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Coronavirus Pandemic

A retrospective study on factors related to in-hospital mortality among patients with COVID-19, March 2020 to November 2021

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Abstract

Introduction: Four years since the pandemic was declared, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains an important cause of illness around the world. Although many countries were able to overcome the health crisis at its peak, there are still individuals at high risk of a severe course of coronavirus disease 2019 (COVID-19). Therefore, it is important to continue research on the factors that could predict disease severity and adverse outcomes.

Methodology: We conducted a retrospective study on 171 consecutive hospitalized cases of COVID-19 from March 2020 to November 2021. Past medical history, drug history, clinical and laboratory parameters on admission, and the choice of treatment during hospital stay were obtained and associated with in-hospital mortality.

Results: Older age was significantly associated with mortality. Non-survivors also showed a significantly lower PaO_2/FiO_2 (P/F) ratio at the time of hospital admission; a lower lymphocyte count; and increased levels of white blood cell count, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and creatinine. Significant differences were also observed with regards to both long-term medications and treatments administered during hospital stay.

Conclusions: Our findings highlight the importance of age, clinical features, biochemical biomarkers, and therapeutic interventions in predicting COVID-19 disease severity and outcomes.

Key words: COVID-19; in-hospital mortality; risk factors.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in late 2019 in Wuhan, China, and rapidly spread worldwide causing a global pandemic. The World Health Organization (WHO) estimated that the infection resulted in 15 million deaths in 2020 and 2021 alone [1], and remains an important cause of illness around the world. The virus has evolved through random mutations leading to the emergence and subsequent dominance of new variants over time, some of which were termed "variants of concern" (VOCs) due to their enhanced risk of transmission and virulence [2,3]. The clinical presentation of coronavirus disease 2019 (COVID-19) is highly heterogeneous, as it can vary from absence of symptoms to respiratory failure, acute respiratory distress syndrome (ARDS), and multi-organ dysfunction. The severity of symptoms affects disease outcome and survival of patients and it depends on a complex interaction between viral and host factors such as age, gender, smoking history, and pre-existing comorbidities [4–10].

Many countries have now moved past the COVID-19 health crisis thanks to the emergence of less virulent variants; and, most importantly, the development of an immune response in a growing number of vaccinated or virus-exposed individuals. However, there are still patients at risk of poorer outcomes, and continued research on patterns that may predict disease severity is therefore essential. In a systematic review and meta-

analysis, Li *et al.* showed that age, obesity and comorbidities such as diabetes and chronic kidney disease are important risk factors of poor outcomes following COVID-19 [6]. In a recent meta-analysis, Djorwè *et al*. showed that demographic characteristics such as age and gender, as well as various comorbidities, are predictive of a severe form of the disease [10]. Over the last years, we have focused on a few biomarkers such as arterial partial pressure of oxygen (PaO_2) to inspired (FiO_2) partial pressure of oxygen ratio (P/F ratio), complete blood cell count (CBC)-derived inflammation indexes, and the De Ritis ratio; and found an association between these parameters and poor COVID-19 outcomes [11–13]. Moreover, Ku *et al.* [14] reported an association between long term glucocorticoid therapy and COVID-19 prognosis, revealing the importance of considering the patient medication history in the investigation. Therefore, in the present study, we aimed to analyze a wider spectrum of clinical parameters which included comorbidities, laboratory measures, patient medication history, and choice of treatment during hospital stay; in order to have a more detailed picture of the factors that can be related to mortality.

Methodology

We conducted a retrospective study of a consecutive series of 171 patients with COVID-19 admitted to the Sub-Intensive Respiratory Unit of the University Hospital of Sassari, North Sardinia, Italy; between March 2020 and November 2021. The presence of COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR). All information was retrospectively collected from the hospital medical records. In particular, demographical, clinical and biometric data; lab test measures; high-resolution chest tomography (HRCT) reports; and drug history were all obtained on admission. Moreover, details about choice of treatment for COVID-19, any clinical complications that occurred during hospital stay, and in-hospital mortality were also gathered.

The study was conducted in accordance with the declaration of Helsinki and was approved by the ethics committee of the University Hospital (AOU) of Cagliari (PG/2020/10915).

Categorical variables (i.e., clinical, demographical, and radiological variables; treatment before and during hospitalization; COVID-19-specific therapies; and complications) were summarized through descriptive analyses presented as absolute numbers and frequencies (percentages) for the entire cohort, as well as for the survivors and non-survivors. Continuous variables (clinical and laboratory data) were expressed as means and standard deviations, or medians and interquartile ranges (IQR), depending on their distribution (normal or non-normal), assessed using the Shapiro-Wilk test.

Table 1. Descriptive analysis of patients' clinical and demographic variables.

