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RESEARCH ARTICLE

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Prognostic factors and combined use of tocilizumab and corticosteroids in a Spanish cohort of elderly COVID-19 patients

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Abstract

Coronavirus disease 2019 (COVID-19) infection in elderly patients is more aggressive and treatments have shown limited efficacy. Our objective is to describe the clinical course and to analyze the prognostic factors associated with a higher risk of mortality of a cohort of patients older than 80 years. In addition, we assess the efficacy of immunosuppressive treatments in this population. We analyzed the data from 163 patients older than 80 years admitted to our institution for COVID-19, during March and April 2020. A Lasso regression model and subsequent multivariate Cox regression were performed to select variables predictive of death. We evaluated the efficacy of immunomodulatory therapy in three cohorts using adjusted survival analysis. The mortality rate was 43%. The mean age was 85.2 years. The disease was considered severe in 76.1% of the cases. Lasso regression and multivariate Cox regression indicated that factors correlated with hospital mortality were: age (hazard ratio [HR] 1.12, 95% confidence interval [CI]: 1.03–1.22), alcohol consumption (HR 3.15, 95% CI: 1.27–7.84), CRP > 10 mg/dL (HR 2.67, 95% CI: 1.36–5.24), and oxygen support with Venturi Mask (HR 6.37, 95% CI: 2.18–18.62) or reservoir (HR 7.87, 95% CI: 3.37–18.38). Previous treatment with antiplatelets was the only protective factor (HR 0.47, 95% CI: 0.23–0.96). In the adjusted treatment efficacy analysis, we found benefit in the combined use of tocilizumab (TCZ) and corticosteroids (CS) (HR 0.09, 95% CI: 0.01–0.74) compared to standard treatment, with no benefit of CS alone (HR 0.95, 95% CI: 0.53–1.71). Hospitalized elderly patients suffer from a severe and often fatal form of

COVID-19 disease. In this regard, several parameters might identify high-risk patients upon admission. Combined use of TCZ and CS could improve survival.

KEYWORDS
corticosteroids, COVID-19, elderly, prognosis, tocilizumab

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a major cause of acute respiratory syndrome and mortality.[1] Initially data from China showed a total case-fatality rate of 2.3%, but in patients, over 80 years this rate may be as high as 14.8%.[2] Spain has been one of the most severely affected European countries reaching up to three times the usual capacity of intensive care units (ICUs).[3] Elderly patients and nursing homes were especially hit by the pandemic. According to the Spanish National Surveillance Net, the 80-years and older population showed the highest hospitalization −44.7%- and mortality −21.8%- rates.[4]

COVID-19 in elderly patients is a matter of great importance for its morbi-mortality. Until now, several reports have tried to establish risk factors for poor outcomes, but few studies have focused on the elderly population[5,6] Furthermore, these patients are underrepresented in clinical trials and the specific use of some treatments should be confirmed in this group of patients. More evidence is needed about SARS-CoV-2 infection in this group of patients.

In this study, we aim to: (a) describe clinical characteristics as well as outcomes of patients over 80 years admitted for COVID-19; (b) identify prognostic factors for risk of death; and (c) assess the efficacy of immunosuppressive treatments - tocilizumab (TCZ) and corticosteroids (CS) - applied to this population.

2 | METHODS

2.1 | Study design

We design a single-center, retrospective observational study that included all patients older than 80 years, admitted into our institution between March 1 and April 30, 2020, with a diagnosis of COVID-19 and followed up until hospital discharge. Due to the difficulties to provide adequate follow-up in that pandemic scenario, patients referred to other hospitals from our Emergency Department were ultimately excluded. The Fuenlabrada University Hospital's local Ethics Committee approved this study (APR 20/26).

2.2 | Procedures and study variables

Diagnosis of confirmed cases was performed by real-time reverse transcription-polymerase chain reaction (PCR) from nasopharyngeal swab samples (platform Roche Cobas Z 480). During the period of greatest healthcare overload, there was no availability of PCR tests for all patients. According to hospital protocols, patients with high clinical suspicion (bilateral pneumonia, lymphopenia, and close contact with positive cases) were defined and managed as probable cases. Probable cases were included in statistical analysis.

The following variables were recorded from electronic medical records.

- Baseline characteristics and comorbidities at the time of initial contact: age, sex, former or current smoker, previous alcohol consumption, hypertension, diabetes mellitus (DM), dyslipidemia, obesity (defined as body mass index (BMI) > 3 kg/m^2), chronic kidney disease (CKD) (glomerular filtration rate <60 ml/min), heart disease (including arrhythmias, ischemic disease, heart failure, and valvular disease), respiratory pathology (chronic obstructive pulmonary disease, asthma, chronic respiratory insufficiency, and use of previous mechanical noninvasive ventilation devices), venous thromboembolic disease (VTE), cirrhosis, neurological conditions (dementia and neurodegenerative disorders, previous stroke, or epilepsy), anemia, history of malignancy (including hematological and solid cancer), autoimmune disease, and autonomy for activities of daily living.
- Previous treatments: antiplatelets, anticoagulants, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptors antagonists type II (ARA-II), nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, and immunosuppressive therapies.
- Symptoms and clinical signs on admission: fever (temperature over 37.8°C), cough, dyspnea, chest pain, digestive symptoms, confusion, blood pressure, heart rate, tachypnea, and mental status.
- Laboratory parameters: lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, D-dimer (DD), creatinine, glomerular filtration rate (GFR), urea, sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), albumin, white cell blood count, neutrophils, lymphocytes, hemoglobin, platelets. Severity of disease on admission: Classified as mild, moderate, or severe according to recommendations from WHO guidelines. Critical cases were re-classified into the severe group.[7] We recorded additional information about oxygen supplementation on entry, and radiological findings on entry.
- Treatments received during the course of the hospital stay: Antibiotics, chloroquine/hydroxychloroquine, ritonavir/lopinavir, interferon beta 1b, CS, TCZ, and heparin (prophylactic or intermediate-high

