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Original article

Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain

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ABSTRACT

Objectives: To analyse the characteristics and predictors of death in hospitalized patients with coronavirus disease 2019 (COVID-19) in Spain.
Methods: A retrospective observational study was performed of the first consecutive patients hospitalized with COVID-19 confirmed by real-time PCR assay in 127 Spanish centres until 17 March 2020. The follow-up censoring date was 17 April 2020. We collected demographic, clinical, laboratory, treatment and complications data. The primary endpoint was all-cause mortality. Univariable and multivariable Cox regression analyses were performed to identify factors associated with death.
Results: Of the 4035 patients, male subjects accounted for 2433 (61.0%) of 3987, the median age was 70 years and 2539 (73.8%) of 3439 had one or more comorbidity. The most common symptoms were a history of fever, cough, malaise and dyspnoea. During hospitalization, 1255 (31.5%) of 3979 patients developed acute respiratory distress syndrome, 736 (18.5%) of 3988 were admitted to intensive care units and 619 (15.5%) of 3992 underwent mechanical ventilation. Virus- or host-targeted medications included lopinavir/ritonavir (2820/4005, 70.4%), hydroxychloroquine (2618/3995, 65.5%), interferon beta (1153/3950, 29.2%), corticosteroids (1109/3965, 28.0%) and tocilizumab (373/3951, 9.4%). Overall, 1131 (28%) of 4035 patients died. Mortality increased with age (85.6% occurring in older than 65 years). Seventeen factors were independently associated with an increased hazard of death, the strongest among them including advanced age, liver cirrhosis, low age-adjusted oxygen saturation, higher concentrations of C-reactive protein and lower estimated glomerular filtration rate.
Conclusions: Our findings provide comprehensive information about characteristics and complications of severe COVID-19, and may help clinicians identify patients at a higher risk of death. **Juan Berenguer, Clin Microbiol Infect 2020;26:1525**

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Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated coronavirus disease 2019 (COVID-19) emerged in China in December 2019 and has spread globally, creating a worldwide pandemic and a public health crisis of historic dimensions [1]. The clinical spectrum of COVID-19 varies widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome (ARDS), multisystem organ failure and ultimately death [2–4].

Several case series or cohorts describing the clinical characteristics and outcomes of patients with severe COVID-19 have been reported summarizing the experience of city or regional hospitals in China [2,5,6], Singapore [7] and New York City [8,9], as well as case series of critically ill patients admitted to intensive care units (ICUs) in China [10], Italy [4] and the United States [11]. However, variations in the rates for COVID-19 hospitalizations and deaths may occur across different areas even in the same country, suggesting differences in population characteristics or inequities in the access to care [12]. We are aware of three prior published nationwide cohorts of hospitalized patients with COVID-19, two from China [3,13] and one from the United Kingdom [14]. None of these three cohorts explored both clinical and laboratory variables associated with hospital death.

Our study aimed to determine the epidemiologic and clinical characteristics of hospitalized patients with COVID-19 in Spain, and to identify clinical and laboratory predictors of death.

Patients and methods

Design and patient selection

COVID-19@Spain is a retrospective nationwide cohort study of patients admitted to Spanish hospitals with laboratory-confirmed COVID-19 infection by real-time PCR (RT-PCR) assay for SARS-CoV-2. Investigators from participating centres were asked to include the first consecutive hospitalized patients (up to 100) meeting the study criteria from the start of the epidemic in Spain until 17 March 2020. The Ethics Committee for Research with Medicines of Hospital General Universitario Gregorio Marañón approved the study and waived informed consent for the collection of clinical data.

Investigations

The data source comprised the electronic medical records. All data were collected using an electronic case report form (eCRF), a modified version of the World Health Organization International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) Core CRF [15]. The eCRF was built using REDCap electronic data capture tools [16] and was hosted at SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology)/GESIDA (AIDS Study Group) Foundation (FSG).

The variables registered included administrative data, epidemiologic information and type of clinical specimen in which the diagnosis was confirmed. We also registered demographics, comorbidities, current medications, signs and symptoms at admission, baseline laboratory tests results, chest radiographic findings at baseline and during follow-up, development of ARDS and other complications during hospitalization, use of medications with purported activity against COVID-19, use of adjunctive medications to modulate the host inflammatory response, admission to a high-dependency unit or ICU, noninvasive ventilation, mechanical ventilation, use of extracorporeal membrane oxygenation, vasopressor agents and renal replacement therapy.

The clinical status of the patients as of 17 April 2020 was categorized as discharged alive (with date of discharge), alive and currently hospitalized or dead (with date of death). For patients who were discharged and subsequently readmitted during the study period, only one hospital admission episode was considered for purposes of analysis.

Outcome

The primary endpoint was all-cause mortality. Baseline was the date of hospital admission. The follow-up censoring date was 17 April 2020.

Definitions

Comorbidities and complications during hospitalization were defined as diagnoses included in the medical record. Cancer was defined as the presence of an active solid or haematologic malignant neoplasm. Obesity was defined as a body mass index of >30 kg/m^2. ARDS was defined as the acute onset or worsening of respiratory symptoms with severe hypoxaemia and bilateral opacities on chest radiograph not fully explained by cardiac failure or fluid overload [17].

Study oversight

The investigators of each participating centre vouch for the completeness and accuracy of the data. FSG monitors maintained close contact with investigators for problem resolution during the period of data retrieval; they checked the database for missing, invalid and inconsistent data; and they managed queries before the analysis.

