Farmacia
HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

ORIGINALS
Bilingual edition English/Spanish

Factors associated with mortality in patients hospitalized for COVID-19 in Spain. Data from the RERFAR registry

Factores asociados a la mortalidad en pacientes hospitalizados por COVID-19 en España. Datos del Registro Español de Resultados de Farmacoterapia frente a COVID-19 (RERFAR)

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Received 21 April 2021;
Accepted 13 October 2021.
Early Access date (01/08/2022).
DOI: 10.7399/fh.11714

How to cite this paper
Olry de Labry-Lima A, Saez-de la Fuente J, Abdel-Kader Martin L, Alegre-del Rey EJ, García-Cabrera E, Sierra-Sánchez JF. Factors associated with mortality in patients hospitalized for COVID-19 in Spain. Data from the RERFAR registry. Farm Hosp. 2022;46(2):57-71.

Abstract

Objective: To determine the baseline characteristics associated with higher mortality at 42 days in patients hospitalized for COVID-19 in Spain.

Method: The study analyzed a prospective cohort of hospitalized COVID-19 patients. The dependent variable was 42-day mortality. Data on the subjects' demographic and clinical characteristics, comorbidities, usual therapy and supportive interventions and treatments was collected within 48 hours from admission. To determine the potential association of the data with mortality, a multivariate analysis was performed using logistic regression.

Results: 15,628 patients were included, 18.2% of whom (n = 2,806) died during the study period. According to the multivariate analysis, the variables that were significantly associated ($p < 0.05$) with mortality upon admission were: being referred from a nursing home (OR 1.9); having a high respiratory rate (OR 1,5); having moderate (OR 1.7) or severe (OR 2.9) pneumonia (CURB-65); aspartate aminotransferase transami-

KEYWORDS
2019-nCoV; SARS-CoV-2; Coronavirus; COVID-19; Mortality; Spain.

Resumen

Objetivo: Determinar las características basales que se asocian a una mayor mortalidad a los 42 días en aquellos pacientes hospitalizados por COVID-19 en España.

Método: Cohorte prospectiva de pacientes COVID-19 hospitalizados. La variable dependiente fue la mortalidad a los 42 días. Además, se recogieron características demográficas, clínicas, comorbilidades, tratamiento habitual, intervenciones de soporte y tratamientos en las primeras 48 horas del ingreso. Para determinar la asociación con la mortalidad, se realizó un análisis multivariante mediante regresión logística.

Resultados: Se incluyeron 15.628 pacientes, de ellos falleció el 18,2% (n = 2.806). El análisis multivariante mostró que las variables asociadas significativamente ($p < 0,05$) con la mortalidad al ingreso fueron: proceder de un centro sociosanitario (*odds ratio* OR 1,9), frecuencia respiratoria (*odds ratio* 1,5), gravedad de neumonía (CURB-65) moderada (*odds ratio* 1,7) o alta (*odds ratio* 2,9), transaminasa aspartato aminotransferasa ≥ 100 UI/l (*odds ratio* 2,1), lactato-deshidrogenasa ≥ 360 UI/l (*odds ratio* 1,6), procal-

PALABRAS CLAVE
2019-nCoV; SARS-CoV-2; Coronavirus; COVID-19; Mortalidad; España.

nase ≥ 100 IU/l (OR 2.1); lactate dehydrogenase ≥ 360 IU/L (OR 1.6); procalcitonin > 0.5 ng/mL (OR 1.8); creatine kinase ≥ 294 U/L (OR 1.5); D-dimer > 3,000 ng/mL (OR 1.5); hemoglobin < 11.6 g/dL (OR 1.4) and C-reactive protein > 120 mg/L (OR 1.2; requiring respiratory support within the first 48 hours (oxygen therapy [OR 2.0], non-invasive ventilation [OR 2.8], and mechanical ventilation [OR 3.5]); and being treated with interferon-beta (OR 1.5). On the contrary, being under 80 years of age was associated with lower mortality.

Conclusions: The analysis, based on the data in the RERFAR registry, showed that the factors associated with poorer prognosis were older age, assessed using the CURB-65 scale, level of respiratory support required, severe pneumonia (CURB-65), hypertransaminasemia, elevated creatine kinase, lactate dehydrogenase, and D-dimer levels, anemia, and elevated respiratory rate.

Conclusiones: El análisis del Registro Español de Resultados de Farmacoterapia frente a COVID-19 muestra que los factores asociados a peor pronóstico son: mayor edad, valoración mediante la escala CURB-65, el nivel de requerimiento de soporte respiratorio, neumonía grave (CURB-65), hipertransaminasemia, elevación de creatina-quinasa, lactato-deshidrogenasa, y dímero-D, anemia y elevación de la frecuencia respiratoria.

Introduction

In December 2019, the first cases of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia, which causes Coronavirus Disease-2019 (COVID-19), were reported in Wuhan city (Hubei province, China). Since then, this virus has spread worldwide in pandemic form.

COVID-19 patients usually present with fever, dry cough, upper respiratory congestion, and shortness of breath. Cases of headache, hemoptysis and diarrhea, loss of smell (anosmia) and loss of taste (ageusia) have also been reported[1,2].

The pandemic has caused an unprecedented situation resulting in a significant number of reported cases, deaths and, ultimately, in a major social and economic upheaval. Science has had to mobilize all its resources to provide an urgent response to the need for evidence. Today, many unknowns remain, and there is a massive and pressing demand for evidence on the treatment of COVID-19. Aware of this urgency, the Spanish Society of Hospital Pharmacists (SEFH) launched, back in March 2020, the Spanish COVID 19 Drug therapy Outcomes Registry (RERFAR). The aim of this study was to determine the baseline characteristics associated with increased 42-day mortality in patients hospitalized for COVID-19 in Spain.

Methods

The present study included a cohort of patients with PCR confirmation of COVID-19 admitted to 174 Spanish hospitals between March 20 and July 15, 2020. A maximum of 200 patients were included from each hospital to avoid overrepresentation of hospitals with a larger number of patients. A simple random sampling procedure produced a total sample of 15,628 patients. Patients with suspected nosocomial infection with COVID-19 (n = 227) were excluded if symptoms began after admission.

