European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Characteristics and outcomes of unvaccinated and vaccinated COVID-19 patients with acute respiratory failure treated with CPAP in a medical intermediate care unit

Dear Editor,

Vaccinations against coronavirus disease 2019 (COVID-19) have undoubtedly conferred widespread protection against infection worldwide and are strongly associated with prevention of serious illness, with a hospitalization rate 10.5 times higher in unvaccinated compared with fully vaccinated persons [1,2].

As vaccination campaigns progress, emerging studies are describing the breakthrough of SARS-CoV-2 infections in vaccinated individuals rising proportionally as vaccine coverage increases.

In Spanish Intensive Care Units (ICU) between January and March 2021, 6.9% of patients have completed the vaccination regimen and were older, with three-fold increase in immunosuppression, higher Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) at admission and more comorbidities, factors that directly impact ICU management (longer ICU length of stay and no differences in mortality rate compared with unvaccinated) [3].

Between March and July 2021, more than a quarter of fully vaccinated patients admitted to hospital has been reported to be severely ill and this could be reflective of SARS-CoV-2 variants that might confer decreased vaccine effectiveness and an ineffective immune response among those with comorbidities [4].

A study on critically ill COVID-19 patients enrolled from September 2021 in the RISC-19-ICU registry discloses how, despite older age and elevated risk profile, vaccinated ICU patients had less severe lung and systemic organ failure (lower sequential organ failure assessment (SOFA)), need for mechanical ventilation, yet still similar ICU mortality [5].

In an original retrospective investigation Grasselli et al. reported that vaccines based on mRNA technology or adenoviral vectors significantly decreased the risk of ICU admission while, analysing data of vaccinated and unvaccinated patients admitted to ICUs in Lombardy (Italy) from August to December 2021 no significant association was detected with ICU and hospital mortality despite unvaccinated patients were younger and with fewer comorbidities [6].

A retrospective analysis on 32 fully vaccinated and 41 unvaccinated COVID-19 critically ill patients admitted between September and December 2021 to an Intermediate Respiratory Care Unit, all treated with high flow nasal oxygen, has reported no significant differences in anamnestic and clinical data; vaccinated patients were older but with less pulmonary ground glass opacities and consolidations, hypothesizing a vaccination protective effect on the extent of lung involvement, but clinical outcomes in the two groups were not significantly different [7].

We would like to briefly report data on 74 consecutive COVID-19 patients admitted from December 2021 to April 2022 to a medical Intermediate Care Unit (ImCU) in Lombardy (Italy) all treated with continuous positive airway pressure (CPAP) for acute respiratory failure (ARF) due to SARS-CoV-2 interstitial pneumonia to highlight the clinical differences between unvaccinated and vaccinated. ARF was defined by an arterial partial pressure of oxygen to inspiratory oxygen fraction ratio (PaO_2/FiO_2) < 300 mmHg or by an arterial partial pressure of oxygen (PaO_2) < 60 mmHg; pneumonia was defined by chest X-ray or computed tomography with COVID-19 related pulmonary interstitial thickenings; SARS-CoV-2 infection was confirmed by PCR assay for nasopharyngeal swab specimens. Negative SARS-CoV-2 patients, positive SARS-CoV-2 patients treated with CPAP with acute respiratory failure not caused by SARS-CoV-2 interstitial pneumonia and patients with respiratory failure due to SARS-CoV-2 interstitial pneumonia treated with CPAP not in the acute phase (patients needing CPAP in the weaning phase from invasive ventilation) were excluded.

35/74 (47.3%) patients were unvaccinated; 17/39 (43.6%) of vaccinated received 3 doses, 19/39 (48.7%) 2 doses, 3/39 (7.7%) received only one dose.

The viral genotyping was available for 47 patients: the Delta variant was identified in 23, the Omicron variant in 24, without differences in mortality (10/23, 43.5%, with Delta vs 10/24, 41.7%, with Omicron) and between unvaccinated and vaccinated.

Comparative statistics between vaccinated and unvaccinated are detailed in Table 1.