Statistical analysis

Univariable and multivariable Cox regression analyses were performed to identify factors associated with death. To obtain a reduced set of variables from the broad set of predictors, we carried out a blockwise forward procedure allocating the predictor variables into five clusters: sociodemographic characteristics, comorbidities, admission signs and symptoms, vital signs and laboratory parameters. A multivariable regression analysis was fitted within each block using two criteria to achieve the best set of predictors: relevance to the clinical situation and statistical significance ($p < 0.10$). We used variance inflation factors to detect collinearity among predictors included in the multivariable models. We carried out a sensitivity analysis in which the order of entry of the blocks was inverted. We checked the proportional hazards assumption. Variables with more than 25% missing values have not been considered, and missing values were treated as a separate category for analysis. Heterogeneity introduced by different hospitals was accounted for by using robust methods to estimate standard errors, and thus to calculate 95% confidence intervals and p values.

Statistical analyses were performed by Stata 15.0 software (StataCorp, College Station, TX, USA). This study was registered with ClinicalTrials.gov as trial NCT04355871. The STROBE guidelines were used to ensure the reporting of the study (Supplementary Table S1).

Results

The final cohort included 4035 hospitalized patients (Supplementary Fig. S1) in whom SARS-CoV-2 was detected by RT-PCR by testing nasopharyngeal swabs (89.6%), pharyngeal swabs (13.4%), low respiratory tract specimens (1.3%) and other specimens (4.4%). The median admission date was 13 March 2020, with little variability among the median admission date between the centres (range from 6 to 17 March). The median follow-up time was 34 days (interquartile range (IQR), 24–37 days). A total of 141 patients (3.6%) were discharged and readmitted during the study period, a median time of 5 days (IQR, 2–9 days) after discharge.

Demographics and presenting clinical features

Patient characteristics, categorized by survival, are shown in Table 1. In brief, male subjects accounted for 61.0%, the median age was 70 years and 25.1% were ≥80 years old. Most patients were Spanish-born whites. The age distribution of patients stratified by sex is shown in Fig. 1(A).

At least one comorbidity was present in 73.8%, and 26.7% had at least three comorbid conditions. The most common comorbidities were arterial hypertension (51.2%), chronic heart disease (23.3%), diabetes mellitus (21.8%), chronic pulmonary disease (not asthma) (17.9%) and obesity (13.8%). Only 0.7% patients had HIV. Before admission, 19.4% patients had been provided angiotensin-converting enzyme (ACE) inhibitors and 17.3% were receiving angiotensin II receptor blockers (Table 1).

The median duration of symptoms before hospitalization was 4 days (IQR, 2–7 days), and the most commonly reported symptoms were history of fever (81.0%), cough (71.8%), malaise (64.0%), dyspnoea (49.1%), upper respiratory tract symptoms (30.8%), myalgia or arthralgia (24.9%) and sputum production (24.1%) (Supplementary Table S2). Abnormal vital signs at admission included fever (40.9%), arterial hypotension (18.8%) and marked tachypnoea (10.9%). Low age-adjusted arterial oxygen saturation (SaO_2) levels on room air were reported in 26.6% patients (Supplementary Table S3).

Chest radiograph findings

Infiltrates on initial chest radiograph were observed in 77.6% patients, of whom 71.3% had bilateral involvement. Over the whole hospital course, worsening of the baseline infiltrates was observed in 64.7% patients, with new lesions in 51.0%.

Laboratory findings

Baseline laboratory findings are shown in Table 2. The most common abnormalities in blood counts included lymphopenia (54.2%) and thrombocytopenia (31.5%). The median neutrophil-to-lymphocyte ratio was 4.5. A prolonged activated partial thromboplastin time was present in 9.4%, and 57.1% had D-dimer levels above the normal range. High serum levels were reported from alanine aminotransferase (25.3%), aspartate aminotransferase (34.7%), lactate dehydrogenase (64.5%), creatine kinase (23.5%), C-reactive protein (91.9%) and procalcitonin (14.2%). Low serum albumin was found in 36.0% patients, and 6.8% had an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Ferritin and interleukin 6 were determined in a limited number of patients, and high concentrations of these parameters were found in 75.1% and 90.0% respectively.

Supportive therapy and medications

High-dependency unit or ICU admission was required for 18.5% patients, 15.5% underwent mechanical ventilation, 11.9% received vasopressors and 3.0% received renal-replacement therapy (Supplementary Table S4). Virus-targeted agents were administered to 82.0% patients: lopinavir/ritonavir to 70.4%, hydroxychloroquine to 65.5% and subcutaneous interferon beta to 29.2%, usually in combination with lopinavir/ritonavir. Host-targeted agents included systemic corticosteroids in 28.0% and tocilizumab in 9.4%. Antibiotics other than azithromycin were administered to 80.9% and antifungals to 3.2% (Supplementary Table S5).

Complications and mortality

The full list of complications during the hospital course is provided in Supplementary Table S6. The most common were ARDS (31.5%), acute kidney injury (15.4%), presumed bacterial pneumonia (10.6%), heart failure (5.8%) and bloodstream infection (4.9%). During the study period, 28.0% patients died, 64.1% were discharged and 7.8% remained hospitalized. The median (IQR) time to death since the beginning of symptoms and since hospital admission was 13 (9–19) days and 10 (6–16) days, respectively. Death was particularly high among patients aged ≥80 years (54.9%) (Fig. 1(B)) and those with three or more comorbid conditions (47.7%). Death was also very high among those with ARDS (59.3%), those who were admitted to the ICU (42.4%) and those who underwent mechanical ventilation (45.7%). The median (IQR) length of stay was 4 (1–9) days for patients who were discharged and 35 (32–38) days for those who remained hospitalized at the censoring date.

