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Short communication

Clinical characteristics and outcome of hospitalized elderly patients with COVID- 19 after vaccine failure

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ABSTRACT

We described clinical characteristics and outcome of 160 patients over 65 years (01 September to 31 August 2021) who had a first positive SARS-CoV-2 PCR- test more than 14 days after full vaccination and were hospitalized with COVID-19. Median age of included patients was 84 years, 61.2% were over 80 years; 50.6% were male and most (82.5%) has at least one comorbidity. Up to 84% received specific treatment against COVID-19, including 76.9% low-flow oxygen therapy. We found that overall mortality was 25.6% and 30.6% in those older than 80 years. A higher mortality was significantly associated with older age and treatment with tocilizumab. Our data showed that although COVID-19 vaccines continue protecting elderly patients against hospitalization and death and might improve the prognosis after hospitalization in patients with breakthrough infections, mortality in this population -especially in those older than 80 years- remains very high.

1. Introduction

There are incomplete data about COVID-19 vaccines efficacy in the elderly, especially in those above 80 years [1–4]. Phase III clinical trials included a limited number of participants over 65 and even fewer over 75, a population in which COVID-19 has been found to have the higher mortality rates [5]. For instance, only 4.4% of patients included in the phase III trial of the BNT162b2 vaccine were older than 75 years [1]; in the mRNA-1273 efficacy clinical trial, although 24.8% of participants were older than 65 years, only 4.6% of them were over 75 [4]. Outside of clinical trials, recent studies have reported significantly lower vaccine effectiveness against COVID-19 hospitalizations among adults aged at least 75 (76%) compared to those aged 18–74 years (89%) [6], also among adults aged at least 65 years (80%) compared to those aged 18–64 years (95%) [7].

Although elderly patients are overrepresented among vaccine failures requiring hospitalization, there is a lack of data about their clinical course and prognosis. It could be possible that having been fully vaccinated improves the outcomes of COVID-19 in elderly patients requiring hospitalization. However, to the best of our knowledge there are no specific studies about the clinical course of hospitalized elderly patients with COVID-19 after vaccine failure. In one report from Israel of 152 fully vaccinated hospitalized COVID-19 patients mean age (±SD) was 71 (14.3) years, but the study was not focused only on elderly patients [8].

Here we describe the clinical course of what is, so far, the largest series of elderly patients hospitalized with COVID-19 despite having received full vaccination.

2. Patients and methods

This retrospective observational study was carried out between 01/06/21 and 31/08/21 in La Paz University Hospital, a 1,270-bed hospital with a catchment area of more than 500,000 individuals in Madrid, Spain. Our hospital had attended 6,811 hospitalized patients with COVID-19, one of the largest single-center cohorts in Europe, since February 2020.

In accordance with case definitions established by the Centers for Disease Control and Prevention, SARS-CoV-2 infections were classified as breakthrough infections if the date of the first positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) was more than 14 days after completion of full vaccination

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[9] (Pfizer/BioNTech's BNT162b2, Moderna's mRNA-1273, Oxford/Astra-Zeneca's ChAdOx1nCoV-19 or Janssen's JNJ-78436735) according to each vaccine label.

We included all patients older than 65 year who were admitted to the hospital during the study period who met the CDC definition for SARS-CoV-2 breakthrough infection and had a definitive outcome of their hospitalization: discharged from the hospital as convalescent or died.

We retrieved from clinical records epidemiological and clinical data including comorbidities, symptoms and laboratory data at admission, treatments, highest level of oxygen delivered, and lung involvement based on computed tomography (CT) imaging or chest X-ray. For each patient whose final outcome was death, the medical records were reviewed to identify the most likely cause of death.

Patients were diagnosed and treated according to the most recent national recommendations for the management of COVID-19 [10]. Diagnosis of SARS-CoV-2 infection was performed by RT-PCR or antigenic testing. Viral genomic sequencing was performed to identify relevant variants on available samples, with results categorized according to the WHO classification [11].

The study was approved by the Research Ethics Committee of La Paz University Hospital (PI-4072) and by the Spanish Agency of Medicines and Medical Devices (HUL-AIN-2020–01). Due to the anonymized retrospective design, informed consent was not required.