Variables

The dependent variable was 42-day mortality. In addition, the following groups of independent variables were collected:

1. Demographic characteristics: sex, age, body mass index (weight [kg]/height [m^2]; lean: < 18.5, normal: 18.5-24.9, overweight: 25-29.9, obese: > 30), whether subjects were healthcare providers and whether they had been referred from a nursing home or other care center.
2. Previous clinical status: hypertension; diabetes mellitus; chronic obstructive pulmonary disease (COPD); asthma; heart failure; ischemic heart disease; renal failure; cirrhosis; neurological disorders; active hematological/oncological neoplasms (active treatment, diagnosis or recurrence/metastasis less than 5 years ago, excluding diagnosis of squamous cell and basal cell carcinoma); and human immunodeficiency virus (HIV).
3. Previous treatments: angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor antagonists (ARA-II), nonsteroidal anti-inflammatory drugs (NSAIDs), H1 antihistamines (antiH1) and montelukast.
4. Clinical situation on arrival at the hospital: respiratory rate (> 24 rpm), fever (≥ 38 °C), oxygen saturation (%) and severity of pneumonia according to the CURB-65 scale.
5. Analytical tests on admission: C-reactive protein (mg/L), aspartate aminotransferase transaminase [AST (U/L)], alanine aminotransferase transaminase [AST (U/L)], lactate dehydrogenase [LDH (U/L)], creatinine (mg/dL), hemoglobin (g/dL), procalcitonin (ng/mL), creatine kinase (CPK (U/L), D-dimer (ng/mL), ferritin (ng/mL), leukocytes (x $10^3/mm^3$), neutrophils (x $10^3/mm^3$), lymphocytes (x $10^3/mm^3$) and platelets (x $10^3/mm^3$).
6. Respiratory support interventions within 48 h from admission: oxygen therapy (high and low flow), non-invasive ventilation and mechanical ventilation.
7. Pharmacological treatments within 48 h from admission[3]: antivirals [lopinavir/ritonavir, remdesivir and other antivirals (darunavir/cobicistat; darunavir/ritonavir; darunavir/cobicistat/tenofovir/emtricitabine and fosamprenavir)]; immunosuppressants [cyclosporine and tacrolimus], low molecular weight heparins (prophylactic or treatment dose], anakinra, tocilizumab, interferon beta, hydroxychloroquine, chloroquine, azithromycin, antimicrobials and corticosteroids (continuous/bolus infusion).

Measuring instruments

Severity of pneumonia was assessed using the CURB-65 mortality prediction score in patients with community-acquired pneumonia. The scale takes into account the following variables: confusion, urea, respiratory rate, blood pressure and age. A score ≥2 implies an increased risk of mortality[4].

Procedure

The study protocol was approved by the Spanish Drugs and Medical Products Agency (AEMPS) and the Terrasa Hospital's Research Ethics Committee (The protocol was registered with ENCePP® under registration number EUPAS34343).

The project was endorsed by the Ethics Committee of the Hospital Universitari Mútua Terrassa on 23 March 2020. The database was anonymized to protect patient confidentiality. All the researchers involved in the project signed a confidentiality agreement with SEFH. The 42-day mortality data was gathered by reviewing the patients' medical records or by contacting patients on the telephone to ascertain that they were alive. If no contact could be established and the clinical record made no mention of a patient's *exitus*, subjects were considered to have survived.

The information was extracted by the hospitals' pharmacy departments from the patients' medical records using REDCap electronic data capture tools, hosted on SEFH's server[5].

Statistical analysis

The usual descriptive statistical parameters (frequencies, means, standard deviation, etc.) were used. First, bivariate analyses were carried out between the different independent variables and 42-day mortality. The measure of association used was the odds ratio (OR) with its 95% confidence interval (OR 95%CI). Confounding factors were controlled by logistic regression. Given the large sample size and long observation time, logistic regression was considered a better alternative than Cox regression for time-to-event modeling as this technique would provide information on the impact of the various factors on the final outcome (i.e., death), differentiating it from possible phenomena associated with a simple delay of the event. Logistic regression included all the variables shown to be statistically significant in the bivariate

analysis; the model was overridden to ensure it included variables which, despite not showing a statistically significant association, were suspected to be associated with the dependent variables or to behave as confounding factors. The models were constructed by the "forward" procedure, where goodness of fit was tested by means of the Hosmer-Lemeshow coefficient. The existence of interactions between variables was also explored. A statistical significance level of $p < 0.05$ was established. The statistical analysis was performed using the R statistical package.

Results

A total of 15,628 patients were included in the study; 2,806 of them (18.2%) died within 42 days. Tables 1-3 show the baseline characteristics of the patients included in the registry, both from a demographic and a clinical point of view, as well as pre-existing comorbidities, their baseline analytical profile, and the different (pharmacological and/or supportive) interventions initiated within 48 hours from admission.

As regards the demographic characteristics of the sample, mean age was 66.29 years (SD: 15.74); 57.2% were men, 15.5% were obese, 11.4% came from nursing homes and 4.5% were healthcare providers. A total of 19.6% of subjects had a respiratory rate > 24 rpm, 47.1% had an oxygen saturation rate below 93%, 40.1% had fever and 11.6% had severe pneumonia (CURB-65).

The most frequent baseline diseases were (Table 1): hypertension (50.1%), diabetes mellitus (21.8%), previous neurological disorders (14.6%), renal failure (9.8%) and ischemic heart disease (9%). At admission, 37.3% and 14.3% of subjects were receiving treatment with ACEI/ARA-II and NSAIDs, respectively.

