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COVID-19: Clinical Presentation and Prognostic Factors of Severe Disease and Mortality in the Oldest-Old Population: A Cohort Study

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Abstract
Introduction: The oldest-old population (80 years or older) has the highest lethality from COVID-19. There is little information on the clinical presentation and specific prognostic factors for this group. This trial evaluated the clinical presentation and prognostic factors of severe disease and mortality in the oldest-old population. ***Methods:*** This is an ambispective cohort study of oldest-old patients hospitalized for respiratory infection associated with COVID-19 and with a positive test by RT-PCR. The clinical presentation and the factors associated with severe disease and mortality were evaluated (logistic regression). All patients were followed up until discharge or death. ***Results:*** A total of 103 patients (59.2% female) were included. The most frequent symptoms were fever (68.9%), dyspnoea (60.2%), and cough (39.8%), and 11.7% presented confusion. Fifty-nine patients (57.3%) presented severe disease, and 59 died, with 43 patients (41.7%) presenting both of these. In the multivariate analysis, female sex (odds ratio [OR] 0.31, 95% confidence interval [95% CI] 0.13–0.73, *p* 0.0074) and serum lactate dehydrogenase (LDH) (OR 2.55, 95% CI 1.21–5.37, *p* 0.0139) were associated with severe disease, and serum sodium was associated with mortality (OR 3.12, 95% CI 1.18–8.26, *p* 0.0222). No chronic disease or pharmacological treatment was associated with worse outcomes. ***Conclusions:*** The typical presenting symptoms of respiratory infection in COVID-19 are less frequent in the oldest-old population. Male sex and LDH level are associated with severe disease, and the serum sodium level is associated with mortality in this population.

Introduction

The pandemic caused by the new severe acute respiratory distress syndrome coronavirus (SARS-CoV-2) represents a priority objective of current medical research, given its global extent. The older population has the highest lethality, having reported a crude fatality ratio of 12%, and this is much higher (approximately 30%) in the oldest-old people (80 or more years old) [1, 2]. Given this population's greater vulnerability, knowledge of this pathology in them is a priority.

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Proper management of affected oldest-old people requires knowledge of the clinical presentation and prognostic factors specific to this group. Most diseases, including infectious diseases, usually include atypical presentations, especially in this population [3–5], and their clinical profile means that the prognostic factors identified in the general adult population cannot be extrapolated.

Data on clinical presentation and prognostic factors have been reported in cohorts of older population [6]. However, most of these are from Asian populations and have a fairly low age cut-off (60–65 years), leaving the oldest-old population under-represented. The results of these studies cannot be extrapolated to the oldest-old population of our environment [7] since the level of autonomy and physical activity of the 60–70-year-old group is more similar to that of the youngest than the oldest patients [7, 8].

There are few studies specifically reporting on clinical presentation and prognostic factors in the oldest-old population [9–11]. The main reported symptoms of clinical presentation have included fever, dyspnoea, cough, and deterioration of functional status ,and factors associated with higher mortality included age, male sex, severe functional dependence, cognitive decline, renal function, and inflammatory markers. However, other relevant variables like previous pharmacologic treatments or other important outcomes such as severe disease have not been specifically evaluated in this population. In the present study, we analysed the clinical presentation and the most important prognostic factors of severe disease and mortality in a cohort of oldest-old people (aged 80 years or more) hospitalized for COVID-19.

Materials and Methods

Design and Sample

The present work is a cohort study based on the previously described ambispective cohort (n = 464) of patients hospitalized for COVID-19 in the hospitals of the Consorci Sanitari de l'Alt Penedès i Garraf (CSAPG) [12]. The CSAPG includes 3 second-level hospitals with a total of 457 hospital beds, including 7 intensive care beds (extended to 24 beds at the peak of the epidemic) and 182 intermediate care beds. Its territorial scope includes an area of Barcelona with a reference population of 247,357 inhabitants.

For this study, patients aged 80 years or older who were admitted for respiratory infection associated with COVID-19 and with pharyngeal, nasal, or sputum smears positive for SARS-CoV-2 (RT-PCR) were included. All patients who were hospitalized through the emergency department were recruited from March 12 to May 2, 2020 and were followed up until hospital discharge or death. Patients with a positive COVID-19 test but without clinical or radiological respiratory involvement and patients with compatible respiratory symptoms who were treated as COVID-19 patients during admission but with negative smears ("COVID-19 clinical") were excluded. Also excluded were patients who, despite meeting the diagnostic inclusion criteria, were not admitted to a hospitalization unit (e.g., due to death in the emergency department or transfer to a tertiary referral centre). In our case, there was no need to transfer patients to other centres of the same level for lack of hospital beds.

Patients were selected from the daily hospitalization census. This census included the medical diagnosis of admission of each patient and a signal that identified the patients who had requested an RT-PCR test for SARS-CoV-2. A predetermined calculation of the sample size was not performed. We included all possible patients who met the admission criteria.

Variables and Information Collection

Information on the variables was collected from the computerized medical records (GoWin program, version 2.4.0). The interviewers (the COVID-19 research group of the CSAPG [30 people]) began the study on April 6 and continued until the discharge or death of the last patient recruited. The information was collected with the help of 2 data collection notebooks (the first for baseline assessment and the second for the follow-up) created with the OpenClinica programme, version 3.14 (Copyright © OpenClinica LLC and collaborators, Waltham, MA, USA). Training sessions for data collection were held by the coordinating researcher of the study, and the quality control process included the review of at least 20% of the data of the main variables of the study to verify their agreement with the source document. If necessary, retraining and supervision sessions were held.