A descriptive-univariate analysis of all variables was carried out. These are presented in absolute and relative frequencies in the case of qualitative variables, and in median and Interquartile Range (IQR) in the case of quantitative variables.

For comparisons of independent samples, Pearson's Chi-Square test was used (or Fisher's exact test for 2X2 tables or likelihood ratio in mXn tables, if necessary) if it was qualitative variables, and Mann's *U* test -Whitney and the Kruskal-Wallis test in the case of quantitative variables. For the multivariate analysis, a multivariate logistic regression was fitted to assess the predictors of hospital death. All variables with a significance level<0.1 were included in the final analysis. For the choice of the optimal model, the BIC criterion was used. The calculations were carried out with the statistical program R (version 4.0.1).

3. Results

3.1. Demographic characteristic

We included a total of 160 patients representing 40.3 % of all COVID-19 patients who were hospitalized during the study period (n = 397). Median age was 84 years (IQR 74.5– 89.5 years), 98 of them (61.2%) were over 80 years old and 40 (25%) older than 90 years; 81 were male (50.6%); most (132; 83.7%) had at least one comorbidity, mainly hypertension (67.5%). Obesity was found to be more prevalent in younger patients (p = 0.047). Patients older than 80 years had more comorbidities than those under 80 years (p = 0.007). BNT162b2 vaccine was the most administered vaccine (138; 86.3%) in general, but significatively more in those at least 80 years old (p greater than 0.001).

Demographic characteristics are summarized in Table 1.

3.2. Clinical characteristics and outcome

Out of the 160 patients, 132 (82.5%) presented symptoms characteristic of COVID-19, including dyspnoea (67; 41.9%) or fever (46; 28.8%). Almost two thirds of patients (97, 61.4%) had a conventional chest radiography and/or CT lung tomography typical of COVID-19 (bilateral reticular pattern, ground-glass opacities or consolidations).

Most patients (122; 76.3%) were diagnosed with SARS-CoV-2 acute infection by nasopharyngeal RT-PCR and in those with this information available (n = 101), almost all were infected with the delta variant (97%). Lower neutrophil count (p = 0.045) and higher D-dimer (p = 0.021) were more frequent in patients older than 80 years.

Most patients (135; 84.4%) received specific treatment against COVID-19, mainly dexamethasone as immunomodulator. The majority (123; 76.9%) were treated with oxygen through low-flow oxygen delivery systems. Only 2 patients, both under 80 years, received ventilatory support in ICU.

Median time elapsed between admission and discharge or death was 11 days (IQR 7–16), with no differences between those younger or older than 80 years. Overall mortality was 25.6% (95% CI 18.7%–32.4%) and 30.6% (95% CI 21.3%-39.9%) in those above

Table 1
Demographics, comorbidities and vaccine administered to elderly hospitalized patients with COVID-19 after complete vaccination (n = 160).

Variable	Total n = 160	<80 years n = 62	≥ 80 years n = 98	*p*-value
Demographics				
Age				
Mean, IQR (years)	84 (74.5–89.5)	73 (38–78)	85 (84–92)	
Gender n (%)				0.493
Male	81(50.6%)	34 (54.8%)	47 (48%)	
Female	79 (49.4%)	28 (45.2%)	51(52%)	
Chronic comorbidities[1] n (%)				1.00
NO	28 (17.5%)	11 (17.7%)	17(17.4%)	
YES:	132 (83.7%)	51 (82.3%)	82 (82.6%)	
Hypertension	108 (67.5%)	40 (64.5%)	68 (69.4%)	0.640
Type-2 Diabetes	60 (37.5)	29 (46.8%)	31 (31.6%)	0.078
Obesity	28 (17.5%)	16 (25.8%)	12 (12.2%)	**0.047**
Other	72(45%)	33 (53.2%)	39(40 %)	0.133
Vaccine administered n *(%)*				**<0.001**
BNT162b2	138 (86.3%)	43 (69.4%)	95(97%)	
JNJ-78436735	9 (5.6%)	8 (12.9%)	1 (1%)	
ChAdOx1n	8 (5%)	8 (12.9%)	0	
mRNA-1273	3 (1.9%)	2 (3.2%)	1 (1%)	
Other[2]	2 (1.4%)	1 (1.6%)	1 (1%)	

[1] Some patients have more than one comorbidity.
[2] Other vaccines administered: inactivated CoronaVac (Sinovac Life Sciences) and BBIBP-CorV (Sinopharm).