Predictors of death

Independent predictors of death in the different clusters of variables are shown in Table 3. In the final adjusted analysis, we found 17 factors independently associated with an increased hazard of death: male sex, older age, arterial hypertension, obesity, liver cirrhosis, chronic neurologic disorder, active cancer, dementia, dyspnoea, confusion, low age-adjusted SaO2 on room air, higher white cell blood count, higher neutrophil-to-lymphocyte ratio, lower platelet count, prolonged international normalized ratio, lower estimated glomerular filtration rate and higher concentrations of C-reactive protein (Fig. 2). No collinearity was detected, the proportional hazards assumption was fulfilled and the results were not changed when the order of entry of the blocks was inverted. Kaplan-Meier plots for death according to age and sex are shown in Fig. 3. The adjusted hazard ratio of death for being admitted early in the epidemic (before 13 March) versus later was 1.07 (95% confidence interval, 0.90–1.28; p 0.407). The variable unilateral or bilateral lung opacities had missing values in 29% individuals and was not included in the final model. However, when this variable was included in the model, the adjusted hazard ratio of death for bilateral opacities compared to unilateral opacities was 1.32 (95% confidence interval, 0.11–1.55; p 0.002). We also carried out two *post hoc* analyses (data not shown). In the first one, the predictors of mortality among patients aged ≤65 years were not substantially different from those found in the whole dataset. In the second analysis, the mortality hazard did not change depending on the seroprevalence of IgG anti–SARS-CoV-2 at the provincial level, according to a recent nationwide study in Spain [18].

Discussion

Our cohort describes the presenting characteristics and outcomes of 4035 patients with COVID-19 admitted to 127 centres in Spain during the first month of the country outbreak. We are aware of three prior published nationwide cohorts of hospitalized patients with COVID-19, two from China [3,13] and one from the United Kingdom. The majority of patients in all four cohorts were male. However, compared to Chinese patients, those from Spain and the United Kingdom were, on average, two decades older and had a prevalence three times higher of comorbid conditions. It is thus not surprising that mortality was substantially higher in Spain (28%) and the United Kingdom (26%) than in China (1.4% and 3.2%). Presenting features were similar in all

Table 1
Demographics, comorbidity data and current medications of 4035 hospitalized patients with COVID-19 stratified according to vital status at study censoring date