doses). Due to its retrospective observational design, the dose of CS administered was not predefined in advance. Our institutional protocol contemplated the possibility of CS use in case of rapidly progressive respiratory failure or elevation of inflammatory parameters (such as CRP > 10 mg/dL), despite antiviral or antimalarial treatment. Although the institutional protocol recommended doses of 20 mg dexamethasone for 5–10 days or 250/500 mg methylprednisolone pulses for 3–5 days, the final dose was individually decided by the treating physician. Data were collected on daily and total doses received, in mg equivalent to prednisone. The use of TCZ (in 2 doses of 600 mg on consecutive days) was restricted during part of the study due to stock-outs. When available, it was used with the same criteria as CS, generally in the absence of response to them.

- Length of stay, complications during hospitalization (bacterial infection, kidney and liver worsening, heart failure, thrombosis, bleeding, confusional syndrome, and blood transfusion), and final outcomes (survival or death).

2.3 | Outcomes

The main outcome was mortality for both analyses: prognostic risk factors and efficacy of treatments. Patients were followed up until discharge or death.

2.4 | Statistical analysis

The descriptive variables were analyzed using means and standard deviations (Student's *t*-test) as well as counts and percentage (χ^2 tests) where appropriate. Given the multitude of baseline variables, we report univariate Cox regression results and chose the least absolute shrinkage and selection operator (Lasso) binary logistic regression model to select and report variables jointly predictive of death. The selected variables were entered into a multivariate Cox regression analysis. To facilitate model interpretation, we transformed the laboratory data continuous variable into bivariate. Cut-off levels were determined according to previous reports[8] or reference values from our laboratory.

In a subsequent step, we evaluated the efficacy of the treatments by creating three patient cohorts: (1) patients without immunomodulatory therapy, (2) patients who received only CS, and (3) patients who received CS and TCZ, and compared them using crude Kaplan–Meier survival curves and adjusted survival analysis for age, sex, the presence of hypertension, diabetes mellitus, previous heart disease, severity of disease, and initial supplemental oxygen requirements on admission. This analysis was not time updated but uses the time from hospitalizations to death or discharge, regardless of when the treatment was administered.

Statistical analysis was performed with R 4.0.1 and the level of statistical significance considered in all univariate analyses and the Kaplan–Meier survival curves was $p = 0.05$.

3 | RESULTS

During the first wave of the COVID-19 pandemic, a total of 1700 patients were admitted to our center. Of them, 163 (9.5%) were over 80 years old and were included in the study.

Baseline characteristics, comorbidities, and previous treatments are presented in Table 1, comparing survivors (93 cases) and deceased (70 cases, 43% of total). Seventy-five (46%) of patients were female. The median age was 85.2 years. None of these patients were admitted to the ICU.

The most frequent comorbidity was hypertension in 82.2% of cases, followed by heart disease 50.9%, CKD 44.1%, neurological conditions 38%, former and current smoker 36.9%-, DM 35.6%, obesity 35.4%, and respiratory diseases 30.7%. CKD was more frequent among patients that died (56.2% vs. 35.2%, $p = 0.02$) while the rest of the variables did not show relevant differences. ACEIs and ARAII were frequently used among patients (91 cases, 55.8%) without differences between both groups. Regarding the remaining drugs, they had similar rates of use, except for immunosuppressive agents, which were more frequently used among patients who eventually died (18.8% vs. 6.5%, $p = 0.03$).

3.1 | Symptoms, clinical signs, and laboratory findings at admission

Data about symptoms, clinical signs, laboratory, and radiological findings, and severity of disease upon admission are shown in Table 2.

Cough and dyspnea were the most frequent symptoms (69.4% and 63.4%), while fever was present in 40.1% of all cases. Notably, digestive symptoms were more frequent in the survival group (25.8% vs. 10%). Tachypnea and tachycardia were more frequent in dead patients (66.7% vs. 27.9% and 95 bpm vs. 86.5 bpm, respectively). In addition, these patients presented more frequently altered mental status (confusion in 24.2% vs. 11.1% and coma in 10.6% vs. 0%).

The mean values of analytical parameters are also shown in Table 2. The dead group had higher levels of LDH (461.2 vs. 272.9 U/L), CRP (14.35 vs. 8.81 mg/dL), creatinine (1.49 vs. 1.2 mg/dL), AST (55.26 vs. 36.56 U/L), GGT (95.05 vs. 54.65 U/L), white blood cell count (12.7 vs. 8.66×10^9/L), neutrophils (10.17 vs. 6.38×10^9/L) with decreased levels of GFR (46.78 vs. 58.85 ml/min/1.73 m^2) and platelets (181.94 vs. 211.39×10^3).