Variables	Total cohort (n = 171)	Alive (n = 107)	Dead (n = 64)	*p* value
Median (IQR) age	73 (66–82)	69 (64–74)	81 (74–85)	**< 0.0001**
Females, n (%)	60 (35.09)	42 (39.25)	18 (28.13)	0.140
Median (IQR) BMI, n = 88	27.5 (25.3–30.0)	27.4 (25.2–30.0)	28.8 (25.4–30.0)	0.660
ICU transfer, n (%)	17 (9.94)	1 (0.93)	16 (25.00)	**< 0.0001**
Diabetes, n (%)	53 (30.99)	31 (28.97)	22 (34.38)	0.46
Hypercholesterolemia, n = 170, n (%)	58 (34.12)	35 (33.02)	23 (35.94)	0.697
Hypertension, n = 170, n (%)	127 (74.71)	80 (75.47)	47 (73.44)	0.768
Smoking history, n = 87				
non-smokers, n (%)	33 (37.93)	24 (42.11)	9 (30.00)	
former smoker, n (%)	45 (51.72)	26 (45.61)	19 (63.33)	0.279
current smoker, n (%)	9 (10.34)	7 (12.28)	2 (6.67)	
Prior angina, n = 161, n (%)	15 (9.32)	9 (8.82)	6 (10.17)	0.777
Prior myocardial infarction, n = 167, n (%)	17 (10.18)	9 (8.49)	8 (13.11)	0.341
Prior PCI, n = 167, n (%)	15 (8.98)	8 (7.55)	7 (11.48)	0.393
Prior CABG bypass, n = 167, n (%)	2 (1.20)	2 (1.89)	0 (0.00)	0.280
Chronic heart failure, n = 167, n (%)	12 (7.19)	5 (4.76)	7 (11.29)	0.114
Atrial fibrillation, n = 169, n (%)	20 (11.83)	13 (12.26)	7 (11.11)	0.822
Pulmonary embolism, n = 169, n (%)	5 (2.96)	1 (0.94)	4 (6.35)	**0.045**
Deep vein thrombosis, n = 168, n (%)	6 (3.57)	2 (1.90)	4 (6.35)	0.133
Transitory ischemic attack, n = 169, n (%)	2 (1.18)	1 (0.94)	1 (1.59)	0.708
Stroke, n = 170, n (%)	13 (7.65)	7 (6.60)	6 (9.38)	0.510
Chronic kidney disease, n (%)	17 (9.94)	10 (9.35)	7 (10.94)	0.736
COPD, n= 170, n (%)	25 (14.71)	12 (11.32)	13 (20.31)	0.109
Asthma, n= 170, n (%)	7 (4.12)	4 (3.77)	3 (4.69)	0.771
Active cancer, n (%)	12 (7.02)	6 (5.61)	6 (9.38)	0.35
Autoimmune disorders, n (%)	23 (13.45)	17 (15.89)	6 (9.38)	0.227

BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronioc obstructive pulmonary disease; ICU: intensive care unit; IQR: interquartile range; PCI: percutaneous coronary intervention. Statistical significances ($p \leq 0.05$) are in bold.

Differences in categorical variables between survivors and non-survivors were evaluated using the χ^2 test, or the Fischer's exact test if the number of patients was less than 10. The Student's *t* or the Mann-Whitney tests were used to analyze between-group differences in continuous variables according to their distribution (parametric and non-parametric, respectively). The duration of hospitalization was defined as the number of days between admission and discharge (survivors) or date of death (non-survivors). The Cox regression model was used to identify factors associated with mortality. The variables found to be statistically significant in univariate analysis were included in the multivariate Cox regression analysis using the backward method. Values of $p < 0.05$ were considered statistically significant; the analyses were conducted using Stata 14 (StataCorp, College Station, TX, USA) and MedCalc 19.6.3 (MedCalc Software Ltd, Ostend, Belgium).

Results

The clinical and demographic variables are summarized in Table 1. The median age of the entire cohort was 73 years (IQR 66–82 years). Females accounted for 35.09% of cases. Deceased patients were significantly older compared to the survivors (median: 81, IQR 74–85 vs. median 69, IQR: 64–74, $p < 0.0001$), and were more likely to have been moved to the intensive care unit (ICU) (25.00% vs 0.93%, $p < 0.0001$). The most frequently reported comorbidity was hypertension, with no differences between the two groups. A significant difference was identified for the presence of pulmonary embolism in deceased patients compared to the survivors (6.35% vs 0.94%, $p = 0.045$).

Table 2 lists the medications normally taken by the patients before hospital admission. Statistical differences between the deceased and survivor groups can be observed with regards to furosemide (25.40% vs 8.45%, $p = 0.003$), inhaled corticosteroid/long-acting beta A07gonist (ICS/LABA) inhaler combination

Table 2. Descriptive analysis of therapy before admission.