In the baseline assessment, sociodemographic, comorbidity, previous pharmacological treatment, and clinical presentation data were collected from the emergency assessment data. The data of comorbidity and previous pharmacological treatments were collected after reviewing all the medical reports available in the computerized clinical history. We recorded the data categorically (yes/no) from a predetermined list prepared by the researchers (Table 1).

The clinical presentation variables were collected from the emergency department medical report and included symptoms and signs (categorically recorded from a predetermined list), oxygen saturation, pulmonary radiological involvement (number of affected lung quadrants, range 0–4), and the level of C-reactive protein (CRP) (hereinafter "emergency CRP"). During each day of the follow-up, the following variables were collected: hospital discharge, oxygenation system (nasal cannulas, mask, non-rebreather mask, non-invasive mechanical ventilation, and orotracheal intubation), and death. For the present study, the laboratory parameters of the first day of hospitalization were also considered, which were extracted automatically by the Department of Informatics to avoid manual registration errors.

The variables considered potentially prognostic were those collected in the baseline assessment and the laboratory parameters of the first day of hospitalization. The outcome variables were 2: mortality and severe disease, which were verified every day of the follow-up. The standard definition of severe disease (dyspnoea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial

Table 1. Baseline assessment of the patients included in the study

Variable	Total	*N* (%)
Block 1: personal background		
Sociodemographic		
Female sex	103	61 (59.2)
Age, years (SD)	103	86.75 (4.65)
Institutionalized	103	63 (61.2)
Autoimmune		
Rheumatoid arthritis	103	0
SLE	103	0
Spondyloarthropathies	103	0
Scleroderma	103	0
Psoriasis	103	0
Other autoimmune disease	103	7 (6.8)
Renal		
Chronic kidney failure	103	34 (33.0)
Peritoneal dialysis	103	0
Haemodialysis	103	1 (1.0)
Cardiovascular disease or risk factors		
Hypertension	103	84 (81.6)
Diabetes mellitus 2	103	35 (34.0)
Dyslipidaemia	103	42 (40.8)
Obesity	103	13 (12.6)
Smoking	103	5 (4.9)
Alcoholism	103	1 (1.0)
Heart failure	103	17 (16.5)
Atrial fibrillation	103	24 (23.3)
Ischaemic heart disease	103	16 (15.5)
Other arterial ischaemia	103	2 (1.9)
Aortic valve disease	103	8 (7.8)
Mitral valve disease	103	7 (6.8)
Prosthetic cardiac valve	103	0
Other heart disease	103	6 (5.8)
Pacemaker carrier	103	4 (3.9)
Stroke	103	13 (12.6)
Pulmonary hypertension	103	2 (1.9)
Psychiatric		
Depression	103	25 (24.3)
Schizophrenia	103	1 (1.0)
Other psychiatric diseases	103	10 (9.7)
Neurodegenerative diseases		
Dementia	103	36 (35.0)
Parkinson disease	103	2 (1.9)
Multiple sclerosis	103	0
Other neurodegenerative diseases	103	4 (3.9)
Digestive		
Gastropathy	103	7 (6.8)
Inflammatory bowel disease	103	4 (3.9)
Cirrhosis	103	0
Celiac disease	103	0
Other liver disease	103	4 (3.9)
Respiratory		
Asthma	103	3 (2.9)
COPD	103	16 (15.5)
Cystic fibrosis	103	0
Other pneumopathy	103	4 (3.9)

Table 1 (continued)

Variable	Total	*N* (%)
Other		
Thyroid disease	103	13 (12.6)
HIV/AIDS	103	0
Organ transplant	103	0
Immunosuppression due to other causes	103	0
Chronic anaemia	103	12 (11.7)
HCV	103	0
Block 2: pharmacological treatments		
Haematological		
Antiplatelet agents	103	33 (32.0)
Anticoagulants	103	17 (16.5)
Analgesics and corticosteroids		
Paracetamol	103	43 (41.7)
NSAIDs	103	8 (7.8)
Opioids	103	13 (12.6)
Systemic corticosteroids	103	5 (4.9)
Antidiabetic		
Insulin	103	10 (9.7)
Metformin	103	20 (19.4)
Other oral antidiabetic drugs	103	9 (8.7)
Cardiovascular		
Lipid-lowering drugs	103	26 (25.2)
Diuretics	103	46 (44.7)
Beta blockers	103	17 (16.5)
ACE inhibitors	103	30 (29.1)
ARA 2	103	21 (20.4)
Other antihypertensives	103	31 (30.1)
Antiarrhythmics	103	9 (8.7)
Respiratory		
Inhaled anticholinergics	103	12 (11.7)
β_2 inhaled agonists	103	14 (13.6)
Inhaled corticosteroids	103	10 (9.7)
Other inhalers	103	2 (1.9)
Home oxygen therapy	103	4 (3.9)
CNS		
Sedatives	103	32 (31.1)
Antidepressants	103	41 (39.8)
Antipsychotics	103	30 (29.1)
Anti-epileptics	103	4 (3.9)
Antiparkinsonians	103	4 (3.9)
Other drugs with effect on CNS	103	14 (13.6)
Other therapies		
Antacids	103	51 (49.5)
Cytotoxic/chemotherapy	103	0
Drugs with immune action	103	0
Antihistamines	103	1 (1.0)

Table 1 (continued)

