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## Clinical course and prognostic factors of COVID-19 infection in an elderly hospitalized population

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### ABSTRACT

**Introduction:** Older subjects have a higher risk of COVID-19 infection and a greater mortality. However, there is a lack of studies evaluating the characteristics of this infection at advanced age.

**Patients and methods:** We studied 404 patients  $\geq 75$  years (mean age  $85.2 \pm 5.3$  years, 55 % males), with PCR-confirmed COVID-19 infection, attended in two hospitals in Madrid (Spain). Patients were followed-up until they were discharged from the hospital or until death.

**Results:** Symptoms started 2–7 days before admission, and consisted of fever (64 %), cough (59 %), and dyspnea (57 %). A total of 145 patients (35.9 %) died a median of 9 days after hospitalization. In logistic regression analysis, predictive factors of death were age (OR 1.086; 1.015–1.161 per year,  $p = 0.016$ ), heart rate (1.040; 1.018–1.061 per beat,  $p < 0.0001$ ), a decline in renal function during hospitalization (OR 7.270; 2.586–20.441,  $p < 0.0001$ ) and worsening dyspnea during hospitalization (OR 73.616; 30.642–176.857,  $p < 0.0001$ ). Factors predicting survival were a female sex (OR 0.271; 0.128–0.575,  $p = 0.001$ ), previous treatment with RAAS inhibitors (OR 0.459; 0.222–0.949,  $p = 0.036$ ), a higher oxygen saturation at admission (OR 0.901; 0.842–0.963 per percentage point increase,  $p = 0.002$ ), and a greater platelet count (OR 0.995; 0.991–0.999 per  $10^6/L$ ,  $p = 0.025$ ).

**Conclusion:** Elderly patients with COVID-19 infection have a similar clinical course to younger individuals. Previous treatment with RAAS inhibitors, and demographic, clinical and laboratory data influence prognosis.

### 1. Introduction

During the last few months, a pandemic of COVID-19 infection has

spread worldwide. Spain has been one of the most affected countries, with more than 200,000 infected subjects and 27,000 deaths registered until the middle of May 2020. Madrid is one of the Spanish regions with

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the highest population density, and the one with the greatest number of confirmed cases.

A few studies have defined the characteristics of those subjects most prone to COVID-19 infection (Guan et al., 2020; Richardson et al., 2020), and the natural course of this disease (Zhou et al., 2020). However, although older patients are the most vulnerable segment of the population in this pandemic (Guan et al., 2020; Richardson et al., 2020), there is a lack of detailed descriptions of the natural progression of this disease in the elderly (Niu et al., 2020). Moreover, although COVID-19 infection affects all age groups, the majority of deaths have been among elderly people, and it is not known whether risk factors associated with a worse prognosis in younger persons, (Zhou et al., 2020) are also present in the older ones.

The objective of the present study was to investigate the clinical course of COVID-19 infection in subjects 75 years or older admitted in two hospitals in Madrid (Spain), and to analyse factors that may contribute to mortality.

## 2. Patients and methods

### 2.1. Methods

#### 2.1.1. Study design

Retrospective cohort study in patients aged 75 or older, with a PCR confirmed diagnosis of COVID-19 infection, admitted to either Carlos III or Cantoblanco Hospitals (Madrid, Spain), between March 1st, 2020 to April 21st, 2020 and discharged by May 10th. During these dates, only COVID-19 infected subjects were hospitalized in these Centers. Both are tributaries of La Paz Hospital, and they only attended subjects with no indication for ICU admission.

#### 2.1.2. Data collection

Demographic, clinical, laboratory, treatments, and outcome data were obtained through manual revision of the Hospital's clinical charts and were anonymized before their inclusion in the database. We selected those treatments that have previously reported to influence the clinical course of COVID-19 infection (statins, ACE inhibitors, Angiotensin II receptor blockers, anticoagulants, and antiplatelet drugs), or those that could theoretically influence its prognosis (steroids and/or immunosuppressive treatment).