Characteristic	Alive (n = 2904)	Dead (n = 1131)	p	Total (N = 4035)
Sex			<0.001	
Male	1666/2868 (58.1)	767/1119 (68.5)		2433/3987 (61.0)
Female	1202/2868 (41.9)	352/1119 (31.5)		1554/3987 (39.0)
Pregnant female	13/1136 (1.1)	2/329 (0.6)	0.395	15/1465 (1.0)
Gestational week, median (IQR)	33 (17–38)	—		33 (17–38)
Age				
Median (IQR) (years)	65 (51–75)	79 (71–86)	<0.001	70 (56–80)
Distribution			<0.001	
0–10 years	13/2901 (0.4)	2/1130 (0.2)		15/4031 (0.4)
11–20 years	18/2901 (0.6)	0/1130 (0)		18/4031 (0.5)
21–30 years	89/2901 (3.1)	2/1130 (0.2)		91/4031 (2.3)
31–40 years	210/2901 (7.2)	5/1130 (0.4)		215/4031 (5.3)
41–50 years	373/2901 (12.9)	18/1130 (1.6)		391/4031 (9.7)
51–60 years	483/2901 (16.6)	68/1130 (6.0)		551/4031 (13.7)
61–70 years	624/2901 (21.5)	167/1130 (14.8)		791/4031 (19.6)
71–80 years	675/2901 (23.3)	357/1130 (31.6)		1032/4031 (25.6)
81–90 years	355/2901 (12.2)	389/1130 (34.4)		744/4031 (18.5)
≥91 years	61/2901 (2.1)	122/1130 (10.8)		183/4031 (4.5)
Country of birth			<0.001	
Spain	2505/2819 (88.9)	1065/1101 (96.7)		3570/3920 (91.1)
Other	314/2819 (11.1)	36/1101 (3.3)		350/3920 (8.9)
Ethnic group			<0.001	
Arab	21/2821 (0.7)	3/1094 (0.3)		24/3915 (0.6)
Asian	16/2821 (0.6)	2/1094 (0.2)		18/3915 (0.5)
Black	12/2821 (0.4)	0		12/3915 (0.3)
Latin American	166/2821 (5.9)	20/1094 (1.8)		186/3915 (4.7)
White	2578/2821 (91.4)	1064/1094 (97.3)		3642/3915 (93.0)
Other	28/2821 (1.0)	5/1094 (0.5)		33/3915 (0.8)
Comorbidity				
Smoking history			<0.001	
Current smoker	134/2123 (6.3)	63/794 (7.9)		197/2917 (6.7)
Former smoker	613/2123 (28.9)	334/794 (42.1)		947/2917 (32.5)
Never smoked	1376/2123 (64.8)	397/794 (50.0)		1773/2917 (60.8)
Comorbid conditions			<0.001	
0	848/2501 (33.9)	52/938 (5.5)		900/3439 (26.2)
1–2	1172/2501 (46.9)	448/938 (47.8)		1620/3439 (47.1)
≥3	481/2501 (19.2)	438/938 (46.7)		919/3439 (26.7)
Types of comorbid conditions				
Hypertension	1251/2885 (43.4)	801/1125 (71.2)	<0.001	2052/4010 (51.2)
Chronic heart disease	488/2875 (17.0)	444/1119 (39.7)	<0.001	932/3994 (23.3)
Diabetes	514/2884 (17.8)	357/1118 (31.9)	<0.001	871/4002 (21.8)
Chronic pulmonary disease (not asthma)	405/2879 (14.1)	310/1116 (27.8)	<0.001	715/3995 (17.9)
Obesity	316/2618 (12.1)	181/988 (18.3)	<0.001	497/3606 (13.8)
Chronic neurologic disorder	203/2886 (7.0)	170/1116 (15.2)	<0.001	373/4002 (9.3)
Dementia	124/2871 (4.3)	191/1108 (17.2)	<0.001	315/3979 (7.9)
Asthma	230/2884 (8.0)	69/1116 (6.2)	0.053	299/4000 (7.5)
Solid neoplasm (active)	146/2882 (5.1)	121/1116 (10.8)	<0.001	267/3998 (6.7)
Inflammatory disease	148/2883 (5.1)	83/1114 (7.4)	0.005	231/3997 (5.8)
Chronic kidney disease stage 4 (eGFR <30 mL/min/1.73 m^2)	87/2882 (3.0)	112/1118 (10.0)	<0.001	199/4000 (5.0)
Haematologic neoplasm (active)	45/2885 (1.6)	47/1120 (4.2)	<0.001	92/4005 (2.3)
Liver cirrhosis	28/2882 (1.0)	26/1116 (2.3)	0.001	54/3998 (1.3)
HIV/AIDS	20/2860 (0.7)	6/1102 (0.5)	0.589	26/3962 (0.7)
Current medications				
Angiotensin-converting enzyme inhibitors	489/2878 (17.0)	283/1105 (25.6)	<0.001	772/3983 (19.4)
Angiotensin II receptor blockers	434/2879 (15.1)	254/1108 (22.9)	<0.001	688/3987 (17.3)
Corticosteroids, inhaled	303/2875 (10.5)	184/1110 (16.6)	<0.001	487/3985 (12.2)
Corticosteroids, systemic	113/2872 (3.9)	95/1110 (8.6)	<0.001	208/3982 (5.2)
Antineoplastic agents	59/2875 (2.0)	49/1110 (4.4)	<0.001	108/3985 (2.7)
Biologic anti-inflammatory drugs	69/2871 (2.4)	27/1106 (2.4)	0.944	96/3977 (2.4)
Antiretroviral drugs	15/19 (78.9)	6/6 (100.0)	0.220	21/25 (84.0)

Values are displayed as n/N with data (%).
eGFR, estimated glomerular filtration rate; IQR, interquartile range.

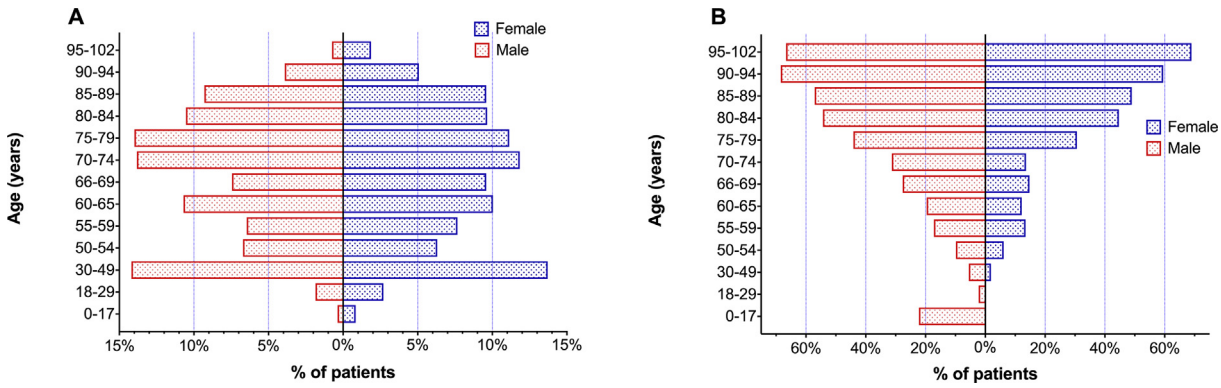

Fig. 1. (A) Distribution of hospitalized patients with coronavirus disease 2019 (COVID-19) stratified by age and sex. (B) Mortality of patients with COVID-19 stratified by age and sex.

