ORIGINAL ARTICLE

Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study

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Abstract:

Background: The clinical course of COVID-19 critically ill patients, during their admission in the intensive care unit (UCI), including medical and infectious complications and support therapies, as well as their association with in-ICU mortality has not been fully reported.

Objective: This study aimed to describe clinical characteristics and clinical course of ICU COVID-19 patients, and to determine risk factors for ICU mortality of COVID-19 patients.

Methods: Prospective, multicentre, cohort study that enrolled critically ill COVID-19 patients admitted into 30 ICUs from Spain and Andorra. Consecutive patients from March 12th to May 26th, 2020 were enrolled if they had died or were discharged from ICU during the study period. Demographics, symptoms, vital signs, laboratory markers, supportive therapies, pharmacological treatments, medical and infectious complications were reported and compared between deceased and discharged patients.

Results: A total of 663 patients were included. Overall ICU mortality was 31% (203 patients). At ICU admission non-survivors were more hypoxemic [SpO_2 with non-rebreather mask, 90 (IQR 83–93) vs 91 (IQR 87–94); $p < 0.001$] and with higher sequential organ failure assessment score [SOFA, 7 (IQR 5–9) vs 4 (IQR 3–7); $p < 0.001$]. Complications were more frequent in non-survivors: acute respiratory distress syndrome (ARDS) (95% vs 89%; $p = 0.009$), acute kidney injury (AKI) (58% vs 24%; $p < 10^{-16}$), shock (42% vs 14%; $p < 10^{-13}$), and arrhythmias (24% vs 11%; $p < 10^{-4}$). Respiratory super-infection, bloodstream infection and septic shock were higher in non-survivors (33% vs 25%; $p = 0.03$, 33% vs 23%; $p = 0.01$ and 15% vs 3%, $p = 10^{-7}$), respectively. The multivariable regression model showed that age was associated with mortality, with every year increasing risk-of-death by 1% (95%CI: 1–10, $p = 0.014$). Each 5-point increase in APACHE II independently predicted mortality [OR: 1.508 (1.081, 2.104), $p = 0.015$]. Patients with AKI [OR: 2.468 (1.628, 3.741), $p < 10^{-4}$)], cardiac arrest [OR: 11.099 (3.389, 36.353), $p = 0.0001$], and septic shock [OR: 3.224 (1.486, 6.994), $p = 0.002$] had an increased risk-of-death.

Conclusions: Older COVID-19 patients with higher APACHE II scores on admission, those who developed AKI grades II or III and/or septic shock during ICU stay had an increased risk-of-death. ICU mortality was 31%.

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Características, evolución clínica y factores asociados a la mortalidad en UCI de los pacientes críticos infectados por SARS-CoV-2 en España: estudio prospectivo, de cohorte y multi-céntrico

Resumen

Antecedentes: No se ha reportado plenamente la evolución clínica de los pacientes críticos de COVID-19 durante su ingreso en la unidad de cuidados intensivos (UCI), incluyendo las complicaciones médicas e infecciosas y terapias de soporte, así como su asociación con la mortalidad en ICU.

Objetivo: El objetivo de este estudio es describir las características clínicas y la evolución de los pacientes ingresados en UCI por COVID-19, y determinar los factores de riesgo de la mortalidad en UCI de dichos pacientes.

Métodos: Estudio prospectivo, multi-céntrico y de cohorte, que incluyó a los pacientes críticos de COVID-19 ingresados en 30 UCIs de España y Andorra. Se incluyó a los pacientes consecutivos de 12 de Marzo a 26 de Mayo de 2020 si habían fallecido o habían recibido el alta de la UCI durante el periodo de estudio. Se reportaron los datos demográficos, síntomas, signos vitales, marcadores de laboratorio, terapias de soporte, terapias farmacológicas, y

complicaciones médicas e infecciosas, realizándose una comparación entre los pacientes fallecidos y los pacientes dados de alta.

Resultados: Se incluyó a un total de 663 pacientes. La mortalidad general en UCI fue del 31% (203 pacientes). Al ingreso en UCI los no supervivientes eran más hipoxémicos [SpO_2 sin mascarilla de no reinhalación, de 90 (RIC 83–93) vs 91 (RIC 87–94); p < 0,001] y con mayor puntuación en la escala SOFA - Evaluación de daño orgánico secuencial - [SOFA, 7 (RIC 5–9) vs 4 (RIC 3–7); p < 0,001]. Las complicaciones fueron más frecuentes en los no supervivientes: síndrome de distrés respiratorio agudo (SDRA) (95% vs 89%; p = 0,009), insuficiencia renal aguda (IRA) (58% vs 24%; $p < 10^{-16}$), shock (42% vs 14%; $p < 10^{-13}$), y arritmias (24% vs 11%; $p < 10^{-4}$). Las súperinfecciones respiratorias, infecciones del torrente sanguíneo y los shock sépticos fueron más frecuentes en los no supervivientes (33% vs 25%; p = 0,03, 33% vs 23%; p = 0,01 y 15% vs 3%, $p = 10^{-7}$), respectivamente. El modelo de regresión multivariable reflejó que la edad estaba asociada a la mortalidad, y que cada año incrementaba el riesgo de muerte en un 1% (95%IC: 1–10, p = 0,014). Cada incremento de 5 puntos en la escala APACHE II predijo de manera independiente la mortalidad [OR: 1,508 (1,081, 2,104), p = 0,015]. Los pacientes con IRA [OR: 2,468 (1,628, 3,741), $p < 10^{-4}$)], paro cardiaco [OR: 11,099 (3,389, 36,353), p = 0,0001], y shock séptico [OR: 3,224 (1,486, 6,994), p = 0,002] tuvieron un riesgo de muerte incrementado.

