COVID-19 in patients aged 80 years and over during the peaks of the first three pandemic waves at a Spanish tertiary hospital

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ABSTRACT

INTRODUCTION COVID-19 disproportionately impacts patients aged ≥80 years, yet few studies have focused on this population. We aimed to investigate the clinical characteristics and outcomes of very elderly patients with COVID-19 across three consecutive waves in Spain.
METHODS We retrospectively evaluated very elderly patients admitted with COVID-19 to a university hospital in Barcelona, Spain, across the three first waves. Main outcomes were ICU admission and 30-day mortality.
RESULTS From March 2020 to February 2021, 3105 patients diagnosed with COVID-19 were admitted. Of these, 655 (21%) were very elderly patients, 50% were female and median age was 86 (83; 89) years. ICU admission and ICU-mortality rates were 11% and 42%, respectively; male sex, respiratory rate ≥25 breaths/min, LDH ≥337.5 U/L and C-reactive protein ≥11.5 mg/dL were significantly associated with ICU admission in the multivariable analysis. Overall, 30-day mortality was 34%. The ICU admission rate was significantly higher during the first wave compared to the third wave (16% vs 8%; p=0.009), whereas no significant differences in 30-day mortality were found between waves (p=0.107).
CONCLUSIONS We observed an increase in the percentage of very elderly patients admitted to the ICU during the three first pandemic peaks. ICU admission more likely occurs in very elderly male patients with higher respiratory rate, with elevate LDH and C-reactive protein. Overall, our 30-day mortality rate was lower compared to other series globally.

INTRODUCTION

Since the beginning of the pandemic, Spain has been hit by five waves of COVID-19. Age was widely used as a prioritizing criterion for ICU admission, which has been one of the most controversial aspects of the pandemic thus far[1]. Numerous studies have found older age to be associated with higher risk of severe illness, complications, and mortality in COVID-19[2]. Despite that patients aged ≥80 years have distinct clinical features and risk factors, notably multiple comorbidities and polypharmacy[3], there is little information on this specific population.

We aimed to describe and compare the clinical characteristics, complications, therapy and outcomes in very elderly patients with COVID-19 during the first three waves of the pandemic in Spain.

METHODS

We retrospectively evaluated all consecutive very elderly patients admitted to Hospital Clinic, Barcelona (Spain). All patients admitted >48 h with a definite diagnosis of COVID-19 (either confirmed by RT-PCR or fulfilling clinical criteria in place) between March 2020 and February 2021 were included. The primary outcome was ICU mortality. Secondary outcomes included length of hospital stay, early mortality (within 5 days of admission), 30-day mortality and need for mechanical ventilation. We divided the study population into three groups for the analysis: first wave (March to June 2020), second wave (July to November 2020) and third wave (December 2020 to February 2021).

Categorical variables were compared between the three groups using the χ² test, while continuous variables with the Kruskal-Wallis test. In the event of a significant overall test, we conducted *post hoc* pairwise comparisons with Bonferroni correction. We examined the association of risk factors with ICU admission using logistic regression models. After bivariate analyses, we selected independent variables at a p<0.25. All the variables were put into a multivariable logistic regression analysis model. Final variable selection was performed using the backward stepwise selection method, except for period, which had to appear in the model. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the final model. The receiver

operating characteristic (ROC) curve was used to assess the discriminatory ability of the model to distinguish ICU patients from ward patients and is expressed as the area under the ROC curve (AUC). The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Statistics version 26.0 (Armonk, New York, USA).

RESULTS

From March 2020 to February 2021, 3105 patients diagnosed with COVID-19 were admitted. A total of 655 (21%) were very elderly patients and were included in our study [first wave 289/1447 (20%); second wave 145/765 (19%); third wave 221/893 (25%)], 50% were females, and median age was 86 (83; 89) years.

The median time from symptoms to COVID-19 diagnosis was 5 (2; 8) days. At least one comorbidity was present in 91% of patients, the most frequent of which were hypertension (74%) and chronic heart disease (53%) (Table 1).

Seventy-four (11%) patients were admitted to the ICU,

51% of whom during the first 48 h of hospital stay. Overall, 30-day mortality was 34%.