Variables	Total cohort (n = 171)	Alive (n = 107)	Dead (n = 64)	*p* value
Aspirin, n = 168, n (%)	38 (22.62)	22 (20.95)	16 (25.40)	0.505
Clopidogrel, n = 167, n (%)	13 (7.78)	7 (6.73)	6 (9.52)	0.514
Ticagrelor, n = 166, n (%)	2 (1.20)	2 (1.94)	0 (0.00)	0.266
Heparin, n = 167, n (%)	7 (4.19)	3 (2.88)	4 (6.35)	0.279
Coumadin, n = 167, n (%)	7 (4.19)	3 (2.88)	4 (6.35)	0.279
DOAC, n = 168, n (%)	12 (7.14)	7 (6.67)	5 (7.94)	0.757
Statins, n= 167, n (%)	43 (25.75)	29 (27.88)	14 (22.22)	0.417
ACE inhibitor, n = 167, n (%)	52 (31.14)	28 (26.92)	24 (38.10)	0.131
ARBs, n = 167, n (%)	41 (24.55)	27 (25.96)	14 (22.22)	0.586
Calcium antagonist, n = 167, n (%)	46 (27.54)	27 (25.96)	19 (30.16)	0.556
Beta blockers, n = 167, n (%)	49 (29.34)	28 (26.92)	21 (33.33)	0.378
Alfa antagonists, n = 167, n (%)	11 (6.59)	7 (6.73)	4 (6.35)	0.923
Antiarrhythmics, n = 167, n (%)	3 (1.80)	2 (1.92)	1 (1.59)	0.874
Digoxin, n = 167, n (%)	2 (1.20)	1 (0.96)	1 (1.59)	0.719
Furosemide, n = 167, n (%)	25 (14.97)	9 (8.65)	16 (25.40)	**0.003**
Thiazides, n = 167, n (%)	29 (17.37)	16 (15.38)	13 (20.63)	0.385
Oral antidiabetics, n = 167, n (%)	27 (16.17)	17 (16.35)	10 (15.87)	0.939
Insulin, n = 167, n (%)	18 (10.78)	11 (10.58)	7 (11.11)	0.914
ICS/LABA combination, n = 167, n (%)	18 (10.78)	6 (5.77)	12 (19.05)	**0.007**
Glucocorticoids, n = 167, n (%)	25 (14.97)	8 (7.69)	17 (26.98)	**0.001**

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; DOAC: direct-acting oral anticoagulants; ICS/LABA: inhaled corticosteroids/long-acting β2-agonist. Statistical significances ($p \leq 0.05$) are in bold.

Table 3. Descriptive analysis of diagnosis at admission.

Variables	Total cohort (n = 171)	Alive (n = 107)	Dead (n = 64)	*p* value
Acute cardiac failure, n (%)	1 (0.58)	0 (0.00)	1 (1.56)	0.195
Pneumonia, n (%)	73 (42.69)	54 (50.47)	19 (29.69)	**0.008**
Acute respiratory failure, n (%)	92 (53.80)	49 (45.79)	43 (67.19)	**0.007**
Acute kidney injury, n (%)	1 (0.58)	1 (0.93)	0 (0.00)	0.438
Myocarditis, n (%)	1 (0.58)	0 (0.00)	1 (1.56)	0.195
Cerebral and pulmonary masses, n (%)	1 (0.58)	1 (0.93)	0 (0.00)	0.438
Giant cell arteritis, n (%)	1 (0.58)	1 (0.93)	0 (0.00)	0.438
Orchiepididymitis, n (%)	1 (0.58)	1 (0.93)	0 (0.00)	0.438
Pulmonary embolism, n (%)	1 (0.58)	0 (0.00)	1 (1.56)	0.195
Sepsis, n (%)	1 (0.58)	0 (0.00)	1 (1.56)	0.195
Stroke, n (%)	1 (0.58)	1 (0.93)	0 (0.00)	0.438

Statistical significances ($p \leq 0.05$) are in bold.

Table 4. Descriptive analysis of HRCT, biometric data, and lab test measures at the time of admission.