A total of 65.5% of the patients received oxygen therapy at baseline, while 5% received noninvasive ventilation and 4.8% were subjected to mechanical ventilation. As for pharmacological treatments, 664 patients (4.3%) did not receive any treatment. The most frequently prescribed drugs in the first 48 hours after admission included hydroxychloroquine (81.3%);

Table 1. Demographics, clinical characteristics and previous treatment and their association with 42-day mortality

Variable		Total	42-day mortality		Unadjusted OR (95%CI)
		N (%)	Deceased	Live	
Sex	Males	8,804 (57.2%)	1,787 (63.7%)	7,017 (55.7%)	
	Females	6,473 (42.0%)	1,018 (36.3%)	5,455 (43.3%)	0.733 (0.673-0.798)
	Not available	124 (0.8%)	1 (0.0%)	123 (1.0%)	0.032 (0.004-0.229)
Age	> 80 years	3,397 (22.2%)	1,425 (50.8%)	1,972 (15.8%)	
	18-29 years old	230 (1.5%)	6 (0.2%)	224 (1.8%)	0.037 (0.016-0.084)
	30-64 years old	6,313 (41.3%)	310 (11.1%)	6,003 (48.1%)	0.071 (0.063-0.082)
	65-79 years	5,348 (35.0%)	1,064 (37.9%)	4,284 (34.3%)	0.344 (0.312-0.378)
Body mass Index	Normal weight	1,430 (9.3%)	267 (9.5%)	1,163 (9.2%)	
	Overweight	2,641 (17.1%)	509 (18.1%)	2,132 (16.9%)	1.040 (0.882-1.226)
	Obese	2,408 (15.6%)	428 (15.3%)	1,980 (15.7%)	0.942 (0.795-1.115)
	Lean	185 (1.2%)	35 (1.2%)	150 (1.2%)	1.016 (0.687-1.503)
	Not available	8,737 (56.7%)	1,567 (55.8%)	7,170 (56.9%)	0.952 (0.824-1.099)
Healthcare provider	No	13,936 (89.2%)	2,758 (96.3%)	11,178 (87.6%)	
	Yes	700 (4.5%)	13 (0.5%)	687 (5.4%)	0.078 (0.045-0.135)
	Not available	992 (6.3%)	93 (3.2%)	899 (7.0%)	0.411 (0.330-0.513)
Referred from nursing home	No	12,914 (83.9%)	1,999 (71.2%)	10,915 (86.7%)	
	Yes	1,749 (11.4%)	687 (24.5%)	1,062 (8.4%)	3.532 (3.173-3.932)
	Not available	738 (4.8%)	120 (4.3%)	618 (4.9%)	1.060 (0.867-1.297)
High respiratory rate **	No	9,341 (60.7%)	1,284 (45.8%)	8,057 (64.0%)	
	Yes	3,016 (19.6%)	984 (35.1%)	2,032 (16.1%)	3.039 (2.760-3.346)
	Not available	3,044 (19.8%)	538 (19.2%)	2,506 (19.9%)	1.347 (1.207-1.504)
Oxygen saturation (%)	> 96	3,047 (19.8%)	238 (8.5%)	2,809 (22.3%)	
	93-96	4,084 (26.5%)	428 (15.3%)	3,656 (29.0%)	1.382 (1.170-1.631)
	88-93	3,504 (22.8%)	800 (28.5%)	2,704 (21.5%)	3.492 (2.993-4.073)
	< 88	3,741 (24.3%)	1,173 (41.8%)	2,568 (20.4%)	5.391 (4.644-6.259)
	Not available	1,025 (6.7%)	167 (6.0%)	858 (6.8%)	2.297 (1.858-2.840)
Fever	No	8,595 (55.8%)	1,582 (56.4%)	7,013 (55.7%)	
	Yes	6,172 (40.1%)	1,156 (41.2%)	5,016 (39.8%)	1.022 (0.939-1.111)
	Not available	634 (4.1%)	68 (2.4%)	566 (4.5%)	0.533 (0.412-0.689)
Severity of pneumonia (Curb-65)	Under	6,903 (44.8%)	386 (13.8%)	6,517 (51.7%)	
	Medium	3,376 (21.9%)	875 (31.2%)	2,501 (19.9%)	5.907 (5.195-6.716)
	High	1,789 (11.6%)	889 (31.7%)	900 (7.1%)	16.677 (14.523-19.151)
	Not available	3,333 (21.6%)	656 (23.4%)	2,677 (21.3%)	4.137 (3.620-4.728)

Table 1 *(cont.).* Demographics, clinical characteristics and previous treatment and their association with 42-day mortality