Blood analysis and a chest x-ray were routinely obtained at admission.

#### 2.1.3. Variables and definitions

Fever was defined as a temperature  $> 37.5^{\circ}\text{C}$ . Worsening dyspnea was considered if, during hospital admission, there was a respiratory failure that required an increased in the administered  $\text{FiO}_2$ . We calculated the ratio of pulse oximetric saturation/ fraction of inspired oxygen ( $\text{SpO}_2/\text{FiO}_2$ ) in all patients (Rice et al., 2007). Diagnosis of acute respiratory distress syndrome (ARDS) and their stages were considered according to the Berlin definition, after excluding congestive heart failure (ARDS task force).

A decline in renal function was considered if creatinine level increased 1.5 times from the one obtained at admission. Hypotension was considered if blood pressure dropped below 90/60 mmHg in two consecutive occasions at least 8-hs apart.

#### 2.1.4. Statistical analysis

The continuous variables with a normal distribution are presented as mean  $\pm$  standard deviation. Non-normally distributed continuous variables are reported as median (IQR). Categorical variables are presented as percentages. Comparisons between continuous variables were performed by the Student *t*-test if they had a normal distribution, or otherwise by the Mann-Whitney *U* test. Comparisons between categorical variables were performed by the  $\chi^2$  test.

We performed separate forward stepwise logistic regression

analyses, in order to evaluate factors associated with death at two different periods: One with data only available at the emergency ward (demography, comorbidities, ambulatory treatments, clinical course of the disease and laboratory values at admission), and another adding data obtained from hospitalization. In each model we have included age, sex, Charlson Comorbidity Index scoring, and those variables significantly associated with death in the univariate analysis ( $p < 0.10$ ), avoiding over adjustment.

Statistical processing of the data was performed with SPSS for windows, v.19.0; IBM Corp, Armonk, New York, USA.

The study protocol was approved by the Research Ethics Committee of La Paz Hospital in Madrid. The study complied with the International Guidelines for Ethical Review of Epidemiological Studies (Geneva, 1991).

## 3. Results

A total of 404 patients were attended in both hospitals, 302 (75 %) in Carlos III and 102 (25 %) in Cantoblanco Hospital. Mean age was  $85.2 \pm 5.3$  years, with a 55 % of males. Overall mortality was 35.9 %; 25 % in subjects 75–79 years, 40.5 % in subjects 80–84 years, 32.1 % in those 85–89 years and 42.7 % in persons older than 90 years.

The clinical characteristics of the patients, ambulatory treatments, laboratory findings and clinical evolution are presented in Table 1.

Symptoms started 2–7 days before admission, and consist in fever, cough, and dyspnea, and less frequently, diarrhea (17.3 %), nausea and vomits (10.1 %), nasal congestion (4.7 %), and odynophagia (3.2 %).

Mortality rate was greater in males, and in subjects with a shorter period of symptoms, presence of fever and dyspnea, and a lower oxygen saturation at admission. Laboratory findings predictive of a worse outcome were a higher concentration of neutrophils, ALT, AST, LDH and C reactive protein (CRP), and in those with a lower lymphocyte and platelet count.

During hospitalization, 43 % of the participants had aggravation of their dyspnea, 37.6 % developed ARDS, 13.1 % had a decline in their renal function, and 24 % a drop in their blood pressure below 90/60 mmHg.

Of those with severe exacerbation of dyspnea ( $\text{StO}_2/\text{FiO}_2 < 100$ ), 81.2 % died. The percentage of deaths was 27.3 % when the deterioration was moderate ( $\text{StO}_2/\text{FiO}_2 100\text{--}200$ ), 12.1 % when it was mild ( $\text{StO}_2/\text{FiO}_2 200\text{--}300$ ), and only 4.1 % when patients did not have dyspnea exacerbation ( $\text{StO}_2/\text{FiO}_2 > 300$ ).