Variables	Total cohort (n = 171)	Alive (n = 107)	Dead (n = 64)	*p* value
HRCT ground glass, n = 157, n (%)	131 (83.44)	86 (84.31)	45 (81.82)	0.688
HRCT interstitial, n = 157, n (%)	49 (31.21)	25 (24.51)	24 (43.64)	**0.014**
HRCT consolidations, n = 156, n (%)	92 (58.97)	58 (57.43)	34 (61.82)	0.594
Heart Rate, n = 98; median (IQR)	83 (77–96)	84 (75–100)	82 (80–90)	0.784
Body Temperature, n = 100; median (IQR)	37.25 (36.3–38.0)	37.3 (36.3–38.0)	37 (36.3–38.05)	0.745
SAO_2, n = 149; median (IQR)	91 (87–94)	92 (89–94)	90 (80.0–94.5)	**0.029**
Systolic Blood Pressure, n = 91; mean (SD)	131.41 (20.62)	130.94 (21.88)	132.05 (18.98)	0.802
P/F, n = 165; mean (SD)	249.45 (89.01)	271.02 (79.48)	214.52 (93.07)	**0.0001**
Platelets $*10^3$ (cmb), n = 165; median (IQR)	207 (150–270)	199 (150–271)	209 (147–270)	0.85
White blood cells $*10^3$ (cmb), n = 165; median (IQR)	7.6 (5.1–11.2)	6.4 (4.8–10.1)	9.8 (6.5–13.0)	**0.0008**
Lymphocytes (%), n = 165; median (IQR)	10.6 (6.4–17.9)	12.8 (7.13–20.83)	9.19 (4.76–13.3)	**0.0043**
APTT (sec), n = 156; median (IQR)	24.55 (22.65–27.05)	24.05 (22.2–26.2)	25.3 (23.0–29.9)	**0.0295**
C-reactive protein (mg/l), n = 160; Median (IQR)	87.4 (33.35–146.9)	71.6 (28.0–132.2)	125.9 (55.6–183.7)	**0.0013**
Lactate dehydrogenase (U/l), n= 142; median (IQR)	317.5 (252–422)	306 (242–367)	387 (303–533)	**0.0004**
D-dimer (ug/l), n = 149; median (IQR)	940 (490–2060)	770 (400–1840)	1305 (750–2660)	**0.0033**
Creatinine (mg/dl), n = 162; median (IQR)	0.98 (0.77–1.35)	0.9 (0.765–1.18)	1.165 (0.8–1.7)	**0.0053**

APTT: activated partial thromboplastin time; HRCT: high resolution computed tomography; IQR: interquartile range; P/F: arterial partial pressure of oxygen (PaO_2) to inspired (FiO_2) partial pressure of oxygen ratio; SAO_2: arterial oxygen saturation. Statistical significances ($p \leq 0.05$) are in bold.

(19.05% vs 5.77%, $p = 0.007$), and corticosteroids (26.98% vs 7.69%, $p = 0.001$).

Table 3 summarizes the analysis of admitting diagnoses. A diagnosis of pneumonia was registered in 42.69% of the cohort, while the 53.80% of the cohort were admitted with acute respiratory failure, which was more likely for patients whose outcome resulted in death (29.69% vs 50.47%, $p = 0.008$; and 67.19% vs 45.79%, $p = 0.007$ respectively).

Table 4 presents a descriptive analysis of clinical parameters registered on hospital admission. A ground glass pattern on HRCT was described in 83.44% of cases without significant differences in the two groups. A statistical difference was observed regarding the presence of crazy paving and consolidation radiological aspects, with the group of non-survivors having a more recurring presence of these patterns compared to survivors (43.64% vs 24.51%, $p = 0.014$). Moreover, the group of deceased patients showed a significantly lower P/F ratio on admission (mean 214.52 ± 93.07 vs 271.02 ± 79.48, $p = 0.0001$), a lower lymphocyte count (median 9.19, IQR 4.76–13.3 vs median 12.8, IQR 7.13–20.83), a higher number of white blood cells (median 9.8, IQR 6.5–13.0 vs median 6.4, IQR 4.8–10.1, $p = 0.0008$); and a higher value of C-reactive protein (CRP) (median 125.9, IQR 55.6–183.7 vs median 71.6, IQR 28.0–132.2, $p = 0.0013$), lactate dehydrogenase (median 387, IQR 303–533 vs median 306, IQR 242–367, $p = 0.0004$), D-dimer (median 1305, IQR 750–2660 vs median 770, IQR 400–1840, $p = 0.0033$), and creatinine (median 1.165, IQR 0.8–1.7 vs median 0.9, IQR 0.765–1.18, $p = 0.0053$).

Table 5 presents an analysis of the medications taken during hospital stay, in addition to the pre-admission therapy. A significant difference was observed for remdesivir and methylprednisolone between the two groups. Both medications were less represented among non-survivors (7.81% vs 29.91%, $p = 0.001$; and 20.31% vs 35.24%; $p = 0.039$ respectively). On the contrary, amiodarone, psychotropic drugs, and opioids were prescribed more frequently in the non-survivor group (9.38% vs 0%, $p = 0.001$; 76.56% vs 32.71%, $p < 0.0001$; and 45.31% vs 2.80%, $p < 0.0001$; respectively).