Variable		Total	42-day mortality		Unadjusted OR (95%CI)
		N (%)	Deceased	Live	
Hypertension	No	7,352 (47.7%)	786 (28.0%)	6,566 (52.1%)	
	Yes	7,716 (50.1%)	1,997 (71.2%)	5,719 (45.4%)	2.917 (2.666-3.191)
	Not available	333 (2.2%)	23 (0.8%)	310 (2.5%)	0.620 (0.403-0.953)
Diabetes mellitus	No	11,676 (75.8%)	1,865 (66.5%)	9,811 (77.9%)	
	Yes	3,359 (21.8%)	918 (32.7%)	2,441 (19.4%)	1.978 (1.807-2.166)
	Not available	366 (2.4%)	23 (0.8%)	343 (2.7%)	0.353 (0.231-0.540)
COPD	No	13,850 (89.9%)	2,385 (85.0%)	11,465 (91.0%)	
	Yes	1,038 (6.7%)	354 (12.6%)	684 (5.4%)	2.488 (2.172-2.849)
	Not available	513 (3.3%)	67 (2.4%)	446 (3.5%)	0.722 (0.556-0.937)
Asthma	No	13,748 (89.3%)	2,563 (91.3%)	11,185 (88.8%)	
	Yes	1,065 (6.9%)	141 (5.0%)	924 (7.3%)	0.666 (0.555-0.799)
	Not available	588 (3.8%)	102 (3.6%)	486 (3.9%)	0.916 (0.737-1.139)
Heart failure	No	13,785 (89.5%)	2,264 (80.7%)	11,521 (91.5%)	
	Yes	1,063 (6.9%)	455 (16.2%)	608 (4.8%)	3.808 (3.345-4.335)
	Not available	553 (3.6%)	87 (3.1%)	466 (3.7%)	0.950 (0.752-1.200)
Ischemic heart disease	No	13,407 (87.1%)	2,228 (79.4%)	11,179 (88.8%)	
	Yes	1,386 (9.0%)	467 (16.6%)	919 (7.3%)	2.550 (2.261-2.876)
	Not available	608 (3.9%)	111 (4.0%)	497 (3.9%)	1.121 (0.908-1.383)
Renal insufficiency	No	13,402 (87.0%)	2,112 (75.3%)	11,290 (89.6%)	
	Yes	1,503 (9.8%)	610 (21.7%)	893 (7.1%)	3.652 (3.262-4.088)
	Not available	496 (3.2%)	84 (3.0%)	412 (3.3%)	1.090 (0.858-1.384)
Cirrhosis	No	14,699 (95.4%)	2,674 (95.3%)	12,025 (95.5%)	
	Yes	132 (0.9%)	37 (1.3%)	95 (0.8%)	1.751 (1.195-2.567)
	Not available	570 (3.7%)	95 (3.4%)	475 (3.8%)	0.899 (0.719-1.125)
Previous neurological disorders	No	12,605 (81.8%)	1,929 (68.7%)	10,676 (84.8%)	
	Yes	2,255 (14.6%)	797 (28.4%)	1,458 (11.6%)	3.025 (2.740-3.340)
	Not available	541 (3.5%)	80 (2.9%)	461 (3.7%)	0.960 (0.754-1.224)
Neoplasms**	No	13,703 (89.0%)	2,383 (84.9%)	11,320 (89.9%)	
	Yes	1,118 (7.3%)	337 (12.0%)	781 (6.2%)	2.050 (1.791-2.346)
	Not available	580 (3.8%)	86 (3.1%)	494 (3.9%)	0.827 (0.655-1.044)
HIV	No	14,299 (92.8%)	2,607 (92.9%)	11,692 (92.8%)	
	Yes	65 (0.4%)	9 (0.3%)	56 (0.4%)	0.721 (0.356-1.459)
	Not available	1,037 (6.7%)	190 (6.8%)	847 (6.7%)	1.006 (0.855-1.184)
Pre-treatment ACEI/ARA-II	No	9,170 (59.5%)	1,360 (48.5%)	7,810 (62.0%)	
	Yes	5,739 (37.3%)	1,380 (49.2%)	4,359 (34.6%)	1.818 (1.672-1.976)
	Not available	492 (3.2%)	66 (2.4%)	426 (3.4%)	0.890 (0.682-1.160)
NSAID pretreatment	No	11,868 (77.1%)	2,133 (76.0%)	9,735 (77.3%)	
	Yes	2,201 (14.3%)	469 (16.7%)	1,732 (13.8%)	1.236 (1.105-1.383)
	Not available	1,332 (8.6%)	204 (7.3%)	1,128 (9.0%)	0.825 (0.706-0.965)
Anti-H1 pretreatment	No	13,785 (89.5%)	2,551 (90.9%)	11,234 (89.2%)	
	Yes	825 (5.4%)	135 (4.8%)	690 (5.5%)	0.862 (0.713-1.041)
	Not available	791 (5.1%)	120 (4.3%)	671 (5.3%)	0.788 (0.645-0.961)
Montelukast pretreatment	No	14,527 (94.3%)	2,684 (95.7%)	11,843 (94.0%)	
	Yes	235 (1.5%)	33 (1.2%)	202 (1.6%)	0.721 (0.498-1.044)
	Not available	639 (4.1%)	89 (3.2%)	550 (4.4%)	0.714 (0.569-0.897)

*Respiratory rate >24 rpm. **Active hematologic/oncologic neoplasm (active treatment, diagnosis or recurrence/metastasis < 5 years, excluding diagnosis of squamous cell and basal cell carcinoma).

Anti-H1: antihistamines; CI95%: 95% confidence interval; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; NSAID: nonsteroidal anti-inflammatory drug; OR: *odds ratio*.

Table 2. Results of baseline analytical parameters and their association with 42-day mortality

