# Higher frequency of comorbidities in fully vaccinated patients admitted to the ICU due to severe COVID-19: a prospective, multicentre, observational study



Received: 18 Aug 2021
Accepted: 13 Nov 2021

*To the Editor*:

The coronavirus disease 2019 (COVID-19) vaccination campaign in Spain began on 27 December 2020 [1]. To date, more than 36 million people have been fully vaccinated, with most of the population, namely 25.3 million people (69.1%), receiving BNT 162b2 (Pfizer/BioNTech) [1]. With respect to other vaccines and figures, 4.8 million (13.2%) people have received AZD1222 (Oxford/AstraZeneca); 4.5 million (12.3%) mRNA-1273 (Moderna); and 2.0 million (5.4%) JNJ-78436735 (Janssen) [1].

Vaccination uptake has radically changed how the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has impacted healthcare systems [2, 3]. Since the initiation of the campaign, a total of 19 705 patients with severe COVID-19 have required admission to intensive care unit (ICU) in Spain, the vast majority with no vaccination or an incomplete regimen [1]. Although vaccination has been shown to be notably effective, a few fully vaccinated patients can develop severe COVID-19 requiring ICU admission. To our knowledge, there is no description of this cohort of patients.

Within the CIBERESUCICOVID consortium [4], we reported a prospective, multicentre and observational study that characterised fully vaccinated patients admitted to seven Spanish ICUs for severe COVID-19 between 25 January and 14 September 2021. These patients developed COVID-19 symptoms at least 2 weeks after administration of either a single-dose COVID-19 vaccine (JNJ-78436735) or the second dose of a two-dose vaccine. Exclusion criteria for this study included unconfirmed SARS-CoV-2 infection; ICU admission due to other causes; or incomplete vaccination status. Data was collected as previously described [4]. For the purpose of comparison, we included 105 consecutive, non-vaccinated adult patients with laboratory-confirmed SARS-CoV-2 infection requiring admission to the same seven ICUs between 25 January and 13 May 2021.

Continuous variables are reported as median (interquartile range) and compared between groups using the Mann–Whitney test. Categorical variables are reported as frequencies (percentages) and compared using Fisher's exact test.

The study received approval by the institution's internal review board (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370), and we obtained informed consent from either patients or their relatives.

During the study period, a total of 1585 patients were admitted to ICUs across seven Spanish hospitals due to COVID-19. Of those, 1314 (82.9%) were unvaccinated; 161 (10.2%) had not completed the vaccination regimen; and 110 (6.9%) were fully vaccinated. Data from 81 (73.6%) fully vaccinated patients were available for the analysis.

Demographics and clinical characteristics of the fully vaccinated population are detailed in table 1. In summary, the median age was 68.0 (60.0–74.0) years; 35 (43.2%) patients were aged ⩾70 years, whilst only five patients were <50 years. 72% (n=58) of these patients were male. All of the patients but two had at least one comorbidity, whereas 69.1% (n=56) had three or more. The most frequent comorbidity was

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**Severe COVID-19 disease requiring ICU admission is possible in the fully vaccinated population, especially in those with immunocompromised status and other comorbidities. Interventions to improve vaccine response might be necessary in this population.** https://bit.ly/3Fw6vCP

**Cite this article as:** Motos A, López-Gavín A, Riera J, *et al*. Higher frequency of comorbidities in fully vaccinated patients admitted to the ICU due to severe COVID-19: a prospective, multicentre, observational study. *Eur Respir J* 2022; 59: 2102275 [DOI: 10.1183/13993003.02275-2021].