### 3.1. Factors associated with mortality at Hospital admission: Multivariate analysis

At hospital admission, the factors associated with an increased mortality in the multivariate analysis were (Table 2), an older age, a shorter duration of symptoms before hospitalization, a faster heart rate, and higher levels of CRP. Factors associated with survival were a female sex, previous treatment with RAAS inhibitors, a higher oxygen saturation in the emergency ward and a higher platelet count.

In order to further explore the association between RAAS inhibitors treatment and mortality, we performed a full adjusted model multivariate analysis, including all previously reported comorbidities associated with COVID-19 mortality and with RAAS inhibitors treatment (hypertension, diabetes, ischemic cardiovascular disease, congestive heart failure and chronic renal failure). The OR of mortality associated with the use of RAAS inhibitors remained significant (OR 0.61; 95 %CI 0.37–0.98).

### 3.2. Overall factors associated with mortality: Multivariate analysis

During hospitalization, factors associated with an increased mortality were dyspnea aggravation, the development of ARDS, a decline in renal function and a drop in blood-pressure below 90/60 mmHg

**Table 1**

Demographic, baseline comorbidities, ambulatory treatments, clinical characteristics and laboratory findings at admission, and clinical course among survivors and non-survivors.

	TOTAL 404	Survivors 259 (64.1 %)	Non-survivors 145 (35.9 %)	p*
Age (years)	85.2 ± 5.3	85.0 ± 5.2	85.7 ± 5.5	0.225
Gender (% males)	54.7	47.5	67.6	0.001
Nursing-home residents (%)	22.6	23.6	20.7	0.496
Hypertension (%)	73.8	76.4	69.0	0.101
Diabetes (%)	28.0	26.6	30.3	0.426
COPD/Asthma (%)	19.9	21.7	16.6	0.213
Atrial Fibrillation (%)	23.5	22.0	26.2	0.340
Congestive Heart Failure (%)	18.8	20.1	16.6	0.384
Chronic Renal Failure (%)	15.6	16.6	13.8	0.455
Dementia (%)	22.5	20.8	25.5	0.281
Atherothrombotic vascular disease	25	22.6	29.3	0.136
Solid neoplasia (%)	18.6	17.9	19.7	0.649
Leukemia/Lymphoma	2.8	2.8	2.8	0.887
Chronic Liver Disease (%)	4.0	3.9	4.1	0.891
Chronic inflammatory disease (%)	6.4	5.8	7.6	0.481
Charlson Comorbidity Index	6 (5–7)	6 (4–7)	6 (5–7)	0.086
Statins (%)	47.5	44.8	52.4	0.141
Antiplatelet drugs (%)	30.4	29.3	32.4	0.520
ACE inhibitors (%)	31.4	33.2	28.3	0.306
Angiotensin II receptor antagonists (%)	21.5	24.3	16.6	0.068
RAAS Blockers (%)	47.5	56.8	44.8	0.021
Anticoagulants (%)	25.5	26.6	23.4	0.480
Steroids/Immunosuppressive (%)	6.9	5.8	9.0	0.228
Days of symptoms before admission	4 (2–7)	5 (2–7)	3 (1–7)	0.006
Fever (%)	63.9	56.8	76.6	0.0001
Dyspnea (%)	56.7	51.4	66.2	0.004
Cough (%)	59.2	61.8	54.5	0.153
Oxygen saturation at admission (%)	93 (89–95)	93 (90–95)	92 (87–95)	0.002
SBP (mmHg)	133 ± 23	133 ± 24	132 ± 22	0.530
DBP (mmHg)	72 ± 12	72 ± 12	71 ± 12	0.846
Heart rate (bmp)	84 ± 17	83 ± 17	87 ± 18	0.016
Hemoglobin, g/dl (404)	13.6 (12.1–14.8)	13.6 (12.2–14.7)	13.6 (11.8–14.8)	0.913
WBC x10 <sup>9</sup> , per L <sup>†</sup> (402)	6.0 (4.5–8.2)	6.0 (4.4–7.8)	6.2 (4.6–8.6)	0.265
Neutrophils x10 <sup>9</sup> , per L <sup>†</sup> (402)	4.4 (3.3–6.5)	4.4 (3.1–6.2)	4.8 (3.6–7.0)	0.051
Lymphocytes x10 <sup>9</sup> , per L <sup>†</sup> (402)	0.78 (0.55–1.14)	0.84 (0.59–1.22)	0.72 (0.10–0.98)	0.002
Platelets x10 <sup>9</sup> , per L (404)	199 (153–280)	213 (163–283)	181 (138.5–252)	0.002
ALT, U/L (387)	36 (25–52)	34 (24–47)	41 (26–62.5)	0.007
AST, U/L (396)	23 (16–36)	23 (15–33)	25 (16.7–37.2)	0.068
LDH, U/L (343)	316 (252–391)	303 (248–376)	344 (258–464)	0.001
CRP, mg/dL (390)	82 (32–145)	57.2 (25.6–123.0)	114.2 (68.8–203.0)	0.001
D Dimer, ng/mL (239)	1153 (680–2550)	1123 (646–2310)	1251 (705–3618)	0.202
Creatinine, mg/dL (404)	0.89 (0.72–1.21)	0.87 (0.7–1.19)	0.99 (0.77–1.26)	0.006
Worsening dyspnea (%)	43.1	15.8	91.7	0.0001
ARDS (%)	37.6	25.5	59.3	0.0001
Days from hospitalization to ARDS	5 (3–7.2)	5.5 (3.25–8.0)	5 (3–7)	
Decline in renal function during hospitalization (%)	13.1	6.6	24.8	0.0001
Hypotension during hospitalization (%)	24.0	18.1	34.5	0.0001