Variable (units)		Total, N (%)	42-day mortality		Unadjusted OR (95%CI)
			Dies N (%)	Alive N (%)	
C reactive protein (mg/L)	< 20	3,685 (23.9%)	427 (15.2%)	3,258 (25.9%)	
	20-60	3,494 (22.7%)	515 (18.4%)	2,979 (23.7%)	1.319 (1.150-1.514)
	60-120	3,299 (21.4%)	594 (21.2%)	2,705 (21.5%)	1.675 (1.465-1.917)
	> 120	3,982 (25.9%)	1,122 (40.0%)	2,860 (22.7%)	2.993 (2.649-3.382)
	Not available	941 (6.1%)	148 (5.3%)	793 (6.3%)	1.424 (1.163-1.744)
AST (U/L)§	< 50	7,604 (49.4%)	1,184 (42.2%)	6,420 (51.0%)	
	50-100	2,186 (14.2%)	469 (16.7%)	1,717 (13.6%)	1.481 (1.314-1.669)
	≥ 100	653 (4.2%)	168 (6.0%)	485 (3.9%)	1.878 (1.559-2.262)
	Not available	4,958 (32.2%)	985 (35.1%)	3,973 (31.5%)	1.344 (1.225-1.476)
ALT (U/L)‖	< 40	9,577 (62.2%)	1,878 (66.9%)	7,699 (61.1%)	
	40-80	2,828 (18.4%)	414 (14.8%)	2,414 (19.2%)	0.703 (0.626-0.789)
	≥ 80	1,137 (7.4%)	162 (5.8%)	975 (7.7%)	0.681 (0.573-0.810)
	Not available	1,859 (12.1%)	352 (12.5%)	1,507 (12.0%)	0.958 (0.844-1.087)
LDH (U/L)	< 280	4,626 (30.0%)	514 (18.3%)	4,112 (32.6%)	
	280-360	3,090 (20.1%)	451 (16.1%)	2,639 (21.0%)	1.367 (1.194-1.566)
	≥ 360	4,786 (31.1%)	1,212 (43.2%)	3,574 (28.4%)	2.713 (2.424-3.036)
	Not available	2,899 (18.8%)	629 (22.4%)	2,270 (18.0%)	2.217 (1.952-2.518)
Creatinine (mg/dL)	0.5-0.9	7,155 (46.5%)	759 (27.0%)	6,396 (50.8%)	
	< 0.5	364 (2.4%)	52 (1.9%)	312 (2.5%)	1.404 (1.037-1.902)
	> 0.9	7,287 (47.3%)	1,952 (69.6%)	5,335 (42.4%)	3.083 (2.814-3.378)
	Not available	595 (3.9%)	43 (1.5%)	552 (4.4%)	0.656 (0.477-0.903)
Hemoglobin (g/dL)	11.6-17	12,222 (79.4%)	1,974 (70.3%)	10,248 (81.4%)	
	< 11.6	1,833 (11.9%)	621 (22.1%)	1,212 (9.6%)	2.660 (2.388-2.964)
	≥ 17	312 (2.0%)	68 (2.4%)	244 (1.9%)	1.447 (1.101-1.901)
	Not available	1,034 (6.7%)	143 (5.1%)	891 (7.1%)	0.833 (0.694-1.001)
Procalcitonin (ng/mL)	< 0.5	8,758 (56.9%)	1,251 (44.6%)	7,507 (59.6%)	
	> 0.5	1,133 (7.4%)	482 (17.2%)	651 (5.2%)	4.443 (3.893-5.070)
	Not available	5,510 (35.8%)	1,073 (38.2%)	4,437 (35.2%)	1.451 (1.327-1.587)
CPK (U/L)	< 32	664 (4.3%)	113 (4.0%)	551 (4.4%)	
	32-294	6,096 (39.6%)	992 (35.4%)	5,104 (40.5%)	0.948 (0.765-1.173)
	≥ 294	898 (5.8%)	281 (10.0%)	617 (4.9%)	2.221 (1.735-2.842)
	Not available	7,743 (50.3%)	1,420 (50.6%)	6,323 (50.2%)	1.095 (0.887-1.352)
D-dimer (ng/mL)	< 500	4,554 (29.6%)	412 (14.7%)	4,142 (32.9%)	
	500-3,000	7,049 (45.8%)	1,351 (48.1%)	5,698 (45.2%)	2.384 (2.120-2.680)
	> 3,000	1,111 (7.2%)	383 (13.6%)	728 (5.8%)	5.289 (4.508-6.206)
	Not available	2,687 (17.4%)	660 (23.5%)	2,027 (16.1%)	3.273 (2.863-3.743)
Ferritin (ng/mL)	< 350	2,239 (14.5%)	248 (8.8%)	1,991 (15.8%)	
	≥ 350	5,291 (34.4%)	818 (29.2%)	4,473 (35.5%)	1.468 (1.262-1.708)
	Not available	7,871 (51.1%)	1,740 (62.0%)	6,131 (48.7%)	2.278 (1.976-2.627)
Leukocytes (x 10^3/mm^3)	4-11	11,279 (73.2%)	1,925 (68.6%)	9,354 (74.3%)	
	< 4	1,989 (12.9%)	306 (10.9%)	1,683 (13.4%)	0.883 (0.775-1.007)
	> 11	1,681 (10.9%)	557 (19.9%)	1,124 (8.9%)	2.408 (2.151-2.695)
	Not available	452 (2.9%)	18 (0.6%)	434 (3.4%)	0.202 (0.125-0.324)
Neutrophils (x 10^3/mm^3)	1.7-7.5	11,446 (74.3%)	1,779 (63.4%)	9,667 (76.8%)	
	< 1.7	474 (3.1%)	84 (3.0%)	390 (3.1%)	1.170 (0.920-1.490)
	≥ 7.5	2,974 (19.3%)	907 (32.3%)	2,067 (16.4%)	2.384 (2.173-2.617)
	Not available	507 (3.3%)	36 (1.3%)	471 (3.7%)	0.415 (0.295-0.585)
Lymphocytes (x 10^3/mm^3)	1-4	6,395 (41.5%)	811 (28.9%)	5,584 (44.3%)	
	> 4	411 (2.7%)	90 (3.2%)	321 (2.5%)	1.930 (1.511-2.467)
	< 1	8,095 (52.6%)	1,868 (66.6%)	6,227 (49.4%)	2.065 (1.888-2.260)
	Not available	500 (3.2%)	37 (1.3%)	463 (3.7%)	0.550 (0.391-0.775)
Platelets (x 10^3/mm^3)	130-450	12,248 (79.5%)	2,094 (74.6%)	10,154 (80.6%)	
	> 450	288 (1.9%)	42 (1.5%)	246 (2.0%)	0.828 (0.595-1.152)
	< 130	2,376 (15.4%)	643 (22.9%)	1,733 (13.8%)	1.799 (1.625-1.992)
	Not available	489 (3.2%)	27 (1.0%)	462 (3.7%)	0.283 (0.192-0.419)

ALT: transaminase alanine aminotransferase; AST: transaminase aspartate aminotransferase; CI95%: 95% confidence interval; CPK: creatine kinase; LDH: lactate dehydrogenase; OR: *odds ratio*.

