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Early View

Research letter

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

Anna Motos, Alexandre López-Gavín, Jordi Riera, Adrián Ceccato, Laia Fernández-Barat, Jesús F Bermejo-Martin, Ricard Ferrer, David de Gonzalo-Calvo, Rosario Menéndez, Raquel Pérez-Arnal, Dario García-Gasulla, Alejandro Rodriguez, Oscar Peñuelas, José Ángel Lorente, Raquel Almansa, Albert Gabarrus, Judith Marin-Corral, Pilar Ricart, Ferran Roche-Campo, Susana Sancho Chinesta, Lorenzo Socias, Ferran Barbé, Antoni Torres

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HIGHER FREQUENCY OF COMORBIDITIES IN FULLY VACCINATED PATIENTS ADMITTED TO ICU DUE TO SEVERE COVID-19: A PROSPECTIVE, MULTICENTER, OBSERVATIONAL STUDY

Anna Motos[1,2*], Alexandre López-Gavín[2*], Jordi Riera[3], Adrián Ceccato[1], Laia Fernández-Barat[1,2], Jesús F Bermejo-Martin[4], Ricard Ferrer[3], David de Gonzalo-Calvo[1,5], Rosario Menéndez[6], Raquel Pérez-Arnal[7], Dario García-Gasulla[7], Alejandro Rodriguez[8], Oscar Peñuelas[1,9], José Ángel Lorente[1,9], Raquel Almansa[4], Albert Gabarrus[2], Judith Marin-Corral[10], Pilar Ricart[11], Ferran Roche-Campo[12], Susana Sancho Chinesta[13], Lorenzo Socias[14], Ferran Barbé, [1,5] Antoni Torres[1,2*] on behalf of the CIBERESUCICOVID Project (COV20/00110, ISCIII)

*AM and ALG equally contributed to the manuscript.

Affiliations:

[1] Centro de Investigación Biomedica En Red – Enfermedades Respiratorias (CIBERES), Barcelona, Spain.

[2] Institut d'Investigacions August Pi i Sunyer (IDIBAPS), Barcelona. Universitat de Barcelona, Barcelona, Spain.

[3] Intensive Care Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca, Barcelona, Spain

[4] Hospital Universitario Río Hortega de Valladolid, Valladolid, Spain; Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Gerencia Regional de Salud de Castilla y León, Spain

[5] Translational Research in Respiratory Medicine, Respiratory Department, Hospital Universitari Aranu de Vilanova and Santa Maria; IRBLleida, Lleida, Spain

[6] Pulmonary Department, University and Polytechnic Hospital La Fe, Valencia, Spain.

[7] Barcelona Supercomputing Centre (BSC), Barcelona, Spain

[8] Critical Care Department, Hospital Joan XXIII, Tarragona, Spain

[9] Hospital Universitario de Getafe, Madrid; Universidad Europea, Madrid; Spain

[10] Critical Care Department, Hospital del Mar-IMIM, Barcelona, Spain

[11] Servei de Medicina Intensiva, Hospital Universitari Germans Trias, Badalona, Spain

[12] Critical Care Department, Hospital Verge de la Cinta, Tortosa, Tarragona, Spain

[13] Servicio de medicina intensiva. Hospital Universitario y Politécnico La Fe, Valencia, Spain.

[14] Intensive Care Unit, Hospital Son Llàtzer, Palma de Mallorca, Illes Balears, Spain.

Corresponding author:

Antoni Torres, MD, PhD

Servei de Pneumologia i Al·lèrgia Respiratòria

Hospital Clínic

Villarroel 170, Esc 6/8 Planta 2

08036 Barcelona

SPAIN

Phone/Fax: (+34) 932275549

Email: atorres@clinic.cat

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AVAILABILITY DATA AND MATERIALS

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

COMPETING INTERESTS

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

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AUTHORS’ CONTRIBUTIONS

AM, ALG, JR, and AT participated in protocol development, study design, study management, statistical analysis and data interpretation, and wrote the first draft of the report. AC, LFB, RP, DGG, OP, JAL, AR, DdG, RA, RM, JBM, RF and FB participated in study design, study management and interpretation, and provided critical review of the first draft of the report. AG performed statistical analysis and provided critical review of the first draft of the report. JMC, PR, FR, SSC, LS participated in data collection and provided critical review of the first draft of the report. CiberesUCICOVID consortium participated in data collection.