Conclusiones: Los pacientes mayores de COVID-19 con puntuaciones APACHE II más altas al ingreso, que desarrollaron IRA en grados II o III y/o shock séptico durante la estancia en UCI tuvieron un riesgo de muerte incrementado. La mortalidad en UCI fue del 31%.

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List of abbreviations

ARDS	acute respiratory distress syndrome
AKI	acute kidney injury
COPD	chronic obstructive pulmonary disease
CI	confidence interval
CRP	C-reactive protein
ECMO	extracorporeal membrane oxygenation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
GPT	glutamic-pyruvic transaminase
HNFT	high flow nasal therapy
ICU	intensive care unit
IQR	interquartile range
IL-6	interleukin-6
KDIGO	kidney disease: improving global outcomes
LDH	lactate dehydrogenase
MV	mechanical ventilation
NIV	non-invasive ventilation
NMB	neuromuscular blockers
OR	odds ratio
PaCO2	carbon dioxide arterial pressure
PaO_2/FiO_2	arterial oxygen pressure to inspiratory oxygen fraction ratio
PCT	procalcitonin
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	standard deviation
SOFA	sequential organ failure assessment
SpO2	peripheral oxyhemoglobin saturation
WHO	World Health Organization

Introduction

On December 31st 2019, the Chinese office of the World Health Organization (WHO) reported a series of cases of pneumonia of unknown origin in Wuhan City, China.[1] On February 11th 2020, the causative agent of the disease named Coronavirus Disease 2019 (COVID-19), a new type of coronavirus named as ''Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)'' was identified. On March 13th 2020, three months after the first case and coinciding with the arrival of the first cases to the intensive care units (ICU) in Spain, the declaration of a pandemic was made.

Within the clinical spectrum of patients infected with COVID-19 some develop a viral pneumonia with severe hypoxemia and characteristic pulmonary infiltrates that can evolve into an acute respiratory distress syndrome (ARDS), the most severe form of acute respiratory failure.[2] The pandemic scenario has pushed the resources of many ICUs to the limit in different countries worldwide. Retrospective data coming from China, Italy, and the United States described the clinical characteristics of critically ill patients, and prognostic factors for ARDS or death as well as ventilation strategies commonly used.[3–9] As it has been shown, many of these patients present with an extremely serious clinical condition, often associating non-respiratory organic dysfunctions or displaying secondary superinfections. However, until today, the clinical course including medical complications or supportive therapies in ICU patients has not been prospectively reported. The present study prospectively describes the clinical course, treatment received, outcomes, and risk factors for in-ICU mortality in critically ill COVID-19 patients admitted to ICUs throughout Spain.

Methods

Study design

This is a prospective, multicentre, observational, cohort study that enrolled critically ill patients with COVID-19 admitted to 30 ICUs in Spain, and Andorra (participating centres are listed in the Supplementary file). The study was approved by the referral Ethics Committee of Euskadi, Spain. The need for written informed consent from participants was considered by each participating centre. This study followed the ''Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)'' statement guidelines for observational cohort studies.[10] Patient and public involvement did not take place in this study.

Study population and data collection

Data from patients' electronic medical records was collected by physicians trained in critical care according to a previously standardized common protocol. Each investigator had a personal username and password and entered data into a specifically pre-designed online data acquisition system (CoVid19.ubikare.io). Patient confidentiality was protected by assigning a de-identified patient code. All consecutive COVID-19 patients included in the dataset from March 12th to May 26th, 2020 were enrolled if they fulfilled the following criteria: (1) >18 years old, and (2) had confirmed SARS-CoV-2 infection from a respiratory tract sample. Exclusion criteria were: (1) patients with non-confirmed SARS-CoV-2 infection according to WHO guidance,[11] and (2) patients that had not accomplished the outcomes of death or ICU discharge by May 26th, 2020.

Recorded data included demographics, symptoms at ICU admission, vital signs, laboratory markers (bloodwork, coagulation, biochemistry), critical care supportive therapies (mechanical ventilation, renal replacement therapy, extracorporeal membrane oxygenation, etc.), pharmacological treatments, medical complications during stay (definitions are described in the Supplementary appendix), disease chronology [time from symptom onset and from hospital admission to ICU admission, to initiation of respiratory support, and to the onset of complications, and ICU length-of-stay (LOS)]. Sequential Organ Failure Assessment (SOFA) and APACHE II scores, and outcomes by May 26th, 2020 were also reported.

We defined baseline as the first day in ICU and a full set of data was collected on this day. We also gathered complete daily information and reported the ''worst'' values during the ICU period (maximum or minimum, depending on the variable). Our case report form collected data every day from ICU admission to either ICU discharge or death, whichever came first. It also allowed us to retrospectively collect data before ICU admission including symptoms at presentation or pharmacological treatment received. Before data were analysed, two independent investigators, and a statistician screened for erroneous data against standardized ranges and contacted local investigators in case of dubious values.

Measurements and outcomes

This study was aimed to describe the clinical characteristics and clinical course of COVID-19 patients admitted to ICU, as well as to determine risk factors for in-ICU mortality in COVID-19 patients.

Statistical analysis

A pre-defined sample size was not estimated for this study. Descriptive variables are expressed as percentage, mean, and standard deviation (SD), or median and interquartile range (IQR), as appropriate for each variable. To compare variables across groups, Student t-test or Mann–Whitney test for numerical variables, and Chi squared test or Fisher exact test for categorical variables were used. Missing data was not imputed. Analyses were performed in a complete case analysis basis. All tests were two-sided, and a P-value <0.05 was considered statistically significant. Further, to explore the risk factors associated with in-ICU mortality, multivariable logistic regression models were computed. Parameters with a p-value less than 0.1 in univariate analysis were included with variables with more than 30% of missing data being excluded. Two different analyses were performed: (1) we investigated baseline factors such as demographics, comorbidities, symptoms and vital signs, laboratory markers, and severity scores at admission and (2) we explored factors related to the clinical course which included medical and infectious complications, and laboratory markers. Pseudo-r is presented as a measure of model fit. All analyses were performed with STATA version 16.

