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

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Highlights

- Those hospitalized for COVID-19 breakthrough were mostly elderly people
- These patients had and elevated comorbidity and high mortality rate
- Predictors of poor outcomes resemble those reported in unvaccinated patients
- Partially vaccinated patients were younger and had less comorbidity
- Outcomes did not differ between the fully or partially vaccinated groups

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

Running title: COVID-19 Vaccine Breakthrough

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Objectives. To describe breakthrough COVID-19 in patients who needed hospitalization and the factors associated with poor outcomes.

Methods. A retrospective study on complete (diagnosed two weeks after the second dose of the Pfizer/Moderna/AstraZeneca or first dose of the Janssen vaccine was administered) or partial vaccine scheme (CV or PV) patients hospitalized for COVID-19 between December 27, 2020, and October 17, 2021, was conducted. 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, estimating the odds ratios (OR; 95% CI).

Results. One hundred and forty-five patients (101 CV) were included. The CV subgroup was mainly composed of elderly males with high comorbidity (Charlson index ≥3, 72%; immunosuppression, 20%), 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%, reaching 15.3% when excluding LTE patients; the global mortality was 22.8% and 41.4% in the subgroup with LTE. Although the PV patients 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. Fully vaccinated patients hospitalized due to breakthrough COVID-19 tend to be elderly, with comorbidities, and have high mortality.

Keywords: breakthrough infection; hospitalization; mortality; vaccine effectiveness; COVID-19; risk factors

Introduction

Vaccine breakthrough SARS-CoV-2, 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 regarding the groups most at risk, and the prognosis and outcomes for hospitalized patients are scarce (CDCMMWR, 2021; Tenforde et al., 2021).

The aim of this study was to study COVID-19 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 vaccinations on December 27, 2020, and 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) means no-resuscitation and no-intubation orders (on

agreement with 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 admission; 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 via 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 (OR; 95% 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 two-tailed, and a *p*-value of less than 0.05 was considered to indicate significance. The final date of follow-up was December 6, 2021, unless censored (due to in-hospital death).

IBM SPSS Statistics v25 (Armonk, NY, USA) was used for the analyses. The HGUA-ISABIAL Ethics Committee approved the study (expedient no. 200145).

Results

Of the 1648 patients hospitalized with COVID-19 in 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 shown in Table 1. The median number of days

at admission since complete vaccination was 81.0 (IQR: 45.0–115.5). All the patients were discharged at the end of the study. The censored time was 118.0 (IQR: 102.5–132.0) days for re-admission.

The epidemiological distribution of SARS-CoV-2 variants according to genomic sequencing in our health area in the study period is provided in the Supplementary Materials (Figure S1). Although the CV subpopulation was admitted between April 16, 2021, and October 17, 2021 (weeks 16 to 41), 98% of them 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 high comorbidity (Charlson index ≥3, 72%; immunosuppression, 20%). After a mean of one week of symptoms, they were admitted to hospital, with bilateral pneumonia in 63.4%. Opacities >50% of the lung surface were found in 14.9% of cases.

In frail, elderly, severely comorbid patients, LTE was agreed upon in 28% (29/101) of the CV cases. Endotracheal intubation was required in 10.9%, reaching 15.3% when LTE patients were excluded from the analysis. The global mortality was 22.8% and 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 (see 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 infiltrates, and a Charlson index ≥

3 were independently associated with a need for invasive mechanical ventilation (see Figure 1).

When the time elapsed since complete vaccination 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 invasive mechanical ventilation requirement (OR: 3.55 (95% CI: 0.75–16.78), after excluding patients with LTE), compared with the three lower quartiles (<115.5 vs. ≥115.5 days).

Although the PV patients 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 hospitalized patients due to breakthrough COVID-19 infection, we reported the clinical profile and evolution by vaccination status, with an overall all-cause mortality rate of around 20%. Why fully vaccinated patients develop severe disease is unknown. While the time elapsed since vaccination (there is a loss of effectiveness after six months) and new variants (Omicron in patients with two 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 seem to be the main risk factors for severe disease and fatal outcomes. In our cohort, the time elapsed since complete vaccination and sample 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 clearly differentiated by age, long-term care residency, and comorbidity from patients with incomplete vaccination; however, the clinical features and outcomes are similar. The independent predictors of critical outcomes (mortality and IMV) are comparable to 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 two groups of patients hospitalized due to 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). According to this evidence, the higher levels of brain natriuretic peptide in our CV patients could translate into a high cardiovascular comorbidity rate and worse renal function, besides 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, when these occur and require hospitalization, this breakthrough could identify patients with extreme vulnerability and a higher risk of poor outcomes.

Limitations

Some important limitations need to be addressed. First, this was a retrospective, single-center study, without a comparison between vaccinated and unvaccinated patients. The population under study received different commercial vaccines. Length of study could entail different scenarios in terms of virus variants and treatment protocols; however, most of the variants detected in our health area were Delta 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. Sample-size limitations prevented analysis by vaccine type, SARS-CoV-2 variant, and time elapsed between vaccination and symptom onset.

Conclusions

Compared to the PV patients, the CV patients that were hospitalized due to breakthrough COVID-19 were older, with more comorbidities, 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 an early therapy 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.

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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.