The complications registered during hospital stay are summarized in Table 6. Circulatory shock and ARDS were more common in the non-survivor group than the survivor group (39.68% vs 1.89%, $p < 0.0001$; and 15.87% vs 1.89%, $p = 0.001$; respectively).

Univariate Cox regression analysis confirmed the association found for age (crude hazard ratio, HR: 1.07; 95% confidence interval, CI 1.04–1.10, $p < 0.0001$) and

Table 5. Descriptive analysis of treatment during hospital stay, in addition to the pre-admission therapy.

Variables	Total cohort (n = 171)	Alive (n = 107)	Dead (n = 64)	*p* value
Amiodarone, n (%)	6 (3.51)	0 (0.00)	6 (9.38)	**0.001**
Psychotropic drugs, n (%)	84 (49.12)	35 (32.71)	49 (76.56)	**< 0.0001**
Opioids, n (%)	32 (18.71)	3 (2.80)	29 (45.31)	**< 0.0001**
Hydroxychloroquine, n = 170, n (%)	11 (6.47)	7 (6.60)	4 (6.25)	0.928
Remdesivir, n (%)	37 (21.64)	32 (29.91)	5 (7.81)	**0.001**
Dexamethasone, n = 170, n (%)	144 (84.71)	90 (84.91)	54 (84.38)	0.926
Methylprednisolone, n = 169, n (%)	50 (29.59)	37 (35.24)	13 (20.31)	**0.039**

Statistical significances ($p \leq 0.05$) are in bold.

Table 6. Descriptive analysis of complications registered during hospital stay.

Variables	Total cohort (n = 171)	Alive (n = 107)	Dead (n = 64)	*p* value
Pulmonary embolism, n = 169, n (%)	3 (1.78)	2 (1.89)	1 (1.59)	0.887
Shock, n = 169, n (%)	27 (15.98)	2 (1.89)	25 (39.68)	**< 0.0001**
ARDS, n = 169, n (%)	12 (7.10)	2 (1.89)	10 (15.87)	**0.001**
Ischemic stroke, n = 169, n (%)	3 (1.78)	0 (0.00)	3 (4.76)	0.23

ARDS: acute respiratory distress syndrome. Statistical significances ($p \leq 0.05$) are in bold.

ICU transfer (crude HR: 2.46, 95% CI 1.39–4.35, p = 0.0019). Moreover, a significant positive association with mortality was found for deep vein thrombosis (crude HR: 2.78, 95% CI 1.00–7.72, p = 0.0493), and active cancer (crude HR: 3.11, 95% CI 1.32–7.33, p = 0.0095) (Table 7). Furosemide, ICS/LABA inhalers, and long-term corticosteroids taken prior to hospital admission were also confirmed to be significantly related to mortality (crude HR: 1.95, 95% CI 1.10–3.45, p = 0.0218; crude HR: 2.65, 95% CI 1.40–4.99, p = 0.0027; and crude HR: 2.95, 95% CI 1.68–5.20, p = 0.0002; respectively) (Table 8).

Several clinical and laboratory measures registered on admission were also confirmed to be related to mortality, such as oxygen saturation (crude HR: 0.94, 95% CI 0.91–0.96, $p < 0.0001$), P/F ratio (crude HR: 0.97, 95% CI 0.99–1.00, p = 0.0120), white blood cell count (crude HR: 1.00, 95% CI 1.00–1.00, p = 0.0001), CRP (crude HR: 1.01, 95% CI 1.00–1.01, p = 0.0036), lactate dehydrogenase (crude HR: 1.00, 95% CI 1.00–1.00, p = 0.0016), and creatinine (crude HR: 1.27, 95% CI 1.09–1.47, p = 0.0016) (Table 9 and 10).

Table 7. Cox proportional-hazards univariate regression test and crude hazard ratio (HR) with 95% confidence interval (CI) of patients' clinical and demographic variables.

Variables	Crude HR	95% CI	*p* value
Age	1.07	1.04–1.10	**< 0.0001**
Gender	1.19	0.69–2.05	0.54
Body Mass Index	1.00	0.91–1.09	0.95
ICU transfer	2.46	1.39–4.35	**0.0019**
Diabetes	1.33	0.79–2.24	0.28
Hypercholesterolemia	1.09	0.65–1.82	0.75
Hypertension	0.79	0.45–1.38	0.40
Smoking history (former + active)	1.40	0.64–3.06	0.40
Prior angina	1.37	0.54–3.21	0.47
Prior myocardial infarction	1.48	0.70–3.12	0.31
Prior PCI	1.43	0.65–3.16	0.37
Prior CABG bypass	0.00	0.00–0.00	0.96
Chronic heart failure	1.51	0.68–3.34	0.31
Atrial fibrillation	1.27	0.57–2.80	0.56
Pulmonary embolism	2.47	0.89–6.84	0.08
Deep vein thrombosis	2.78	1.00–7.72	**0.0493**
Transitory ischemic attack	1.41	0.19–10.24	0.74
Stroke	1.06	0.46–2.46	0.89
Chronic kidney disease	1.35	0.62–2.97	0.45
COPD	1.27	0.69–2.35	0.44
Asthma	1.58	0.49–5.08	0.45
Active cancer	3.11	1.32–7.33	**0.0095**
Autoimmune disorders	0.62	0.27–1.45	0.27

ICU: intensive care unit; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease. Statistical significances ($p \leq 0.05$) are in bold.