Results

Characteristics

Over a period of 80 days (between March 12th and May 26th, 2020), 663 patients with a definitive outcome of ICU discharge or death were admitted to 30 ICUs in Spain and Andorra. The enrolment of patients is still ongoing, and as of May 26th, 2020 297 (30%) patients were still in the ICU and therefore were not included in the analysis. Patients demographics, comorbidities and previous pharmacological treatments are shown in Table 1. The median days from symptom onset to hospital and ICU admission were 7 [IQR 5.0–9.0] and 9 [IQR 7.0–13.0], respectively with no differences between survivors and non-survivors (Table 1). Fever (83%) and dyspnoea (71%) were the most frequent symptoms at ICU admission. Among other symptoms, no differences were found between survivors and non-survivors. At ICU admission, non-survivors were sicker as shown by the substantial differences found in the severity scores [APACHE II, 17 (IQR 13–21) vs 11 (IQR 8–15); p < 0.001 and SOFA, 7 (IQR 5–9) vs 4 (IQR 3–7); p < 0.001]. Arterial blood gases at ICU admission showed that severe ARDS ($PaO_2/FiO_2 < 100$ mmHg) was more frequent in non-survivors (43% vs 28%; p = 0.006] (Table 1). The multivariable regression model showed that older age was associated with higher ICU mortality risk [OR 1.05; (95%CI: 1.011–1.099), p = 0.014], and that for each 5-point increase in APACHE II, the mortality risk increased by

Table 1 Demographic, comorbidities, pharmacological treatment, symptoms, scores, vital signs and laboratory markers on admission.

	All (n = 663)	Survivors (n = 460)	Non-survivors (n = 203)	P value
Patients demographics and comorbidities				
Age, years	64 [56−72]/661	62 [53−71]/458	68 [62−73]/203	**<10^{−9}**
Females	219/660 (33.18%)	150/459 (32.68%)	69/201 (34.33%)	0.720
Body mass index (BMI), kg/m^2	28.3 [25.5−32.2]/554	28.6 [25.7−32.4]/398	27.7 [25.3−31.6]/156	0.466
Arterial hypertension	329/663 (49.62%)	214/460 (46.52%)	115/203 (56.65%)	**0.018**
Diabetes mellitus	151/663 (22.78%)	90/460 (19.57%)	61/203 (30.05%)	**0.004**
Chronic heart failure	9/663 (1.36%)	3/460 (0.65%)	6/203 (2.96%)	**0.027**
Chronic kidney disease	38/663 (5.73%)	20/460 (4.35%)	18/203 (8.87%)	**0.029**
Asthma	17/663 (2.56%)	13/460 (2.83%)	4/203 (1.97%)	0.605
COPD	28/663 (4.22%)	19/460 (4.13%)	9/203 (4.43%)	0.836
Dyslipidaemia	90/663 (13.57%)	55/460 (11.96%)	35/203 (17.24%)	0.084
Malignancy	23/663 (3.47%)	11/460 (2.39%)	12/203 (5.91%)	0.035
Pharmacological treatment				
Antihypertensives	300/663 (45.25%)	199/460 (43.26%)	101/203 (49.75%)	0.128
Hypoglycaemic agents	94/663 (14.18%)	57/460 (12.39%)	37/203 (18.23%)	0.053
Antiplatelet agents	84/663 (12.67%)	51/460 (11.09%)	33/203 (16.26%)	0.076
Anticoagulants	51/663 (7.69%)	30/460 (6.52%)	21/203 (10.34%)	0.113
Bronchodilators	166/663 (25.04%)	107/460 (23.26%)	59/203 (29.06%)	0.120
Lipid lowering agents	44/663 (6.64%)	30/460 (6.52%)	14/203 (6.90%)	0.866
Thyroid hormone replacement	62/663 (9.35%)	45/460 (9.78%)	17/203 (8.37%)	0.665
Immunossupresors	24/663 (3.62%)	13/460 (2.83%)	11/203 (5.42%)	0.115
Corticosteroids	30/663 (4.52%)	14/460 (3.04%)	16/203 (7.88%)	**0.008**
Chronology (days from symptom onset)				
To hospital admission	7 [5−9]/654	7 [5−9]/455	7 [4−9]/199	0.693
To ICU admission	9 [7−13]/653	9 [7−12]/454	10 [7−13]/199	0.873
Symptoms				
Fever	551/663 (83.11%)	380/460 (82.61%)	171/203 (84.24%)	0.654
Cough	401/663 (60.48%)	284/460 (61.74%)	117/203 (57.64%)	0.343
Dyspnoea	477/663 (71.95%)	324/460 (70.43%)	153/203 (75.37%)	0.223
Myalgia	109/663 (16.44%)	80/460 (17.39%)	29/203 (14.29%)	0.364
Headache	47/663 (7.09%)	34/460 (7.39%)	13/203 (6.40%)	0.744
Rhinorrhoea	8/663 (1.21%)	5/460 (1.09%)	3/203 (1.48%)	0.706
Vomiting	54/663 (8.14%)	35/460 (7.61%)	19/203 (9.36%)	0.445
Arthralgia	39/663 (5.88%)	31/460 (6.74%)	8/203 (3.94%)	0.209
Chest pain	53/663 (7.99%)	39/460 (8.48%)	14/203 (6.90%)	0.538
Increased sputum production	77/663 (11.61%)	48/460 (10.43%)	29/203 (14.29%)	0.188
Anosmia	28/663 (4.22%)	22/460 (4.78%)	6/203 (2.96%)	0.402
Pharyngodynia	23/663 (3.47%)	15/460 (3.26%)	8/203 (3.94%)	0.650
Diarrhoea	76/663 (11.46%)	51/460 (11.09%)	25/203 (12.32%)	0.692
Fatigue	24/663 (3.62%)	15/460 (3.26%)	9/203 (4.43%)	0.500
Scores				
APACHE II	12 [9−17]/458	11 [8−15]/332	17 [13−21]/126	**<10^{−15}**
SOFA	5 [3−7]/446	4 [3−7]/327	7 [5−9]/119	**<10^{−8}**
Vital Signs				
Temperature, ºC	36.7 [36.0−37.5]/568	36.7 [36.0−37.5]/402	36.7 [36.0−37.5]/166	0.988
Mean arterial pressure, mmHg	86.7 [78.0−96.7]/566	87.3 [78.7−96.7]/397	84.0 [74.3−94.3]/169	0.058
Heart rate, bpm	83 [72−96]/576	82 [71−95]/404	86 [75−100]/172	**0.044**
SpO$_2$, %	91 [86−94]/566	91 [87−94]/396	90 [83−93]/170	**<0.001**
Respiratory rate, rpm	25 [20−30]/539	25 [20−30]/381	26 [20−31]/158	0.077