Variable	Total	*N* (%)
Block 3: clinical presentation		
Fever	103	71 (68.9)
Dyspnoea	103	62 (60.2)
Cough	103	41 (39.8)
Diarrhoea	103	16 (15.5)
Arthromyalgia	103	6 (5.8)
Asthenia	103	22 (21.4)
Anosmia	103	0
Altered taste	103	0
Skin lesions	103	0
Headache	103	0
Confusion	103	12 (11.7)
Psychomotor agitation, %	103	3 (2.9)
Chest X-ray (affected quadrants)	103	
0		12 (12.6)
1		15 (15.8)
2		36 (37.9)
3		15 (15.8)
4		17 (17.9)
CRP, mg/L in emergencies, mean (SD)	34	151.03 (110.72)
Basal oxygen saturation (emergency), mean (SD)	93	86.82 (10.56)
Block 4: laboratory parameters (day 1 of admission)	n	Mean (SD)
Haemoglobin, g/dL	87	12.53 (2.21)
Platelets, 10^9/L	85	232.79 (117.17)
Neutrophils, 10^9 L	82	7.27 (4.38)
Lymphocytes, 10^9/L	87	1.16 (0.89)
Eosinophils, 10^9/L	87	0.32 (0.63)
Prothrombin time (INR)	84	1.28 (0.48)
D-dimer, ng/mL	71	2,842.82 (3,468.59)
Fibrinogen, mg/dL	15	614.67 (242.51)
Glucose, mg/dL	87	149.44 (64.36)
Sodium, mEq/L	87	141.64 (8.25)
Cr, mg/dL	87	1.49 (0.92)
Urea, mg/dL	87	78.36 (54.11)
Alkaline phosphatase, IU/L	50	73.99 (30.42)
AST, IU/L	60	44.85 (44.22)
ALT, IU/L	66	28.15 (14.57)
GGTP, IU/L	53	50.57 (27.47)
Total bilirubin, mg/dL	70	0.66 (0.49)
LDH, U/L	73	325.01 (131.48)
CRP at admission, mg/L	80	13.37 (10.83)
Ferritin, μg/L	48	518.44 (491.55)
Procalcitonin, ng/mL	30	0.80 (1.34)
Lactate, mmol/L	20	2.14 (1.79)
Arterial oxygen, mm Hg	61	73.61 (30.30)
Carbon dioxide, mm Hg	61	24.45 (4.32)
Serum bicarbonate, mmol/L	71	24.79 (3.38)
pH	61	7.46 (0.05)

SD, standard deviation; SLE, systemic lupus erythematosus; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HCV, hepatitis C virus; NSAIDs, non-steroidal anti-inflammatory drugs; ACE inhibitors, inhibitors of the angiotensin-converting enzyme; ARA 2, angiotensin 2 receptor antagonists; CNS, central nervous system; CRP, C-reactive protein; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase.

oxygen to the fraction of inspired oxygen of <300 mm Hg, or infiltrates in >50% of the lung field) [13] was considered too broad for our study since the majority of hospitalized patients would meet the criteria of this definition. For this reason, in this study, severe disease was defined as the need for oxygen therapy with a reservoir mask, mechanical ventilation (invasive or non-invasive), or high-flow nasal cannulas. This definition is similar to the categories 6–9 of the Clinical Progression Scale of the World Health Organisation [14].

Regarding the prognostic factor-outcome variable association, age and sex were considered a priori as potential confounding variables and/or effect modifiers of all other variables evaluated. The data collection notebooks with the complete lists of variables are available in see online suppl. material 1 and 2; for all online suppl. material, see www.karger.com/doi/10.1159/000515159.

Statistical Analysis

For the analysis of the prognostic factors of death and severe disease, the potential prognostic variables were grouped into 4 blocks: age-sex-comorbidity (block 1); previous pharmacological treatment (block 2); variables of clinical presentation, including pulmonary radiological involvement and CRP in the emergency room (block 3); and variables of laboratory parameters (block 4). Within each block and for each outcome variable, a bivariate analysis was performed with each prognostic variable (χ^2 or Fisher's test for categorical variables, the *T*-test or Mann-Whitney test for quantitative variables), and a multivariate model was built using logistic regression, except for block 3 (in this block, it was considered more relevant to evaluate the individual prognostic capacity of each parameter).

In the bivariate analysis and given the multiplicity of analyses performed, the statistical significance was adjusted by the false discovery rate method [15]. In all the planned multivariate models, age and sex were included, given their status as potential confounding variables. The variables with significant associations (unadjusted $p < 0.05$) found in the bivariate analysis were preselected for the models. As the primary objective of our study was the identification of the prognostic factors with high associative strength and considering the high number of potential prognostic factors to be evaluated, the least absolute shrinkage and selection operator (LASSO) method was used for the final selection of the variables to be included in the models. The LASSO method [16] is not based on *p* values (which could induce the inclusion of superfluous clinical variables in the final model) but on a modification of the minimum quadratic estimation. Its objective is to select a smaller subset of explanatory variables (but with greater strength of association) with which to finally adjust the model without significantly losing any explanatory quality of the model. This procedure is considered superior to eliminating the prognostic variables according to *p* value, and it reduces the risk of multicollinearity problems, which may arise in models with a large number of potential prognostic variables [17]. Variables with >30% missing values were excluded from the multivariate models, as were those with 15 or fewer individuals with the evaluated condition. Finally, based on the results of the bivariate analysis and to avoid collinearity, Cr was excluded from the models when it coincided in the preselection with the urea variable.

Quantitative variables were not categorized. The laboratory parameters were transformed logarithmically to improve their fit to a normal distribution and were scaled to allow a comparison of their odds ratios (ORs).

Regarding the missing data, in case there were no laboratory parameters from the first day of hospitalization, these variables were imputed from their values of the second day of hospitalization if the latter were available. No missing data of other variables were imputed. R version 3.6.1 (R Project for Statistical Computing) and IBM SPSS version 26 were used.

Results

During the recruitment period, 464 people (113 aged 80 or older) were hospitalized for suspected infection with COVID-19, of whom 418 had respiratory infection with a positive RT-PCR test for SARS-CoV-2. Of this last group, 89 people (21%) were aged 80 or more years. Additionally, 14 patients aged 80 years or older identified after a second review of the hospitalization censuses were included, so 103 oldest-old people were included in the end.