**TABLE 1** Characteristics of fully and non-vaccinated, intensive care unit (ICU)-admitted patients with COVID-19

| | Fully vaccinated patients (n=81) | Non-vaccinated patients (n=105) | p-value |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age, years | 68.0 (60.0–74.0) | 65.0 (55.0–73.0) | 0.24 |
| Male | 58 (71.6%) | 71 (67.6%) | 0.63 |
| BMI, $kg \cdot m^{-2}$ | 27.6 (24.9–31.7) | 30.1 (26.5–33.7) | **0.010** |
| **Comorbidities** | | | |
| Number of comorbidities | 3 (2–4) | 2 (1–4) | **0.005** |
| Hypertension | 61 (75.3%) | 52 (49.5%) | **<0.001** |
| Chronic cardiac disease | 15 (18.5%) | 15 (14.3%) | 0.55 |
| Chronic respiratory disease[#] | 21 (25.9%) | 16 (15.2%) | 0.095 |
| Chronic renal disease | 16 (19.8%) | 10 (9.5%) | 0.055 |
| Obesity (BMI $\geqslant$30 $kg \cdot m^{-2}$) | 30 (37.0%) | 57 (54.3%) | **0.026** |
| Diabetes mellitus | 35 (43.2%) | 26 (24.8%) | **0.011** |
| Immunosuppression[¶] | 28 (34.6%) | 11 (10.5%) | **<0.001** |
| Solid organ transplant | 13 (46.4%) | 8 (72.7%) | |
| Active malignancy | 11 (39.3%) | 0 | |
| Autoimmune disease | 3 (10.7%) | 2 (18.2%) | |
| Chronic immunosuppressor treatment | 1 (3.6%) | 1 (5.6%) | |
| Active or former smoker | 30 (37.0%) | 42 (40.0%) | 0.76 |
| **Disease chronology** | | | |
| Days from last vaccine dose to COVID-19 symptoms | 75.0 (47.0–95.0) | | |
| Days from COVID-19 onset to hospital admission | 6.0 (4.0–8.0) | 8.0 (6.0–10.0) | **<0.001** |
| Days from hospital admission to ICU admission | 1.0 (0–3.0) | 1.0 (0–3.0) | 0.20 |
| Days from ICU admission to IMV | 1.0 (0–3.0) | 0 (0–1.0) | **0.001** |
| **ICU admission** | | | |
| APACHE II score | 12 (9–17) | 10 (8–13) | **0.003** |
| SOFA score | 4 (3–5) | 4 (3–6) | 0.64 |
| **Adjuvant treatments** | | | |
| COVID-19 therapies | 28 (34.6%) | 12 (11.4%) | **<0.001** |
| Remdesivir | 21 (75.0%) | 7 (58.3%) | |
| Tocilizumab | 14 (50.0%) | 3 (25.0%) | |
| Convalescent plasma | 3 (10.7%) | 2 (16.7%) | |
| Subcutaneous heparin | 77 (95.1%) | 104 (99.0%) | 0.17 |
| Low dose ($\leqslant$1 $mg \cdot kg^{-1}$ per day) | 61 (75.3%) | 76 (73.1%) | |
| High dose (>1 $mg \cdot kg^{-1}$ per day) | 16 (19.8%) | 28 (26.9%) | |
| Vasopressor treatment | 37 (45.7%) | 58 (55.2%) | 0.24 |
| Continuous neuromuscular blockers | 39 (48.1%) | 70 (66.7%) | **0.016** |
| Corticosteroids | 76 (93.8%) | 104 (99.0%) | 0.087 |
| **Supportive therapies** | | | |
| High-flow oxygen cannula | 65 (80.2%) | 56 (53.3%) | **<0.001** |
| NIMV | 21 (25.9%) | 25 (23.8%) | 0.86 |
| IMV | 45 (55.6%) | 76 (72.4%) | **0.020** |
| Prone position | 42 (51.9%) | 62 (59.0%) | 0.23 |
| ECMO support | 1 (1.2%) | 1 (1.0%) | 1.00 |
| Renal replacement therapy | 10 (12.3%) | 4 (3.8%) | **0.047** |
| Limitation of life-sustaining care | 16 (19.7%) | 7 (6.7%) | **0.012** |
| **Complications** | | | |
| Nosocomial bacterial pneumonia[+] | 22 (27.2%) | 45 (42.9%) | **0.032** |
| Ventilator-associated pneumonia | 16 (72.7%) | 35 (77.8%) | 0.76 |
| Microbiological diagnosis[§] | 18 (81.8%) | 42 (93.3%) | 0.21 |
| *Pseudomonas aeruginosa* | 7 (38.9%) | 10 (23.8%) | |
| *Klebsiella* spp. | 4 (22.2%) | 2 (4.8%) | |
| *Staphylococcus aureus* | 3 (16.7%) | 11 (26.2%) | |
| *Acinetobacter baumannii* | 2 (11.1%) | 2 (4.8%) | |
| Other | 5 (27.8%) | 20 (47.6%) | |
| Acute renal injury[f] | 23 (28.4%) | 25 (23.8%) | 0.50 |
| Pulmonary embolism | 6 (7.4%) | 8 (7.6%) | 1.00 |
| Myocardial infarction | 1 (1.2%) | 1 (1.0%) | 1.00 |
| Heart failure | 3 (3.7%) | 2 (1.9%) | 0.65 |
| Stroke | 0 (0%) | 2 (1.9%) | 0.51 |
| Liver dysfunction[##] | 32 (39.5%) | 32 (30.5%) | 0.22 |