No significant differences were observed regarding age, sex, or time from onset of symptoms to COVID-19 diagnosis between patients in the three waves (Table 1). A significantly higher proportion of COPD patients were admitted during the second (17%) and third (14%) waves, than in the first wave (8%). No other significant differences were observed in other comorbidities between groups by wave (Table 1).

On admission, patients in the second and third waves more frequently presented tachypnea than patients in the first wave. Patients in the first wave presented the highest median levels of D-dimer. Overall, the use of drugs widely varied across waves, particularly in the case of hydroxychloroquine, lopinavir-ritonavir, azithromycin, and ceftriaxone (whose usage decreased with time), remdesivir and dexamethasone (increasingly used, Table 1).

ICU admission rates rose significantly, from 8% in the first wave to 16% in the third wave (p=0.009). Forty-eight (7%) patients received mechanical ventilation (5% non-invasive

Table 1. Demographics and clinical characteristics of COVID-19 patients hospitalized during the three waves

Characteristics	Total (n=655) Median (Q1; Q2) or n (%)	1st wave (n=289) Median (Q1; Q2) or n (%)	2nd wave (n=145) Median (Q1; Q2) or n (%)	3rd wave (n=221) Median (Q1; Q2) or n (%)	p
Age (years)	86 (83; 89)	86 (83; 89)	85 (82; 89)	86 (83; 89)	0.468
Sex (male)	327 (50)	134 (46)	73 (50)	120 (54)	0.205
Comorbidity	594 (91)	271 (94)	129 (89)	194 (88)	0.050
Chronic heart disease	348 (53)	155 (54)	76 (52)	117 (53)	0.969
Diabetes mellitus	180 (27)	83 (29)	34 (23)	63 (29)	0.467
Hematological disease	53 (8)	20 (7)	14 (10)	19 (9)	0.581
Chronic kidney disease	179 (27)	79 (27)	37 (26)	63 (29)	0.821
Chronic liver disease	32 (5)	13 (4)	7 (5)	12 (5)	0.889
Hypertension	485 (74)	218 (75)	102 (70)	165 (75)	0.505
Cancer	163 (25)	66 (23)	35 (24)	62 (28)	0.391
Solid organ transplantation	4 (1)	4 (1)	0 (0)	0 (0)	0.078
Chronic lung disease	205 (31)	83 (29)	51 (35)	71 (32)	0.372
Asthma	26 (4)	8 (3)	7 (5)	11 (5)	0.375
Bronchiectasis	38 (6)	10 (3)	11 (8)	17 (8)	0.075
COPD	81 (12)	24 (8)	25 (17)	32 (14)	**0.014**[ab]
Pulmonary hypertension	21 (3)	10 (3)	4 (3)	7 (3)	0.926
Symptoms onset to COVID-19 diagnosis (days)	5 (2; 8)	5 (2; 8)	5 (3; 8)	5 (2; 7)	0.653
Heart rate (beats/min)	89 (80; 101)	89 (80; 102)	89 (81; 101)	89 (80; 100)	0.877
Respiratory rate (breaths/min)	23 (20; 28)	21 (18; 28)	24 (20; 28)	24 (20; 28)	**0.001**[ab]
Oxygen saturation (%)	95 (94; 97)	95 (93; 97)	95.5 (94; 97)	95 (94; 97)	0.349
Diastolic blood pressure (mmHg)	70 (61; 78)	69 (60; 77)	70 (61.5; 80)	70 (62; 78)	0.634