The baseline assessment data are shown in Table 1. The mean age was 86.75 (standard deviation [SD] 4.65; maximum age 99) years. Sixty-one patients (59.2%) were female, and 63 (61.2%) came from a nursing home (institutionalized), and 99 patients (96.1%) had 2 or more chronic diseases. The most frequent symptoms of clinical presentation were fever (68.9%), dyspnoea (60.2%), and cough (39.8%).

All patients were followed up until discharge or death. The median follow-up was 6.0 (interquartile range 8) days for the whole sample, 11 days for who survived, 5 days for who presented severe disease criteria, and finally 3 days for who died. Fifty-nine patients (57.3%) had severe disease, and 59 patients died, with both events occurring in 43 patients. In 16 patients who died (1.1 out of every 4 patients who died), no criteria for severe disease were previously detected. In order to exclude medical indication for exclusive palliative care including palliative sedation as cause for not detecting criteria of severe disease, we reviewed individually these cases, and only 2 patients with medical indication for exclusive palliative care were detected.

The results of the bivariate analysis are shown in Table 2. (Table with more extensive data on bivariate analysis including the number of patients of each group is available as supplementary material.) Significant prognostic variables (unadjusted *p* value) were found for both outcome variables only in the blocks of clinical presentation variables (dyspnoea, radiological involvement, and oxygen saturation) and of laboratory parameters (aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and CRP on admission), although out of all of

Table 2. Bivariate analysis of the variables of severe disease and mortality

Variable	Severe disease			Mortality		
	OR (95% CI)[a]	*p* value	p_{adj}	OR (95% CI)[a]	*p* value	p_{adj}
Block 1: personal background						
Sociodemographic						
Sex, woman/man	0.32 (0.13–0.73)	0.01	0.16	0.49 (0.21–1.10)	0.10	0.64
Age, years[b]	−0.79 (−1.04 to 2.64)	0.39	0.96	0.43 (−2.28 to 1.41)	0.64	1.00
Autoimmune						
Other autoimmune disease	0.98 (0.20–5.59)	1.00	1.00	0.55 (0.10–2.74)	0.46	1.00
Renal						
Chronic kidney failure	1.10 (0.48–2.57)	1.00	1.00	1.31 (0.57–3.11)	0.53	1.00
Cardiovascular						
High blood pressure	0.97 (0.34–2.69)	1.00	1.00	1.62 (0.59–4.56)	0.44	1.00
Diabetes mellitus	2.03 (0.87–4.97)	0.14	0.70	1.41 (0.61–3.33)	0.53	1.00
Dyslipidaemia	2.28 (1.01–5.35)	0.07	0.47	1.16 (0.52–2.62)	0.84	1.00
Obesity	1.21 (0.37–4.39)	1.00	1.00	1.76 (0.52–7.13)	0.39	1.00
Smoking	2.82 (0.37–79.06)	0.39	0.96	0.49 (0.06–3.38)	0.65	1.00
Alcoholism	0.75 (0.09–57.36)	1.00	1.00	0.75 (0.09–57.36)	1.00	1.00
Heart failure	0.81 (0.28–2.39)	0.79	1.00	1.95 (0.65–6.73)	0.29	0.97
Ischaemic heart disease	0.53 (0.17–1.57)	0.28	0.89	0.53 (0.17–1.57)	0.28	0.97
Pulmonary hypertension	1.52 (0.18–82.65)	0.51	1.00	0.74 (0.02–29.56)	1.00	1.00
Aortic valve disease	1.24 (0.28–6.74)	1.00	1.00	5.12 (0.84–134.25)	0.13	0.72
Mitral valve disease	0.98 (0.20–5.59)	1.00	1.00	0.98 (0.20–5.59)	1.00	1.00
Pacemaker	2.11 (0.24–61.97)	0.63	1.00	3.14 (0.38–137.63)	0.13	0.72
Other heart disease	1.47 (0.26–12.36)	1.00	1.00	4.89 (0.59–197.27)	0.04	0.36
Stroke	4.49 (1.10–33.13)	0.04	0.35	0.85 (0.26–2.91)	1.00	1.00
Atrial fibrillation	1.32 (0.52–3.51)	0.64	1.00	1.65 (0.64–4.55)	0.35	0.97
Psychiatric						
Depression	0.93 (0.37–2.37)	1.00	1.00	0.76 (0.30–1.90)	0.64	1.00
Schizophrenia	0.00 (0.00–6.13)	0.43	0.96	0.00 (0.01–6.13)	0.43	1.00
Other psychiatric diseases	0.17 (0.02–0.74)	0.02	0.23	0.29 (0.06–1.16)	0.09	0.62
Neurodegenerative diseases						
Dementia	0.76 (0.33–1.73)	0.54	1.00	1.81 (0.78–4.34)	0.21	0.97
Parkinson's disease	0.74 (0.02–29.56)	1.00	1.00	0.74 (0.02–29.56)	1.00	1.00
Other neurodegenerative disease	0.26 (0.01–2.32)	0.31	0.89	0.74 (0.07–7.34)	1.00	1.00
Digestive						
Gastropathy	1.86 (0.36–14.99)	0.70	1.00	0.98 (0.20–5.59)	1.00	1.00
Inflammatory bowel disease	0.74 (0.07–7.34)	1.00	1.00	0.26 (0.01–2.32)	0.31	0.97
Other liver disease	3.14 (0.38–137.63)	0.13	0.69	2.11 (0.24–61.97)	0.63	1.00
Respiratory						
Asthma	1.42 (0.11–45.48)	1.00	1.00	0.39 (0.01–4.94)	0.57	1.00
COPD	1.28 (0.43–4.14)	0.79	1.00	0.95 (0.32–2.93)	1.00	1.00
Other lung disease	2.11 (0.24–61.97)	0.63	1.00	0.74 (0.07–7.34)	1.00	1.00
Other						
Thyroid disease	0.60 (0.18–2.00)	0.55	1.00	0.42 (0.12–1.40)	0.23	0.97
Chronic anaemia	0.72 (0.20–2.53)	0.76	1.00	1.04 (0.30–3.87)	1.00	1.00