Table 2
Laboratory findings of 4035 hospitalized patients with COVID-19 stratified according to vital status at study censoring date

Laboratory parameter	Alive (n = 2904)	Death (n = 1131)	p	Total (N = 4035)
Haemoglobin				
No. of patients with data	2860	1120		3980
Median (IQR) (g/L)	13.8 (12.6–14.9)	12.9 (11.5–14.4)	<0.001	13.6 (12.3–14.8)
Haematocrit				
No. of patients with data	2832	1105		3937
Median (IQR) (%)	41.0 (37.9–44.0)	39.1 (34.8–43.0)	<0.001	40.6 (37.0–44.0)
WBC count				
Median (IQR) ($\times 10^9$/L)	5635 (4330–7420)	6900 (5000–9470)	<0.001	5910 (4490–7990)
Distribution			<0.001	
>12 000 $\times$ 10^9/L	152/2854 (5.3)	160/1117 (14.3)		312/3971 (7.9)
<4000 $\times$ 10^9/L	529/2854 (18.5)	137/1117 (12.3)		666/3971 (16.8)
Neutrophil count				
Median (IQR) (/μL)	3920 (2800–5560)	5300 (3530–7700)	<0.001	4200 (2920–6120)
<1000/μL	51/2848 (1.8)	24/1113 (2.2)	0.448	75/3961 (1.9)
Lymphocyte count				
Median (IQR) (/μL)	1000 (700–1360)	780 (540–1160)	<0.001	900 (640–1300)
<1000/μL	1423/2852 (49.9)	727/1111 (65.4)	<0.001	2150/3963 (54.2)
Neutrophil-to-lymphocyte ratio				
Median (IQR)	3.9 (2.5–6.5)	6.6 (3.7–11.4)	<0.001	4.5 (2.7–7.7)
Distribution				
Tertile 1	1094/2839 (38.5)	222/1106 (20.1)	<0.001	1316/3945 (33.4)
Tertile 2	1005/2839 (35.4)	309/1106 (27.9)		1314/3945 (33.3)
Tertile 3	740/2839 (26.1)	575/1106 (52.0)		1315/3945 (33.3)
Platelets				
Median (IQR) ($\times 10^9$/L)	181 000 (143 000–229 000)	168 000 (130 000–221 000)	<0.001	178 000 (139 000–226 000)
Platelets <150 000 $\times$ 10^9/L	831/2842 (29.2)	416/1118 (37.2)	<0.001	1247/3960 (31.5)
Prolonged APTT (>39.2 seconds or ratio >1.25)	161/2232 (7.2)	133/880 (15.1)	<0.001	294/3112 (9.4)
INR				
Median (IQR)	1.1 (1.0–1.2)	1.2 (1.1–1.3)	<0.001	1.1 (1.0–1.2)
INR > 1.1	954/2376 (40.1)	549/925 (59.3)	<0.001	1503/3301 (45.5)
D-dimer				
Median (IQR) (ng/mL)	548 (328–934)	740 (410–1590)	<0.001	580 (339–1040)
High D-dimer levels (>500 ng/mL)	639/1184 (54.0)	253/379 (66.7)	<0.001	892/1563 (57.1)
Glucose				
No. of patients with data	2766	1084		3850
Median (IQR) (mg/dL)	106 (93–126)	125 (104–165)	<0.001	110 (95–136)
Creatinine				
No. of patients with data	2832	1111		3943
Median (IQR)	0.88 (0.72–1.07)	1.10 (0.84–1.46)	<0.001	0.92 (0.74–1.18)
eGFR (mL/min/1.73 m^2) (CKD-EPI)				
Median (IQR)	84.1 (65.3–97.4)	60.2 (40.1–80.4)	<0.001	78.4 (56.5–93.6)
Distribution			<0.001	
>60 mL/min/1.73 m^2	2234/2797 (79.9)	552/1098 (50.3)		2786/3895 (71.5)
30–59 mL/min/1.73 m^2	456/2797 (16.3)	388/1098 (35.3)		844/3895 (21.7)
<30 mL/min/1.73 m^2	107/2797 (3.8)	158/1098 (14.4)		265/3895 (6.8)
Sodium				
No. of patients with data	2825	1109		3934
Median (IQR) (mEq/L)	138 (135–140)	137 (135–140)	0.008	138 (135–140)
Potassium				
No. of patients with data	2770	1070		3840
Median (IQR) (mEq/L)	4.1 (3.8–4.4)	4.2 (3.8–4.6)	<0.001	4.1 (3.8–4.4)

(*continued on next page*)

Table 2 (*continued*)