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Cardina Fernández, Laura Carrión García, Sula Carvalho, Núria Casacuberta-Barberà, Manuel Castellà, Andrea Castellví, Pedro Castro, Mercedes Catalán-González, Ramon Cicuendez Ávila, Catia Cillóniz, Luisa Clar, Cristina Climent, Jordi Codina, Pamela Conde, Sofía Contreras, María Cruz Martin, Maria del Carmen de la Torre, Raul de Pablo Sánchez, Diego De Mendoza, Cecilia del Busto Martínez, Yolanda Díaz, Emili Díaz, María Digna Rivas Vilas, Cristina Dólera Moreno, Irene Dot, Pedro Enríquez Giraudo, Inés Esmorís Arijón, Ángel Estella, Teresa Farre Monjo, Javier Fernández, Carlos Ferrando, Albert Figueras, Eva Forcadell-Ferreres, Lorena Forcelledo Espina, Nieves Franco, Àngels Furro, Cristóbal Galbán, Elena Gallego, Eugenia García, Felipe García, Beatriz García, Emilio García Prieto, Carlos García Redruello, Amaia García Sagastume, José Luis García Garmendia, José Garnacho-Montero, José M. Gómez, Maria Luisa Gascón Castillo, Gemma Gomà, Vanesa Gómez Casal, Silvia Gómez, Carmen Gómez Gonzalez, Jessica González, Federico Gordo, Maria Pilar Gracia, Víctor D. Gumucio- Sanguino, Alba Herraiz, Arturo Huerta, Rubén Herrán-Monge, Mercedes Ibarz, Silvia Iglesias, Maria Teresa Janer, Gabriel Jiménez, Ruth Noemí Jorge García, Mar Juan Díaz, Karsa Kiarostami, Juan I Lazo Álvarez, Miguel León, Ana López Lago, Ana Loza-Vázquez, Desire Macias Guerrero, Nuria Mamolar Herrera, Rafael Mañez Mendiluce, Cecilia L Mantellini, Gregorio Marco Naya, Pilar Marcos, Enrique Marmol Peis, Cinta Marsà-Fadurdo, Paula Martín Vicente, María Martínez, Amalia Martínez de la Gándara, Carmen Eulalia Martínez Fernández, Maria Dolores Martínez Juan, Ignacio Martínez Varela, Juan Fernando Masa Jimenez, Joan Ramon Masclans, Emilio Maseda, Eva María Menor Fernández, Juan Lopez Messa, Mar Miralbés, Josman Monclou, Juan Carlos Montejo-González, Neus Montserrat, María Mora Aznar, Pedro Moral-Parras, Dulce Morales, Sara Guadalupe Moreno Cano, David Mosquera Rodríguez, Guillermo M Albaiceta, Rosana Muñoz-Bermúdez, José María Nicolás, Ramon Nogue Bou, Rafaela Nogueras Salinas, Mariana Andrea Novo, Marta Ocón, Ana Ortega, Sergio Ossa, Pablo Pagliarani, Yhivian Peñasco, Anna Parera Pous, Francisco Parrilla, Leire Pérez Bastida, Purificación Pérez, Gloria Pérez Planelles, Eva Pérez Rubio, David Pestaña Laguna, Àngels Piñol-Tena, Juan Carlos Pozo-Laderas, Javier Prados, Andrés Pujol, Núria Ramon Coll, Gloria Renedo Sanchez-Giron, Laura Rodriguez, Felipe Rodríguez de Castro, Silvia Rodríguez, Covadonga Rodríguez Ruiz, Jorge Rubio, Alberto Rubio López, Miriam Ruiz Miralles, Pablo Ryan Murúa, Eva Saborido Paz, Ana Salazar Degracia, Inmaculada Salvador-Adell, Miguel Sanchez, Ana Sánchez, Angel Sánchez-Miralles, Bitor Santacoloma, Maria Teresa Sariñena, Marta Segura Pensado, Lidia Serra, Mireia Serra-Fortuny,

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To the Editor,

The 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/Astrazenca); 4.5 million (12.3%) mRNA-1273 (Moderna); and 2.0 million (5.4%) JNJ-78436735 (Janssen) [1].

The vaccination uptake has radically changed how the SARS-CoV-2 infection has impacted health care 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 could 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 two 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 1,585 patients were admitted to ICUs across seven Spanish hospitals due to COVID-19. Of those, 1,314 (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.