Without significant differences in disease severity at admission according to PaO_2/FiO_2 values and NEWS, SOFA and APACHE II scores, vaccinated were older and with a significantly higher number of underlying pathologies, as demonstrated by the absolute count (3[2–4] vs 2[0.5–3], $p = 0.017$) and by the Charlson's Comorbidity Index - CCI (6 [4.5–7.5] vs 5 [2.5–7], $p = 0.047$). Considering complementary diagnoses (sepsis, acute kidney injury, heart failure, arrhythmias, pneumothorax, deep venous thrombosis, pulmonary embolism, and delirium), 22/35 (62.8%) of unvaccinated had ≥ 1 complications versus 26/39 (66.7%) of vaccinated, without statistical difference.

https://doi.org/10.1016/j.ejim.2023.01.003
Received 30 December 2022; Accepted 3 January 2023
Available online 5 January 2023

Table 1
Baseline clinical characteristics and outcomes (n. (%) or median [IQR]).

	All $n = 74$	Unvaccinated $n = 35$	Vaccinated $n = 39$	p-value
Age	77 [67.5–81.7]	71 [65.5–81]	79 [71–82.5]	0.075
Female	33 (44.6%)	18 (51.4%)	15 (38.5%)	0.350
VoC: Delta	23	12	11	0.773
VoC: Omicron	24	11	13	
Symptom Onset (days)	5 [3–9]	7 [4–10]	4.5 [2–7]	**0.013**
Hypertension	47	18 (51.4%)	29 (74.4%)	0.056
CVD/HF	26	12 (34.3%)	14 (35.9%)	1.000
COPD	22	9 (25.7%)	13 (33.3%)	0.612
Diabetes	13	5 (14.3%)	8 (20.5)	0.552
Renal Failure	12	4 (11.4%)	8 (20.5%)	0.355
Cancer	16	5 (14.3%)	11 (28.2%)	0.169
Rheumatological Disease	10	5 (14.3%)	5 (12.8%)	1.000
Cerebral Vasculopathy	16	6 (17.1%)	10 (25.6%)	0.411
Immunodepression*	18	5 (14.3%)	13 (33.3%)	0.065
N. diseases	3 [1–4]	2 [0.5–3]	3 [2–4]	**0.017**
CCI	5.5 [3–7]	5 [2.5–7]	6 [4.5–7.5]	**0.047**
NEWS	6 [4–7]	6 [4–7]	6 [3.5–8]	0.863
SOFA	4 [3–5]	4 [3–4]	4 [3–5]	0.857
APACHE II	15 [12–17]	14 [10–16.5]	16 [13–17.5]	0.127
PaO_2 (mmHg)	65 [56.2–76.0]	69 [58.0–76.5]	62 [56.4–75.0]	0.442
PaO_2/FiO_2	119.5 [98.3–156.6]	115 [92.6–149.8]	124.3 [109.3–157]	0.135
CPAP FiO_2 (%)	60 [50–60]	60 [50–60]	50 [50–60]	0.360
CPAP PEEP (cmH_2O)	7.5 [7.5–10]	7.5 [7.5–8]	7.5 [7.5–10]	0.324
LoS-CPAP (days)	7 [3.5–10.5]	9 [4–11]	5.5 [3–9.7]	0.141
ICU transfer for IMV	1	0	1 (2.6%)	1.000
In hospital mortality	34	10 (28.6%)	24 (61.5%)	**0.006**
Mortality within 72 h	7	0	7 (17.9%)	**0.012**
LoS-in hospital (days)	17 [13–23.7]	18 [13.5–23–5]	16 [10–23.5]	0.164

VoC: variant of concern; LoS: Length of Stay; CVD: cardiovascular disease; HF: heart failure; COPD: chronic obstructive pulmonary disease; CCI: Charlson's Comorbidity Index; NEWS: national early warning score; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation; CPAP: continuous positive airway pressure; ICU: intensive care unit; IMV: invasive mechanical ventilation.

* Hematologic diseases, organ transplantations, HIV, chronic immunosuppressive medication.

Comorbidities and immunosuppression represent the most relevant issue related to the higher in-hospital mortality observed in vaccinated, 24/39 (61.5%) vs 10/35 (28.6%), $p = 0.006$ (Fig. 1).

Nevertheless, in survival analysis according to multivariable Cox proportional Hazard regression, stratifying patients for age and CCI (threshold ≥ 70 and ≥ 5, respectively, by the best Youden's index), all variables were removed from the model, including vaccination status (aHR 1.74, 95%CI 0.80–3.78, $p = 0.16$).

