Hospitalized patients with breakthrough COVID-19: Clinical features and poor outcome predictors

Oscar Moreno-Perez [1,2,*], Isabel Ribes [3,*], Vicente Boix [2,4], María Ángeles Martinez-García [5], Silvia Otero-Rodriguez [4], Sergio Reus [2,4], Rosario Sánchez-Martínez [3], Jose Manuel Ramos [2,6], Pablo Chico-Sánchez [7], Esperanza Merino [8,**], On behalf the COVID-19 ALC research group

[1] Endocrinology and Nutrition Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain
[2] Clinical Medicine Department, Miguel Hernández University of Elche, Spain
[3] Internal Medicine Department, Alicante General University Hospital - Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain
[4] Unit of Infectious Diseases, Alicante General University Hospital - Alicante Institute of Health and Biomedical Research (ISABIAL), Alicante, Spain
[5] Pneumology Department, Alicante General University Hospital - Alicante Institute of Health and Biomedical Research (ISABIAL), Alicante, Spain
[6] Internal Medicine Department, Alicante General University Hospital - Alicante Institute of Health and Biomedical Research (ISABIAL), Alicante, Spain
[7] Preventive department, Alicante General University Hospital - Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain
[8] Unit of Infectious Diseases, Alicante General University Hospital - Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain

A B S T R A C T

Objectives: To describe breakthrough COVID-19 infection in patients who needed hospitalization and the factors associated with poor outcomes.
Methods: We conducted a retrospective study on patients hospitalized with COVID-19 between December 27, 2020, and October 17, 2021, with either a complete vaccination (CV) scheme (diagnosed 2 weeks after the second dose of the Pfizer/Moderna/AstraZeneca or first dose of the Janssen vaccine was administered) or a partial vaccination (PV) scheme. The main outcomes were all-cause mortality and the need for invasive mechanical ventilation (IMV). The baseline factors associated with the outcomes were analyzed by multiple logistic regression to estimate the odds ratios (odds ratio [OR]; 95% confidence interval [CI]).
Results: A total of 145 (101 CV) patients were included. The CV subgroup was mainly composed of older males with high comorbidity (Charlson Index ≥ 3, 72%; immunosuppression, 20%) and with bilateral pneumonia in 63.4%. Limited therapeutic effort (LTE) was agreed upon for 28% of the patients. In the CV subgroup, endotracheal intubation was required in 10.9% of patients, reaching 15.3% when excluding LTE patients; the global mortality was 22.8%, reaching 41.4% in the subgroup with LTE. Although the patients with PV were younger and had fewer comorbidities, the main outcomes did not differ significantly between the CV and PV groups. The predictors of poor outcomes were age ≥ 65 years, confusion, ferritin > 500 mg/L, extensive lung infiltrates, and a Charlson Index ≥ 3.
Conclusions: Patients with CV hospitalized because of breakthrough COVID-19 infection tend to be older persons, with comorbidities, and have a high mortality.

** Corresponding author: Hospital General Universitario de Alicante -ISABIAL. C/ Maestro Alonso s/n. CP 03010, Alicante, Spain. Tel: 0034 699438674
E-mail addresses: omorenoperez@hotmail.es (O. Moreno-Perez), isa.rimen@gmail.com (I. Ribes), boix_vic@gva.es (V. Boix), mangelesmartinezg92@gmail.com (M.Á. Martinez-García), o.silvia.r@gmail.com (S. Otero-Rodriguez), reus_ser@gva.es (S. Reus), sanchez_rosmar@gva.es (R. Sánchez-Martínez), jose.ramosr@umh.es (J.M. Ramos), chico_pab@gva.es (P. Chico-Sánchez), merino_luc@gva.es (E. Merino).
* These authors contributed to the manuscript equally and share the first authorship.

Introduction

Vaccine breakthrough SARS-CoV-2 infection, that is, COVID-19 appearing in fully vaccinated patients, is an emerging challenge (Bahl et al., 2021). The severity of the disease in vaccinated patients has not often been described, and data are scarce regarding the groups most at risk and the prognosis and outcomes for patients who are hospitalized. (CDCMMWR, 2021; Tenforde et al., 2021).

Table 1
Demographic characteristics, comorbidities, clinical presentation, and clinical outcomes by vaccination status.