The first assessment of the severity of the disease was clearly different between the groups. 90% of all patients who died had a severe disease on admission (65.6% among survivors). Furthermore, important differences were found in the need for oxygen support upon admission. The group of survivors had more cases with no support (64.5 vs. 25.7%) while a high number of dead patients required a reservoir oxygen mask (37.1% vs. 3.2%). When considering the 29 cases that required a reservoir in the emergency department, only 3 of 29 eventually survived. Regarding the radiological patterns, those patients who died presented more often with bilateral pneumonia (72.9% vs. 52.7%), while in the survivors' group unilateral pneumonia (30.1% vs. 18.6%) and no pneumonia (17.2% vs. 8.6%) were more common.

TABLE 1 Differences in baseline characteristics between survivors and deceased groups

Baseline characteristics	Overall (*n* = 163)	Survivors (*n* = 93)	Dead (*n* = 70)	*p*
Age (mean, year (sd))	85.23 (4.11)	85.18 (4.19)	85.29 (4.03)	0.875
Sex (female, %)	75 (46.0%)	47 (50.5%)	28 (40.0)	0.239
Comorbidities, *n* (%)				
Smoker	59 (36.9)	29 (31.5)	30 (44.1)	0.142
Alcohol consumption	11 (6.7)	3 (3.2)	8 (11.4)	0.08
Hypertension	134 (82.2)	78 (83.9)	56 (80.0)	0.665
Diabetes mellitus	58 (35.6)	32 (34.4)	26 (37.1)	0.845
Obesity	51 (35.4)	31 (37.3)	20 (32.8)	0.697
Chronic kidney disease	67 (44.1)	31 (35.2)	36 (56.2)	0.016
Heart disease	83 (50.9)	44 (47.3)	39 (55.7)	0.366
Respiratory disease	50 (30.7)	24 (25.8)	26 (37.1)	0.167
Previous thrombosis	20 (12.3)	11 (11.8)	9 (12.9)	1
Cirrhosis	2 (1.2)	1 (1.1)	1 (1.4)	1
Neurological disease	62 (38.0)	35 (37.6)	27 (38.6)	1
Anemia	44 (27.5)	27 (30.0)	17 (24.3)	0.532
Malignancy	47 (28.8)	24 (25.8)	23 (32.9)	0.419
Autoimmune disease	11 (6.7)	4 (4.3)	7 (10.0)	0.263
Dependency	61 (37.7)	31 (33.7)	30 (42.9)	0.304
Previous treatments, *n* (%)				
Antiplatelets	51 (31.7)	34 (36.6)	17 (25.0)	0.166
Anticoagulants	53 (32.7)	27 (29.0)	26 (37.7)	0.322
ACEI-ARAII	91 (55.8)	54 (58.1)	37 (52.9)	0.615
NSAID	5 (3.1)	2 (2.2)	3 (4.3)	0.743
Inhaled corticosteroids	19 (11.7)	12 (12.9)	7 (10.1)	0.77
Immunosupresive drugs	19 (11.8)	6 (6.5)	13 (18.8)	0.031

Note: *p*-values represent the comparison between survivors and dead groups.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARAII, angiotensin receptors antagonists type II; NSAIDs, nonsteroidal anti-inflammatory drugs.

3.2 | Length of stay, treatments, and complications

In relation to the length of stay, treatments and complications suffered during hospitalization are shown in Table 3. The time from the onset of self-reported symptoms to emergency department admission was 5.73 days in general, slightly shorter among the patients who died (4.89 vs. 6.32 days).

Most of the patients received antibiotics (90.9% at least one dose), chloroquine/hydroxychloroquine (95.8%), and lopinavir/ritonavir (77.4%) following the established institutional protocol. Corticosteroids (expressed in equivalent doses to mg of prednisone) were used in 52.4% of cases, with greater frequency in patients who died (67.1% vs. 41.5%) at higher cumulative (553 vs. 475 mg), and medium daily doses (217 vs. 118 mg). In addition, tocilizumab was used in 11 patients (in nine with simultaneous corticosteroid treatment) mainly in the survivors' group. Heparin either in intermediate or therapeutic doses was prescribed in 34.4% of patients.

Among the complications, acute kidney failure was the most prevalent, in 22% of the cases; followed by confusional syndrome in 14.6%. Bacterial infections were documented in 8.5%, similarly among groups.

3.3 | Uni and multivariate analysis for risk factors

We first performed a univariate Cox regression analysis to identify prognostic factors associated with death. In a first step, we included 55 variables relatives to comorbidities, previous treatments, symptoms on admission, laboratory data, and severity of the disease. Results with correspondent hazard ratio (HR) and confidence intervals (CI) are presented in Table 4. In the univariate analysis, the

TABLE 2 Differences in clinical signs, symptoms, and laboratory values on admission