Table 1 (*Continued*)				
	All (n = 663)	Survivors (n = 460)	Non-survivors (n = 203)	P value
Arterial blood gas				
PaO_2/FiO_2 <100	167/517 (32.30%)	104/370 (28.11%)	63/147 (42.86%)	**0.006**
PaO_2/FiO_2	241/517 (46.62%)	182/370 (49.19%)	59/147 (40.14%)	
PaO_2/FiO_2 >200	109/517 (21.08%)	84/370 (22.70%)	25/147 (17.01%)	
Ventilatory ratio	1.94 [1.51–2.61]/207	1.93 [1.52–2.61]/139	1.94 [1.46–2.66]/68	0.746
Laboratory findings				
Ferritin, ng/mL	1265 [598–1960]/285	1174 [553–1882]/227	1480 [918–2358]/58	**0.010**
ᴅ-dimer, ng/mL	1017 [600–2300]/477	940 [576–2030]/348	1599 [697–3810]/129	**0.002**
CPR, mg/dL	20.7 [8.8–92.0]/569	20.2 [8.5–86.6]/410	21.8 [9.5–112.0]/159	0.234
Leukocytes, $10^3/\mu L$	7.76 [5.75–11.16]/593	7.67 [5.60–10.90]/417	8.30 [5.95–11.95]/176	0.173
Lymphocyte count per μL	0.69 [0.41–0.94]/595	0.70 [0.46–1.00]/422	0.60 [0.40–0.90]/173	0.083
CRP/lymphocyte ratio	34.9 [13.0–108.9]/564	31.2 [12.9–101.3]/405	42.1 [13.5–143.7]/159	0.119
IL-6, pg/mL	107 [40–225]/79	96 [38–203]/59	144 [82–493]/20	0.063
LDH, U/L	432 [348–536]/633	404 [339–514]/384	487 [393–643]/152	**<10^{-6}**
Procalcitonin, ng/mL	0.20 [0.10–0.56]/422	0.18 [0.09–0.50]/305	0.28 [0.13–0.86]/117	**<0.001**
Platelets, 1000/mm^3	220 [164–298]/601	224 [165–302]/405	214 [156–284]/176	0.312
Bilirubin, mg/dL	0.65 [0.42–0.98]/522	0.61 [0.40–0.93]/379	0.70 [0.42–1.00]/143	0.535
GPT, U/L	38 [25–63]/580	38 [26–63]/414	37 [25–59]/166	0.514
Creatinine, mg/dL	0.85 [0.69–1.13]/592	0.83 [0.67–1.04]/421	0.96 [0.72–1.42]/171	**<10^{-4}**
Urea, mg/dL	40 [29–57]/436	36 [26–50]/295	47 [35–69]/141	**<10^{-8}**
Troponin, ng/mL	12.3 [5.0–28.0]/319	11.0 [4.7–22.7]/233	15.9 [5.8–53.0]/86	**0.006**
NT-proBNP, pg/mL	456 [125–1206]/87	326 [123–896]/54	603 [288–1638]/33	**0.034**
Haematocrit, %	39.0 [35.7–43.0]/560	39.1 [36.0–43.0]/394	38.5 [35.0–42.0]/166	**0.041**
Lactate, mmol/L	1.50 [1.11–2.00]/402	1.41 [1.10–1.83]/286	1.67 [1.21–2.20]/116	**0.002**

Data are expressed as median [interquartile range] or count (percentage). For numeric variables, total counts are presented for each cell. P values were calculated with Mann–Whitney test for numerical variables, and Fisher exact test for categorical variables. COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; SpO_2: peripheral oxyhaemoglobin saturation; PaO_2/FiO_2: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; $PaCO_2$: partial pressure of carbon dioxide; CRP: C-reactive protein; IL-6: interleukin 6; LDH: lactate dehydrogenase; GPT: pyruvic glutamic transaminase; NT-proBNP: N-terminal pro-brain natriuretic peptide. Mg/mL: milligram per millilitre, ng/mL: nanogram per millilitre, pg/mL: picogram per millilitre, and mmol/L: millimoles per litre, μL: microlitre, U/L: units per litre.