Characteristics of patients	Total [n = 145]	Complete vaccination [n = 101]	Partial vaccination [n = 44]	P*
Demographics				
Age (years), median (IQR)	69 (53-81)	72 (56-81)	60 (44-75)	**.003**
Age > 65, %	80/145 (55.2)	65/101 (64.4)	15/44 (34.1)	**.001**
Males, %	89/145 (61.4)	62/101 (61.4)	27/44 (61.4)	1.00
Nosocomial, %	10/145 (6.9)	10/101 (9.9)	0/44 (0.0)	**.031**
Long-term care resident, %	11/145 (7.6)	2/101 (2.0)	9/44 (20.5)	**<0.001**
Health professional, %	1/145 (0.7)	-	1/44 (2.3)	.300
Comorbidities				
Diabetes, %	40/145 (27.6)	30/101 (29.7)	10/44 (22.7)	.39
Hypertension, %	81/145 (55.9)	64/101 (63.4)	17/44 (38.6)	**.006**
Chronic respiratory disease	37/145 (25.5)	29/101 (28.7)	8/44 (18.2)	.18
Smoker (current or former), %	43/139 (30.9)	34/96 (35.4)	9/43 (20.9)	.088
Immunosuppression, %	22/145 (15.9)	20/101 (19.8)	2/44 (4.5)	**.019**
Charlson comorbidity index, median (IQR)	4 (1-6)	5 (2-6)	2 (0-5)	**<0.001**
Charlson comorbidity index ≥3, %	91/144 (63.2)	72/100 (72.0)	19/44 (43.2)	**.001**
Obesity (BMI ≥30), %	48/113 (42.5)	29/77 (37.7)	19/36 (52.8)	.13
Initial assessment				
Oximetry at room air (%), median (IQR)	94 (92-96)	94 (92-96)	94 (92-96)	0.84
Oximetry at room air < 94%, median (IQR)	54/130 (41.5)	40/88 (45.5)	14/42 (33.3)	.19
Respiratory rate (breaths/min), median (IQR)	16 (16-16)	16 (16-16)	16 (16-24)	.057
Lymphocytes (per mm^3), median (IQR)	1050 (690-1360)	1070 (760-1420)	900 (680-1250)	.19
Lymphopenia (<1000/mm^3), %	68/145 (46.9)	42/101 (41.6)	26/44 (59.1)	.052
C-reactive protein > 10 mg/dl, %	47/145 (32.4)	31/101 (30.7)	16/44 (36.4)	.50
Procalcitonin > 0.5 ng/mL, %	9/134 (6.7)	6/91 (6.6)	3/43 (7.0)	.93
Ferritin > 500 mg/L, %	73/136 (53.7)	46/95 (48.4)	27/41 (65.9)	.061
Lactate dehydrogenase > 250 U/L, %	66/125 (52.8)	38/83 (45.8)	28/42 (66.7)	**.027**
D-dimers > 1 mg/mL, %	43/120 (35.8)	33/81 (40.7)	10/39 (25.6)	.11
Troponine T > 14 ng/L	47/124 (37.9)	37/86 (43.0)	10/38 (26.3)	.077
Brain natriuretic peptide > 125 pg/ml, %	67/125 (53.6)	55/87 (63.2)	12/38 (31.6)	**.001**
eGFR < 60 ml/min/m^2, %	46/145 (31.7)	36/101 (35.6)	10/44 (22.7)	.12
IL6 > 10 pg/ml, %	86/111 (77.5)	63/81 (77.8)	23/30 (76.7)	.90
Clinical presentation				
Clinical duration (days)[b], median (IQR)	7 (3-8)	6 (3-8)	8 (4-9)	.17
Fever, %	96/145 (66.2)	63/101 (62.4)	33/44 (75.0)	.14
Cough, %	104/145 (71.7)	73/101 (72.3)	31/44 (70.5)	.82
Dyspnea, %	75/145 (51.7)	49/101 (48.5)	26/44 (59.1)	.24
Anosmia-dysgeusia, %	24/145 (16.6)	18/101 (17.8)	6/44 (13.6)	.53
Myalgias-arthralgias, %	24/145 (16.6)	12/101 (11.9)	12/44 (27.3)	**.022**
Fatigue, %	38/145 (26.2)	31/101 (30.7)	7/44 (15.9)	.063
Diarrhea, %	31/145 (21.4)	18/101 (17.8)	13/44 (29.5)	.11
Confusion, %	28/145 (19.3)	19/101 (18.8)	9/44 (20.5)	.82
Radiological characteristics				.78
Bilateral pneumonia, %	91/144 (63.2)	64/101 (63.4)	27/43 (62.8)	
Unilateral pneumonia, %	17/144 (11.8)	13/101 (12.9)	4/43 (9.3)	
Opacities >50% of lung surface on X-Rays,%	23/145 (15.8)	15/101 (14.9)	8/44 (18.2)	.47
Vaccine manufacturer				**.013**
Pfizer, %	90/145 (62.5)	67/101 (66.3)	23/44 (52.3)	
Moderna, %	11/145 (7.6)	7/101 (6.9)	4/44 (9.1)	
Janssen, %	31/145 (21.4)	23/101 (22.8)	8/44 (18.2)	
Astra-Zeneca, %	13/145 (9.0)	4/101 (4.0)	9/44 (20.5)	
Treatment				
Remdesivir, %	44/145 (30.3)	34/101 (33.7)	10/44 (22.7)	.19
Dexametasone, %	105/145 (72.4)	68/101 (67.3)	37/44 (84.1)	**.038**
Another corticosteroid, %	20/141 (14.2)	12/98 (12.2)	8/43 (18.6)	.32
Tocilizumab, %	46/144 (31.9)	28/100 (28.0)	18/44 (40.9)	.13
Hiperimmune plasma, %	2/145 (1.4)	2/101 (2.0)	-	1.
Antibiotics, %	94/145 (64.8)	68/101 (67.3)	26/44 (59.1)	.34
Clinical outcomes				
Length hospital stay (days), median (IQR)	7 (4-12)	7 (4-12)	7 (4-12)	.68
COVID-19 main cause of admission, %	133/145 (91.7)	90/101 (89.1)	43/44 (97.7)	.083
Noninvasive respiratory support, %	35/145 (24.1)	27/101 (26.7)	8/44 (18.2)	.27
Type of noninvasive respiratory support, %				.83
HFNC, %	23/35 (65.7)	18/27 (66.7)	5/8 (62.5)	
NIMV, %	12/35 (34.3)	9/27 (33.3)	3/8 (37.5)	
ICU admission, %	18/145 (12.4)	13/101 (12.9)	5/44 (11.4)	.80
Length ICU stay (days), median (IQR)	12 (6-33)	16 (8-37)	6 (3-10)	**.011**
Invasive mechanical ventilation, %				
Global, %	14/145 (9.7)	11/101 (10.9)	3/44 (6.8)	.45
Group with LTE, %	0/41 (0.0)	0/29 (0.0)	0/12 (0.0)	-
Group with maximum care, %	14/104 (13.5)	11/72 (15.3)	3/32 (9.4)	.42
Days of IMV, median (IQR)	11 (7-34)	16 (7-38)	5 (0-)	**.014**
Readmitted, %	5/117 (4.3)	4/80 (5.0)	1/37 (2.7)	1.
Limited therapeutic effort, %	41/145 (28.3)	29/101 (28.7)	12/44 (27.3)	.86