	Overall (*n* = 163)	Survivors (*n* = 93)	Dead (*n* = 70)	*p*
Symptoms on admission, *n* (%)				
Fever	97 (59.5)	51 (54.3)	46 (66.7)	0.111
Cough	111 (69.4)	68 (73.1)	43 (64.2)	0.3
Dyspnea	102 (63.4)	53 (57.0)	49 (72.1)	0.073
Chest pain	7 (4.5)	5 (5.5)	2 (3.1)	0.759
Digestive symptoms	31 (19.0)	24 (25.8)	7 (10.0)	0.019
Confusion	25 (15.9)	9 (9.8)	16 (24.6)	0.023
Clinical signs on admission				
Temperature (mean, °C [*SD*])	36.63 (1.09)	36.56 (1.11)	36.75 (1.06)	0.306
Systolic BP (mean, mmHg [*SD*])	130.62 (25.00)	131.45 (24.92)	129.49 (25.25)	0.628
Diastolic BP (mean, mmHg [*SD*])	71.52 (13.18)	71.92 (12.71)	70.96 (13.86)	0.649
Heart rate (mean, bpm [*SD*])	90.18 (20.88)	86.58 (14.00)	95.06 (26.97)	0.011
Tachypnea (*n*, %)	66 (44.3)	24 (27.9)	42 (66.7)	<0.001
Mental status (*n*, %)				<0.001
Normal	123 (78.8)	80 (88.9)	43 (65.2)	
Altered	26 (16.7)	10 (11.1)	16 (24.2)	
Coma	7 (4.5)	0 (0.0)	7 (10.6)	
Laboratory findings				
LDH (mean, U/L [*SD*])	352.19 (420.20)	272.91 (120.99)	461.21 (619.11)	0.017
CRP (mean, mg/dL [*SD*])	11.10 (9.17)	8.81 (8.26)	14.35 (9.47)	<0.001
Procalcitonin (mean, ng/ml [*SD*])	1.55 (8.29)	1.62 (10.80)	1.46 (3.72)	0.923
D-Dimer (mean, mg/L [*SD*])	4.55 (15.78)	5.02 (18.83)	3.90 (10.30)	0.685
Creatinine (mean, mg/dL [*SD*])	1.32 (0.79)	1.20 (0.76)	1.49 (0.81)	0.022
GFR (mean, ml/min/1.73 m^2 [*SD*])	53.53 (23.05)	58.85 (22.13)	46.78 (22.61)	0.003
Urea (mean, mg/dL [*SD*])	70.14 (46.39)	62.59 (46.31)	79.63 (45.37)	0.105
Sodium (mean, mmol/L [*SD*])	138.30 (7.01)	138.32 (6.35)	138.28 (7.95)	0.975
AST (mean, U/L ([*SD*])	43.95 (34.08)	36.56 (27.86)	55.26 (39.68)	0.012
ALT (mean, U/L [*SD*])	29.85 (34.12)	25.76 (24.58)	35.39 (43.51)	0.1
GGT (mean, U/L [*SD*])	72.40 (94.92)	54.65 (71.68)	95.05 (114.88)	0.015
Albumin (g/dL, mean [*SD*])	3.31 (0.45)	3.27 (0.42)	3.36 (0.48)	0.381
White cell blood count (mean, 10^9/9 L [*SD*])	10.38 (18.96)	8.66 (4.66)	12.70 (28.50)	0.181
Neutrophils (mean, 10^9/L [*SD*])	8.00 (17.25)	6.38 (3.88)	10.17 (26.00)	0.168
Lymphocytes (mean, 10^9/L [*SD*])	1.30 (1.43)	1.32 (0.96)	1.29 (1.90)	0.92
Hemoglobin (mean, g/dL [*SD*])	12.91 (2.18)	12.86 (2.10)	12.98 (2.29)	0.726
Platelets (mean, 10^9/L [*SD*])	198.85 (95.22)	211.38 (100.95)	181.94 (84.71)	0.051
Severity of illness				
Severity classification				0.001
Mild	11 (6.7)	8 (8.6)	3 (4.3)	
Moderate	28 (17.2)	24 (25.8)	4 (5.7)	
Severe	124 (76.1)	61 (65.6)	63 (90.0)	

TABLE 2 (Continued)

	Overall (*n* = 163)	Survivors (*n* = 93)	Dead (*n* = 70)	*p*
Oxygen support at entry				<0.001
No support	78 (47.9)	60 (64.5)	18 (25.7)	
Nasal ducts	43 (26.4)	27 (29.0)	16 (22.9)	
VentiMask	13 (8.0)	3 (3.2)	10 (14.3)	
Reservoir	29 (17.8)	3 (3.2)	26 (37.1)	
Radiology findings				0.03
No pneumonia	22 (13.5)	16 (17.2)	6 (8.6)	
Unilateral pneumonia	41 (25.2)	28 (30.1)	13 (18.6)	
Bilateral pneumonia	100 (61.3)	49 (52.7)	51 (72.9)	

Note: *p*-values represent a comparison between survivors and dead groups.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; *SD*, standard deviation.