Laboratory parameter	Alive ($n = 2904$)	Death ($n = 1131$)	p	Total ($N = 4035$)
ALT				
Median (IQR) (U/L)	27 (18–42)	25 (17–38)	0.003	26 (18–41)
High serum levels ≥40 U/L and ≤200 U/L	630/2369 (26.6)	190/870 (21.8)	0.021	820/3239 (25.3)
High serum levels >200 U/L	23/2369 (1.0)	8/870 (0.9)		31/3239 (1.0)
AST				
Median (IQR) (U/L)	31 (23–45)	34 (23–52)	0.033	32 (23–48)
High serum levels ≥ 40 U/L and ≤200 U/L	680/2051 (33.1)	291/750 (38.8)	0.011	971/2801 (34.7)
High serum levels >200 U/L	17/2051 (0.8)	9/750 (1.2)		26/2801 (0.9)
AST/ALT ratio			<0.001	
<1	675/2013 (33.5)	166/733 (22.6)		841/2746 (30.6)
≥1	1338/2013 (66.5)	567/733 (77.4)		1905/2746 (69.4)
Total bilirubin				
No. of patients with data	1920	730		2650
Median (IQR) (mg/dL)	0.50 (0.37–0.71)	0.56 (0.39–0.87)	<0.001	0.50 (0.37–0.80)
Serum albumin				
Median (IQR) (g/dL)	3.6 (3.2–4.0)	3.4 (3.0–3.8)	<0.001	3.5 (3.2–3.9)
Low albumin levels (<3.4 g/dL)	310/991 (31.3)	198/420 (47.1)	<0.001	508/1411 (36.0)
Lactate dehydrogenase				
Median (IQR) (U/L)	281 (215–382)	318 (250–463)	<0.001	290 (224–403)
High lactate dehydrogenase (>250 U/L)	1154/1895 (60.9)	510/683 (74.7)	<0.001	1664/2578 (64.5)
CRP				
Median (IQR) (mg/L)	44 (16–95)	87 (38–168)	<0.001	54 (20–116)
High CRP levels (>5 mg/L)	2388/2654 (90.0)	990/1023 (96.8)	<0.001	3378/3677 (91.9)
Procalcitonin				
Median (IQR) (μg/L)	0.09 (0.05–0.16)	0.22 (0.10–0.56)	<0.001	0.11 (0.06–0.25)
High procalcitonin levels (>0.50 μg/L)	105/1135 (9.2)	119/439 (27.1)	<0.001	224/1574 (14.2)
Creatine kinase				
Median (IQR) (U/L)	90 (56–169)	101 (56–217)	0.048	92 (56–182)
High creatine kinase levels (>190 U/L)	184/882 (20.9)	102/336 (30.4)	<0.001	286/1218 (23.5)
Ferritin				
Median (IQR) (μg/L)	611 (278–1238)	792 (400–1670)	0.002	649 (301–1363)
High ferritin levels (>300 μg/L)	315/433 (72.7)	125/153 (81.7)	0.028	440/586 (75.1)
Interleukin 6				
Median (IQR) (pg/mL)	33 (13–77)	117 (40–512)		42 (16–105)
High interleukin levels (>4.3 pg/mL)	175/201 (87.1)	58/58 (100.0)	0.004	233/259 (90.0)

Values are displayed as *n/N* with data (%) unless otherwise indicated.
ALT, alanine, aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; WBC, white blood cell count.

cohorts. However, dyspnoea was less frequent in Chinese patients, suggesting a more severe course in the older Spanish and British patients. In our cohort, age was the main determinant of death, as has been in other series of hospitalized patients with COVID-19 [3,8,9,14,19].

Independent of the higher prevalence of comorbidities, it cannot be ruled out that older patients could not have been prioritized to receive ICU treatment. Death was also significantly higher in men than in women, as has also been described in other cohorts [3,8,9,13,14]. There are sex differences in innate and adaptive immune responses that might have an impact on the inflammatory response and outcomes of COVID-19 and therefore deserve further investigation [20]. Hypertension was not only the most common comorbidity in our cohort, as in other studies, but it was an independent predictor of mortality. The association between hypertension and poor outcomes in COVID-19 does not seem to be simply a matter of high prevalence; alternative explanations include pre-existing hypertensive end-organ or endothelial damage, and interactions between COVID-19 and antihypertensive medications [21]. Many patients with hypertension were receiving ACE inhibitors or angiotensin II receptor blockers, but these drugs did not increase mortality. Obesity was the fifth most common comorbidity in our cohort, but one with the highest hazard of mortality. Obesity has been found to increase the risk of hospitalization and severe outcomes during influenza seasons [22]. Recent studies of COVID-19 patients indicate that younger hospitalized individuals are more likely to be obese [23] and that obesity is associated with severe clinical pictures [23–25] and increased mortality [14]. Other underlying conditions associated with an increased hazard of death were active cancer and cirrhosis, as has been reported elsewhere [26,27], meaning that clinicians should consider patients with these underlying conditions to be at high risk for COVID-19 [27]. We identified several routine laboratory markers as predictors of mortality, including the neutrophil-to-lymphocyte ratio, an indicator of systemic inflammation that has been found to be of prognostic utility in sepsis [28] and COVID-19 [29,30].

Our study is limited by the retrospective design and the high number of sites, which might have jeopardized the quality of the data. We tried to solve this by selecting simple and well-defined variables and by carefully monitoring of the data. Admission criteria might have differed between the sites; nevertheless, we controlled the site effect in the analysis. We could not include in the multivariable model some potentially interesting laboratory parameters; nor could we include changes in laboratory findings over time. The study's strengths include the large sample size, which allowed the identification of a high number of predictors of death at admission, the analysis of clinical and laboratory variables, and the inclusion of sites from areas with different incidence rates.

In summary, here we report the clinical characteristics of a large cohort of patients with COVID-19 consecutively admitted to