Table 1 (*continued*)

Characteristics of patients	Total [n = 145]	Complete vaccination [n = 101]	Partial vaccination [n = 44]	P*
Deaths, %				
Global, %	30/145 (20.7)	23/101 (22.8)	7/44 (15.9)	.35
Group with LTE, %	17/41 (41.5)	12/29 (41.4)	5/12 (41.7)	.99
Group with maximum care, %	13/104 (12.5)	11/72 (15.3)	2/32 (6.3)	.20
Endotracheal intubation, %	9/14 (64.3)	7/11 (63.6)	2/3 (66.7)	.92
Cause of death				.16
COVID, %	19/30 (63.3)	13/23 (56.5)	6/7 (85.7)	
Other causes				
Bacterial infection, %	6/30 (20.0)	5/22 (21.7)	1/7 (14.3)	
CV event, %	1/30 (3.3)	1/22 (4.3)	0/7	
Other, %	4/30 (13.3)	4/22 (17.4)	0/7	

BMI: body mass index; BP: blood pressure; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate (by CKD-EPI formula); HFNC: high-flow nasal cannula; ICU: intensive care unit; IL6: interleukin-6; IMV: invasive mechanical ventilation; IQR: interquartile rate; LTE: limited therapeutic effort; NIMV: noninvasive mechanical ventilation.

[a] 10-years expected survival derived from Charlson comorbidity index score.

[b] Days of symptoms before admission.The laboratory variables have been dichotomized, according to clinically relevant cut-off points or, failing that, according to the upper limit of the reference values of the center (Bzeizi et al., 2021; Calvo-Fernández et al., 2021; Deng et al., 2020; Garcia-Vidal et al., 2022; Sisó-Almirall et al., 2020; Wagner et al., 2021). For the following variables, standard categorizations were followed: age ≥65 years, eGFR < 60 ml/min/m2, respectively.