Table 2
Clinical characteristics and outcome of elderly hospitalized patients with COVID-19 after complete vaccination (n = 160).

Variable	Total n = 160	<80 years n = 62	≥ 80 years n = 98	*p*-value
Symptoms at admission[1] n (%)				0.258
COVID19- related	**132 (82.5%)**	**48 (77.4%)**	**84 (87.7%)**	
Dyspnoea	67 (41.9%)	27 (43.6%)	40 (40.8%)	0.809
Fever	46 (28.6%)	19 (30.7%)	27 (27.6%)	0.672
Cough	36 (22.5%)	10 (16.1%)	26 (26.5%)	0.180
Others[2]	29 (18.1%)	10(16.1%)	19 (19.4%)	0.602
Symptoms not related to COVID[3]				
Radiological findings[4] *(158 with data available)* n (%)				0.328
COVID19- related		38 (62.3%)	59 (60.8%)	
Non COVID-19 related	97 (61.4%)	11(18%)	11 (11.3%)	
Without abnormal findings	22(13.9%)	12 (19.7%)	27 (27.8%)	
First positive test n (%)				0.640
RT PCR	122 (76.3%)	49 (79%)	73 (74.5%)	
Antigen test	38 (23.8%)	13 (21%)	25 (25.5%)	
Variants (*101 with data available*) n (%)				0.085
Delta variant	98 (97%)	32 (31.7%)	66 (65.3%)	
Beta variant	3 (3%)	2 (2%)	1 (1%)	
First positive test n (%)				0.640
RT PCR	122 (76.3%)	49 (79%)	73 (74.5%)	
Antigen test	38 (23.8%)	13 (21%)	25 (25.5%)	
Variants (*101 with data available*) n (%)				0.085
Delta variant	98 (97%)	32 (31.7%)	66 (65.3%)	0.640
Beta variant	3 (3%)	2 (2%)	1 (1%)	
Not available				
Laboratory findings at admission (median, IQR)				
Lymphocyte count (x10^9/L)	920 (640–1420)	920 (720–1490)	930 (550–1355)	0.476
Neutrophil count (x10^9/L)	4625(3310–7240)	5575 (3690–7790)	4380(3010–6610)	0.045
Fibrinogen (mg/dL) *(156 with data available)*	594 (453–793)	681(435–840)	580 (472–776)	0.358
Ferritin (ng/mL) *(142 with data available)*	277 (142–608)	345 (138.5–761)	269.5 (148–540)	0.590
D-dimer (ng/mL) *(141 with data available)*	840 (500–1580)	640 (450–1400)	915 (550–2040)	0.021
C- reactive protein (mg/L) *(157 with data available)*	42.1 (15.7–92	55.5 (23.6–114.7)	37.5 (12.8–86.9)	0.290
Treatment n (%)				
Dexamethasone	135 (84.4%)	52 (83.9%)	83 (84.7%)	0.889
Remdesivir	17 (10.6%)	10 (16.1%)	7 (7.1%)	0.125
Tocilizumab	18 (11.3%)	11 (17.7%)	7 (7.1%)	0.070
Highest oxygen supplement administered n (%)				0.437
None	20 (12.5%)	7 (11.3%)	13 (13.3%)	
Low-flow Oxygen delivery Systems[5]	123 (76.9%)	46 (74.2%)	77 (78.6%)	
High-flow Oxygen delivery Systems[6]	17 (10.6%)	9 (14.5%)	8 (8.2%)	
Outcome n (%)				**0.103**
Discharged	119 (74.4%)	51 (82.3%)	68 (63.4%)	
Death	41 (25.6%)	11(17.7%)	30 (30.6%)	

[1] some patients have more than one symptom.
[2] included: headache, asthenia, myalgias, throat pain, anosmia and vomits.
[3] included: head trauma (3), decreased oral intake (3), tract urinary infection (2) and epistaxis, vomits, metastatic pleural effusion, anaemia, psychiatric disorder and neurological disorder (one each).
[4] some patients have more than one radiological finding.
[5] included: simple face masks, non-re-breath face mask and nasal prongs.
[6] included: high flow nasal prong, CPAP/BiPaP drivers, orotracheal intubation.