Table 2 (continued)

Variable	Severe disease			Mortality		
	OR (95% CI)[a]	*p* value	p_{adj}	OR (95% CI)[a]	*p* value	p_{adj}
Block 2: pharmacological treatments						
Haematological						
Antiplatelet agents	1.46 (0.63–3.53)	0.40	0.96	1.22 (0.52–2.89)	0.67	1.00
Anticoagulants	0.81 (0.28–2.39)	0.79	1.00	1.43 (0.49–4.58)	0.60	1.00
Analgesics						
Paracetamol	0.77 (0.35–1.71)	0.55	1.00	1.47 (0.66–3.33)	0.42	1.00
NSAIDs	0.24 (0.03–1.13)	0.07	0.47	0.43 (0.08–1.93)	0.28	0.97
Opioids	0.85 (0.26–2.91)	1.00	1.00	0.85 (0.26–2.91)	1.00	1.00
Systemic corticosteroids	4.00 (0.48–166.87)	0.07	0.47	1.10 (0.16–9.81)	1.00	1.00
Antihistamines	0.75 (0.09–57.36)	1.00	1.00	0.75 (0.09–57.36)	1.00	1.00
Antidiabetic						
Insulin	0.72 (0.18–2.87)	0.74	1.00	0.47 (0.11–1.81)	0.32	0.97
Metformin	1.48 (0.54–4.35)	0.46	1.00	1.48 (0.54–4.35)	0.46	1.00
Other oral antidiabetic drugs	2.67 (0.59–20.59)	0.29	0.89	0.92 (0.22–4.10)	1.00	1.00
Cardiovascular						
Lipid-lowering drugs	1.56 (0.62–4.11)	0.37	0.96	0.45 (0.18–1.11)	0.11	0.64
Diuretics	0.69 (0.31–1.52)	0.42	0.96	1.11 (0.50–2.46)	0.84	1.00
Beta blockers	0.46 (0.15–1.34)	0.18	0.80	0.35 (0.11–1.01)	0.06	0.48
ACE inhibitors	1.41 (0.59–3.50)	0.51	1.00	1.72 (0.72–4.36)	0.27	0.97
ARA 2	2.12 (0.77–6.56)	0.22	0.89	0.62 (0.23–1.64)	0.33	0.97
Other antihypertensives	0.60 (0.25–1.41)	0.28	0.89	1.04 (0.44–2.50)	1.00	1.00
Antiarrhythmics	2.67 (0.59–20.59)	0.29	0.89	2.67 (0.59–20.50)	0.29	0.97
Respiratory						
Inhaled anticholinergics	1.04 (0.30–3.87)	1.00	1.00	0.72 (0.20–2.53)	0.76	1.00
β2 inhaled agonists	1.38 (0.43–4.94)	0.77	1.00	0.71 (0.22–2.30)	0.57	1.00
Inhaled corticosteroids	1.78 (0.45–9.18)	0.51	1.00	1.12 (0.29–4.82)	1.00	1.00
Other inhalers	0.74 (0.02–29.56)	1.00	1.00	0.74 (0.02–29.56)	1.00	1.00
CNS						
Sedatives	1.64 (0.70–4.04)	0.29	0.89	0.78 (0.33–1.84)	0.67	1.00
Antidepressants	1.09 (0.49–2.45)	1.00	1.00	0.78 (0.35–1.75)	0.68	1.00
Antipsychotics	1.72 (0.72–4.36)	0.27	0.89	1.72 (0.72–4.36)	0.27	0.97
Anti-epileptics	2.11 (0.24–61.97)	0.63	1.00	2.11 (0.24–61.97)	0.63	1.00
Antiparkinsonians	2.11 (0.24–61.97)	0.63	1.00	0.74 (0.07- (7.34)	1.00	1.00
Other drugs with effect on the CNS	0.37 (0.10–1.18)	0.09	0.54	0.52 (0.15–1.64)	0.26	0.97
Other therapies						
Antacids	1.32 (0.60–2.93)	0.55	1.00	0.97 (0.44–2.13)	1.00	1.00
Block 3: clinical presentation						
Dyspnoea	2.92 (1.30–6.78)	0.01	0.21	2.92 (1.30–6.78)	0.014	0.21
Cough	0.92 (0.41–2.07)	1.00	1.00	0.34 (0.15–0.77)	0.014	0.21
Fever	2.20 (0.94–5.26)	0.09	0.53	1.28 (0.54–2.99)	0.67	1.00
Diarrhoea	0.71 (0.24–2.13)	0.58	1.00	0.71 (0.24–2.13)	0.59	1.00
Arthromyalgia	0.73 (0.12–4.47)	1.00	1.00	0.15 (0.01–1.03)	0.08	0.57

Table 2 (continued)