* P-value corresponds to the comparison between the complete and partial vaccination groups, obtained using Mann-Whitney U test, chi-squared or Fisher exact test, as appropriate.

This study aimed to study breakthrough COVID-19 infection in SARS-CoV-2-vaccinated patients who needed hospitalization and the factors associated with poor outcomes.

Materials and Methods

This was a retrospective study of the 145 SARS-CoV-2-vaccinated patients admitted with COVID-19 at the Hospital General Universitario de Alicante, Spain, between the start of vaccination schemes on December 27, 2020, to October 17, 2021. The vaccine most commonly administered was Pfizer, followed by Janssen, AstraZeneca, and Moderna. We defined complete vaccination (CV) as symptom onset 14 days after the second dose of a vaccine (or a single Janssen dose), and partial vaccination (PV) as the administration of only the first dose or symptom onset within 13 days after the second dose (or a single dose of Janssen). The vaccine administration date was obtained from the electronic medical record.

All the clinical and laboratory parameters were recorded at admission. Limited therapeutic effort (LTE) is defined as no-resuscitation and no-intubation orders (with consent from the family); however, these patients could benefit from noninvasive mechanical ventilation or a high-flow nasal cannula. The main outcomes were 1) the all-cause mortality during hospital stay; 2) the need for invasive mechanical ventilation (IMV); and 3) identified associated risk factors.

Statistics

The results were stratified by vaccination status, comparing the CV and PV groups using the Mann-Whitney U test (for numeric traits), the chi-squared test, and Fisher's exact test (for binary outcomes), as appropriate.

The baseline factors associated with outcomes were analyzed by multiple logistic regression estimating the odds ratios (odds ratio [OR]; 95% confidence intervals [CI]). Explanatory variables were included as covariates if they showed significant associations in simple models. The variables unavailable in more than 15% of the population were excluded.

All the tests were 2-tailed, and a *p*-value of less than 0.05 was considered significant. The final follow-up date was December 6, 2021, unless censored (because of in-hospital death).

IBM SPSS Statistics Version 25.0 (Armonk, New York, United States) was used for the analyses. The HGUA-ISABIAL Ethics Committee approved the study (expedient no. 200145).

Results

Of the 1,648 patients hospitalized with COVID-19 during the study period, only 145 met the inclusion criteria and were included in the analysis. The types of vaccines administered, basal demographic characteristics, comorbidities, clinical presentations, and outcomes by vaccination status are listed in Table 1. After CV, the median number of days at admission was 81.0 (interquartile [IQR]: 45.0–115.5). All the patients were discharged at the end of the study. For re-admission, the censored time was 118.0 days (IQR: 102.5–132.0).

The epidemiological distribution of SARS-CoV-2 variants according to genomic sequencing in our health area during the study period is provided in the Supplementary Materials (Figure S1). Although the CV subpopulation was admitted to the hospital between April 16, 2021, and October 17, 2021 (weeks 16 to 41), 98% of patients arrived from week 28, when Delta was the predominant variant (causing >80% of infections).

The CV subgroup was composed mainly of males (61.4%), with a median age of 72 years. They had a high comorbidity (Charlson Index ≥3, 72%; immunosuppression, 20%). Patients were admitted to the hospital after a mean of 1 week of symptoms, with bilateral pneumonia affecting 63.4%. Opacities greater than 50% of the lung surface were found in 14.9% of cases.

LTE was agreed upon in 28% (29 of 101) of the CV cases in frail, older patients who have severe comorbidities. Endotracheal intubation was required in 10.9%, reaching 15.3% when LTE patients were excluded from the analysis. The global mortality was 22.8%, 41.4% in the subgroup with LTE, and 15.3% in the rest of the cohort.

In the multivariate analysis, after adjusting for confounding factors, age ≥ 65 years, confusion, and ferritin > 500 mg/L at admission were independently associated with mortality (Figure 1); a Charlson Index ≥3, basal oximetry ≤94% or nosocomial COVID-19 were close to statistical significance (*p* < 0.09); and the time from vaccination showed no association.