ACE = Angiotensin converting enzyme. ARDS = Acute respiratory distress syndrome. ALT = alanine aminotransferase. AST = aspartate aminotransferase. COPD = Chronic obstructive pulmonary disease. CRP = C-reactive protein. DBP = Diastolic blood pressure. LDH = Lactate dehydrogenase. RAAS = renin angiotensin aldosterone system. SBP = Systolic blood pressure. WBC = White Blood Count.

\* p for Survivors vs non-survivors. Data are mean ± SD, median (IQR), or percentages. p values were calculated by the Student t-test, the Mann-Whitney U test or χ<sup>2</sup> test. Number of patients with value in parenthesis.

<sup>†</sup> Two patients with chronic lymphocytic leukemia were excluded.

(Table 1).

We performed a second stepwise logistic regression analysis to evaluate the effect of both, prehospitalization and hospitalization factors on mortality (Table 2). Overall, older age, male sex, a lower oxygen saturation at admission, a faster heart rate, a lower platelet count, and worsening dyspnea and declining renal function during hospitalization were associated with a worse outcome. Subjects taking RAAS inhibitors before admission had a lower mortality rate.

#### 4. Discussion

Several studies have demonstrated that the lethality rate of COVID-19 infection in older patients is extremely high. Despite this, only a few studies have specifically evaluated its characteristics in the elderly (Niu et al., 2020). We assessed the clinical course of this disease and the

factors associated with mortality in patients admitted in 2 hospitals in Madrid (Spain). Our results demonstrate that the clinical evolution of COVID-19 infection in elderly patients, does not differ from the clinical course previously reported in younger subjects (Zhou et al., 2020). Symptoms start 2–7 days before admission, generally with fever and cough, and are followed by shortness of breath, which brings the patient to the Hospital. Three to seven days after admission (7–13 after the initiation of symptoms), many patients may develop respiratory failure, progressing to ARDS, and death. It must be considered that our population consists of hospitalized patients, and for that reason of subjects with a more severe infection. The proportion of deaths was 36 %, much higher than the observed in China (Guan et al., 2020; Niu et al., 2020) and lower than the reported in United States (Richardson et al., 2020) for the same age ranges. There are no clear explanations for these differences, except for race or the threshold severity required

**Table 2**  
Logistic regression analysis of factors associated with mortality, at hospital admission and during the complete clinical course.