Treatment taken during hospital stay, in addition to pre-admission therapy was also investigated to identify factors related to mortality. The analysis confirmed a negative effect on survival for amiodarone (crude HR: 2.83, 95% CI 1.21–6.60, p = 0.0160), psychotropic drugs (crude HR: 2.62, 95% CI 1.47–4.69, p = 0.0011), and opioids (crude HR: 3.38, 95% CI 2.06–5.54, $p <$ 0.0001); and a positive effect for remdesivir (crude HR: 0.26, 95% CI 0.10–0.65, p = 0.0038) and methylprednisolone (crude HR: 0.41, 95% CI 0.22–

Table 8. Cox proportional-hazards univariate regression test and crude hazard ratio (HR) with 95% confidence interval (CI) of therapy before admission.

Variables	Crude HR	95% CI	*p* value
Aspirin	0.90	0.50–1.61	0.73
Clopidogrel	1.27	0.54–2.95	0.58
Ticagrelor	0.00	0.00–0.00	0.96
Heparin	2.20	0.79–6.08	0.13
Coumadin	1.55	0.56–4.29	0.40
DOAC	1.21	0.48–3.02	0.69
Statins	0.75	0.41–1.36	0.34
ACE inhibitor	1.32	0.79–2.20	0.29
ARBs	0.90	0.49–1.66	0.74
Calcium antagonist	0.94	0.55–1.62	0.82
Beta blockers	1.16	0.68–1.96	0.59
Alfa antagonists	1.35	0.49–3.76	0.56
Antiarrhythmics	1.76	0.24–12.86	0.58
Digoxin	1.08	0.15–7.93	0.94
Furosemide	1.95	1.10–3.45	**0.0218**
Thiazides	1.28	0.69–2.37	0.43
Oral antidiabetics	1.00	0.51–1.97	1.00
Insulin	1.39	0.63–3.07	0.41
ICS/LABA combination	2.65	1.40–4.99	**0.0027**
Glucocorticoids	2.95	1.68–5.20	**0.0002**

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; DOAC: direct-acting oral anticoagulants; ICS/LABA: inhaled corticosteroids/long-acting β2-agonist. Statistical significances ($p \leq 0.05$) are in bold.

Table 9. Cox proportional-hazards univariate regression test and crude hazard ratio (HR) with 95% confidence interval (CI) of diagnosis at admission.

Variables	Crude HR	95% CI	*p* value
Acute cardiac failure	3.18	0.43–23.18	0.25
Pneumonia	0.64	0.38–1.10	0.11
Acute respiratory failure	1.41	0.84–2.38	0.20
Acute kidney injury	0.00	0.00–0.00	0.96
Myocarditis	1.65	0.23–11.97	0.63
Cerebral and pulmonary masses	0.00	0.00–0.00	0.96
Giant cell arteritis	0.00	0.00–0.00	0.97
Orchiepididymitis	0.00	0.00–0.00	0.96
Pulmonary embolism	0.64	0.09–4.62	0.66
Sepsis	2.71	0.37–19.74	0.33
Stroke	0.00	0.00–0.00	0.96

0.76, $p = 0.0046$) (Table 11). Moreover, complications that emerged during hospital stay such as circulatory shock and ischemic stroke were found to be correlated with patient mortality (crude HR: 3.28, 95% CI 1.98–5.43, $p < 0.0001$; and crude HR: 8.31, 95% CI 2.52–27.46, $p = 0.005$; respectively) (Table 12). The Cox multivariate regression analysis with backward elimination confirmed the significant relation of some of these variables (age, active cancer, pre-admission corticosteroids, P/F ratio, white blood cells, activated partial thromboplastin time (APTT), opioids, methylprednisolone, ischemic stroke) to mortality after eliminating the confounding effect of other parameters (ICU transfer, intubation, furosemide, ICS/LABA inhaler combination, arterial oxygen saturation (SaO_2), CRP, lactate dehydrogenase, creatinine, amiodarone, psychotropic drugs, remdesivir, circulatory shock during hospitalization) (Table 13).

Table 10. Cox proportional-hazards univariate regression test and crude hazard ratio (HR) with 95% confidence interval (CI) of high-resolution chest tomography (HRCT), biometric data, and lab test measures at admission.