Table 1. Continued

Characteristics	Total (n=655) Median (Q1; Q2) or n (%)	1st wave (n=289) Median (Q1; Q2) or n (%)	2nd wave (n=145) Median (Q1; Q2) or n (%)	3rd wave (n=221) Median (Q1; Q2) or n (%)	p
Systolic blood pressure (mmHg)	127 (114; 144)	127 (114; 145)	128 (117.5; 146)	127 (112; 141)	0.578
Temperature (℃)	37.2 (36.6; 37.8)	37.2 (36.5; 37.8)	37.3 (36.7; 38)	37.1 (36.6; 37.8)	0.611
ALT (U/L)	21 (14; 33)	21 (13.5; 32)	19 (14; 34)	21 (13.5; 34)	0.877
AST (U/L)	34 (25; 51)	34 (23; 52.5)	32.5 (25; 48)	35 (26; 53)	0.386
Creatinine (mg/dL)	1.18 (0.89; 1.65)	1.10 (0.86; 1.62)	1.13 (0.87; 1.58)	1.25 (0.94; 1.83)	0.056
D-dimer (ng/mL)	1200 (700; 2950)	1400 (800; 4000)	1100 (600; 2400)	1200 (700; 2300)	**0.047[c]**
Ferritin (ng/mL)	443.5 (185; 1003)	464 (196; 1088)	436 (167; 871)	402.5 (208; 1086)	0.330
Glucose (mg/dL)	129 (105; 165)	123 (103; 163)	135 (106.5; 158.5)	133 (108; 178)	0.227
C-reactive protein (mg/dL)	9 (4; 16.7)	8.7 (4; 17.3)	8.6 (4.1; 16)	9.1 (3.8; 16.6)	0.718
Procalcitonin (ng/mL)	0.17 (0.08; 0.46)	0.18 (0.08; 0.45)	0.15 (0.09; 0.37)	0.19 (0.09; 0.53)	0.478
LDH (U/L)	309 (240; 402)	309 (237; 422)	318 (245; 391)	300 (235; 395)	0.827
Troponin (ng/L)	28.4 (14.5; 77.3)	26.5 (13.6; 76.5)	28.4 (16.4; 68.5)	34.6 (15.4; 111.4)	0.406
Leucocyte count (×10⁹/L)	7.05 (5.24; 9.91)	7.12 (5.24; 10.03)	6.59 (5.08; 9.50)	7.18 (5.33; 9.71)	0.344
Platelet count (×10⁹/L)	186 (141; 245)	188 (143; 250)	181 (148; 232)	186 (131; 243)	0.313
Lymphocyte count (×10⁹/L)	0.90 (0.60; 1.20)	0.85 (0.60; 1.20)	0.90 (0.70; 1.20)	0.90 (0.60; 1.20)	0.463
Neutrophil-to-lymphocyte ratio	6.2 (3.7; 10.3)	6.3 (3.8; 10.9)	5.3 (3.4; 9.8)	6.4 (4; 9.9)	0.117
Noninvasive mechanical ventilation	33 (5)	8 (3)	9 (6)	16 (7)	0.056
Invasive mechanical ventilation	15 (2)	5 (2)	7 (5)	3 (1)	0.066
LOS (days)	8 (5; 14)	8 (4; 13)	9 (6; 14)	9 (5; 15)	**0.011[ab]**
ICU admission	74 (11)	22 (8)	16 (11)	36 (16)	**0.009[b]**
Hydroxychloroquine	220 (34)	220 (76)	0 (0)	0 (0)	**<0.001[ab]**
Lopinavir/ritonavir	157 (24)	157 (54)	0 (0)	0 (0)	**<0.001[ab]**
Azithromycin	257 (39)	224 (78)	15 (10)	18 (8)	**<0.001[ab]**
Ceftriaxone	349 (53)	170 (59)	74 (51)	105 (48)	**0.033[b]**
Remdesivir	70 (11)	4 (1)	33 (23)	33 (15)	**<0.001[ab]**
Corticosteroids	389 (59)	123 (43)	99 (68)	167 (76)	**<0.001[ab]**
Dexamethasone	223 (34)	5 (2)	76 (52)	142 (64)	**<0.001[ab]**
Methylprednisolone	206 (31)	105 (36)	34 (23)	67 (30)	**<0.001[a]**
Prednisone	112 (17)	49 (17)	23 (16)	40 (18)	0.166
ICU mortality[d]	31 (42)	12 (55)	4 (25)	15 (42)	0.190
Early mortality	99 (15)	64 (22)	12 (8)	23 (10)	**<0.001[ab]**
30-day mortality	223 (34)	111 (38)	43 (30)	69 (31)	0.107

COPD: chronic obstructive pulmonary disease. ICU: intensive care unit. LOS: length of hospital stay. Q1: first quartile. Q3: third quartile. LDH: lactate dehydrogenase. a p<0.05 for comparison between the groups of 1st wave and 2nd wave. b p<0.05 for comparison between the groups of 1st wave and 3rd wave. c p<0.05 for comparison between the groups of 2nd wave and 3rd wave. d 74 patients were used to calculate the percentages (22 patients in the 1st wave, 16 in the 2nd wave, and 36 in the 3rd wave).

and 2% invasive mechanical ventilation), with no differences between waves.