Continued

**TABLE 1** Continued

| | Fully vaccinated patients (n=81) | Non-vaccinated patients (n=105) | p-value |
|---|---|---|---|
| **Outcomes** | | | |
| 28-day mortality | 24 (29.6%) | 27 (25.7%) | 0.62 |
| ICU mortality | 27 (33.3%) | 30 (28.6%) | 0.52 |
| In-hospital mortality | 28 (34.6%) | 30 (28.6%) | 0.43 |
| Length of IMV, days | 19.0 (9.0–28.0) | 20.0 (10.0–29.0) | 0.51 |
| Length of ICU stay, days | 11.0 (7.0–30.0) | 15.0 (9.0–30.0) | **0.044** |
| Length of hospital stay, days | 19.0 (14.0–36.0) | 21.0 (14.0–36.0) | 0.31 |

Continuous variables are reported as median (interquartile range) and categorical variables as frequencies (%). Sample sizes were indicated for each variable and percentages were calculated in accordance with available data. Missing data were only present for APACHE II and SOFA scores. Specifically, data were available for 171 and 169 patients, respectively. p-values <0.05 were considered significant and are shown in bold. APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; SOFA: Sepsis-related Organ Failure Assessment. [#]: chronic respiratory disease includes any of COPD, cystic fibrosis, bronchiectasis, interstitial lung disease, asthma, or pre-existing requirement for long-term oxygen therapy. [¶]: immunosuppression includes current solid organ or haematological malignancy, AIDS/HIV, solid organ transplant, haematopoietic cell transplant, autoimmune diseases and any immunosuppressant treatment taken within 14 days of hospital admission. [+]: clinically or radiologically diagnosed bacterial pneumonia managed with antimicrobials; bacteriological confirmation was not required. [§]: three patients had polymicrobial pneumonia in the fully vaccinated group, two in the non-vaccinated group. [f]: acute renal injury was defined as an increase in serum creatinine by $\geqslant$0.3 mg·dL$^{-1}$ within 48 h or as an increase in serum creatinine $\geqslant$1.5 times more than baseline. [##]: liver dysfunction was defined as an increase in blood bilirubin, alanine transaminase or aspartate transaminase twice the upper limit of the normal range.

hypertension, being present in 61 (75.3%) patients. 28 (34.6%) patients had an immunocompromised status. The percentage of obese (BMI $\geqslant$30 kg·m$^{-2}$) patients was 37.0% (n=30). Patients required ICU admission after a median time of 82.0 (55.0–101.0) days since vaccination, and APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sepsis-related Organ Failure Assessment) scores at this time point were 12 (9–17) and 4 (3–5), respectively. All patients showed bilateral pulmonary infiltrates. Additionally, 35 of 81 (43.2%) vaccines administered were BNT 162b2; 26 (32.1%) JNJ-78436735; 16 (19.8%) mRNA-1273; and four (4.9%) AZD1222.

Amongst the fully vaccinated population, 45 (55.6%) received invasive mechanical ventilation. 42 (51.9%) patients were placed in the prone position, and only one patient received extracorporeal membrane oxygenation support. All but five (93.8%) patients received corticosteroids. Furthermore, all patients but four (95.1%) received subcutaneous anticoagulation; 72 (88.9%) underwent antimicrobial therapies. 22 (27.2%) patients were diagnosed with nosocomial bacterial pneumonia, whilst 23 (28.4%) patients suffered acute kidney failure.

The in-hospital mortality rate was 34.6%, and the main causes of death included respiratory failure (n=19, 67.9%) and multiorgan failure (n=4, 14.3%). The median duration of invasive mechanical ventilation was 19.0 (9.0–28.0) days, and the median length of ICU stay was 11.0 (7.0–30.0) days.

To our knowledge, this study is the first descriptive report of fully vaccinated patients requiring ICU admission due to severe COVID-19. The main finding of this study is that patients with specific comorbidities and full vaccination regimen may be at risk of developing severe COVID-19, even though vaccines have proven to be greatly effective in the general population [2, 3, 5]. Importantly, only 7% of patients with severe COVID-19 were fully vaccinated. We observed a notably high incidence of comorbidities in this population, especially as they relate with vascular disease (*i.e.* hypertension, diabetes mellitus and chronic renal disease) and immunosuppression status. When we compared this incidence with that of a non-vaccinated group of patients requiring ICU admission during coinciding periods, we observed a three-fold increase in immunosuppression; chronic respiratory disease, renal disease, diabetes mellitus and hypertension rates almost doubled. Of note, the median time between the onset of symptoms and hospital admission was significantly shorter for fully vaccinated cases than unvaccinated patients with COVID-19.