Table 3. Treatments initiated within 48h from hospital admission

Variable		Total, N (%)	42-day mortality		Unadjusted OR (95%CI)
			Deceased	Live	
Oxygen therapy*	No	5,317 (34.5%)	490 (17.5%)	4,827 (38.3%)	
	Yes	10,084 (65.5%)	2,316 (82.5%)	7,768 (61.7%)	2.937 (2.647-3.259)
Non-invasive ventilation	No	14,630 (95.0%)	2,451 (87.3%)	12,179 (96.7%)	
	Yes	771 (5.0%)	355 (12.7%)	416 (3.3%)	4.240 (3.657-4.917)
Mechanical ventilation	No	14,657 (95.2%)	2,484 (88.5%)	12,173 (96.6%)	
	Yes	744 (4.8%)	322 (11.5%)	422 (3.4%)	3.739 (3.214-4.350)
Lopinavir/Ritonavir	No	7,027 (45%)	1,353 (47.2%)	5,674 (44.5%)	
	Yes	8,601 (55%)	1,511 (52.8%)	7,090 (55.5%)	0.894 (0.824-0.969)
Remdesivir	No	15,596 (99.8%)	2,863 (100.0%	12,733 (99.8%)	
	Yes	32 (0.2%)	1 (0.0%)	31 (0.2%)	0.143 (0.020-1.051)
Interferon beta	No	14,415 (92.2%)	2,484 (86.7%)	11,931 (93.5%)	
	Yes	1,213 (7.8%)	380 (13.3%)	833 (6.5%)	2.191 (1.926-2.492)
Hydroxychloroquine	No	2,925 (18.7%)	697 (24.3%)	2,228 (17.5%)	
	Yes	12,703 (81.3%)	2,167 (75.7%)	10,536 (82.5%)	0.657 (0.597-0.724)
Chloroquine	No	15,101 (96.6%)	2,758 (96.3%)	12,343 (96.7%)	
	Yes	527 (3.4%)	106 (3.7%)	421 (3.3%)	1.127 (0.907-1.400)
Other antivirals†	No	15,462 (98.9%)	2,825 (98.6%)	12,637 (99.0%)	
	Yes	166 (1.1%)	39 (1.4%)	127 (1.0%)	1.374 (0.957-1.971)
Tocilizumab	No	14,917 (95.5%)	2,695 (94.1%)	12,222 (95.8%)	
	Yes	711 (4.5%)	169 (5.9%)	542 (4.2%)	1.414 (1.184-1.689)
Immunosuppressants‡	No	15,559 (99.6%)	2,851 (99.5%)	12,708 (99.6%)	
	Yes	69 (0.4%)	13 (0.5%)	56 (0.4%)	1.035 (0.565-1.894)
Anakinra	No	15,598 (99.8%)	2,854 (99.7%)	12,744 (99.8%)	
	Yes	30 (0.2%)	10 (0.3%)	20 (0.2%)	2.233 (1.044-4.775)
Azithromycin	No	6,932 (44.4%)	1,374 (48.0%)	5,558 (43.5%)	
	Yes	8,696 (55.6%)	1,490 (52.0%)	7,206 (56.5%)	0.836 (0.771-0.907)
Antimicrobial	No	4,892 (31.3%)	607 (21.2%)	4,285 (33.6%)	
	Yes	10,736 (68.7%)	2,257 (78.8%)	8,479 (66.4%)	1.879 (1.706-2.070)
LMWH prophyl	No	3,986 (25.5%)	824 (28.8%)	3,162 (24.8%)	
	Yes	11,642 (74.5%)	2,040 (71.2%)	9,602 (75.2%)	0.815 (0.745-0.892)
LMWH tx	No	13,062 (83.6%)	2,152 (75.1%)	10,910 (85.5%)	
	Yes	2,566 (16.4%)	712 (24.9%)	1,854 (14.5%)	1.947 (1.765-2.147)
Corticosteroids	No	13,012 (83.3%)	2,041 (71.3%)	10,971 (86.0%)	
	Yes	2,616 (16.7%)	823 (28.7%)	1,793 (14.0%)	2.497 (2.243-2.713)
Corticosteroid bolus	No	14,503 (92.8%)	2,517 (87.9%)	11,986 (93.9%)	
	Yes	1,125 (7.2%)	347 (12.1%)	778 (6.1%)	2.124 (1.858-2.428)

*High- and low-flow oxygen therapy; †Other antivirals: darunavir/cobicistat; darunavir/ritonavir; darunavir/cobicistat/tenofovir/emtricitavine and fosamprenavir; ‡: Immunosuppressants: cyclosporine and tacrolimus. CI95%: 95% confidence interval; LMWH prophyl: low molecular weight heparin at prophylactic doses; LMWH tx: low molecular weight heparin at therapeutic doses; OR: *odds ratio*.

low molecular weight heparins at prophylactic doses (74.5%); antimicrobials (68.7%), of which the most frequent was azithromycin (in 55.6% of all patients); lopinavir/ritonavir (55%): and corticosteroids (16.7%).

Tables 1-3 show the results of a bivariate analysis of the relationship between each of the variables and 42-day mortality. Table 4 shows the results of the multivariate analysis. With regard to the baseline demographic and clinical characteristics, coming from a nursing home (OR 1.938; 95%CI: 1.686-2.227); presenting with a higher respiratory rate (OR 1.511; 95%CI: 1.330-1.717); and having diabetes (OR 1.221; 95%CI: 1.089-1.368), heart failure (OR 1.477; 95%CI: 1.256-1.736) and moderate (OR 1.738; 95%CI: 1.492-2.025) or severe (OR 2.940; 95%CI: 2.746-3.491) pneumonia were associated with higher mortality. In contrast, being female (OR 0.769; 95%CI: 0.684-0.863) and young (18-29 years: OR 0.097; 95%CI: 0.039-0.24; 30-64 years OR 0.162; 95%CI: 0.136-0.194; 65-79 years: OR 0.428; 95%CI: 0.379-0.483), having asthma (OR 0.770; 95%CI: 0.618-0.961) and being a healthcare provider (OR 0.433; 95%CI: 0.238-0.787) were associated with lower mortality. As shown in table 4, baseline alterations in various analytical values (leukocytes, lymphocytes, platelets, AST, LDH, procalcitonin, CPK, D-dimer, hemoglobin, C-reactive protein and creatinine) were associated with increased mortality, with values ranging from an OR of 1.200 (95%CI 1.040-1.384) for D-dimer levels between 500 and 3,000 ng/mL to an OR of 2.175 (95%CI 1.601-2.954) for AST levels > 100 U/L. A platelet count > 450 x 10 ^{3}platelets/mm^{3} was associated with a reduction in mortality

Table 4. Factors associated with 42-day mortality in patients admitted for COVID-19: multivariate analysis