Early mortality was 15% (99), with a significant decrease, from 22% in the first wave to 10% in the third wave (p<0.001). ICU mortality was 42% (31), with no differences between waves. There were 223 (34%) patients who died at 30 days after admission, with no differences between waves. Male sex, respiratory rate ≥25 breaths/min, LDH ≥337.5 U/L and C-reactive protein ≥11.5 mg/dL were significantly associated with ICU admission in the multivariable analysis

Table 2. Significant univariate logistic regression analysis for variables associated with ICU admission and independent predictors of ICU admission determined by multivariable logistic regression analysis[a]

Variable	Univariate[b]			Multivariable (n=279)[cd]			Multivariable (n=279)[ce]		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Period			0.028			0.080			0.076
First wave (Ref.)	1	-	-	1	-	-	1	-	-
Second wave	1.09	0.54–2.22	0.811	0.87	0.37–2.06	0.752	0.93	0.40–2.16	0.874
Third wave	2.12	1.16–3.88	0.015	2.03	0.93–4.44	0.076	2.08	0.98–4.43	0.058
Male sex	3.06	1.73–5.40	<0.001	2.41	1.19–4.88	0.014	2.30	1.16–4.53	0.017
Heart rate (+1 beats/min)[f]	1.01	1.00–1.03	0.052	-	-	-	-	-	-
Respiratory rate (+1 breaths/min)[f]	1.15	1.10–1.21	<0.001	1.13	1.07–1.20	<0.001	-	-	-
Respiratory rate ≥25 breaths/min[g]	5.60	3.17–9.89	<0.001	-	-	-	4.28	2.24–8.18	<0.001
Oxygen saturation (+1%)[f]	0.90	0.83–0.97	0.009	-	-	-	-	-	-
Diastolic blood pressure (+1 mmHg)[fh]	0.96	0.94–0.99	0.001	-	-	-	-	-	-
Systolic blood pressure (+1 mmHg)[f]	0.99	0.98–1.00	0.123	-	-	-	-	-	-
Temperature (+1°C)[f]	1.23	0.92–1.64	0.154	-	-	-	-	-	-
ALT (+1 U/L)[f]	1.01	1.00–1.02	0.059	-	-	-	-	-	-
AST (+1 U/L)[fh]	1.02	1.00–1.03	0.011	-	-	-	-	-	-
Creatinine (+1 mg/dL)[f]	1.15	0.92–1.44	0.208	-	-	-	-	-	-
Glucose (+1 mg/dL)[f]	1.01	1.00–1.01	0.001	-	-	-	-	-	-
LDH (+1 U/L)[f]	1.01	1.00–1.01	<0.001	1.01	1.00 – 1.01	0.001	-	-	-
LDH ≥337.5 U/L[g]	3.92	2.24–6.87	<0.001	-	-	-	2.41	1.22–4.76	0.011
C-reactive protein (+1 mg/dL)[f]	1.08	1.05–1.12	<0.001	1.06	1.01–1.10	0.010	-	-	-
C-reactive protein ≥11.5 mg/dL[g]	3.49	2.03–6.00	<0.001	-	-	-	2.38	1.22–4.67	0.011
Neutrophil-to-lymphocyte ratio (+1)[f]	1.07	1.03–1.12	<0.001	-	-	-	-	-	-

ALT: indicates alanine transaminase. AST: aspartate transaminase. CI: confidence interval. LDH: lactate dehydrogenase. OR: odds ratio. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the ICU admission group. The OR represents the odds that the presence of ICU admission will occur given exposure of the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure; for continuous predictors, the OR represents the increase in odds of the outcome of interest with every one unit increase in the input variable. The p-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). aPatients who were not admitted to ICU and with a DNR were excluded. bThe variables analyzed in the univariate analysis were sex, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, hypertension, COPD, heart rate, respiratory rate, oxygen saturation, diastolic blood pressure, systolic blood pressure, temperature, ALT, AST, creatinine, glucose, LDH, C-reactive protein, leucocytes, neutrophil-to-lymphocyte ratio, and platelets. cAdjusted for period of admission. dHosmer–Lemeshow goodness-of-fit test, p=0.684. Area under the ROC curve, AUC=0.82 (95% CI: 0.76–0.88). e Hosmer–Lemeshow goodness-of-fit test, p=0.086. Area under the ROC curve, AUC=0.80 (95% CI: 0.73–0.87). f '+1' indicates an increase by one unit. gCut-off obtained from ROC curve. hVariable excluded of multivariable analysis because of collinearity with another significant variable.