Table 3
Independent predictors of death in different clusters of variables

Characteristic	HR (95% CI)	p
Sociodemographic characteristics		
Male sex	1.52 (1.33–1.73)	<0.001
Age (ref. 0–49 years)		
50–65 years	3.76 (2.43–5.83)	<0.001
66–79 years	8.87 (5.85–13.43)	<0.001
80+ years	20.75 (13.72–31.37)	<0.001
Comorbidities		
Hypertension	1.81 (1.56–2.09)	<0.001
Chronic heart disease	1.58 (1.38–1.81)	<0.001
Diabetes	1.23 (1.07–1.41)	0.003
Chronic pulmonary disease (not asthma)	1.40 (1.21–1.61)	<0.001
Obesity	1.21 (1.01–1.44)	0.036
Chronic kidney disease stage 4 (eGFR <30 mL/min/1.73 m^2)	1.55 (1.26–1.91)	<0.001
Liver cirrhosis	1.59 (1.03–2.43)	0.034
Chronic neurologic disorder	1.30 (1.08–1.57)	0.006
Cancer	1.59 (1.33–1.90)	<0.001
Dementia	2.28 (1.90–2.73)	<0.001
Admission signs and symptoms		
Headache	0.50 (0.37–0.68)	<0.001
Myalgia/arthralgia	0.70 (0.59–0.84)	<0.001
Anosmia	0.50 (0.22–1.14)	0.099
Cough	0.70 (0.60–0.80)	<0.001
Sputum production	1.26 (1.09–1.47)	0.002
Dyspnea	1.93 (1.69–2.19)	<0.001
Chest pain	0.64 (0.51–0.81)	<0.001
Vomiting/nausea	0.77 (0.62–0.95)	0.016
Altered consciousness	2.26 (1.93–2.66)	<0.001
Vital signs		
Low SaO_2 (age-adjusted)[a]	2.62 (2.29–3.00)	<0.001
Laboratory parameters		
WBC count (ref. <4000 × 10^9/L)		
4000–12 000 × 10^9/L	1.11 (0.91–1.35)	0.323
>12 000 × 10^9/L	1.54 (1.18–2.01)	0.002
Neutrophil count (ref. ≥1000/μL)		
<1000/μL	1.77 (1.12–2.79)	0.015
Neutrophil-to-lymphocyte ratio (ref. <3.22 (tertile 1))		
3.22–6.33 (tertile 2)	1.41 (1.17–1.69)	<0.001
>6.33 (tertile 3)	2.38 (1.99–2.84)	<0.001
Platelets (ref. ≥150 000 × 10^9/L)		
<150 000 × 10^9/L	1.41 (1.24–1.60)	<0.001
Prolonged APTT (>39.2 seconds or ratio >1.25)	1.34 (1.09–1.64)	0.006
INR (ref. ≤1.1)		
>1.1	1.49 (1.28–1.73)	<0.001
eGFR (ref. > 60 mL/min/1.73 m^2)		
30–59 mL/min/1.73 m^2	2.24 (1.95–2.58)	<0.001
<30 mL/min/1.73 m^2	2.68 (2.21–3.25)	<0.001
ALT (ref. <40 U/L)		
40–200 U/L	0.84 (0.71–0.99)	0.042
>200 U/L	0.86 (0.42–1.78)	0.692
CRP (ref. ≤5 mg/L)		
>5 mg/L	2.43 (1.69–3.49)	<0.001

ALT, alanine, aminotransferase; APTT, activated partial thromboplastin time; CI = confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR = hazard ratio; INR, international normalized ratio; SaO_2, arterial oxygen saturation; WBC, white blood cell count.
[a] Age-adjusted low SaO_2 ≤90% for patients aged >50 years and ≤93% for patients aged ≤50 years.

hospitals in Spain during the first month of the epidemic. Our findings provide comprehensive information about the characteristics and complications of severe COVID-19, and may help us identify patients at hospital admission with a higher risk of death.

Transparency declaration

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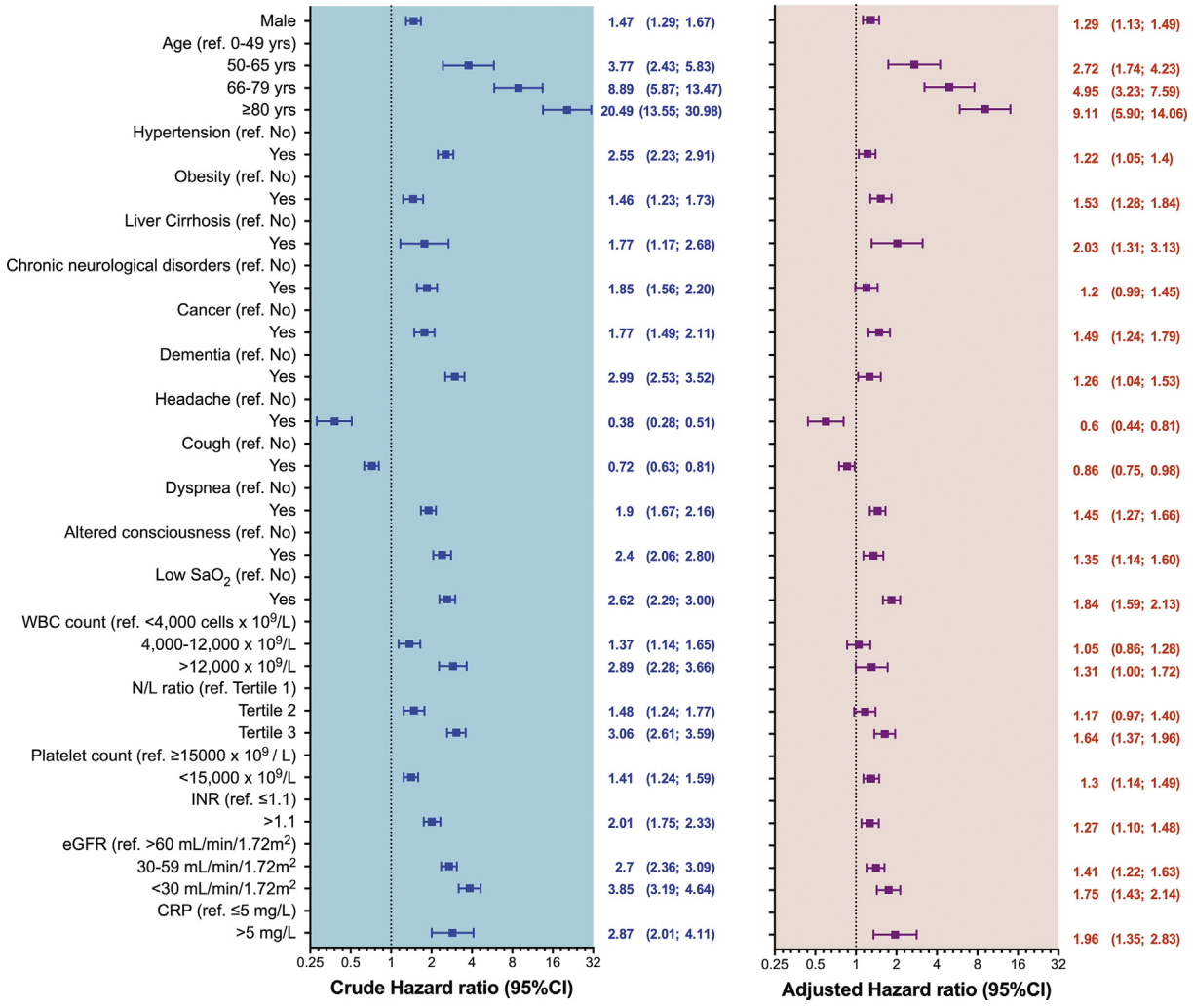