These results prove that in the severe disease stage few factors, including vaccines, influence outcome: all CPAP patients received steroid but were not eligible for antiviral or monoclonal therapy, and a no significant proportion could be treated with immunomodulators considering the high risk of bacterial superinfection.

Once severe SARS-CoV-2 illness develops, mortality is definitely high in both unvaccinated and vaccinated and that's why the vaccines are strongly recommended to elderly and frail patients, emphasizing that the benefits of adequate adherence to the vaccination campaign is mainly aimed to reduce risk of critical illness and hospitalization and consequently to reduce the COVID-19 related mortality risk on the overall population.

The poor dismal outcome enhances the clinical complexity of this cohort of critical patients in a medical intermediate care setting, with a comparable disease severity to ICU data, but for whom CPAP has been considered in large proportion as ceiling treatment according to denied indication to further escalate care intensity.

The major limitations of this study consist in its small sample size and monocentric design and in the missing data about the vaccine type and vaccination date.

The updated study period provides a preliminary focus on different SARS-CoV-2 variants and vaccination spread scenarios (when most frail patients in Italy have been fully vaccinated), excluding those SARS-CoV-2 positive patients that, especially during Omicron surge, have been admitted in hospital for reasons other than COVID-19 and for whom hospitalization and death may not be an enough specific marker to monitor the waning vaccine effectiveness over time.

These preliminary remarks about the ongoing hospitalized population characteristics highlight the decisive role of the internist in the interdisciplinary approach to COVID-19 patients admitted in ImCU for ARF due to SARS-CoV-2 pneumonia but with more active diseases.

Future real-life wider studies are needed to better characterize comorbid and immunocompromised patients with breakthrough infections developing critical disease.

In these "new" COVID-19 complex patients, the analyses of protection against severe disease would improve public health recommendations for adequate vaccine schedules and the identification of the ultimate causes of a consistently high in-hospital mortality rate would improve clinical management in critical ones.