80 years of age. Of the 41 deceased patients, in only 3 cases the cause of death could not be directly attributed to COVID-19 (intestinal perforation in a patient with gastrointestinal tract cancer, fracture of multiple vertebrae with neurological compromise and sepsis of urinary tract origin).

Data on clinical characteristics and outcome are summarized in Table 2.

In the univariant analysis lower mortality was associated to a higher lymphocyte count (p = 0.049), lower C-reactive protein (p = 0.003) and lower ferritin levels (p = 0.026). Those who finally died, received more frequently high-flow oxygen, compared to those discharged alive (p = 0.014) (Table 3).

The multivariate model showed that age over 80 years and treatment with Tocilizumab were associated to higher probability of death (Table 3): for every year increase in age, the probability of dying was 4 times higher and patients who have received Tocilizumab were 5 times more likely to die.

4. Discussion

Here we report what it is to the best of our knowledge the largest series of patients over 65 years old hospitalized with COVID-19 after a vaccine breakthrough infection. The mortality of these hospitalized elderly patients remained high (25.6%) but might be lower than the mortality of unvaccinated hospitalized elderly patients. Almost all of our patients had multiple comorbidities and a considerable proportion presented without typical symptoms or signs of COVID-19.

In the present study, mortality in patients older than 80 years was half (30.6%) than the mortality registered during the first wave (25 February to 19 April 2020) of the COVID-19 pandemic in our hospital which exceeded 60% in unvaccinated patients in the same age strata [12]. Although it is tempting to attribute this reduction in mortality to the enduring protective effects of vaccines, other factors such a lower hospital burden, early use of oxygen, less

Table 3
Factors associated to mortality in elderly hospitalized patients with COVID-19 after complete vaccination (n = 160).

Variable	Live discharges (n = 119)	Deaths (n = 41)	*p*-value	OR (95 %CI)
Univariate analysis				
Age (median, IQR)	82.00 (73.00, 88.50)	84.00 (80.00, 91.00)	0.087	
Gender, n (%)				
Male	60 (50.4%)	21 (51.2%)	1.000	
Female	59 (49.6%)	20 (48.8%)		
Chronic comorbidities[1], n (%)			0.784	
NO	22 (18.5%)	6 (14.6%)		
YES	97 (81.5%)	35 (85.4%)		
Hypertension	81 (68.1%)	27 (65.9%)	0.946	
Type-2 Diabetes	47 (39.5%)	13 (31.7%)	0.483	
Obesity	22 (18.5%)	6 (14.6%)	0.748	
Other	53 (44.5%)	19 (46.3%)	0.985	
Vaccine administered, n (%)				
BNT162b2	100 (84%)	38 (92.7%)	0.261	
Others[2]	19 (16%)	3 (7.3%)		
Symptoms at admission[3], n (%)			0.268	
COVID19-related	101 (84.9%)	31 (75.6%)		
Fever	37 (31.1%)	9 (22%)	0.360	
Cough	28 (23.5%)	8 (19.5%)	0.753	
Symptoms not related to COVID	18 (15.1%)	10 (24.4%)	0.268	
Laboratory findings at admission (median, IQR)				
Lymphocyte count (x109/L)	960 (700–1535)	830 (500–1220)	**0.049**	
Neutrophil count (x109/L)	4470 (3440–7240)	5670 (3090–6840)	0.598	
Fibrinogen (mg/dL)	594 (459.3783.5)	599.5 (442.5–823.5)	0.703	
Ferritin (ng/mL)	271 (108.5–502)	351.5 (228.3–696.8)	**0.026**	
D-dimer (ng/mL)	850 (500–1625)	830 (510–1405)	0.619	
C- reactive protein (mg/L)		66.85 (32.2–137.1)	**0.003**	
Treatment regimens, n (%)				
Remdesivir	15 (12.6%)	2 (4.9%)	0.277	
Tocilizumab	9 (7.6%)	9 (22%)	0.026	
Highest oxygen supplement administered, n (%)			**0.014**	
None	19 (16%)	1 (2.4%)		
Low-flow Oxygen delivery System[4]	91 (76.5%)	32 (78%)		
High-flow Oxygen delivery Systems[5]	9 (7.6%)	8 (19.5%)		
Multivariate Analysis				
	β	**SE(β)**	***p*-value**	OR(CI95%)
Age ≥ 80 years	1.43	0.55	**0.01**	4.18 (1.51–13.58)
Lymphocyte count (x109/L)	0.00	0.00	0.89	–
Ferritin (ng/mL)	0.00	0.00	0.13	–
C- reactive protein (mg/L)	0.01	0.00	0.10	1.01 (1.00–1.02)
Low-flow Oxygen delivery System[4]	1.56	1.09	0.15	–
High-flow Oxygen delivery Systems[5]	1.47	0.78	0.28	–
Tocilizumab	1.61	0.78	**0.04**	5 (1.10–25.02)