TABLE 3 Differences in time to admission, mean stay, treatments received, and complications

Variable	Overall (*n* = 163)	Survivors (*n* = 93)	Dead (*n* = 70)	*p*
Time symptoms to admission (mean, days [*SD*])	5.73 (5.95)	6.32 (6.46)	4.89 (5.07)	0.138
Mean stay (mean, days [*SD*])	9.45 (7.12)	12.08 (7.56)	6.04 (4.69)	<0.001
Treatments (*n*, %)				
Antibiotics	149 (90.9)	87 (92.6)	62 (88.6)	0.382
Chloroquine	33 (20.2)	18 (19.4)	15 (21.4%)	0.744
Hydroxychloroquine	124 (75.6)	77 (81.9)	47 (67.1)	0.029
Lopinavir/ritonavir	127 (77.4)	72 (76.6)	55 (78.6)	0.765
Interferon	4 (2.4)	2 (2.1)	2 (2.9)	0.765
Corticosteroids	86 (52.4)	39 (41.5)	47 (67.1)	0.001
Total dose (mg PDN, [*SD*])	508.91 (708.53)	475.78 (773.72)	553.4 (612.8)	0.489
Mean dose (mg PDN, [*SD*])	172.96 (112.17)	118.31 (63.92)	217.36 (123.4)	<0.001
Tocilizumab	11 (6.7)	10 (10.8)	1 (1.4)	0.025
Heparin	56 (34.4)	38 (40.9)	18 (25.7)	0.044
Complications				
Bacterial infection	14 (8.5)	8 (8.5)	6 (8.6)	0.989
Kidney injury	36 (22)	16 (17)	20 (28.6)	0.077
Liver injury	5 (3)	1 (1.1)	4 (5.7)	0.087
Heart failure	20 (12.2)	8 (8.5)	12 (17.1)	0.095
Thrombosis	4 (2.4)	4 (4.3)	0	0.137
Bleeding	4 (2.4)	1 (1.1)	3 (4.3)	0.314
Confusional syndrome	24 (14.6)	12 (12.8)	12 (17.1)	0.433
Transfusion	7 (4.3)	6 (6.4)	1 (1.4)	0.240

Note: *p*-values represent the comparison between survivors and dead groups.

Abbreviations: PDN, prednisone; *SD*, standard deviation.

TABLE 4 Univariate Cox regression for prognostic factors associated with death

Univariate Cox analysis											
Prognostic factors	**HR (95% CI)**	***p*-value**	**Prognostic factors**	**HR (95% CI)**	***p*-value**	**Prognostic factors**	**HR (95% CI)**	***p*-value**	**Prognostic factors**	**HR (95% CI)**	***p*-value**
Age	1.02 (0.97–1.08)	0.457	Antiplatelets	0.62 (0.36–1.09)	0.112	Mental status (*n*, %)			Neutrophils > 7.5×10^3/L	1.3 (0.8–2.13)	0.304
Sex (female)	0.88 (0.54–1.41)	0.612	Anticoagulants	1.25 (0.76–2.03)	0.380	Normal	1		Lymphocytes <1×10^3/L	1.96 (1.2–3.19)	0.008
Smoker	1.43 (0.89–2.31)	0.153	ACEIs-ARAII	0.96 (0.6–1.54)	0.882	Altered	2.18 (1.25–3,88)	0.010	Hemoglobin < 13 g/dL	0.87 (0.54–1.4)	0.578
Alcohol consumption	2.24 (1.07–4.68)	0.036	NSAIDs	1.62 (0.51–5.19)	0.428	Coma	6.82 (3.03–15.33)	<0.001	Platelets <150×10^3/L	1.29 (0.8–2.1)	0.295
Hypertension	0.87 (0.48–1.56)	0.669	Inhaled corticosteroids	0.75 (0.34–1.63)	0.467	LDH > 250 U/L	3.2 (1.5–6.86)	0.003	Severity classification		
Diabetes	0.93 (0.57–1.52)	0.784	Immunosupresive drugs	1.95 (1.06–3.57)	0.036	CRP > 10 mg/dL	2.35 (1.43–3.85)	0.001	Mild	1	
Obesity	0.98 (0.57–1.67)	0.930	Fever	1.4 (0.85–2.32)	0.187	Procalcitonin > 0.5 ng/ml	1.97 (1.06–3.64)	0.042	Moderate	0.4 (0.09–1.78)	0.231
Chronic kidney disease	1.83 (1.17–3)	0.019	Cough	0.85 (0.51–1.4)	0.519	D-Dimer > 0.5 mg/L	1.17 (0.56–2.48)	0.681	Severe	1.67 (0.53–5.36)	0.394
Cardiopathy	1.42 (0.89–2.27)	0.160	Dyspnea	2.16 (1.26–3.69)	0.016	Creatinine > 1.17 mg/dL	1.97 (1.06–3.64)	0.004	Oxygen support		
Neumopathy	1.32 (0.81–2.15)	0.275	Chest pain	0.75 (0.18–3.1)	0.711	GFR < 60 ml/min/1.73 m^2	2.05 (1.15–3.67)	0.017	No support	1	
Previous thrombosis	0.99 (0.49–2)	0.986	Digestive symptoms	0.43 (0.2–0.94)	0.040	Urea > 49 mg/dL	1.59 (0.76–3.33)	0.224	Nasal ducts	1.72 (0.87–3.36)	0.123
Cirrhosis	1.56 (0.21–11.3)	0.685	Confusion	2.12 (1.24–3.74)	0.011	Sodium > 145 mmol/L	1.4 (0.6–3.27)	0.321	VentiMask	7.31 (3.35–15.94)	<0.001
Neurological disease	1.09 (0.67–1.77)	0.726	Temperature	1.12 (0.9–1.4)	0.333	AST > 50 U/L	3.4 (1.7–6.75)	0.001	Reservoir	6.31 (3.45–11.55)	<0.001
Anemia	0.76 (0.44–1.32)	0.344	Systolic BP	1 (0.99–1)	0.838	ALT > 50 U/L	1.4 (0.66–2.96)	0.390	Radiology findings		
Malignancy	1.18 (0.71–1.93)	0.530	Diastolic BP	1 (0.97–1.01)	0.486	GGT > 85 U/L	1.63 (0.9–2.94)	0.112	No pneumonia	1	
Autoimmune disease	2.03 (0.92–4.46)	0.083	Heart rate	1.02 (1.01–1.04)	<0.001	Albumin <3.5 g/dL	0.7 (0.36–1.37)	0.226	Unilateral pneumonia	1.08 (0.41–2.84)	0.882
Dependency	1.29 (0.80–2.07)	0.296	Tachypnea (n, %)	3.36 (1.99–5.69)	<0.001	WBC > 11.6×10^3/L	1.24 (0.71–2.18)	0.640	Bilateral pneumonia	2.03 (0.87–4.77)	0.091