After excluding patients with LTE and adjusting for confounding factors in the multivariate analysis, age ≥ 65 years, extensive lung
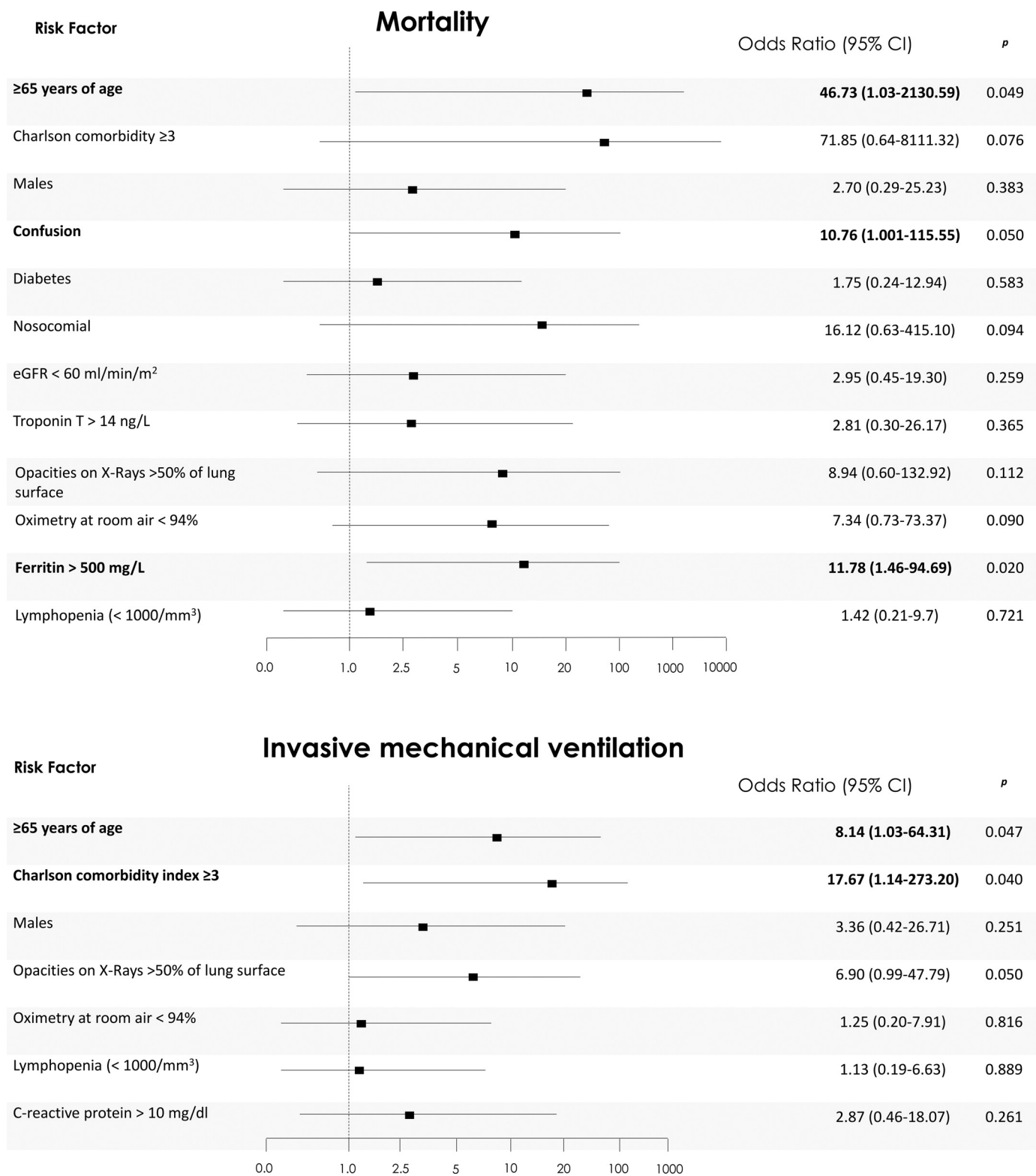
Mortality

Risk Factor	Odds Ratio (95% CI)	p
≥65 years of age	**46.73 (1.03-2130.59)**	0.049
Charlson comorbidity ≥3	71.85 (0.64-8111.32)	0.076
Males	2.70 (0.29-25.23)	0.383
Confusion	**10.76 (1.001-115.55)**	0.050
Diabetes	1.75 (0.24-12.94)	0.583
Nosocomial	16.12 (0.63-415.10)	0.094
eGFR < 60 ml/min/m²	2.95 (0.45-19.30)	0.259
Troponin T > 14 ng/L	2.81 (0.30-26.17)	0.365
Opacities on X-Rays >50% of lung surface	8.94 (0.60-132.92)	0.112
Oximetry at room air < 94%	7.34 (0.73-73.37)	0.090
Ferritin > 500 mg/L	**11.78 (1.46-94.69)**	0.020
Lymphopenia (< 1000/mm³)	1.42 (0.21-9.7)	0.721