(Table 2). The AUC was 0.80 (95% CI: 0.73–0.87) for the predictive model.

DISCUSSION

In accordance with data from other regions[4,5], where elderly patients were reported to be the population most affected by COVID-19, the burden of COVID-19 in very elderly patients remained high throughout the three first waves in Spain. The proportion of patients with COPD increased between the first and third waves. Despite the reported overall relatively low incidence of COVID-19 in COPD patients (1.1–10%)[6,7], COPD patients have an increased risk of severe disease and poor outcomes[8]. Thus, the increase in COPD across waves may be explained because this population may have taken isolation measures more seriously and, consequently, reduced their rates of infection, provided that it was made clear from the early stages of the pandemic that SARS-CoV-2 severely affected the lungs. Also, the use of inhaled corticosteroids may

offer a protective effect in these patients, as recently reported[9].

In our study, 91% of our patients presented at least one comorbidity, 15% of the patients died in the first 5 days after admission, and ICU mortality was 42%, which shows the disproportionate impact of COVID-19 on these patients; this increased impact has also been widely reported for the elderly population though not specifically in very elderly patients[10]. Early recognition of severe COVID-19 in very elderly patients may allow prompt complication management, thus improving outcomes or optimizing comfort in patients who are not candidates for aggressive therapeutic measures. During the pandemic peaks, we observed a significant increase in the use of remdesivir and corticosteroids, whereas hydroxycloroquine, lopinavir/ ritonavir, and azythromycin were progressively abandoned, which is in line with the results of the main platform clinical trials on COVID-19 (i.e. WHO Solidarity trial[11], RECOVERY[12], REMAP-CAP[13]). Overall, 11% of very elderly patients were admitted to the ICU, with rates increasing between the first and third waves (8–16%), which are likely related to the availability of ICU beds. During the first wave, the Spanish health system, including ICUs, was largely overwhelmed and prioritization criteria that included advanced age or reduced functionality in nursery homes residents were implemented in many hospitals[1]. We found that male sex, respiratory rate, and C-reactive protein were associated to a higher likelihood of ICU admission, which has already been reported[5,6,10,14]. Meanwhile, 30-day mortality rates, although remarkably lower overall (34%) compared to other series worldwide (46–54%)[2,14,15], are strikingly high figures that highlight the vulnerability of very elderly patients to COVID-19 and therefore the relevance of preventive measures.

Strengths and limitations

The strengths of this study include the large sample size, the special focus on very elderly patients, and the information on three consecutive COVID-19 wave peaks. The study does, however, have some limitations that need to be addressed. The data were collected from a single academic teaching hospital in Spain; it may not be possible to extrapolate results to patients admitted to different hospitals or in other countries. Second, data on quality of life, frailty, and/or functional status were not recorded, which may have led to an underestimation of their potential predictive value.

CONCLUSIONS

We observed an increase in the percentage of very elderly patients admitted to the ICU during the three first pandemic peaks. ICU admission more likely occurs in very elderly male patients with higher respiratory rate, with elevated LDH and C-reactive protein. Overall, our 30-day mortality rate was lower compared to other series globally.

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ETHICAL APPROVAL AND INFORMED CONSENT

The study was approved by the local Institutional Review Board (HCB/2020/0273). The need for written informed consent was waived due to the non-interventional design of the study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

CC, FM, GD and AS conceived the study. CC, FM, GD and JG executed the search and extracted data. FM, GD and AG performed the analysis of data, with inputs from CC, MC, PP, NC, VR, AT, CG and AS. All authors contributed to the interpretation of data. CC, FM, GD and AS wrote the initial draft of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version. AS and CC are guarantors for the study.

PROVENANCE AND PEER REVIEW

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