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; ARAII, angiotensin receptors antagonists type II; AST, aspartate aminotransferase; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; LDH, lactate dehydrogenase; NSAIDs, nonsteroidal anti-inflammatory drugs.

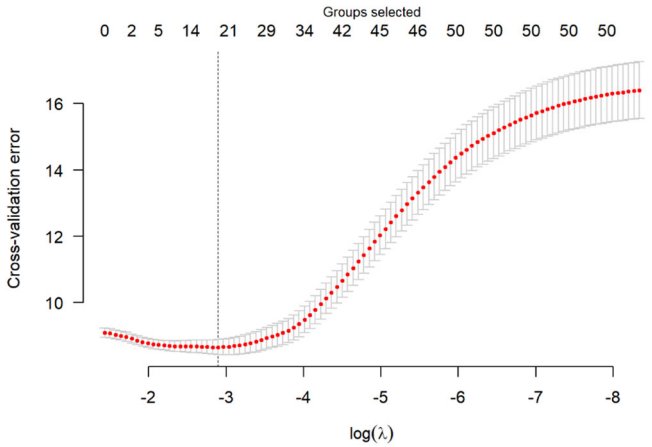

FIGURE 1 The selection of the variables by Lasso regression was controlled by lambda to select the most accurate model

factors associated with poor outcomes were: alcohol consumption, chronic kidney disease, previous immunosuppressive drugs, dyspnea, confusion, tachypnea, altered mental status, increased LDH, CRP, PCT, creatinine or AST, decreased GFR, lymphopenia, and the type of oxygen support. Digestive symptoms were the only factor with a protective role.

Due to an imbalanced proportion between baseline variables and the number of patients, we then performed a Lasso shrinkage regression for variable selection. After controlling for the most accurate model (Figure 1), 19 variables were selected and entered into a multivariate Cox regression analysis. NSAIDs were excluded for creating instability in the model, due to a low frequency of use. The results of the multivariate analysis are shown in Table 5. Finally the variables that remained as independent prognostic factors for mortality were: age (HR 1.12, 95% CI: 1.03–1.22), alcohol consumption (HR 3.15, 95% CI: 1.27–7.84), CRP > 10 mg/dL (HR 2.67, 95% CI: 1.36–5.24), and oxygen support with Venturi Mask (HR 6.37, 95% CI: 2.18–18.62), or reservoir (HR 7.87, 95% CI: 3.37–18.38). Previous treatment with antiplatelets was the only beneficial factor for survival (HR 0.47, 95% CI: 0.23–0.96).

TABLE 5 Multivariate Cox regression for prognostic factors associated with death

Multivariate Cox analysis			
Prognostic factors	**HR**	**95% CI**	***p*-value**
Age	1.12	1.03–1.22	0.012
Alcohol consumption	3.15	1.27–7.84	0.013
Antiplatelets	0.47	0.23–0.96	0.037
CRP > 10 mg/dL	2.67	1.36–5.24	0.004
Platelets < 150×10^3/L	2.29	1.21–4.31	0.11
Oxygen support on admission:			
No support	1		
Nasal ducts	1.78	0.72–4.37	0.209
Venturi Mask	6.37	2.18–18.62	0.001
Reservoir	7.87	3.37–18.38	<0.001

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio;.

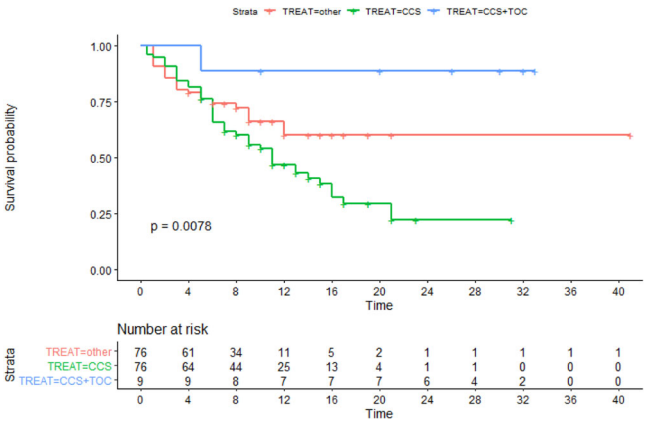

FIGURE 2 Unadjusted Kaplan–Meier curve for survival of each treatment group. CCS, corticosteroids; TOC, tocilizumab

3.4 | Efficacy of treatments: Corticosteroids and tocilizumab

We assessed the efficacy of treatments with survival analysis of three groups: no immunosuppressive therapy (76 patients), CS alone (76 patients), or in combination with TCZ (9 patients).