[1] Some patients have more than one comorbidity.
[2] Other vaccines administered: JNJ-78436735, ChAdOx1n, mRNA-1273**,** inactivated CoronaVac (Sinovac Life Sciences) and BBIBP-CorV (Sinopharm).
[3] Some patients have more than one symptom.
[4] Included: simple face masks, non-re-breath face mask and nasal prongs.
[5] Included: high flow nasal prong, CPAP/BiPaP drivers, orotracheal intubation.

aggressive measures, different variants a better general supportive care, the use of steroids and other therapeutics that improve survival such as dexamethasone might also have contributed to the reduced mortality observed in the present series. However, it is interesting that we are seen this possible decrease in mortality in a series of patients who were almost exclusively infected with the delta variant. In unvaccinated patients, recent data have shown higher hospital admission or emergency care attendance risk for patients with COVID-19 infected with the delta variant compared with the alpha variant [13]. A Brazilian study exploring the impact of vaccination against COVID-19 on deaths among elderly people infected mostly with gamma or P.1 variant, showed a mortality rate lower than that observed in our series (12.5% vs. 25.6%) [14]. Therefore, the delta variant predominant in our series might be in part responsible of our higher mortality compared to the Brazilian study (but still lower than in unvaccinated persons during the first wave).

In our study the proportion of patients with co-morbidities was very high (83.7%) compared with large case series on unvaccinated hospitalized elderly patients with COVID-19 (65–70%, depending on the studies) [15,16]. This difference could be explained by our high percentage of patients with advanced age.

We found that 17.5% of our patients presented without specific symptoms or signs of COVID-19. Other studies have reported that elderly patients are more likely to present atypical symptoms, such as decreased oral intake, anorexia and fallings [15], so it is necessary to be alert to atypical symptoms that happens to an elderly person, as it could forewarn the presence of a SARS-CoV-2 infection.

We found a very low percentage of patients receiving enhanced respiratory support in line with other series [15] thus reflecting the therapeutic restrictions that applies to elderly patients. According to Spanish consensus of expertś guidelines, patients older than 80 years of age with comorbidity may preferably receive non-invasive respiratory therapies [17].

In our study, risk factors associated to death in old patients indicated that those receiving tocilizumab had 5 times more probability of dying. This might probably be explained because tocilizumab is more likely to be administered to more severely ill patients who are, therefore, more likely also to die. For each year increase in age,

the probability of dying was 4 times higher, in line with other series of unvaccinated hospitalized patients [18,19].

Our study has some limitations: this is a single site study, and the findings may not be generalizable to other populations. In addition, this case series has no control group, although a control group of unvaccinated hospitalized elderly patients is not available because the rate of full vaccination in Spain in the population above 65 years old approaches 100% [20]. We did not have results of serology of other biomarkers of immune response to vaccinees. Finally, we did not conduct a follow-up of the patients after discharge. Large sample size and longer follow-up studies would help to better characterize clinical characteristics and outcome of hospitalized elderly patients with COVID-19 after vaccine failure. Nevertheless, our study helps to inform the current debate about the need of improved strategies of vaccination in the elderly -such as booster doses- by showing that vaccine failures in the elderly can still lead to substantial mortality if patients are admitted to the hospital.

In conclusion although COVID-19 vaccines continue protecting elderly patients against hospitalization and death and might improve the prognosis after hospitalization in patients with breakthrough infections, mortality in this population - especially in those older than 80 years- remains very high. Improved strategies for preventing breakthrough infections in the elderly are clearly needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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