Variable	Severe disease			Mortality		
	OR (95% CI)[a]	*p* value	p_{adj}	OR (95% CI)[a]	*p* value	p_{adj}
Asthenia	0.55 (0.21–1.43)	0.23	0.89	0.20 (0.07–0.56)	0.003	0.09
Confusion	0.50 (0.13–1.71)	0.35	0.96	2.37 (0.64–11.82)	0.23	0.97
Psychomotor agitation	0.39 (0.01–4.94)	0.57	1.00	2.32 (0.28–109.54)	0.26	0.97
X-ray, affected quadrants[b]	2.42 (1.05) vs. 1.68 (1.37)	0.004	0.10	2.33 (1.2) vs. 1.8 (1.25)	0.039	0.36
CRP, mg/dL in emergency department[b]	187.84 (110.14) vs. 104.4 (95.56)	0.027	0.30	175.82 (118.44) vs. 105.58 (80.72)	0.08	0.57
Basal oxygen saturation (emergency department)[b]	83.35 (11.47) vs. 91.84 (6.46)	0.0001	0.006	83.74 (11.34) vs. 90.9 (7.87)	0.001	0.036
	Mean dif. (95% CI)	*p* value	p_{adj}	Mean dif. (95% CI)	*p* value	p_{adj}
Block 4: laboratory parameters[c]						
Haemoglobin, g/L	−0.03 (−0.99 to 0.93)	0.95	1.00	−0.07 (−1.03 to 0.88)	0.96	1.00
Platelets, 10^9/L	47.16 (−3.27 to 97.58)	0.037	0.35	12.10 (−39.12 to 63.32)	0.94	1.00
Neutrophils, 10^9/L	0.12 (−1.84 to 2.08)	0.79	1.00	−1.24 (−3.10 to 0.62)	0.38	1.00
Lymphocytes, 10^9/L	0.44 (0.02–0.87)	0.06	0.47	0.38 (0.01–0.76)	0.022	0.24
Eosinophils, 10^9/L	0.24 (−0.05 to 0.53)	0.019	0.29	0.07 (−0.21 to 0.34)	0.60	1.00
Prothrombin time, INR	0.12 (−0.13 to 0.36)	0.55	1.00	0.00 (−0.21 to 0.22)	0.53	1.00
D-dimer, ng/mL	−695.79 (−2,349.74 to 911.78)	0.26	0.89	−1,503.07 (−3,038.81 to 32.67)	0.06	0.48
Fibrinogen, mg/dL	−142.73 (−448.44 to 162.99)	0.54	1.00	−7.78 (−294.29 to 278.74)	0.88	1.00
Glucose, mg/dL	−20.55 (−48.34 to 7.24)	0.18	0.80	−8.41 (−36.37 to 19.55)	0.33	0.97
Serum sodium, mEq/L	0.32 (−3.28 to 3.93)	0.87	1.00	−6.56 (−9.67 to −3.46)	0.0001	0.006
Cr, mg/dL	−0.12 (−0.52 to 0.28)	0.07	0.47	−0.38 (−0.77 to 0.01)	0.005	0.12
Urea, mg/dL	−0.74 (−24.40 to 22.92)	0.25	0.89	−38.43 (−58.56 to −18.30)	0.0001	0.006
Alkaline phosphatase, IU/L	13.63 (−3.52 to 30.79)	0.12	0.69	−7.66 (−25.01 to 9.69)	0.30	0.97
AST, IU/L	−19.65 (−42.3 to 2.83)	0.028	0.30	−21.06 (−43.56 to 1.44)	0.016	0.21
ALT, IU/L	−8.31 (−15.24 to −1.38)	0.012	0.21	−1.28 (−8.55 to 5.98)	0.92	1.00
GGTP, IU/L	−9.36 (−24.45 to 5.73)	0.40	0.96	−6.41 (−21.66 to 8.85)	0.31	0.97
Total bilirubin, mg/dL	0.08 (−0.16 to 0.32)	0.67	1.00	0.13 (−0.11 to 0.37)	0.69	1.00
LDH, U/L	−111.27 (−167.70 to −54.83)	0.0001	0.006	−82.88 (−139.31 to −26.44)	0.006	0.12
CRP at admission, mg/L	−5.75 (−10.49 to −1.02)	0.004	0.10	−55.8 (−103.5 to −8.2)	0.019	0.22
Ferritin, µg/L	−387.82 (−642.31 to −133.33)	0.004	0.10	206.55 (−58.34 to 471.45)	0.68	1.00
Procalcitonin, ng/mL	−0.01 (−1.13 to 1.10)	0.27	0.89	−0.10 (−1.13 to 0.93)	0.70	1.00
Lactate, mmol/L	0.07 (−1.74 to 1.88)	0.31	0.89	−1.03 (−2.71 to 0.66)	0.18	0.88
Arterial oxygen, mm Hg	6.30 (−9.32 to 21.93)	0.53	1.00	12.42 (−3.00 to 27.85)	0.36	1.00
Arterial carbon dioxide, mm Hg	0.89 (−1.34 to 3.12)	0.81	1.00	1.70 (−0.50 to 3.91)	0.42	1.00
Serum bicarbonate, mmol/L	1.00 (−0.73 to 2.73)	0.51	1.00	1.24 (−0.49 to 2.97)	0.65	1.00
Blood pH	0.01 (−0.01 to 0.04)	0.32	0.89	−0.00 (−0.03 to 0.03)	1.00	1.00

OR, odds ratio; SD, standard deviation; 95% CI, confidence interval; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; ACE inhibitors, inhibitors of the angiotensin-converting enzyme; ARA2, angiotensin 2 receptor antagonists; CNS, central nervous system; CRP, C-reactive protein; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase.
[a] In the case that any cell had a value of 0, for the calculation of the OR, a normal approximation was performed with adjustment for small samples. [b] For these variables, the results represent mean (SD). [c] For the laboratory parameters, the values of *p* and p_{adj} come from the bivariate analysis of the logarithmically transformed parameter.