No statistically significant differences were noted between groups regarding age, sex, and comorbidities. The proportions of severity and oxygen support in the groups receiving CS alone or combined with TCZ were higher than in the group of patients who did not receive either of these drugs. No statistically significant differences were observed when comparing the groups treated with immunomodulatory therapy. The analysis controlled for potential baseline confounding effects such as age, sex, comorbidities, the severity of disease, and the need for supportive oxygen at admission.

The final Kaplan-Meier curve for the survival of each group is presented in Figure 2. The adjusted estimates for treatment efficacy were: (a) non immunomodulatory therapy (reference treatment HR = 1), (b) patients receiving CS (HR 0.95, 95% CI: 0.53–1.71), and (c) patients receiving CS and TCZ (HR 0.09, 95% CI: 0.01–0.74).

4 | DISCUSSION

In this study we present the characteristics and outcomes of 163 elderly patients admitted to our institution during the first wave of the pandemic in Spain. Population over 80 years represent the largest group by age (23.8% of the cases confirmed until the end of May 2020).[4] Advanced age is a well-known independent factor for mortality and the overall mortality rate in this group ranges between 15%–35%.[2]

In our hospital, the mortality rate for those over 80 years of age was 43%. During the greatest hospital overload, mild cases were transferred to other hospitals, and severe/critical cases represented 76% of our series. The need for ICU was assessed on a case-by-case basis, although none of the patients were considered for admission to ICU, due to previous comorbidities and the decision algorithms to rationalize resources in a context of high demand. These reasons may explain higher mortality compared with other cohorts[5,9]

In the elderly population, COVID-19 infection evolves rapidly to death in many cases. Once hospitalized, the time to death in our study was half of the time to recovery. Our analysis tries to clarify which symptoms, vital signs, laboratory data, and radiological findings on admission may be useful to better identify patients of high risk. The multivariate model regression finally selected age, alcohol consumption, elevated CRP, low platelets, and oxygen supplementation as the most important factors related to the risk of death. Previous treatment with antiplatelets was considered a protective factor. The results of our model are strongly concordant with existing literature.

Elderly patients suffer from several of the comorbidities that have been already associated with COVID-19 risk mortality: cardiovascular disease, DM, hypertension, respiratory disease, cancer, CKD, obesity, smoking, and alcoholism[10–12] Dementia, which is a frequent condition in elderly patients, has also been related to mortality in specific studies in older people.[5] In our cohort, these conditions were highly represented and the univariate analysis showed a risk increase in most of them. The subsequent Lasso-Cox regression selected age itself and alcohol consumption as relevant factors for poor outcomes. A remarkable result was obtained with the beneficial role of previous antiplatelets use. Larger cohorts have already associated antiplatelets with better in-hospital outcomes[13,14] We may hypothesize that antiplatelets reduce the COVID-19 related thrombosis risk. But the number of events, predominantly in the survivors' groups, is too small to analyze properly this issue. Previous treatment with anticoagulants did not have the same protective effect.

Regarding the prognostic role of laboratory markers, previous reports have emphasized the value of lymphopenia, thrombocytopenia, elevated LDH, CRP or D-dimer[5,8,15] Our model finally selected CRP and platelets count as the most important parameters which may guide the therapeutic decision algorithms.

The most consistent risk factor in our study was the type of oxygen supplementation on admission. Hypoxemia or dyspnea have already been linked to poor outcomes by other authors[5,16] The risk of death with Venturi mask or reservoir increased by six or seven times, respectively. WHO proposed a classification for COVID-19 cases into mild, moderate, severe, and critical. But considering the high proportion of elderly patients with the last forms, oxygen demand on admission may be a more accurate form to stratify the risk in this population.

Our study has some limitations in evaluating the efficacy of treatments, mainly due to its retrospective observational design, dose variability in therapies, and the small number of patients treated with the combined treatment. At the time these patients were treated, no treatment had shown an improvement in survival.[17] Most received antimalarials and lopinavir/ritonavir, which were later shown to be ineffective and excluded for the analysis[18,19] Remdesivir was not available so no patient received it.

According to the postulated theories about a cytokine storm causing the lung damage[20,21] CS and an interleukine-6 blocker (TCZ) were prescribed in some cases. CS has subsequently been validated in later studies as a mortality-reducing treatment in clinical trials in patients requiring oxygen therapy,[22] while some controversies remain about TCZ.[23–25] Some studies propose an extra benefit for TCZ when using it in addition to CS, rather than separately.[26]

We found of special interest the role of immunosuppressive treatments in this special population. Aging itself is a predisposing condition to cytokine dysregulation and hyperinflammatory states, which may explain the higher mortality rates in the elderly.[27,28] Interleukine-6 is considered a hallmark of inflammatory changes related to aging.[29] Despite a small number of patients treated with the combination of TCZ and CS, the adjusted model showed statistically significant benefit in terms of survival. The results should be interpreted with caution due to a wide confidence interval.