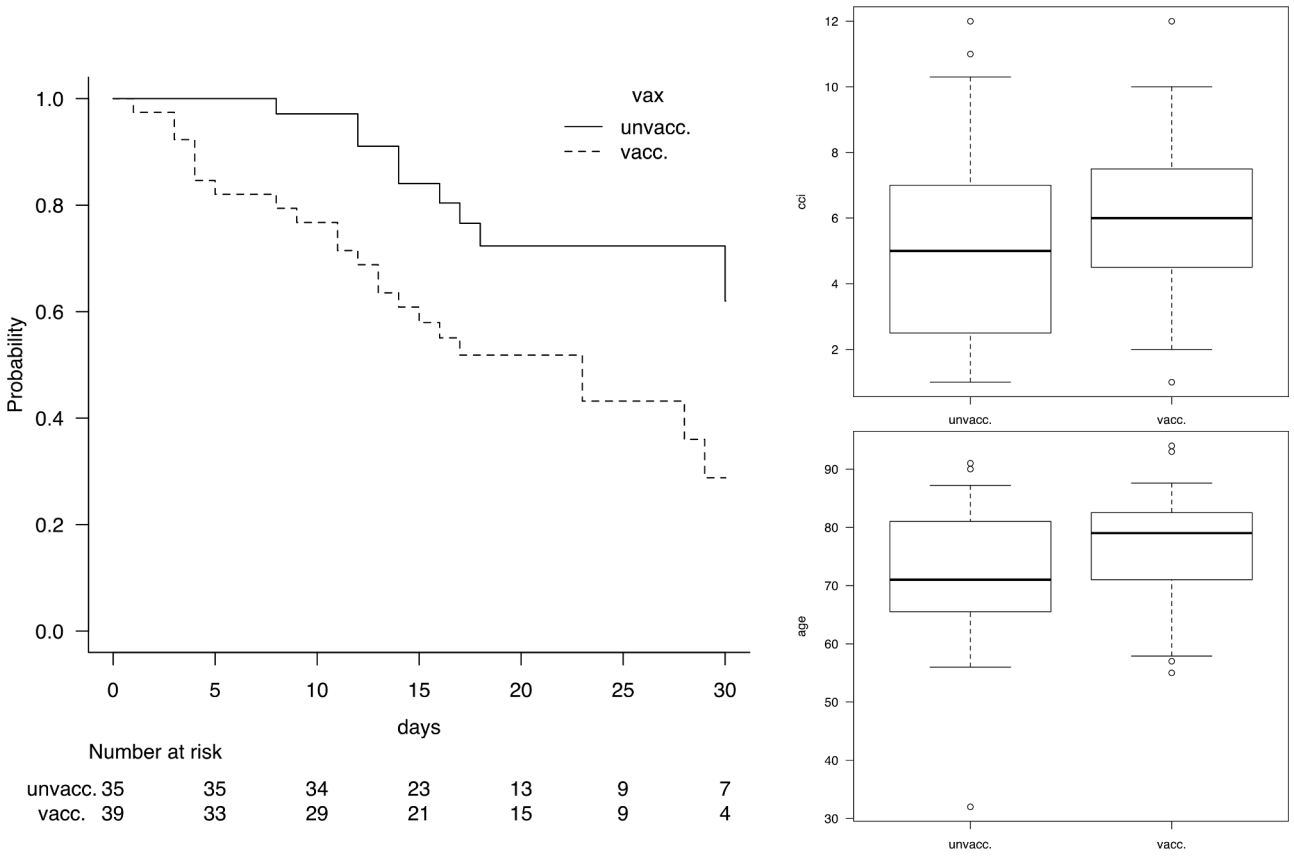

Fig. 1. Kaplan-Meier survival curve and box and whiskers (median, 95%CI) for Charlson's Comorbidity Index and Age by vaccination status.

References

[1] Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326:2043–54. https://doi.org/10.1001/jama.2021.19499.

[2] Havers FP, Pham H, Taylor CA, et al. COVID-19 associated hospitalizations among vaccinated and unvaccinated adults 18 years or older in 13 US states, January 2021 to April 2022. JAMA Intern Med 2022;182(10):1071–81. https://doi.org/10.1001/jamainternmed.2022.4299.

[3] Motos A, Lopez-Gavin A, Riera J, et al. CIBERESUCICOVID Project (COV20/00110, ISCCIII). Higher frequency of comorbidities in fully vaccinated patients admitted to the ICU due to severe COVID-19: a prospective, multicentre, observational study. Eur Resp J 2022;59(2):2102275. https://doi.org/10.1183/13993003.02275-2021.

[4] Juthani PV, Gupta A, Borges KA, et al. Hospitalization among vaccine breakthrough COVID-19 infections. Lancet Infect Dis 2021;21:1485–6. https://doi.org/10.1016/S1473-3099(21)00558-2.

[5] Hilty MP, Keiser S, Wendel Garcia PD, et al. RISC-19-ICU investigators for Switzerland. mRNA-based SARS-CoV-2 vaccination is associated with reduced ICU admission rate and disease severity in critically ill COVID-19 patients treated in Switzerland. Intensive Care Med 2022;48(3):362–5. https://doi.org/10.1007/s00134-021-06610-z.

[6] Grasselli G, Zanella A, Carlesso E, et al. Association of COVID-19 vaccinations with intensive care units admissions and outcomes of critically ill patients with COVID-19 pneumonia in Lombardy, Italy. JAMA Netw Open 2022;5(10):e2238871. https://doi.org/10.1001/jamanetworkopen.2022.38871.

[7] Giraudo C, Guarnieri G, Molena B, et al. The lung-protective effect of prior mRNA vaccination on breakthrough COVID-19 patients receiving high flow nasal oxygen for hypoxemic acute respiratory failure. Pulmonology 2022;13:57. https://doi.org/10.1016/j.pulmoe.2022.07.003.

Silvia Accordino[a,*], Ciro Canetta[a], Francesco Blasi[b,c]

[a] *High Care Internal Medicine Unit, Internal Medicine Department, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy*

[b] *Pulmonology and Cystic Fibrosis Unit, Internal Medicine Department, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy*

[c] *Department of Pathophysiology and Transplantation, University of Milan, Italy*

[*] Corresponding author.
E-mail address: silvia.accordino@policlinico.mi.it (S. Accordino).