We detailed demographic and clinical characteristics of the fully vaccinated population in **Table 1**. In summary, the median age was 68.0 [60.0 – 74.0] years; 35 (43.2%) patients aged ≥70 years whilst only five patients aged < 50 years. Seventy-two percent (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 hypertension, being present in 61 (75.3%) patients. Twenty-eight (34.6%) patients had an immunocompromised status. The percentage of obese (BMI ≥ 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 and SOFA 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 4 (4.9%) AZD1222. Amongst the fully vaccinated patients, 50 (61.7%) have since been discharged from the hospital; 27 (33.3%) died in the ICU; 1 (1.2%) discharged from the ICU but remains at hospital; and 3 (3.7%) still require ICU admission at the time of writing this publication.

Amongst the fully vaccinated population, 45 (55.6%) received invasive mechanical ventilation. Forty-two (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. Twenty-two (27.2%) patients were diagnosed with nosocomial bacterial pneumonia, whilst twenty-three (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.

Investigators Contou et al. [6] published a study describing 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] had performed small reports of fully vaccinated patients that required hospitalization, 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. found that the significant association between hospitalization for COVID-19 and decreased likelihood of vaccination was weaker in immunocompromised patients than immunocompetent patients [9].

The implications of our findings are manyfold. 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.

Second, 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%) 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.

Table 1. Characteristics of fully and non-vaccinated, ICU-admitted patients with COVID-19.

	Fully vaccinated patients n=81	**Non-vaccinated patients n=105**	**p-value**
Baseline characteristics			
Age, median (IQR), years	68.0 [60.0– 74.0]	65.0 (55.0 – 73.0)	0.24
Male, n (%)	58 (71.6%)	71 (67.6%)	0.63
BMI, median (IQR), kg/m^2	27.6 (24.9 – 31.7)	30.1 (26.5 – 33.7)	**0.010**
Comorbidities, n (%)			
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 [a]	21 (25.9%)	16 (15.2%)	0.095
Chronic renal disease	16 (19.8%)	10 (9.5%)	0.055
Obesity (BMI ≥ 30 kg/m^2)	30 (37.0%)	57 (54.3%)	**0.026**
Diabetes mellitus	35 (43.2%)	26 (24.8%)	**0.011**
Immunodepression [b]	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, median (IQR)			
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, median (IQR)			
APACHE II score	12 (9 – 17)	10 (8 – 13)	**0.003**
SOFA score	4 (3 – 5)	4 (3 – 6)	0.64
Adjuvant treatments, n (%)			
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 (≤1mg/kg/day)	61 (75.3%)	76 (73.1%)	-
High doe (>1 mg/kg/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, n (%)			
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, n (%)			
Nosocomial bacterial pneumonia [c]	22 (27.2%)	45 (42.9%)	**0.032**
Ventilator-associated pneumonia	16 (72.7%)	35 (77.8%)	0.76
Microbiological diagnosis[d]	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 [e]	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 [f]	32 (39.5%)	32 (30.5%)	0.22
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, median (IQR)	19.0 (9.0 – 28.0)	20.0 (10.0 – 29.0)	0.51
Length of ICU stay, days, median (IQR)	11.0 (7.0 – 30.0)	15.0 (9.0 – 30.0)	**0.044**
Length of hospital stay, days, median (IQR)	19.0 (14.0 – 36.0)	21.0 (14.0 – 36.0)	0.31

Table 1 caption. Continuous variables are reported as median (Interquartile range) whilst categorical variables as frequencies (percentages). 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. A p value < 0.05 was considered as significant. APACHE-II; Acute Physiology and Chronic Health Evaluation II; BMI, Body Mass Index; ECMO, Extracorporeal Membrane Oxygenation; ICU, Intensive Care Unit; IMV, Invasive Mechanical Ventilation; NIMV, Non-Invasive Mechanical Ventilation; SOFA, Sepsis-related Organ Failure Assessment [a] Chronic respiratory disease includes any of chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, interstitial lung disease, asthma, or pre-existing requirement from long-term oxygen therapy. [b] Immunosuppression includes current solid organ or haematologic malignancy, AIDS/HIV, solid organ transplant, haematopoietic cell transplant, autoimmune diseases and any immunosuppressant treatment taken within 14 days of hospital admission. [c] Clinically or radiologically diagnosed bacterial pneumonia managed with antimicrobials. Bacteriologic confirmation was not required. [d] Three patients had polymicrobial pneumonia in the fully vaccinated group, whilst two patients in the non-vaccinated group. [e] Acute renal injury was defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or as an increase in serum creatinine ≥1.5 times more than baseline. [f] Liver dysfunction was defined as an increase in blood bilirubin, alanine transaminase or aspartate transaminase twice the upper limit of the normal range.

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