0.0   1.0   2.5   5   10   20   100   1000   10000

Invasive mechanical ventilation

Risk Factor	Odds Ratio (95% CI)	p
≥65 years of age	**8.14 (1.03-64.31)**	0.047
Charlson comorbidity index ≥3	**17.67 (1.14-273.20)**	0.040
Males	3.36 (0.42-26.71)	0.251
Opacities on X-Rays >50% of lung surface	6.90 (0.99-47.79)	0.050
Oximetry at room air < 94%	1.25 (0.20-7.91)	0.816
Lymphopenia (< 1000/mm³)	1.13 (0.19-6.63)	0.889
C-reactive protein > 10 mg/dl	2.87 (0.46-18.07)	0.261

0.0   1.0   2.5   5   10   20   100   1000

Figure 1. Predictors of mortality and invasive mechanical ventilation according to multivariable logistic regression analysis
The 95% confidence intervals (CIs) of the odds ratios have been adjusted for multiple testing. Explanatory variables (demographic characteristics, comorbidities, and clinical presentation, shown in Table 1) were included as covariates in the logistic regression models, if they showed significant associations in simple models, and are represented as risk factors in the figure. In bold are the independent predictors associated with the outcomes. For the purpose of the logistic regression, variables were categorized according to clinically relevant cutoff points or, failing that, according to the upper limit of the reference values of the center (Bzeizi et al., 2021; Calvo-Fernández et al., 2021; Deng et al., 2020; Garcia-Vidal et al., 2022; Sisó-Almirall et al., 2020; Wagner et al., 2021). For the following variables, standard categorizations were followed: age ≥65 years and eGFR (estimated glomerular filtration rate) < 60 mL/min/m², respectively.

infiltrates, and a Charlson Index ≥ 3 were independently associated with a need for IMV (Figure 1).

When the time elapsed after CV was categorized into quartiles, those in the upper quartile did not show a significant increase in mortality rate (OR: 1.33; 95% CI: 0.49–3.65) or IMV requirement (OR: 3.55; 95% CI: 0.75–16.78) (after excluding patients with LTE), compared with the 3 lower quartiles ($<$115.5 vs $\geq$115.5 days).

Although the patients with PV were younger and had fewer comorbidities, the clinical features and main outcomes did not differ significantly between the CV and PV groups.

Discussion

In this cohort of patients hospitalized because of breakthrough COVID-19 infection, we reported the clinical profile and evolution by vaccination status, with an overall all-cause mortality rate of about 20%. It is unknown why patients who are fully vaccinated develop severe disease symptoms. Although the time elapsed after vaccination (there is a loss of effectiveness after 6 months) and new variants (Omicron in patients with 2 or fewer doses of the vaccine) are important factors in breakthrough infection, COVID-19 vaccination reduces hospitalizations and mortality in the long term (Holtkamp N, et al., 2021; Lin et al., 2022). Therefore, host characteristics appear to be the most important risk factors for severe disease and fatal outcomes. In our cohort, the time elapsed after CV and host characteristics (high comorbidity and immunosuppression) suggest that waning immunity and impaired immune responses after vaccination could help to explain the high mortality rate.

The CV subpopulation is differentiated from patients with incomplete vaccination by age, long-term care residency, and comorbidity. However, the clinical features and outcomes are similar. The independent predictors of critical outcomes (mortality and IMV) are comparable with those in published series for unvaccinated patients (Alimohamadi et al., 2021; Andrés et al., 2021; Berenguer et al., 2020).

The clinical and baseline characteristics of our cohort are similar to those of the other 2 groups of patients hospitalized because of breakthrough COVID-19 (Bosch et al., 2021; Brosh-Nissimov et al., 2021). Compared to unvaccinated COVID-19 admissions, those patients appear to be older, are more likely to be immunosuppressed, and have more comorbidities (Alimohamadi et al., 2021; Andrés et al., 2021; Berenguer et al., 2020). In accordance to this evidence, the higher levels of brain natriuretic peptide in our patients with CV could translate into a high cardiovascular comorbidity rate and worse renal function, in addition to being a biomarker of myocardial damage in COVID-19 (Calvo-Fernández et al., 2021).

Our mortality rate and that found by Brosh-Nissimov (Brosh-Nissimov et al., 2021) in 152 fully vaccinated hospitalized breakthrough cases from Israel (22%) are similar, and a composed primary outcome of IMV or death is overlapping (26.7 vs 25%).

Although vaccines are very effective at preventing severe cases of COVID-19, this study on breakthrough infection could help identify patients with extreme vulnerability and a higher risk of poor outcomes when they do occur and patients require hospitalization.

