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**LETTER**

# SARS-CoV-2 breakthrough infections in vaccinated individuals requiring ventilatory support for severe acute respiratory failure

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Dear Editor,

SARS-CoV-2 infections are expected in ~ 10% of the vaccinated population (breakthrough infection) [1]. Although early data showed that progression to critical illness was less likely among vaccinated than unvaccinated patients [2], recent data show that mortality in patients requiring admission to the intensive care unit (ICU) did not differ [3], or was higher [4, 5] in vaccinated than unvaccinated patients.

This study sets up to test the hypothesis that when age, comorbidities, and pathophysiological conditions are considered, vaccines are effective to prevent deaths in patients requiring ICU admission for breakthrough infection.

This prospective multicenter observational study enrolled patients from 27 ICUs in Italy (June 1st, 2021–June 31st, 2022). Entry criteria were age ≥ 18 and respiratory failure associated to coronavirus disease 2019 (COVID-19) with a P/F < 300. Exclusion criteria were (a) pre-existing limitations on the use of life-sustaining treatments; (b) no/incomplete information on vaccination status.

Study endpoint was hospital mortality. Age, comorbidities, arterial-to-inspiratory $O_2$ ratio (P/F), Simplified Acute Physiology Score (SAPS) II, and Sequential Organ Failure Assessment (SOFA) score were collected. Patients were classified as "vaccinated" (two-dose of mRNA vaccines or single-dose vaccine) and "unvaccinated" (one-dose of mRNA vaccines or no dose). Hospital mortality was adjusted using a multivariate logistic regression model that included age, comorbidities, clinical conditions at ICU admission, vaccination status, period of admission to the ICU (June 1st, 2021–December 31st, 2021, vs. January 1st, 2022–June 31st, 2022) and their interaction (online supplement). A sensitivity analysis was conducted comparing predicted vs. observed mortality in vaccinated and unvaccinated patients [6].

Among the 916 patients admitted, 262 were vaccinated (28.6%) (Fig. 1, online supplement). Vaccinated patients were older (71 vs. 63 years $p < 0.001$), with more comorbidities (91.2% vs. 65.7%, $p < 0.001$), had more renal and metabolic failures (40.5% vs. 25.1% and 26.3% vs. 18.5%, respectively; $p < 0.001$), and had higher SAPS II and SOFA scores (39 vs. 32 and 6 vs. 4, respectively; $p < 0.001$) (Table 1, online supplement).

Crude hospital mortality and risk of death in vaccinated were higher than in unvaccinated [54.7% vs. 41.3%, $p < 0.001$; OR 1.72 (95%CI: 1.28–2.30); $p < 0.001$, respectively]. After adjusting for covariates, risk of death in vaccinated was lower than in unvaccinated patients [OR 0.66 (95%CI: 0.44–0.98); $p = 0.04$)]. Neither year of admissions nor its interaction with vaccination status was statistically significant (Figs. 2 and 3**,** online supplement). In vaccinated patients, observed hospital mortality was lower than expected hospital mortality (Fig. 1, $p = 0.047$).

Lack of information regarding (a) time and vaccine brand; (b) whether the patients received a third booster dose; (c) the type of the SARS-CoV-2 variants infecting

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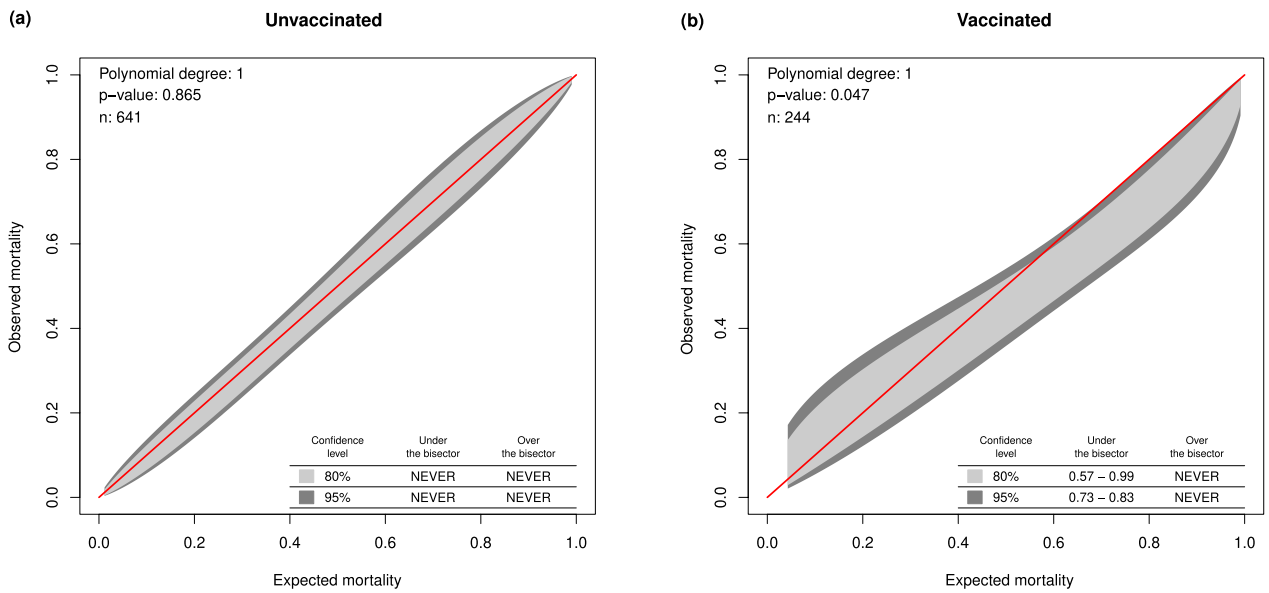


**Fig. 1** Calibration belts (light and dark gray: 80% and 95% confidence levels, respectively) comparing observed and expected mortality for unvaccinated (**a**) and vaccinated patients (**b**). A calibration belt below the line of identity indicates that observed mortality is lower than mortality expected according to the model

the patient are the major limitations of the present analysis. Although other techniques are available to deal with confounding factors, the granularity of the identified risk factors and the inclusion of the non-linear behavior of some of these factors allowed our logistic regression model to correct the observed risk of death [6]. The robustness of these methods may explain the difference in vaccination efficacy to reduce the risk of death also in ICU patients with outbreak infection observed in the present study but not reported in previous studies [3–5] in vaccinated than unvaccinated patients.

Our study therefore confirms the effectiveness of vaccination to reduce the risk of death also in ICU patients with breakthrough infection.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06952-2.

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**Author contributions**
All authors have contributed substantially to the conception and design of the study, the acquisition of data, or the analysis and interpretation of the data. All authors drafted or provided critical revision of the article. All authors provided the final approval of the version submitted for publication.

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**Data availability**
Data are available upon request at stefano.finazzi@marionegri.it.

**Declarations**

**Conflicts of interest**
CR declared consultancy fees for ad hoc advisory board meeting and honoraria for Lecture from Seqirus, MSD, Sanofi, outside from the submitted work. All other authors declare no conflicts of interest.

## Publisher's Note


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