Table 3. Results of the multivariate analysis for the variables of severe disease and mortality

Model[a]	Severe disease			Mortality		
	OR[b]	95% CI	*p* value	OR[b]	95% CI	*p* value
Model 1: Personal history						
Female sex	0.31	0.13–0.73	0.007			
Model 2: Pharmacological treatments						
Female sex	0.31	0.13–0.73	0.007	0.48	0.21–1.10	0.082
Model 3: Laboratory parameters						
Female sex	0.29	0.09–0.95	0.041	0.40	0.11–1.45	0.161
Serum LDH	2.55	1.21–5.37	0.014	1.65	0.88–3.10	0.121
CRP on admission	1.93	0.89–4.17	0.094			
Serum sodium				3.12	1.18–8.26	0.022
Serum urea				1.49	0.66–3.39	0.339
Lymphocytes				0.78	0.39–1.56	0.484
Model 4: Laboratory parameters and oxygen saturation						
LDH	2.54	1.03–6.23	0.042	1.60	0.87–2.93	0.128
CRP on admission	2.11	0.83–5.38	0.118			
Basal oxygen saturation	0.94	0.86–1.04	0.222			
Serum sodium				2.60	1.05–6.44	0.0394
Serum urea				1.54	0.70–3.38	0.281

OR, odds ratio; 95% CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase. [a] In each model, the variables age and sex were included, except in model 4. [b] Laboratory parameters (LDH, CRP, sodium, urea, and lymphocytes) were subjected to logarithmic transformation and then scaled, so their ORs cannot be compared with those of the other variables (sex and oxygen saturation).

them, only oxygen saturation survived the adjustment of multiple tests (false discovery rate method). The urea and sodium parameters were significantly associated with mortality.

The results of the multivariate models are shown in Table 3. By the criterion of >30% missing data or fewer than 16 positive individuals with the evaluated parameter, the variables of stroke, psychiatric disease, emergency CRP, AST, alanine aminotransferase, and ferritin were excluded from the severe disease models, and the variables AST and "other heart disease" were excluded from the mortality models. With respect to the outcome severe disease, the variable female sex (OR 0.31, 95% confidence interval [95% CI] 0.13–0.73, *p* 0.0074) was significantly associated with it in block 1, as was serum LDH (OR 2.55, 95% CI 1.21–5.37, *p* 0.0139) in block 4. Regarding the mortality outcome, only serum sodium (block 4) was significantly associated with it (OR 3.12, 95% CI 1.18–8.26, *p* 0.0222). Given this last result, we built a model including laboratory parameters and oxygen saturation. In this model, serum sodium continued to be associated with higher mortality (OR 2.60, 95% CI 1.05–6.44, *p* 0.0394).

Discussion/Conclusion

Main Results

The most frequent symptoms of clinical presentation were fever, dyspnoea, and cough; hospital mortality was quite high; male sex and serum LDH level were associated with severe disease; and serum sodium concentration was associated with mortality.

Clinical Presentation

Although the most frequent symptoms were the same as in the hospitalized adult population [12, 18–20], they were less frequent than has been reported in this population (especially cough and fever), even though the diagnosis of respiratory infection was an inclusion criterion in our study. In general population, cohorts of COVID-19-hospitalized patients [18–20] have reported prevalence of fever and cough between 72 and 88 and between 65 and 73%, respectively. On the other hand, confusion stands out as a symptom present in 11% of our sample. Gutiérrez-Rodríguez et al. [11] and Annweiler et al. [21] reported frequencies similar to ours in the subgroup of patients 80 years or older. These findings are in line with those observed in the majority of diseases of this popula-

tion (including infections), in which less symptomatic or atypical presentations are more frequently observed [3–5]. This reinforces the need for a lower suspicion threshold in this population, especially when evaluated in an emergency department.

A low frequency of non-respiratory symptoms was observed. However, given the absence of a systematic search for these symptoms, we cannot exclude an information bias whereby patients who reported respiratory symptoms at the beginning of the evaluation were not also asked about non-respiratory symptoms, resulting in undetected symptoms.

Prognostic Factors of Severe Disease and Mortality

Age, unlike in the younger population [2, 6, 22, 23], did not bring an added risk in any of the models built here, and male sex was associated with severe disease but not mortality. The trials by Gutiérrez-Rodríguez et al. [11] and Covino et al. [10] did not find that age or sex was associated with mortality either. However, Ramos-Rincon et al. [9] reported age and male sex as variables associated with mortality from a multicentre cohort of 2,772 very old hospitalized patients, so we cannot rule out a lack of statistical power of our sample in these results. Institutionalization was not included in our analysis due to the fact that the registration of this variable was not as reliable as the other included variables. Furthermore, we consider that institutionalization, in contrast to variables like chronic diseases or previous pharmacological treatments, is an external indicator, instead of being an intrinsic factor of a patient. For this reason, the evaluation of institutionalization as a prognostic factor (in difference to its evaluation as predictor factor) might not be recommended.

Unlike laboratory parameters and those related to emergency assessment (some of which were associated with worse prognosis), no chronic disease or previous pharmacological treatment was associated with worse or better outcomes. Previous treatments have not been evaluated as prognostic factors in the aforementioned trials [9–11], so we cannot compare our results with them. In a younger cohort, Mostaza et al. [24], in people older than 75 years, did find a better prognosis in patients who previously took renin-angiotensin-aldosterone system antagonists. Regarding previous chronic diseases, it is remarkable that in contrast to studies in younger populations [25], no chronic disease was associated with mortality. Although we cannot exclude a lack of statistical power for this result, it is similar to the study by Ramos-Rincon et al. [9], which also did not find an association between chronic diseases and mortality (except for obesity which was significantly associated with mortality in the bivariant analysis, although it was not included in the multivariant models). In another study with a very old population, Covino et al. [10] reported severe dementia as an independent risk factor for death, although age, since it was not apparently included in their multivariate analysis, cannot be rule out as a confounding factor.