Fig. 2. Univariable (A) and multivariable (B) Cox proportional hazards model of variables associated with death. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; N/L, neutrophil-to-lymphocyte ratio; WBC, white blood cell count.

from ViiV Healthcare, outside the submitted work. The other authors report no conflicts of interest relevant to this article.

Appendix

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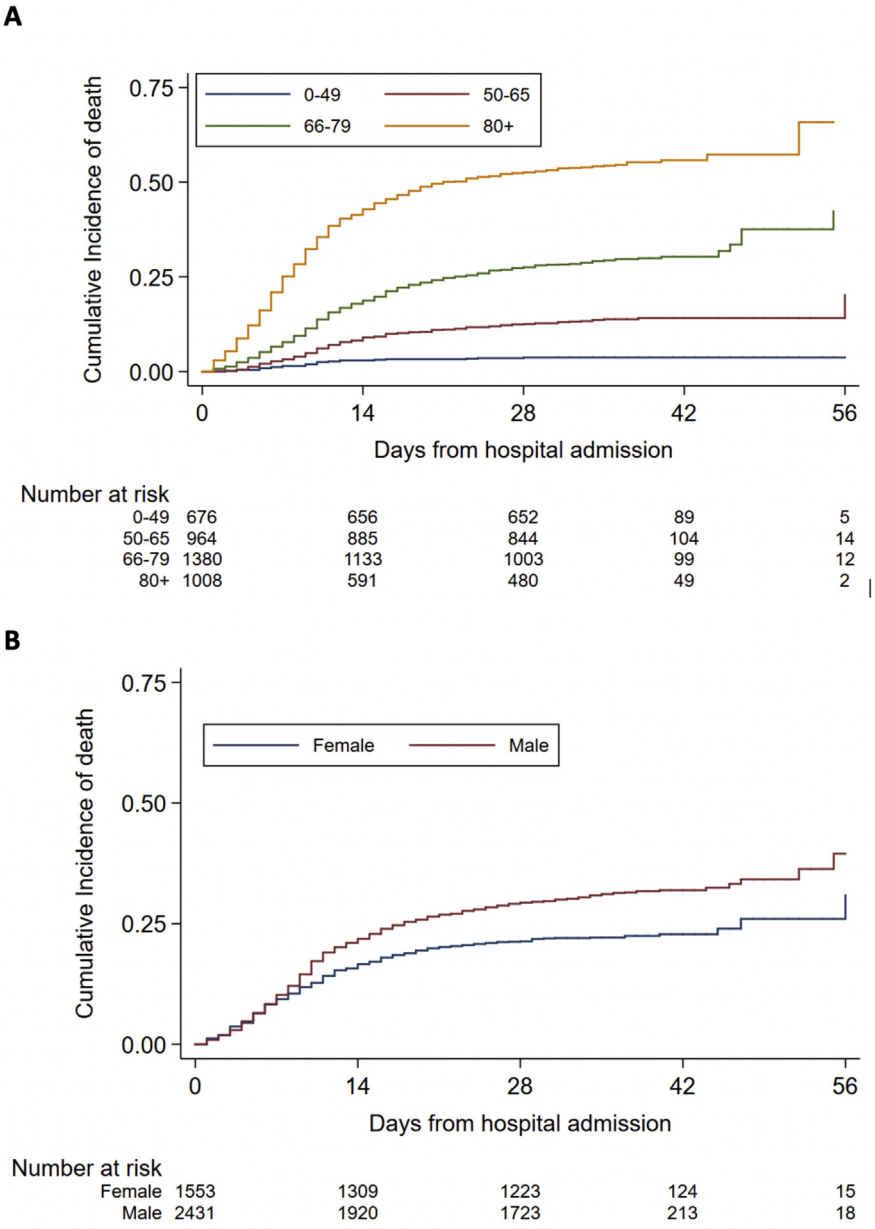

Fig. 3. Kaplan-Meier plots for death according to age (A) and sex (B).

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Appendix A. Supplementary data

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