Factors		OR (95%CI)
Age	> 80 years	
	18-29 years old	0.097 (0.039-0.240)
	30-64 years old	0.162 (0.136-0.194)
	65-79 years	0.428 (0.379-0.483)
Sex	Male	
	Female	0.769 (0.684-0.863)
Referred from nursing home	No	
	Yes	1.938 (1.686-2.227)
	Not available	1.65 (1.252-2.175)
Healthcare provider	No	
	Yes	0.433 (0.238-0.787)
	Not available	0.712 (0.536-0.945)
Severity of pneumonia (Curb-65)	Under	
	Medium	1.738 (1.492-2.025)
	High	2.940 (2.476-3.491)
	Not available	1.98 (1.678-2.338)
Oxygen saturation (%)	> 96	
	93-96	1.021 (0.84-1.242)
	88-93	1.559 (1.294-1.879)
	< 88	1.751 (1.452-2.111)
	Not available	1.187 (0.91-1.549)
Respiratory rate*	No	
	Yes	1.511 (1.330-1.717)
	Not available	1.08 (0.935-1.248)
Diabetes mellitus	No	
	Yes	1.221 (1.089-1.368)
	Not available	0.467 (0.253-0.864)
Asthma	No	
	Yes	0.770 (0.618-0.961)
	Not available	1.182 (0.842-1.659)
Heart failure	No	
	Yes	1.477 (1.256-1.736)
	Not available	1.255 (0.869-1.813)
Leukocytes (x 10^3/mm^3)	4-11	
	< 4	1.102 (0.929-1.308)
	> 11	1.328 (1.146-1.540)
	Not available	0.126 (0.038-0.419)
Lymphocytes (x 10^3/mm^3)	1-4	
	> 4	1.241 (0.910-1.691)
	< 1	1.338 (1.194-1.499)
	Not available	2.211 (1.127-4.334)
Platelets (x 10^3/mm^3)	130-450	
	> 450	0.593 (0.391-0.897)
	< 130	1.571 (1.372-1.798)
	Not available	0.819 (0.337-1.987)
AST (U/L)	<50	
	50-100	1.349 (1.137-1.601)
	≥100	2.175 (1.601-2.954)
	Not available	1.237 (1.086-1.409)
ALT (U/L)	< 40	
	40-80	0.726 (0.617-0.854)
	≥ 80	0.490 (0.373-0.643)
	Not available	0.859 (0.713-1.036)
LDH (U/L)	< 280	
	280-360	1.264 (1.072-1.490)
	≥ 360	1.629 (1.403-1.892)
	Not available	1.451 (1.221-1.725)
Procalcitonin (ng/mL)	< 0.5	
	> 0.5	1.844 (1.557-2.183)
	Not available	1.275 (1.136-1.431)
CPK (U/L)	< 32	
	32-294	1.135 (0.875-1.473)
	≥ 294	1.581 (1.161-2.153)
	Not available	1.271 (0.982-1.645)
D dimer (ng/mL)	< 500	
	500-3,000	1.200 (1.040-1.384)
	> 3,000	1.543 (1.263-1.885)
	Not available	2.167 (1.817-2.584)
Hemoglobin (g/dL)	11.6-17	
	< 11.6	1.45 (1.261-1.668)
	≥ 17	1.194 (0.846-1.685)
	Not available	1.297 (1.001-1.680)
C reactive protein (mg/L)	< 20	
	20-60	1.140 (0.965-1.348)
	60-120	1.166 (0.987-1.376)
	> 120	1.235 (1.053-1.450)
	Not available	1.335 (1.004-1.773)
Creatinine (mg/dL)	0.5-0.9	
	< 0.5	0.676 (0.468-0.976)
	> 0.9	0.951 (0.659-1.373)
	Not available	0.563 (0.305-1.039)
Non-invasive ventilation	No	
	Yes	2.877 (2.378-3.480)
Mechanical ventilation	No	
	Yes	3.471 (2.825-4.266)
Oxygen therapy**	No	
	Yes	1.987 (1.739-2.271)
LMWH prophyl	No	
	Yes	0.836 (0.741-0.942)
Hydroxychloroquine	No	
	Yes	0.707 (0.615-0.813)
Corticosteroids	No	
	Yes	1.425 (1.248-1.627)
Lopinavir/Ritonavir	No	
	Yes	1.158 (1.033-1.300)
Interferon beta	No	
	Yes	1.507 (1.266-1.794)
Tocilizumab	No	
	Yes	0.761 (0.603-0.960)
Azithromycin	No	
	Yes	0.870 (0.779-0.970)
Corticosteroid bolus	No	
	Yes	1.421 (1.179-1.712)

*Respiratory rate > 24 rpm; **High and low flow oxygen therapy.

ALT: transaminase alanine aminotransferase; AST: transaminase aspartate aminotransferase; CI95%: 95% confidence interval; CPK: creatine kinase; LMWH prophyl: low molecular weight heparin at prophylactic doses; LDH: lactate dehydrogenase; OR: *odds ratio*.

(OR 0.593; 95%CI 0.391-0.897), as was an ALT value between 40-80 U/L (OR 0.726, 95%CI 0.617-0.854) and > 80 U/L (OR 0.490, 95%CI 0.373-0.643) and creatinine values < 0.5 mg/dL (OR 0.676, 95%CI 0.468-0.976). Finally, as regards treatments initiated within 48 h from hospital admission, the different modes of respiratory support were associated with greater mortality (oxygen therapy: OR 1.987, 95%CI 1.739-2.271; noninvasive ventilation: OR 2.877, 95%CI 2.348-3.480; and mechanical ventilation: OR 3.471, 95%CI 2.825-4.266). Pharmacotherapy with interferon beta (OR 1.507; 95%CI: 1.266-1.794), corticosteroids (by continuous [OR 1.425; 95%CI: 1.248-1.627] and bolus [OR 1.421; 95%CI: 1.179-.712] infusion), and lopinavir/ritonavir (OR 1.158; 95%CI: 1.033-1.300) were associated with higher mortality; conversely treatments associated with lower mortality included hydroxychloroquine (OR 0.707; 95% CI: 0.615-0.813), tocilizumab (OR 0.761; 95%CI: 0.603-0.960), low-molecular-weight heparin at prophylactic doses (OR 0.836; 95%CI: 0.741-0.942) and azithromycin (OR 0.870; 95%CI: 0.779-0.970).

Discussion

This article analyzes the association between 42-day mortality and a wide range of clinical and demographic variables and analytical parameters related to COVID-19 patients, collected at hospital admission. The study of the factors associated with mortality was intended to gain a better understanding of the disease and coming up with a better stratification of patients so as to allow for a more efficiently management of the resources dedicated to treatment. The use of 42-day mortality as an outcome variable extends beyond in-hospital mortality and includes potential mortality after discharge. SEFH's Spanish COVID 19 Drug therapy Outcomes Registry includes a large number of hospitals from the entire Spanish territory as well as a high number of patients, 80% of whom were included in March 2020 (first COVID-19 wave). This offers a significant degree of homogeneity across the different cases included. For logistic simplification, the number of included patients per center was limited to 200, which may lead to an overrepresentation of small hospitals. In large hospitals, on the other hand, only the first patients admitted were included, which means that the level of experience with and evidence on the treatments in those cases is probably lower. To reduce this selection bias, all hospitals with more than 200 patients hospitalized for COVID-19 that participated in the registry were randomly sampled.