Only the serum LDH level was associated with severe disease among laboratory parameters. We have not found studies that evaluated the factors associated with this result in the older or oldest-old population. In adult population studies, LDH is one of the most powerful factors associated with severe disease among laboratory parameters [26–29]. Thus, in the meta-analysis of Zhang et al. [28], LDH was the only laboratory parameter associated with both adult respiratory distress syndrome and indication for intensive care unit admission. LDH is present in body tissues and is released from damaged cells [30, 31], increases lactate production [32], and is a good predictor of lung injury [30].

Serum sodium was associated with mortality in our sample. Of the aforementioned studies, Gutiérrez-Rodríguez et al. [11] did not find a significant association in their bivariate analysis, and Ramos-Rincon et al. [9] and Covino et al. [10] did not include this parameter in their reports. Below, we propose a hypothesis for this result.

Among the laboratory parameters, it stands out that the parameters associated with worse prognosis were different for severe disease and mortality, although both outcome variables are closely related. We highlight the fact that 1.1 out of every 4 people who died did not previously present any criteria of severe disease. Given the definition of this in our study based on strict respiratory criteria, we hypothesize that some of the patients could have died from complications in other body systems (cardiovascular, thrombotic, metabolic, and renal complications have been described [33]) and not so much from severe respiratory involvement. In this sense, serum sodium (a marker of metabolic alteration or renal function) would predominate as a prognostic factor for mortality and not as much for severe respiratory disease. That the association of this parameter with mortality was maintained, despite adjusting the model for oxygen saturation reinforces our hypothesis.

With respect to our analyses of severe disease, we have to comment the possibility of competing risk factors when the patients died without severe disease criteria (in these patients, dead competes with the severe disease outcome). This would be significant if the proportion of patients who died without severe disease criteria had been similar or larger than the proportion of patients with se-

vere disease, or if the follow-up time had been very long (>5 years) [34]. In our study, the proportion of patients who died without severe disease criteria (15.5%) was significantly lower than the patients with severe disease (57.3%), and the follow-up time of our cohort was very short. Thus, we consider the impact of a situation of competing risk factors insignificant or improbable in our trial.

In-Hospital Mortality

Although the highest lethality of COVID-19 is seen in the older population, especially among the hospitalized population, the hospital mortality found in our sample was higher than that of other hospital series of oldest-old populations in Spain (35–47%). We highlight the high proportion of institutionalized patients in our sample (61%), reflecting a population with greater clinical fragility and therefore with less ability to respond to an organic stressor. Thus, the series reported by Gutiérrez-Rodríguez et al. [11] had a mortality (41%) and a proportion of institutionalized patients (70%) more similar to those of our sample than those reported by Mostaza et al. [24] (mortality 35% and proportion of institutionalized 23%). In neighbouring countries, Zerah et al. [35] (France) reported a lower lethality (31%) in a cohort of 821 hospitalized patients aged 70 years or older, although with a proportion of institutionalized patients much lower than that in our sample (29%). Finally, we have to mention, in relation to the high mortality in our sample, the high pressure to which the Spanish Sanitary System was exposed during this time, which might have influenced or limited the access for this population group to certain health care resources including admission to intensive care units [36].

External Validity

Regarding the extrapolation or comparison of our results with the results in other samples, it is important to consider, in addition to the high mortality and high proportion of institutionalized patients, that our patients were managed in secondary referral centres, so our results cannot be extrapolated to populations treated on an outpatient basis or in centres of maximum complexity (tertiary), such as patients undergoing organ transplants. Furthermore, in our sample, only 4 patients had less than 2 chronic diseases, which means that our results cannot be extrapolated to patients without significant comorbidity.

Limitations

The sample size of our study does not allow us to take the results as conclusive. Some laboratory parameters (AST, aspartate aminotransferase, ferritin, and Cr), despite having significant associations with some of the outcome variables in the bivariate analysis, could not be included in the multivariate models due to significant data loss.

Most likely, some COVID-19 patients were already admitted with severe disease criteria. In these cases, the validity of our results regarding the variables of clinical presentation and laboratory parameters (including serum LDH level) may be affected. The sample size prevented us to perform any sensitivity analysis whereby we recognize this limitation. However, the variables of chronic diseases and previous treatments would continue to be valid in these patients because the temporal relationship remains accurate. Finally, we were unable to evaluate variables of previous functional status, a variable of known prognostic association in most diseases in this population, including COVID-19 [35, 37].

In conclusion, the symptoms of clinical presentation typical of respiratory infection by SARS-CoV-2 (fever, dyspnoea, and cough) are less frequent in the oldest-old population, and male sex and LDH level are associated with severe disease, and serum sodium is associated with mortality.

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Statement of Ethics

The present study has been performed in accordance with the Declaration of Helsinki, and it was approved by the Research Ethics Committee of the Hospital Universitari de Bellvitge (act 12/20, PR 252/20, date June 25, 2020), which approved the study without the need for the informed consent of the patients, given the observational nature of the study and the anonymous nature of the data collected.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

César Gálvez-Barrón and Marta Arroyo-Huidobro analysed and interpreted the data and wrote the manuscript. Alejandro Rodríguez-Molinero designed the trial and analysed and interpreted the data. Antonio Miñarro analysed and interpreted the data. Gemma Añaños, Antonio, Chamero, Mireia Martín, Clara Gris, Jose L. Avalos, Anna M. Capielo, Ester Ventosa, and Gemma Tremosa collected and analysed the data. All authors read and approved the final manuscript. A preprint version of this article is available on Research Square [38].

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