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

	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	94 (92-96)	94 (92-96)	94 (92-96)	0.84

(IQR)				
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
Diarrhoea, %	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 Bilateral pneumonia, % Unilateral pneumonia, %	 91/144 (63.2) 17/144 (11.8)	 64/101 (63.4) 13/101 (12.9)	 27/43 (62.8) 4/43 (9.3)	.78
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
Non-invasive respiratory support, %	35/145 (24.1)	27/101 (26.7)	8/44 (18.2)	.27
Type of non-invasive respiratory support, % HFNC, % NIMV, %	 23/35 (65.7) 12/35 (34.3)	 18/27 (66.7) 9/27 (33.3)	 5/8 (62.5) 3/8 (37.5)	.83
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, % Group with LTE, % Group with maximum care, %	 14/145 (9.7) 0/41 (0.0) 14/104 (13.5)	 11/101 (10.9) 0/29 (0.0) 11/72 (15.3)	 3/44 (6.8) 0/12 (0.0) 3/32 (9.4)	 .45 - .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
Deaths, % Global, % Group with LTE, % Group with maximum care, % Endotracheal intubation, %	 30/145 (20.7) 17/41 (41.5) 13/104 (12.5) 9/14 (64.3)	 23/101 (22.8) 12/29 (41.4) 11/72 (15.3) 7/11 (63.6)	 7/44 (15.9) 5/12 (41.7) 2/32 (6.3) 2/3 (66.7)	 .35 .99 .20 .92
Cause of death COVID, % Other causes Bacterial infection, %	 19/30 (63.3) 6/30 (20.0)	 13/23 (56.5) 5/22 (21.7)	 6/7 (85.7) 1/7 (14.3)	.16

CV event, % Other, %	1/30 (3.3) 4/30 (13.3)	1/22 (4.3) 4/22 (17.4)	0/7 0/7	

Table legend:

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: non-invasive 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.

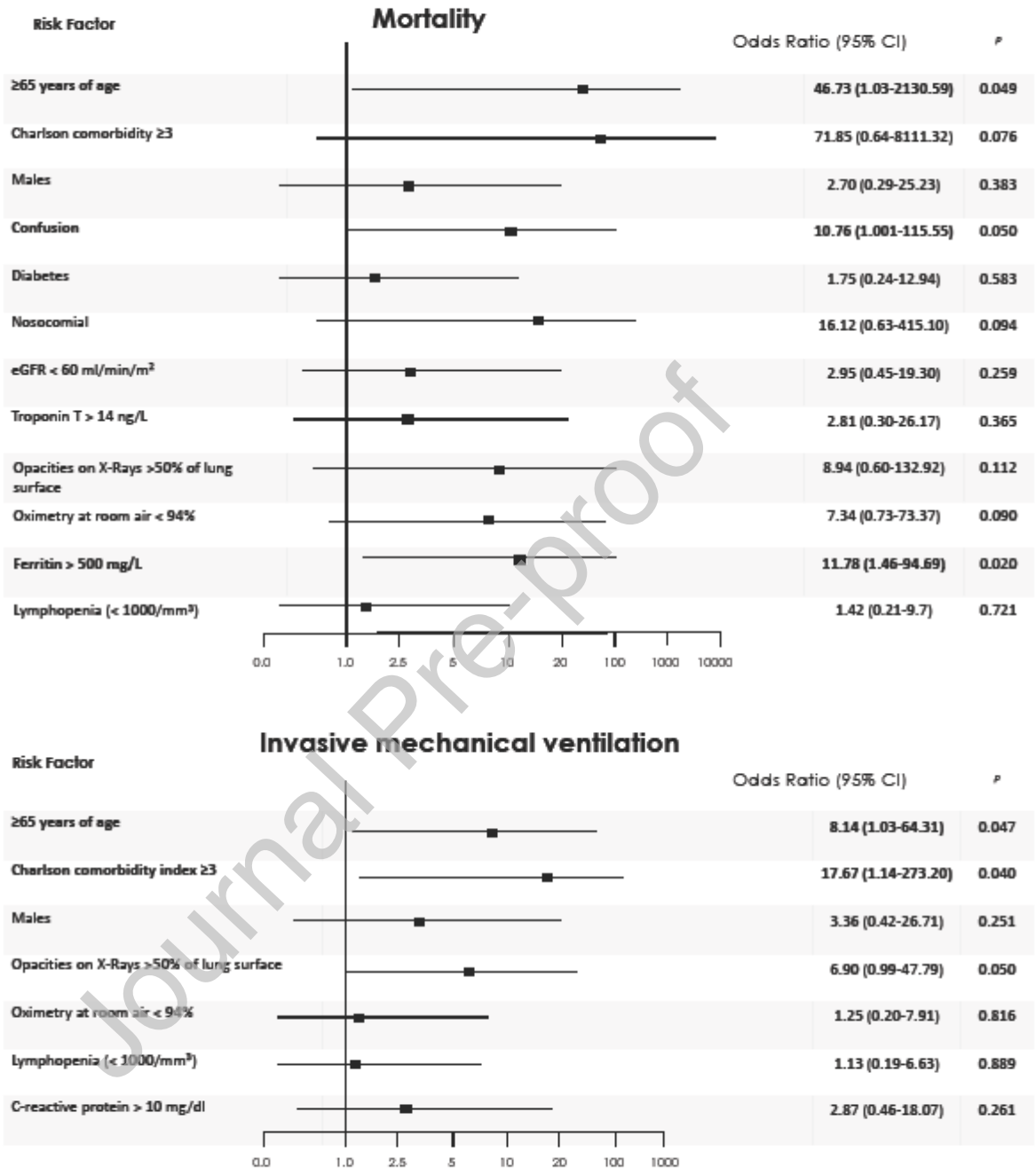

Figure 1. Predictors of mortality and invasive mechanical ventilation according to multivariable logistic regression analysis.

Figure legend:

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/m^2, respectively.