Limitations

Some important limitations of this study need to be addressed. First, this was a retrospective, single-center study without a comparison between vaccinated and unvaccinated patients. The population we studied received different commercial vaccines. This study period could have included different scenarios in terms of virus variants and treatment protocols. However, most of the cases

in our health area were the Delta variant, and there were no substantial changes in treatment protocols during 2021. Although an effort was made to control for relevant confounders, unmeasured confounding variables may still have been present. Finally, sample-size limitations prevented analysis by vaccine type, SARS-CoV-2 variant, and time elapsed between vaccination and symptom onset.

Conclusions

Compared with the patients with PV, the patients with CV hospitalized because of breakthrough COVID-19 were older, with more comorbidity, and had a high mortality rate. Therefore, it is essential to incorporate additional measures in this subgroup of patients, such as reinforcing the vaccination calendar with boosters to prevent severe disease and early treatment of mild symptomatic infection with monoclonal antibodies in immunocompromised patients. To validate the effectiveness of these measures, this population must be specifically addressed in future research.

Disclosure Statement

The authors have nothing to disclose.
This manuscript has not been previously published, and it is not being considered for publication elsewhere.

Funding

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.
Availability of data and material: O.M-P, I.R, and E.M have full access to the data and are the guarantor for the data.

Authors'contributions

We encourage authors to disclose their personal contribution to the research and article (Writing – Original Draft: I.R, E.M. and O.M-P.; Writing – Review & Editing: I.R., E.M., O.M-P., J.M-R, V.B., R.S-M., M.A.M-G., S.O-R., P.C-S., S.R.; Conceptualization: I.R, E.M. and O.M-P.; Investigation: I.R., E.M., O.M-P., J.M-R, V.B., R.S-M., M.A.M-G., S.O-R., P.C-S., S.R.; Methodology: I.R, E.M. and O.M-P.; Formal Analysis: I.R, E.M. and O.M-P.; Project Administration: E.M; Funding Acquisition: not applicable).

Ethics approval

HGUA-ISABIAL Ethics Committee approved the study (expedient no. 200145).
Consent to participate: written informed consent was obtained from all the participants.

Acknowledgments

Violeta Esteban, Isabel Ribes, Julia Portilla, Cristina Herreras, Alejando Cintas, Alicia Ferradas, Ana Martí, Blanca Figueres, Marcelo Giménez, María-Ángeles Martínez, María-Mar García-Mullor, María Angeles Martínez, Irene Calabuig, Marisa Peral, Ernesto Tovar, M Carmen López, Paloma Vela, Pilar Bernabeú, Ana Yuste, José Ponce, Bertomeu Massuti, Vicente Climent, Vicente Arrarte, Fernando Torres, Laura Valverde, Laura Delegido, Cristina Cambra, Miriam Sandín, Teresa Lozano, Amaya García-Fernández, Alejandro Do Campo, Eduardo Vergara, Nicolás López, Elena Elvira, Fátima López, Fernando Dahl, Blanca Serrano, Sarai Moliner, Carmina Díaz, Dolores Castaño, Beatriz López; Antonio Picó, Joaquín Serrano, Sol Serrano, María Marín-Barnuevo, María Díaz, Cristina Gilabert, Estela Martínez, Elena Vivó, Noelia Balibrea, Miguel Perdiguero, Carolina Mangas, Lucía Medina, Oscar Murcia, María Rodríguez, Rodrigo Jover, Javier López, Marina Morillas, Mercedes Khartabil, Cristina Gil, Carlos Salazar, Eva Vera, Helena López, Vanesa Rodríguez, Sandra Baile, Norma Guerra, Mar Blanes, Jaime Guijarro, José Carlos Pascual, Iris Gonzalez, Pedro Sanso, José Manuel Ramos, Jaime Javaloy, Clara Llopis, Olga Coronado, Esther García, Gonzalo Rodríguez, Paola Melgar, Mariano Franco, Félix Lluís, Carmen Zaragoza, Cándido Alcaraz, Ana Carrión, Celia Villodre, Emilio Ruiz de la Cuesta, Cristina Alenda, Francisca Peiró, María Planelles, Laura Greco, Sandra Silvia, Antonio Francia, Iván Verdú, Juan Sales, Ana Palacios, Hortensia Ballester, Antonio García-Valentín, Marta Márquez, Eva Canelo, Andrea Juan, Elena Vives, Andrea Revert, Gonzalo Fuente, Ester Nofuentes, Carolina Mangas, Eva Vera, Alicia Ferradas, Helena López, Cristian Herrera, Beatriz López, Marina Morillas, Vanesa Rodríguez, Mercedes Khartabil, Mario Giménez, Ernesto Tovar, Estela Martínez, Lucia Medina, Sandra Baile, Carlos Salazar, Norma Guerra, Sarai Moliner, Mari-Carmen López-González, Blanca Figueres.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.007.