Predictor	Exp (B)	95 % upper CI for Exp (B)	95 % lower CI for Exp (B)
Forward selection logistic regression analysis of factors predicting mortality at hospital admission*			
Age (per year)	1.077	1.025	1.132
Gender (Female vs male)	0.434	0.258	0.730
Previous treatment with RAAS inhibitors (yes/no)	0.589	0.362	0.961
Symptoms duration (per day)	0.921	0.864	0.983
Oxygen saturation at admission (per 1 %)	0.929	0.888	0.972
Heart rate (per beat)	1.025	1.010	1.040
CRP levels (per mg/dL)	1.007	1.003	1.010
Platelet count (per x10 <sup>6</sup> , per L)	0.995	0.991	0.998
Forward selection logistic regression analysis of all factors predicting mortality**			
Age (per year)	1.086	1.015	1.161
Gender (Female vs male)	0.271	0.128	0.575
Previous treatment with RAAS inhibitors (yes/no)	0.459	0.222	0.949
Oxygen saturation at admission (per 1 %)	0.901	0.842	0.963
Heart rate (per beat)	1.040	1.018	1.061
Platelet count (per x10 <sup>6</sup> , per L)	0.995	0.991	0.999
Worsening dyspnea during hospitalization (yes/no)	73.616	30.642	176.857
Decline in renal function during hospitalization (yes/no)	7.270	2.586	20.441

Results are for 370 patients with a complete set of variables.

\* Variables included in the model were age, gender, Charlson Comorbidity Index, previous treatment with RAAS inhibitors, duration of symptoms before admission, presence of fever, heart rate, oxygen saturation at admission, lymphocyte count, neutrophil count, platelet count, and blood concentration of ALT, CRP and creatinine.

\*\* Variables included in the model were the same as before plus worsening dyspnea, decline renal function and hypotension during hospitalization.

for hospitalization. As previously indicated, younger patients were not transferred to our Hospitals, and remained in La Paz Hospital. The mortality rate for these younger subjects were, 0.5 % for those below 40 years, 1.5 % for those 40–49 years, 3.8 % for those 50–59 years, and 11 % for those 60–69 years (Borobia et al., 2020).

As previously reported, women also had a lower mortality than men in this elderly population. Although the reasons for this gender difference are unknown, it has been suggested that males and females differ in their immunological responses and in their susceptibility to infection (Klein & Flanagan, 2016).

Some studies have proposed that different comorbidities, i.e. hypertension and cardiovascular disease, may increase the risk of COVID-19 infection (Mancia, Rea, Ludernani, Apolone, & Corrao, 2020), a finding that could be explained by a greater contact of these subjects with the health system, increasing their risk of exposure to the virus. They also suggest that patients with these comorbidities may have a greater risk of death (Mancia et al., 2020). Our data do not support that some previously reported comorbidities influence the outcome of elderly patients. COVID infection severity is related to age (Guan et al., 2020; Richardson et al., 2020), and older subjects have an increased prevalence of different comorbidities, i.e. COPD, hypertension, cardiovascular disease, congestive heart failure, arrhythmia, and/or diabetes. Some studies that have found a relationship between comorbidities and COVID mortality, did not control by age (Guan et al., 2020; Richardson et al., 2020) or have found that this relationship disappears after age adjustment (Zhou et al., 2020).