In addition to the ones mentioned above, the work presents several limitations that should be taken into consideration for the interpretation of results. Given the observational nature of the study and its design as a retrospective collection of data, the associations described between each variable and mortality may be subject to biases or confounding factors. This design is not suitable for testing the effect of treatments. Firstly, as patient inclusion started at the beginning of the pandemic, there was a lack of evidence about the treatments selected and most patients received multiple treatments during their hospitalization. On the other hand, as pharmacotherapy was one of the different baseline characteristics included in the analysis, a 48- hour period from admission was set to determine which patient had received a treatment. This complicated interpretation of the results of the multivariate pharmacotherapeutic analysis as patients who did not receive a given treatment within 48 h from admission could have received it later. Moreover, by the time they received it, their final health status may have changed, which introduced a difficult-to-eliminate source of bias.

The scarcity of available evidence at the beginning of the pandemic resulted in the main treatment for COVID-19 in our cohort being hydroxychloroquine, used in more than 80% of patients[6]. This explains discrepancies with currently available evidence, which has shown hydroxychloroquine to lead to no benefits regarding mortality and to increased adverse events[7,8]. Dexamethasone is currently the standard treatment for patients requiring respiratory support[9,10], who accounted for 75.3% of the patients in this registry. Even so, only 16.7% received corticosteroid treatment in the first 48 hours. In the present analysis, patients who received corticosteroids after the first 48 hours were classified as patients not treated with corticosteroids. However, in light of the existing evidence, it is very plausible that these patients may have obtained a benefit from corticosteroid therapy which means that classifying them as not treated with corticosteroids in the statistical analysis could constitute a contradiction with respect to the results of RECOVERY[11]. In addition, it is also likely that patients who received corticosteroids were the ones with most severe forms of the disease, implying a selection bias[12]. Subsequent evidence has shown the use of corticosteroids to be indicated in severe and critically ill patients but to provide no benefit in mild[10,13] and moderate cases[14]. The other treatment that has shown some effect on mortality reduction is tocilizumab[15]. According to the SEFH registry data, it was administered to 4.5% of patients within the first 48 hours. The initial bivariate analysis showed an OR of 1.414 (95%CI 1.184-1.689) while, when adjusted for the remaining variables, the analysis pointed to a protective effect of tocilizumab on 42-day mortality, with an of OR 0.768 (95%CI 0.609-0.969). This is consistent with the results of the only two studies where tocilizumab has been shown to reduce mortality, the REMAP-CAP study[16] and the RECOVERY study[11], and could be indicative of the use of tocilizumab in patients with progressive COVID-19 (C-reactive protein ≥ 75 mg/L and O_2 Sat < 92%) or in critically ill patients within the first 48 hours of admission[11].

The adjusted multivariate model found diabetes and male sex to be associated with mortality. According to the literature, this association may be explained by the increased expression of angiotensin-converting enzyme peptidase 2 (ACE2), which is the gateway for the SARS-CoV-2 virus[17]. Specifically, patients with diabetes-derived hyperglycemia present with an increased expression of ACE2, which seems to favor penetration of the virus into immune cells; patients with asthma, in contrast, have a decreased expression of this enzyme[18]. As for sex differences, in addition to the anatomical, hormonal and lifestyle differences observed during the SARS epidemic of 2003[19], it seems that differences also exist with respect to the immune response, whereby men would seem to be more vulnerable to infection with COVID-19[19].

Regarding the association between mortality and the analytical parameters of our analysis, it is well known that lymphocytes play an essential role in controlling viral infection, specifically the inflammatory response and homeostasis. Lymphopenia due to lymphocyte destruction (particularly T lymphocytes) and depletion caused by virus invasion has consistently been shown to be a poor prognostic factor[20,21]. The findings of our study coincide with those of the literature in that the clinical parameters associated with the increased severity and mortality of COVID-19 include elevated levels of LDH, C-reactive protein, procalcitonin, CPK, platelets and D-dimer[22,23].

An expected finding from the registry was an increase in mortality among patients who required externally supplied oxygen (oxygen therapy, noninvasive ventilation, or mechanical ventilation) to maintain adequate saturation, as well as among patients with higher CURB-65 scores. These findings are consistent with those reported by other authors[24,25].

The 42 day-mortality follow-up applied in this study, aimed at identifying potential increases in residual mortality after discharge, constitutes a more comprehensive follow-up than that found in other observational studies[6,26,27] and clinical trials[11,28], which typically analyze mortality at 28 days. In our study, mortality after hospital discharge was 0.7%, which increased overall mortality from 17.5% to 18.2%. This higher mortality highlights the need to follow up the outcomes of the different studies on COVID-19 over longer periods of time.

The results of SEFH's Spanish COVID 19 Drug therapy Outcomes Registry, which contains a broad representation of the population admitted to hospital for COVID-19 during the first wave of the pandemic and which followed up patient mortality for longer than most studies in the literature, show the possible prognostic usefulness of the baseline analytical and clinical parameters used, which may contribute to improving the management of a disease.

Funding

No funding.

Acknowledgments

The authors would like to thank María del Carmen Valcárcel Cabrera from the Andalusian School of Public Health as well as all who contributed to putting together the RERFAR registry (Annex 1).

Conflict of interest

No conflict of interest.

Protocol

The protocol was published on the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. It is available at: http://www.encepp.eu/encepp/viewResource.htm?id=34344

Presentation at congresses

The preliminary results of this article was presented in the XXXIX Annual Meeting of the Spanish Epidemiology Society (SEE) - XVI congress of the Portuguese Epidemiology Association - IX SESPAS congress. LEÓN, SEPTEMBER 7-10, 2021.

Contribution to the scientific literature

The economic and social impact of the SARS-CoV-2 coronavirus pandemic was unprecedented, causing a severe death toll. This study reports on the data collected by the Spanish COVID-19 Drug therapy Outcomes Registry, which includes more than 15,000 hospitalized patients. The results are consistent with those of other studies showing the association of certain baseline analytical values and sociodemographic characteristics with mortality from COVID-19.

Annex 1. Healthcare providers who contributed to the study

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Poniente Public Health Agency	JUAN ENRIQUE MARTÍNEZ DE LA PLATA, ALBA MARTOS ROSA
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