51% [OR 1.508 (1.081, 2.104), p = 0.015] (Table 4). Worst values during admission and its relationship to ICU mortality are presented in Tables S1 and S2.

Laboratory findings

Important inflammatory markers were significantly higher for non-survivors at ICU admission (Table 1): ferritin [1480 (IQR: 918–2358) vs 1174 (IQR: 553–1882); p = 0.010], ᴅ-dimer [1599 (697–3810) vs 940 (IQR: 576–2030); p = 0.002], procalcitonin (PCT) [0.28 (IQR: 0.13 to 0.86) vs 0.18 (IQR: 0.09 to 0.50); p < 0.001] and lactate dehydrogenase (LDH) [487 (IQR: 393–643) vs 404 (IQR: 339–514); p < 0.001]. High-sensitivity troponin I [16 (IQR: 5–53) vs 11 (IQR: 4–22); p = 0.006], N terminal prohormone of brain natriuretic peptide (NT-proBNP) [603 (IQR: 288–1638) vs 326 (IQR: 123–896); p = 0.034], lactate [1.6 (IQR: 1.1–2.2) vs 1.4 (IQR: 1.1–1.8); p = 0.002] and creatinine [0.96 (IQR: 0.72–1.42) vs 0.83 (IQR: 0.67–1.04); p < 0.001)] were also significantly higher in non-survivors. The same finding was observed between survivors and non-survivors for the differences between the worst peak values for each laboratory marker (Table S1). The multivariable regression model showed that during ICU stay, PCT (OR 1.06; 95%CI: 1.01–1.11, p = 0.010) and platelets (OR 0.97; 95%CI: 0.993–1.000, p = 0.045) were associated to a higher risk of death (Table S2).

Respiratory support and adjunctive strategies

In 199 out of 667 patients high flow nasal therapy (HFNT) or non-invasive ventilation (NIV) were chosen as the first therapeutic option for respiratory support, with HFNT (165, 24%) being more common than NIV (34, 5.1%). Besides, HFNT was used as first line treatment for respiratory support in 30% of survivors while in only 11% of non-survivors (p < 0.001). Invasive respiratory support was needed in 494 (74%) of patients, being required in 182 out of 203 non-survivors (89%), which was significantly higher (p < 0.001) than in survivors (312, 67%). The 19 non-survivors in whom invasive respiratory support was not instituted had not-to-intubate orders. The median time from symptom onset and from hospital admission to mechanical ventilation were 10 (IQR: 8–14) and 3 (IQR:1–6) days, respectively with no differences between survivors and non-survivors (Table 2). Regarding adjunctive therapies, lung recruitment manoeuvre was the commonest as it was applied in 78% of patients

Table 2 Ventilation, adjunctive therapies and pharmacological treatment during ICU stay.

	All (n = 663)	Survivors (n = 460)	Non-survivors (n = 203)	P value
Modes of ventilation				
Mechanical ventilation	494/663 (74.51%)	312/460 (67.83%)	182/203 (89.66%)	**<10⁻⁹**
Mechanical ventilation as 1st intention	419/663 (63.20%)	259/460 (56.30%)	160/203 (78.82%)	**<10⁻⁷**
Days from symptoms onset to mechanical ventilation	10 [8–14]/488	10 [7–14]/308	11 [8–15]/180	0.108
Days from hospital admission to mechanical ventilation	3 [1–6]/494	3 [1–6]/312	4 [1–7]/182	0.097
HFNT as 1st intention	165/663 (24.89%)	142/460 (30.87%)	23/203 (11.33%)	**<10⁻⁷**
HFNT after extubation	112/419 (26.73%)	103/259 (39.77%)	9/160 (5.62%)	**<10⁻¹⁵**
NIV as 1st intention	34/663 (5.13%)	22/460 (4.78%)	12/203 (5.91%)	0.568
NIV after extubation	27/419 (6.44%)	25/259 (9.65%)	2/160 (1.25%)	**<0.001**
Adjunctive therapies				
Recruitment manoeuvres	296/375 (78.93%)	194/241 (80.50%)	102/134 (76.12%)	0.355
Prone positioning	395/635 (62.20%)	250/445 (56.18%)	145/190 (76.32%)	**<10⁻⁵**
Neuromuscular blocking agents	326/472 (69.07%)	191/305 (62.62%)	135/167 (80.84%)	**<10⁻⁴**
ECMO	15/647 (2.32%)	6/453 (1.32%)	9/194 (4.64%)	**0.019**
CO₂ removal	10/647 (1.55%)	1/453 (0.22%)	9/194 (4.64%)	**<0.001**
Renal replacement	60/647 (9.27%)	18/453 (3.97%)	42/194 (21.65%)	**<10⁻¹⁰**
Pharmacological treatment				
Lopinavir/Ritonavir	432/663 (65.16%)	302/460 (65.65%)	130/203 (64.04%)	0.724
Hydroxychloroquine	597/663 (90.05%)	418/460 (90.87%)	179/203 (88.18%)	0.324
Remdesivir	19/663 (2.87%)	16/460 (3.48%)	3/203 (1.48%)	0.208
Interferon	168/663 (25.34%)	106/460 (23.04%)	62/203 (30.54%)	0.043
Tocilizumab	282/663 (42.53%)	195/460 (42.39%)	87/203 (42.86%)	0.932
Azithromycin	496/663 (74.81%)	354/460 (76.96%)	142/203 (69.95%)	0.065
Corticosteroids	506/663 (76.32%)	353/460 (76.74%)	153/203 (75.37%)	0.693
Prophylactic antibiotics	604/663 (91.10%)	419/460 (91.09%)	185/203 (91.13%)	0.999
Anticoagulation	106/663 (15.99%)	59/460 (12.83%)	47/203 (23.15%)	**0.001**
Vasoactive drugs	436/663 (65.76%)	273/460 (59.35%)	163/203 (80.30%)	**<10⁻⁷**