Variables	Crude HR	95% CI	*p value*
HRCT ground glass	0.67	0.33–1.33	0.25
HRCT interstitial	1.51	0.89–2.58	0.13
HRCT consolidations	0.97	0.56–1.67	0.91
Heart Rate	1.00	0.99–1.02	0.93
Body Temperature	0.96	0.81–1.15	0.67
SAO_2	0.94	0.91–0.96	**< 0.0001**
Systolic Blood Pressure	1.01	0.99–1.02	0.41
P/F	0.97	0.99–1.00	**0.0120**
Platelets (cmb)	1.00	1.00–1.00	0.51
White blood cells (cmb)	1.00	1.00–1.00	**0.0001**
Lymphocytes (%)	0.99	0.96–1.02	0.51
APTT (sec)	1.05	1.01–1.10	**0.0230**
C-Reactive Protein (mg/l)	1.01	1.00–1.01	**0.0036**
Lactate dehydrogenase	1.00	1.00–1.00	**0.0016**
D-dimer (ug/l)	1.00	1.00–1.00	0.20
Creatinine (mg/dl)	1.27	1.09–1.47	**0.0016**

HRCT: high resolution computed tomography; SAO_2: arterial oxygen saturation; P/F: arterial partial pressure of oxygen (PaO_2) to inspired (FiO_2) partial pressure of oxygen ratio; APTT: activated partial thromboplastin time. Statistical significances ($p \leq 0.05$) are in bold.

Table 11. Cox proportional-hazards univariate regression test and crude hazard ratio (HR) with 95% confidence interval (CI) of treatment during hospital stay in addition to the pre-admission therapy.

Variables	Crude HR	95% CI	*p value*
Amiodarone	2.83	1.21–6.60	**0.0160**
Psychotropic drugs	2.62	1.47–4.69	**0.0011**
Opioids	3.38	2.06–5.54	**< 0.0001**
Hydroxychloroquine	2.67	0.94–7.62	0.066
Remdesivir	0.26	0.10–0.65	**0.0038**
Dexamethasone	0.52	0.26–1.04	0.063
Methylprednisolone	0.41	0.22–0.76	**0.0046**

Statistical significances ($p \leq 0.05$) are in bold.

Discussion

The period of time investigated in our study was marked by the most severe expression of SARS-CoV-2 infection, and vaccination coverage was still absent. We registered an overall in-hospital mortality rate of 37%. We observed a mortality rate of 28% among the patients who were not admitted to ICU and remained in our sub-intensive respiratory unit.

Upon admission, most patients presented a diagnosis of pneumonia and acute respiratory failure. As expected, the presence of acute respiratory failure was significantly related to mortality. The presence of crazy paving and consolidation pattern on HRCT scan was associated with a significant increase in mortality, as reported in the literature [15]. We also found that older age was a significant risk factor for mortality, and this is also a well-established observation across studies on COVID-19 [16–18]. When reviewing the case histories of our cohort, hypertension was the most frequently observed comorbidity on admission, followed by diabetes, hypercholesterolemia, and chronic obstructive pulmonary disease (COPD). Chronic kidney disease, atrial fibrillation, chronic heart failure, active cancer, and autoimmune disorders were described as well, to a lesser extent. Although several

Table 12. Cox proportional-hazards univariate regression test and crude hazard ratio (HR) with 95% confidence interval (CI) of complications registered during hospital stay.

Variables	Crude HR	95% CI	*p* value
Pulmonary embolism	0.64	0.09–4.62	0.66
Shock	3.28	1.98–5.43	**< 0.0001**
ARDS	1.65	0.84–3.26	0.15
Ischemic stroke	8.31	2.52–27.46	**0.0005**

ARDS: acute respiratory distress syndrome. Statistical significances ($p \leq 0.05$) are in bold.

Table 13. Cox proportional-hazards multivariate regression test and adjusted hazard ratio (HR) with 95% confidence interval (CI), backward method. The following variables were selected from the univariate analysis but were excluded by the backward model if $p > 0.05$: ICU transfer, furosemide, beta2 agonist, SaO_2, CRP, lactate dehydrogenase, creatinine, amiodarone, psychotropic drugs, remdesivir, shock during hospitalization.