Aside from male sex, we found that previous treatment with RAAS inhibitors was associated with a better prognosis. SARS CoV-2 enters the cell through the angiotensin-converting enzyme 2 (ACE2). It has been postulated that the use of RAAS inhibitors may up-regulate its

tissue expression, favoring the virus infectivity (Sommerstein, Kochen, Messerli, & Gräni, 2020). Despite this, there is no clinical data suggesting a causal relationship between the use of RAAS inhibitors and increased infectivity or a worse prognosis. Moreover, some authors have suggested that there are theoretical actions of RAAS inhibition that could lead to a better outcome (Kuster et al., 2020). In fact, several epidemiological studies demonstrate that this relation looks spurious (Mancia et al., 2020; Reynolds et al., 2020). We found that the use of RAAS inhibitors reduces mortality even after adjusting for age, sex, hypertension, and other comorbidities associated with a greater use of these drugs. No other treatments did modify the prognosis. The potential benefit of RAAS inhibitors on survival should be confirmed in clinical trials, as our study cannot assume a cause and effect relationship.

We also observed that a sudden initiation of symptoms, a higher prevalence of fever and dyspnea, a lower oxygen saturation at admission, and an increased inflammatory reaction, with higher levels of inflammatory markers, and with a lower platelet count, were associated with a poorer outcome. Probably, all these factors identify a subgroup of the infected individuals with an abrupt and dysfunctional immune response to disease progression, that leads to organ failure and death (Qin et al., 2020). The amplified inflammatory response against the viral infection, may allow researchers to explore potential therapeutic interventions that target immunoregulation (Tay, Poh, & Rénia, 2020).

Our study has some limitations. Only patients with a more severe disease, requiring hospitalization, were included. Some important data were not collected due to their poor consistency, like smoking habit and weight. And some important variables, like LDH or D-dimer, were not included in the multivariate analysis because they were measured in a limited number of patients. However, the advantage of the present study is the homogeneous sample, with a complete manual collection of data and follow-up of the population.

We conclude that elderly patients with COVID-19 infection have a similar clinical course to younger individuals. Factors associated with an increased mortality were older age, male sex, an abrupt onset of symptoms, a greater inflammatory reaction, and the development of ARDS, renal failure or a blood pressure fall during admission. Treatment with RAAS inhibitors before admission was associated with a better outcome.

#### Data distribution statement

De-identified participant data from the final research dataset used in this manuscript will be shared under the terms of a Data Use Agreement. Requests may be directed to the corresponding author.

#### CRediT authorship contribution statement

**Jose M. Mostaza:** Conceptualization, Project administration, Writing - original draft. **Francisca García-Iglesias:** Investigation, Writing - review & editing. **Teresa González-Alegre:** Investigation, Writing - review & editing. **Francisco Blanco:** Conceptualization, Investigation, Writing - review & editing. **Marta Varas:** Investigation, Writing - review & editing. **Clara Hernández-Blanco:** Investigation, Writing - review & editing. **Victor Hontañón:** Investigation, Writing - review & editing. **María J. Jaras-Hernández:** Investigation, Writing - review & editing. **Mónica Martínez-Prieto:** Investigation, Writing - review & editing, Visualization. **Araceli Menéndez-Saldaña:** Investigation, Writing - review & editing, Visualization. **María L. Cachán:** Data curation, Formal analysis. **Eva Estirado:** Data curation, Formal analysis. **Carlos Lahoz:** Conceptualization, Writing - review & editing. **Rosa de Miguel:** . **Miriam Romero:** . **Mar Lago:** . **Cristina García-Quero:** . **Cristina Plaza:** . **Talía Sainz-Costa:** . **Susana Rivas-Vila:** . **Blanca Sánchez:** . **Celia García Torres:** . **Lucía Martínez-Tobar:** . **María Hernandez-Pérez:** . **Pablo Racionero:** . **Patricia Mir-Ihara:** . **Jesús Peña-López:** . **Marta Bautista-Barea:** . **Alexa P.**

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#### Declaration of Competing Interest

The authors have no conflicts.

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