Data are expressed as median [interquartile range] or count (percentage). For numeric variables, total counts are presented for each cell. P values were calculated with Mann–Whitney test for numerical variables, and Fisher exact test for categorical variables. HFNT: high flow nasal therapy; NIV: non-invasive ventilation; ECMO: extracorporeal membrane oxygenation; CO_2: carbon dioxide.

with no differences between survivors and non-survivors. Other therapies, such as prone positioning and the use of neuromuscular blocking agents were also frequently used [395 (62%) and 326 (69%), respectively], and they were clearly more frequently applied in deceased patients [145 (76%) vs 250 (56%); p < 0.001 and 135 (80%) vs 191 (62%); p < 0.001] (Table 2).

Pharmacological treatment

Treatments provided are shown in Table 2. We did not observe differences in the pharmacological treatment between survivors and non-survivors except for the use of vasoactive drugs [273 (59%) vs 183 (80%); p < 0.001] (Table 2). Among the antiviral drugs used, the use of hydroxychloroquine administered to 597 (90%) patients stood out. The use of remdesivir 19 (3%) was anecdotal. Regarding anti-inflammatory drugs, both corticosteroids 506 (76%) and tocilizumab 282 (42%) were frequently administered. It should be noted that full anticoagulant doses of heparin were used in 106 (15%) of the patients, being used more often in deceased patients (23% vs 13%, p < 0.001).

Medical and infectious complications

Complications are shown on Table 3. Acute respiratory distress syndrome (ARDS) was the most commonly diagnosed complication in 597 (90%) patients followed by acute kidney injury (227; 34%). Less common complications, but still clinically relevant were shock (150; 23%), arrhythmias (97; 15%) and pulmonary embolism (72; 11%). Some were more frequent in non-survivors such as ARDS (95% vs 89%; p = 0.009), acute kidney injury (AKI) (58% vs 24%; p < 10⁻¹⁶), shock (42% vs 14%; p < 10⁻¹³), and arrhythmias (24% vs 11%; p < 10⁻⁴). Also, respiratory super-infection, bloodstream infection and septic shock were higher in non-survivors (33% vs 25%; p = 0.03, 33% vs 23%; p = 0.01 and 15% vs 3%, p = 10⁻⁷), respectively. However, pulmonary embolism was not different between groups (12% vs 10%, p = 0.59). Bacterial/fungal respiratory super-infection (176; 26%), and bloodstream infection (172; 25%) were very frequent and stood out above the rest of reported infections. Both, together with septic shock, were more frequent in non-survivors (33% vs 25%; p = 0.029, 33% vs 23%; p = 0.010 and 15% vs 3%, p < 0.0001). Patients with AKI [OR: 2.468 (1.628, 3.741), p < 10⁻⁴)], cardiac arrest [OR: 11.099 (3.389, 36.353), p = 0.0001], and septic shock [OR: 3.224

Table 3 ICU complications and outcomes.

	P value (n = 663)	Survivors (n = 460)	Non-survivors (n = 203)	
Medical complications				
ARDS	601/663 (90.65%)	408/460 (88.70%)	193/203 (95.07%)	**0.009**
Shock	150/663 (22.62%)	65/460 (14.13%)	85/203 (41.87%)	**<10^{-13}**
Bleeding	52/663 (7.84%)	35/460 (7.61%)	17/203 (8.37%)	0.755
Thromboembolism	72/663 (10.86%)	48/460 (10.43%)	24/203 (11.82%)	0.590
Cardiac arrest	26/663 (3.92%)	4/460 (0.87%)	22/203 (10.84%)	**<10^{-8}**
Heart failure	22/663 (3.32%)	8/460 (1.74%)	14/203 (6.90%)	**0.001**
Arrhythmias	97/663 (14.63%)	49/460 (10.65%)	48/203 (23.65%)	**<10^{-4}**
Ischemic stroke	12/663 (1.81%)	5/460 (1.09%)	7/203 (3.45%)	0.053
Acute kidney injury	227/663 (34.24%)	109/460 (23.70%)	118/203 (58.13%)	**<10^{-16}**
Elevated liver enzymes	324/663 (48.87%)	226/460 (49.13%)	98/203 (48.28%)	0.866
Nonspecific neurological complications	33/663 (4.98%)	28/460 (6.09%)	5/203 (2.46%)	0.053
Pneumothorax	33/663 (4.98%)	24/460 (5.22%)	9/203 (4.43%)	0.847
Failed extubation	34/663 (5.13%)	19/460 (4.13%)	15/203 (7.39%)	0.087
Hyperglycaemia	156/663 (23.53%)	102/460 (22.17%)	54/203 (26.60%)	0.234
Infectious complications				
Respiratory super-infection	180/663 (27.15%)	113/460 (24.57%)	67/203 (33.00%)	0,029
Pneumonia	42/663 (6.33%)	27/460 (5.87%)	15/203 (7.39%)	0,490
Bacteraemia	174/663 (26.24%)	107/460 (23.26%)	67/203 (33.00%)	0,010
Urinary tract infection	79/663 (11.92%)	54/460 (11.74%)	25/203 (12.32%)	0,897
Septic shock	42/663 (6.33%)	12/460 (2.61%)	30/203 (14.78%)	**<10^{-7}**
Outcomes				
ICU length of stay	12 [6−21]/663	12 [6−21]/460	13 [6−20]/203	0.561
Ventilator days|	13 [7−21]/494	12 [7−20]/312	15 [8−22]/182	**0.009**
Ventilator-free days	8 [0−20]/663	16 [7−22]/460	0 [0−0]/203	**<10^{-67}**
Weaning failures	33/663 (6.68%)/494	22/312 (7.05%)	11/182 (6.04%)	0.713
Days from symptoms to ICU discharge or death	24 [12−42]/662	24 [12−42]/459	26 [12−40]/203	0.591