Covariates	Adjusted HR	95% CI	*p* value
Age	1.06	1.01–1.11	**0.0300**
Active cancer	4.17	1.49–11.62	**0.0064**
Glucocorticoids	4.28	1.66–11.03	**0.0027**
P/F	0.99	0.99–1.00	**0.0491**
White blood cells	1.00	1.00–1.00	**0.0071**
APTT	1.08	1.00–1.16	**0.0474**
Opioids*	2.71	1.20–6.13	**0.0169**
Methylprednisolone*	0.37	0.16–0.85	**0.0187**
Ischemic stroke*	11.33	2.08–61.82	**0.0050**

Case summary: events = 39; censored = 67; total = 106. * During hospitalization. APTT: activated partial thromboplastin time; P/F: arterial partial pressure of oxygen (PaO_2) to inspired (FiO_2) partial pressure of oxygen ratio. Statistical significances ($p \leq 0.05$) are in bold.

studies have reported an association between these comorbidities and mortality [18–20], our analysis did not show any significant association with prognosis except for pulmonary embolism, deep vein thrombosis, and active cancer; although very few patients were concerned.

Our study also evidenced a correlation between some laboratory variables registered on admission and mortality. In particular, low oxygen saturation, low P/F ratio, lower lymphocyte counts; as well as higher values of CRP, lactate dehydrogenase, D-dimer, and creatinine were found to be associated with higher mortality. These results confirmed previously reported data on the predictive role of markers of hypoxemia such as low peripheral oxygen saturation and P/F ratio; markers of inflammation such as CRP, lactate dehydrogenase; and coagulation abnormalities; for in-hospital mortality [21–23]. Our analysis also confirms that transfer to ICU was associated with a more severe prognosis [21].

Our study covered data pertaining medication history referred on admission, as well as the drugs prescribed during hospital stay. In this regard, our analysis showed that patients who were on long-term treatment with furosemide, ICS/LABA inhalers, and oral corticosteroids presented a higher mortality. Furosemide is a loop diuretic that is widely used in heart failure, kidney disease and high blood pressure. A relation between the consumption of furosemide prior to the hospitalization and worse patient survival has been described in literature in a real-world study that considered a population of about 16,000 COVID-19 hospitalized patients [24]. Long-term use of corticosteroids has also been associated with an increased risk of hospitalization and mortality in COVID-19 patients [14,25]. In our study, the negative impact of prior long-term use of corticosteroid on mortality was confirmed with regression analysis after adjusting for confounding variables such as age and comorbidities. This result can be explained by the well-established immunosuppressive effect of corticosteroid therapy, a condition that can increase infection susceptibility [26]. The negative effect of ICS/LABA inhaler combination on mortality for patients with obstructive airway disease (asthma and COPD) has also been described in a large observational study [27].

When it comes to treatment administered during hospital stay, our analysis showed that the use of remdesivir and methylprednisone had a positive effect on survival; while the use of amiodarone, opioids, and psychotropic drugs was associated with an increased mortality. Corticosteroids were widely used during the COVID-19 pandemic as a treatment option for patients with severe illness, and demonstrated positive effects on disease progression as shown in randomized controlled trials, and systematic reviews and meta-analyses [28–30]. In particular, treatment with methylprednisolone was associated with reduced mortality through the reduction of systemic inflammatory response in severe COVID-19 [31]. Also, the use of the antiviral drug remdesivir has been described to reduce mortality in the treatment of COVID-19 [32], which is in line with our findings. As regards to amiodarone, our results showed that this anti-arrhythmic drug prescribed during hospital stay was significantly related to mortality. In fact, amiodarone was not effective in improving the clinical outcomes of COVID-19 patients in a randomized clinical trial [33]; and was related to higher ICU admission, intubations, and length of hospital stay in another cohort of hospitalized COVID-19 patients [34]. Moreover, our study showed that patients prescribed with psychotropic drugs and opioids during hospitalization had a higher mortality rate. It is known that pre-existing psychiatric disorders can increase the risk of more severe COVID-19-related outcomes [35]. It should be considered that opioids are prescribed for pain relief and sedation in patients with severe disease that need non-invasive ventilation.

Our study has several limitations, mostly inherent to its retrospective nature and the biases of a single center. However, we believe that it can contribute to a deeper understanding of the factors associated with mortality in hospitalized COVID-19 patients, because the analysis pertains quite a large assortment of information in a real-world medical experience.

Conclusions

Our findings highlight the importance of age, clinical features, biomarkers, and therapeutic interventions in predicting disease severity and outcomes. These insights can help in defining targeted interventions and therapeutic strategies to improve the prognosis of COVID-19 in patients at higher risk of adverse outcomes. Further research is warranted to validate our findings in larger and more heterogeneous populations, while also considering the continuously evolving viral variants and treatment protocols. The common goal is to optimize clinical management and enhance patient outcomes in the ongoing fight against COVID-19.

Authors' contributions

Conceptualization: AZ, PP; methodology: BD, SZ, MCP, AGF; data curation and investigation: EZ, SSF, BD, BP, LT,

CC; original draft preparation: EZ, SSF, PP; review and editing: EZ, SSF, AZ, AAM, PP.

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Conflict of interests

No conflict of interests is declared.

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