References

Alimohamadi Y, Tola HH, Abbasi-Ghahramanloo A, Janani M, Sepandi M. Case fatality rate of COVID-19: a systematic review and meta-analysis. J Prev Med Hyg 2021;62:E311–20. doi:10.15167/2421-4248/jpmh2021.62.2.1627.

Andrés M, Leon-Ramirez J-M, Moreno-Perez O, Sánchez-Payá J, Gayá I, Esteban V, et al. Fatality and risk features for prognosis in COVID-19 according to the care approach - a retrospective cohort study. PLoS One 2021;16. doi:10.1371/journal.pone.0248869.

Bahl A, Johnson S, Maine G, Garcia MH, Nimmagadda S, Qu L, et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: A multicenter cohort study. Lancet Reg Health Am 2021;4. doi:10.1016/j.lana.2021.100065.

Berenguer J, Ryan P, Rodríguez-Baño J, Jarrín I, Carratalà J, Pachón J, et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect 2020;26:1525–36. doi:10.1016/j.cmi.2020.07.024.

Bosch W, Cowart JB, Bhakta S, Carter RE, Wadei HM, Shah SZ, et al. COVID-19 Vaccine-Breakthrough Infections Requiring Hospitalization in Mayo Clinic Florida through August 2021. Clin Infect Dis 2021 ciab932. doi:10.1093/cid/ciab932.

Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect 2021;27:1652–7. doi:10.1016/j.cmi.2021.06.036.

Bzeizi K, Abdulla M, Mohammed N, Alqamish J, Jamshidi N, Broering D. Effect of COVID-19 on liver abnormalities: a systematic review and meta-analysis. Sci Rep 2021;11:10599. doi:10.1038/s41598-021-89513-9.

Calvo-Fernández A, Izquierdo A, Subirana I, Farré N, Vila J, Durán X, et al. Markers of myocardial injury in the prediction of short-term COVID-19 prognosis. Rev Esp Cardiol (Engl Ed) 2021;74:576–83. doi:10.1016/j.rec.2020.09.011.

CDCMMWR. COVID-19 Vaccine Breakthrough Infections Reported to CDC − United States, January 1–April 30, 2021. MMWR Morb Mortal Wkly Rep 2021;70. doi:10.15585/mmwr.mm7021e3.

Holtkamp N, Kolbe A, Beleche T. COVID-19 Vaccination Associated with Reductions in COVID-19 Mortality and Morbidity in the United States, and an Approach to Valuing these Benefits. ASPE n.d 2021. https://aspe.hhs.gov/reports/economic-health-benefits-covid-19-vaccination (accessed January 30, 2022).

Deng P, Ke Z, Ying B, Qiao B, Yuan L. The diagnostic and prognostic role of myocardial injury biomarkers in hospitalized patients with COVID-19. Clin Chim Acta 2020;510:186–90. doi:10.1016/j.cca.2020.07.018.

Garcia-Vidal C, Moreno-García E, Hernández-Meneses M, Puerta-Alcalde P, Chumbita M, Garcia-Pouton N, et al. Personalized Therapy Approach for Hospitalized Patients with Coronavirus Disease 2019. Clin Infect Dis 2022;74:127–32. doi:10.1093/cid/ciaa964.

Lin D-Y, Gu Y, Wheeler B, Young H, Holloway S, Sunny S-K, et al. Effectiveness of Covid-19 Vaccines over a 9-Month Period in North Carolina. N Engl J Med 2022. doi:10.1056/NEJMoa2117128.

Sisó-Almirall A, Kostov B, Mas-Heredia M, Vilanova-Rotllan S, Sequeira-Aymar E, Sans-Corrales M, et al. Prognostic factors in Spanish COVID-19 patients: A case series from Barcelona. PLoS One 2020;15. doi:10.1371/journal.pone.0237960.

Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. JAMA 2021;326:2043–54. doi:10.1001/jama.2021.19499.

Wagner J, Garcia-Rodriguez V, Yu A, Dutra B, Larson S, Cash B, et al. Elevated transaminases and hypoalbuminemia in Covid-19 are prognostic factors for disease severity. Sci Rep 2021;11:10308. doi:10.1038/s41598-021-89340-y.