Contou *et al.* [6] have described a second-wave French cohort of non-vaccinated patients. This cohort had similar or slightly increased comorbidity rates compared to those of our non-vaccinated group, albeit lower than that of our fully vaccinated patients. Juthani *et al.* [7] and Brosh-Nissimov *et al.* [8] have reported small series of fully vaccinated patients that required hospitalisation, including mild to severe patients. Like our study, both investigations found a high rate of comorbidities amongst severe or critically ill patients [7, 8].

In a case–control study including 35 fully vaccinated patients admitted to the ICU, Tenforde *et al*. [9] found that the significant association between hospitalisation for COVID-19 and decreased likelihood of vaccination was weaker in immunocompromised patients than immunocompetent patients.

The implications of our findings are manifold. First, these findings encourage discussion on the possible need for further interventions, such as the use of COVID-19 vaccine boosters, in this population. Some recent studies have already debated the practicality of a third dose of the vaccine [10–12]. Our data suggest that patients with comorbidities may benefit from these strategies.

Secondly, the substantial number of immunocompromised patients also suggests a poorer immune response in this population. Previous data have already demonstrated that some of these patients had low antibody levels after full vaccination [13, 14]. In this context, more personalised management of immunosuppressed patients, *e.g.* measuring antibody levels after vaccination, could prove to be a reasonable option.

Lastly, an increase in comorbidities directly impacts ICU management and the clinical outcomes of a fully vaccinated population. Some studies have already discussed prognosis in patients with previous comorbidities who develop COVID-19 [15, 16]. Indeed, we still observed high ICU mortality rate in fully vaccinated patients, reaching similar levels to previous reports, including those in fully vaccinated patients [6–8, 17, 18]. Worsening of underlying illnesses and/or lower vaccine effectiveness in those patients may provide an explanation for these high rates [8]. Nevertheless, we observed no differences in mortality between both groups, despite higher rates of comorbidities in fully vaccinated patients. Of note, a final decision to not increase supportive measures was made in 16 (19.8%) fully vaccinated patients.

Our study has some limitations, however. First, we collected data from a small cohort. A larger sample size would be ideal to confer a more robust generalisation of our results. Second, our control group was a small sample of the large, non-vaccinated population. As both study periods partially overlapped, it is also worth considering the role of emerging SARS-CoV-2 variants in these scenarios. Finally, we were not able to know the SARS-CoV-2 viral load and variant, or antibody titres before COVID-19 onset.

To conclude, only 7% of patients with severe COVID-19 were fully vaccinated. Nonetheless, a clinical scenario of severe COVID-19 disease requiring ICU admission is possible amongst the vaccinated population, especially in those with comorbidities and/or immunosuppression. Therefore, further interventions to improve vaccine response, including an additional dose, might be necessary for this population.

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Acknowledgements: The authors are indebted to Maria Arguimbau, Raquel Campo, Natalia Jarillo, Javier Muñoz, Elisabeth Sancho and Manuel Sanchez for their extensive support in project management and article preparation.

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Data sharing: The datasets used and/or analysed during the current study are available from the corresponding author per reasonable request.

Author contributions: A. Motos, A. López-Gavín, J. Riera and A. Torres participated in protocol development, study design, study management, statistical analysis and data interpretation, and wrote the first draft of the report. A. Ceccato, L. Fernández-Barat, R. Pérez-Arnal, D. García-Gasulla, O. Peñuelas, J.Á. Lorente, A. Rodriguez, D. de Gonzalo-Calvo, R. Almansa, R. Menéndez, J.F. Bermejo-Martin, R. Ferrer and F. Barbé participated in study design, study management and interpretation, and provided critical review of the first draft of the report. A. Gabarrus performed statistical analysis and provided critical review of the first draft of the report. J. Marin-Corral, P. Ricart, F. Roche-Campo, S. Sancho Chinesta and L. Socias participated in data collection and provided critical review of the first draft of the report. The CIBERESUCICOVID consortium participated in data collection.

Conflict of interest: The authors have disclosed that they do not have any conflicts of interest.

Support statement: Financial support was provided by the Instituto de Salud Carlos III de Madrid (COV20/00110, ISCIII), Fondo Europeo de Desarrollo Regional (FEDER), “Una manera de hacer Europa”, and Centro de Investigación Biomedica En Red – Enfermedades Respiratorias (CIBERES). D. de Gonzalo-Calvo has received financial support from the Instituto de Salud Carlos III (Miguel Servet 2020: CP20/00041), co-funded by European Social Fund (ESF)/“Investing in your future”. Funding information for this article has been deposited with the Crossref Funder Registry.

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