Data are expressed as median [interquartile range] or count (percentage). For numeric variables, total counts are presented for each cell. P values were calculated with Mann–Whitney test for numerical variables, and Fisher exact test for categorical variables. ARDS: acute respiratory distress syndrome; ICU: intensive care unit. Acute kidney injury (AKI) refer to stages II or III on the KDIGO classification. |Ventilator days include only patients that received mechanical ventilation.

(1.486, 6.994), p = 0.002] had an increased risk-of-death (Table 4).

The chronology of complications and treatments is shown on Figs. 1 and S1.

Outcomes

The overall ICU mortality found was 31% (203 patients). Median ICU length of stay was 12 [6–21], with no differences between survivors and deceased patients 12 [6–21] vs 13 [6–20]; p = 0.56.

Discussion

In this nationwide prospective cohort study in COVID-19 critically ill patients, ageing men with prevalent comorbidities such as hypertension, obesity and diabetes were overrepresented, which is in line with previous reports.[3–9] Non-survivors were often sicker as shown by the APACHE II, and SOFA scores, and baseline oxygenation parameters, as well as by the higher use of mechanical ventilation. However, on multivariable analysis using data collected at

baseline, only age, and APACHE II remained as predictors of ICU mortality, thus making baseline prediction of mortality difficult. Indeed, a significant number of patients who received mechanical ventilation could be successfully discharged from ICU after two weeks of admission. Overall ICU mortality was 31%, which is similar to reports of non-COVID-19 ARDS.[12]

A wide array of complications was recorded. AKI stage II or III was among the commonest, being diagnosed in 1 out of 3 patients, and it was associated with a higher risk of mortality. 50% of patients presenting with this complication died in the ICU, a value that rose to 70% when renal replacement techniques were needed. In multivariable analysis, AKI stage II-III conferred an odds ratio for ICU mortality of 1.9. Considering prediction of mortality at baseline was poor, and that this complication often appeared early, AKI could represent a step-up for realistically characterizing the expected clinical picture of an individual COVID-19 patient. Cardiac complications had a similar prevalence than in previous studies, without differences between groups.[3,9] Moreover, pulmonary embolism, although frequent did not increase the risk of death. Pulmonary embolism is a difficult complication to confirm since radiology is needed. Whether

Table 4   Risk factors associated with in-ICU mortality — multivariable logistic regression.

Baseline risk factors for ICU mortality (N = 270)

Variables	Multivariate OR (95% CI)	P value
Age, years	1.054 (1.011, 1.099)	**0.014**
SOFA	1.099 (0.947, 1.275)	0.215
APACHE II per 5-point increase	1.508 (1.081, 2.104)	**0.015**
Diabetes Mellitus	1.831 (0.428, 7.838)	0.415
Chronic kidney disease	0.914 (0.226, 3.691)	0.900
Malignancy	1.866 (0.360, 9.678)	0.458
Chronic corticosteroid use	3.030 (0.573, 16.027)	0.192
Antiplatelet agents	1.175 (0.422, 3.270)	0.758
Dyspnoea	0.716 (0.216, 2.368)	0.584
Mean arterial pressure, mmHg	1.005 (0.981, 1.029)	0.706
PaO_2/FiO_2 <100	1 (Ref.)	–
PaO_2/FiO_2 100—200	0.629 (0.293, 1.350)	0.234
PaO_2/FiO_2 >200	0.659 (0.203, 2.139)	0.488
Ventilatory ratio	1.072 (0.591, 1.946)	0.819
Lymphocyte count per mL	1.038 (0.570, 1.889)	0.903
CPR/lymphocyte ratio	1.001 (0.998, 1.004)	0.625
Creatinine, mg/dL	2.560 (0.842, 7.784)	0.097
Haematocrit, %	0.964 (0.873, 1.066)	0.477
D-dimer per 100 ng/mL increase	0.997 (0.982, 1.011)	0.644
Overall Pseudo-R^2 0.277		
Complications associated with ICU mortality (N = 660)		
Age, years	1.049 (1.029, 1.069)	<0,0001
ARDS	1.504 (0.683, 3.309)	0,3106
Shock	2.150 (1.347, 3.432)	0,0013
Bleeding	0.521 (0.247, 1.096)	0,0856
Cardiac arrest	11.099 (3.389, 36.353)	0,0001
Heart failure	2.670 (0.959, 7.428)	0,0600
Arrhythmias	1.288 (0.753, 2.202)	0,3553
Ischemic stroke	3.516 (0.962, 12.856)	0,0573
Acute kidney injury	2.468 (1.628, 3.741)	<0,0001
Respiratory co-infection	1.119 (0.712, 1.757)	0,6260
Pneumonia	0.979 (0.462, 2.076)	0,9557
Bacteraemia	1.271 (0.803, 2.010)	0,3057
Septic shock	3.224 (1.486, 6.994)	0,0030
Overall Pseudo-R^2 0.207		

Two multivariable logistic regression models are presented: the first one using predictors on admission to ICU, and the second one using complications as predictors. OR: odds ratio; SOFA: sequential organ failure assessment; SpO2: peripheral oxyhaemoglobin saturation; PaO_2/FiO_2: partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; $PaCO_2$: partial pressure of carbon dioxide; CRP: C-reactive protein; ARDS: acute respiratory distress syndrome. Mg/mL: milligram per millilitre, ng/mL: nanogram per millilitre.