The evolution of those who received only CS seems worse than those who did not receive any treatment, but after the adjustment for severity, the survival curves become similar. It should be noted that in our institutional protocol, CS and TCZ were started under certain severity criteria but TCZ availability was limited for some periods of time. This fact justifies a more widespread use of corticosteroids. Very high doses were often prescribed in a setting of lack of evidence or availability of other treatments. Consequently, the proportion of seriously ill patients was higher in the corticosteroids-treated group. Despite the adjustment of the model for severity, the bias caused may have been sufficient to explain this result. We must also consider a harmful influence of the dose used as the dose shown to be beneficial in the studies is significantly lower than that received by our patients.

In conclusion, in this study, we extensively describe the clinical evolution of a cohort of elderly patients over 80 years of age with COVID-19 and highlight the most relevant prognostic factors. Bearing in mind the high mortality rate and the concerns about effective therapeutic interventions, it is necessary to know the prognostic tools that allow better adaptation of medical care. Combined treatment with TCZ and CS may have a potential role in reducing mortality even in the elderly population.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests. The main author corroborates on behalf of Dr. Stefan Walter that no conflicts of interest affected his work in this study.

AUTHORS CONTRIBUTIONS

All authors contributed to data collection, analysis, and writing of the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Harvard Dataverse, V1 at doi:10.7910/DVN/YUAPGS, reference number UNF:6:I3kmpBRlT4FMbJUR9ng3tw==.

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REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020; 395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA - J Am Med Assoc*. 2020; 323(13):1239-1242. doi:10.1001/jama.2020.2648
3. Condes E, Arribas JR. Impact of COVID-19 on Madrid hospital system. *Enferm Infec Microbiol Clin*. 2020;39:256-257. doi:10.1016/j.eimc.2020.06.005
4. Covid-19 cases notified to the Epidemiological Net of Surveillance in Spain. Accessed May 9, 2020. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx
5. Covino M, De Matteis G, Santoro M, et al. Clinical characteristics and prognostic factors in COVID-19 patients aged ≥80 years. *Geriatr Gerontol Int*. 2020;20(March):1-5. doi:10.1111/ggi.13960
6. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80(6):639-645. doi:10.1016/j.jinf.2020.03.019
7. Clinical management of COVID-19 patients: Clinical guidance. January 2021.
8. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032
9. Mostaza JM, García-Iglesias F, González-Alegre T, et al. Clinical course and prognostic factors of COVID-19 infection in an elderly hospitalized population. *Arch Gerontol Geriatr*. 2020;91(July): 104204. doi:10.1016/j.archger.2020.104204
10. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020; 584:430-436. doi:10.1038/s41586-020-2521-4
11. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Int Urol Nephrol*. 2020;52:1193-1194. doi:10.1007/s11255-020-02451-9.
12. Bhalla S, Sharma B, Smith D, et al. Unhealthy alcohol use is an independent risk factor for increased COVID-19 disease severity: observational cross-sectional study. *JMIR Public Health Surveill*. 2021;7:33022. doi:10.2196/33022
13. Santoro F, Nuñez-Gil IJ, Vitale E, et al. Antiplatelet therapy and outcome in COVID-19: the Health Outcome Predictive Evaluation Registry. *Heart Br Card Soc*. Published online October 5, 2021. doi:10.1136/heartjnl-2021-319552
14. Sisinni A, Rossi L, Battista A, et al. Pre-admission acetylsalicylic acid therapy and impact on in-hospital outcome in COVID-19 patients: the ASA-CARE study. *Int J Cardiol*. Published online October 4, 2021. doi:10.1016/j.ijcard.2021.09.058
15. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA - J Am Med Assoc*. 2020;323:1061-1069. doi:10.1001/jama.2020.1585
16. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80(6):639-645. doi:10.1016/j.jinf.2020.03.019
17. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA - J Am Med Assoc*. 2020;2019:1824-1836. doi:10.1001/jama.2020.6019
18. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med*. 2020;383:2041-2052. doi:10.1056/nejmoa2019014
19. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med*. 2020;382(19): 1787-1799. doi:10.1056/NEJMoa2001282
20. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020; 130(5):2620-2629. doi:10.1172/JCI137244
21. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet*. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0
22. RECOVERY Collaborative G, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/nejmoa2021436
23. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2:591. doi:10.1016/S2665-9913(20)30173-9
24. Salama C, Han J, Yau L, et al. Tocilizumab in nonventilated patients hospitalized with Covid-19 pneumonia. *medRxiv*. 2020;384(650): 20-30. doi:10.1056/NEJMoa2030340
25. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med*. 2020;383: 2333-2344. doi:10.1056/nejmoa2028836
26. Remap-Cap I, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384(16):1491-1502.
27. Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. *Science*. 2020;369(6501):256-257. doi:10.1126/science.abb0762
28. Saghazadeh A, Rezaei N. Expert Review of Clinical Immunology Immune-epidemiological parameters of the novel coronavirus: a perspective. *Expert Rev Clin Immunol*. 2020;00(00):1-6.
29. Chen Y, Klein SL, Garibaldi BT, et al. Aging in COVID-19: vulnerability, immunity and intervention. *Ageing Res Rev*. 2021;65(October 2020):101205. doi:10.1016/j.arr.2020.101205

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