the latter underestimated the incidence in the most severe cases is unknown. Indeed, non-survivors were anticoagulated twofold more often, a fact that might have been triggered by higher levels of D-dimer in this subgroup. However, neither baseline nor maximal D-dimer independently predicted mortality in this cohort, a finding that is differential from previous studies. Our results reinforce the need to better characterize this phenomenon and to properly address the effect of using prophylactic therapeutic anticoagulation in the sickest patients, which was common in our cohort of patients, a strategy not devoid of potential complications. Although bleeding rate was not significantly different between groups, our methodology does not allow us to answer whether this strategy could be considered safe or effective in this population. Finally, 26% of patients were

diagnosed with a respiratory super-infection and 25% with a bloodstream infection, both prevailing in non-survivors. When these complications further evolved into septic shock, the odds of mortality were threefold higher.

For laboratory markers, only maximal procalcitonin level and platelet count were predictive of mortality in multivariate analysis. Maximal interleukin-6 levels were higher in non-survivors; but peak values were far away from those described in the cytokine storm syndrome,[13] an entity that some researchers have used to advocate for the use of anti-inflammatory treatment.[14,15] In this line, ferritin levels were also much lower than those previously reported in severe forms of hemophagocytic lymphohistiocytosis (HLH) suggesting these two processes do not play a significant role in the outcome of COVID-19 patients.[16] Despite this,
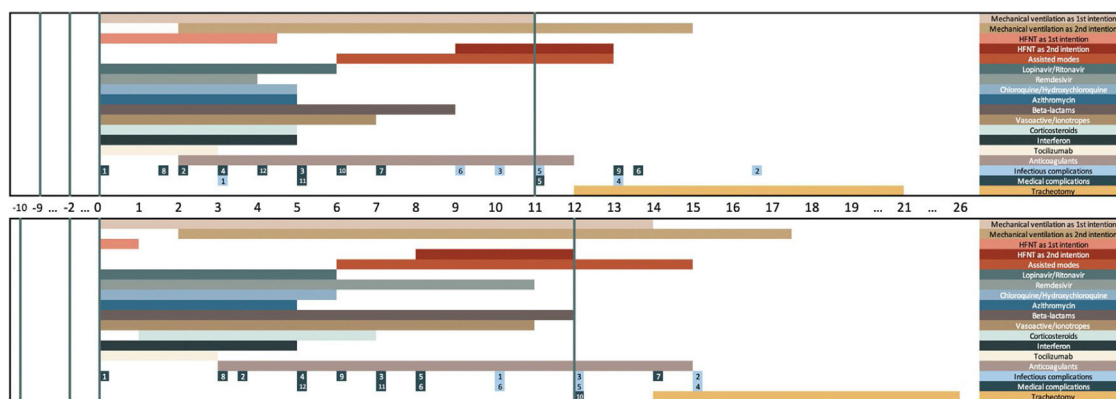
Figure 1 Chronology of treatments and complications during ICU stay for discharged (upper graph) and deceased (lower graph) patients.

The upper part of the graph represents discharged patients. The lower part of the graph represents deceased patients. Day 0 is the day of ICU admission. The vertical lines represent day of symptoms onset, day of hospital admission, day of ICU admission (day 0), and day of discharged (upper graph) or death (lower graph). Each horizontal bar plots the median day of start and median day of end of each treatment among patients with the treatment. Complications are represented at the median day of onset among patients with the complication. Infectious complications: 1 Septic shock; 2 Pneumonia; 3 Bacteraemia; 4 Urinary infection; 5 Respiratory co-infection; 6 Other infectious complication.

Medical complications: 1 ARDS; 2 Acute renal failure; 3 Arrhythmias; 4 Shock; 5 Bleeding; 6 Nonspecific neurological complications; 7 Thromboembolism; 8 Heart failure; 9 Cardiac arrest; 10 Ischemic Stroke; 11 Elevated liver enzymes; 12 Hyperglycaemia.

both groups received often pharmacological treatment, and steroids were given to 3 out of 4 patients, and tocilizumab to roughly 40%, with no differences between groups. In our opinion, this is of high concern given the paucity of data about the efficacy and safety of these treatments.

This study has several strengths. First, this multicentre study provided a highly detailed description of the clinical picture in COVID-19 ICU patients, after including 663 patients with complete outcome data. Second, to the best of our knowledge this is the first study that prospectively explores the association between ICU features at admission and ICU mortality, and the association of the ICU clinical course to the risk of death. However, we acknowledge some limitations. First, observational studies, especially when multicentre in nature, are prone to induce errors while collecting data. For this reason, a concise manual was provided to all the researchers at the beginning of the study. Also, two investigators checked for the accuracy of the data and disregarded occasional unreliable values. Second, it is plausible that due to the burden of care experienced by participating clinicians during the study period, some of the patients admitted to the ICU were not included in the database. However, due to the nature of the registry, we consider that a selection bias was not favoured. Third, at the time of this analysis, as this information was not initially collected, we had no data on the different pharmacological treatments administered before ICU admission. Finally, at the time of the analysis 297 (30%) patients did not have a definitive outcome regarding ICU discharge or death and therefore were not included in the analysis.

Conclusions

COVID-19 critically ill patients often present with an acute respiratory failure with high ICU mortality, which is similar to other non-COVID ARDS cases. Acute kidney injury and septic shock are common and confer an increased risk of mortality.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Euskadi, Spain. The need for written informed consent from participants was considered by each participating center.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.redare.2020.07.001.

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