

# Risk factors for intensive care unit admission and death from COVID-19 in fully vaccinated patients hospitalized for severe COVID-19, Brazil, 2021–2022

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**Suggested citation** Houvèssou GM, Vargas PCG, Jacques N, Leventhal DGP. Risk factors for intensive care unit admission and death from COVID-19 in fully vaccinated patients hospitalized for severe COVID-19, Brazil, 2021–2022. *Rev Panam Salud Publica*. 2022;46:e203. <https://doi.org/10.26633/RPSP.2022.203>

## ABSTRACT

**Objectives.** To assess factors associated with admission to an intensive care unit (ICU) and death from coronavirus disease 2019 (COVID-19) in fully vaccinated patients with severe COVID-19 in Brazil and the association between ICU admission and death from COVID-19.

**Methods.** This was retrospective study of patients hospitalized for COVID-19 from February 12, 2021 to January 10, 2022 across Brazil who were fully vaccinated against COVID-19 before hospitalization. Outcomes were admission in an ICU for COVID-19 and death from COVID-19. Variables evaluated were: sex; age; self-reported skin color; macroregion; comorbidities; time between full vaccination and onset of symptoms; and time between onset of symptoms and hospitalization. A Poisson regression model was used to estimate crude and adjusted risk ratios.

**Results.** Of 74 991 patients hospitalized for severe COVID-19, 67.28% were  $\geq 70$  years and 68.32% had at least one comorbidity. Men, patients aged 60–69 years, and patients aged 18–39 years with obesity had the greatest risk of ICU admission. Patients aged 18–39 years with obesity, diabetes, or renal diseases had the highest risk of death from COVID-19. When age and time between onset of symptoms and hospitalization were considered effect modifiers, patients admitted to an ICU 9–13 days after symptom onset in each age category had the greatest risk of death from COVID-19.

**Conclusion.** Although older patients were at greatest risk of ICU admission and death from COVID-19, the difference in the risk of dying from COVID-19 between patients admitted to an ICU and those not admitted was greatest for young adults.

## Keywords

COVID-19; vaccination; intensive care units; mortality; Brazil.

The ongoing pandemic caused by the new coronavirus began in Wuhan, China, and was characterized as a pneumonia of unknown etiology until the end of December 2019 (1). On January 9, 2020, the new coronavirus (now referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) was confirmed as the causative agent of coronavirus disease 2019 (COVID-19) (2–4) and the ensuing global public health crisis (5). The risk factors for severe symptoms of COVID-19 and

associated death include older age, diabetes, hypertension (6), and obesity (7). The severity of symptoms is also related to their duration: for mild cases, symptoms may last 2 weeks, while for severe cases, duration varies from 3 to 6 weeks (8).

Efforts to control the spread of COVID-19 have been implemented through both personal preventive measures, such as social distancing and the use of masks, as well as country-level initiatives. However, these measures have been insufficient

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for total control of the COVID-19 pandemic. Vaccination on a national and global scale has offered an opportunity for pandemic control. The primary focus of these efforts has been the reduction of deaths and, to a great extent, assigned priority groups have already been fully vaccinated (9, 10).

Brazil, an upper middle-income country with an estimated population of more than 213 million inhabitants in 2021 (11), is third among countries most affected by COVID-19, with more than 24 million confirmed cases reported as of January 25, 2022 (12) and a mortality rate greater than 296 per 100 000 inhabitants as of January 25, 2022 (13). COVID-19 vaccine rollout in Brazil began on January 17, 2021 and prioritized the most vulnerable groups and frontline health professionals. As of January 4, 2022, 143 707 365 people, or more than 67% of the population aged 12 years and older, had been vaccinated with either two-dose or single-dose (Johnson & Johnson/Janssen) COVID-19 vaccines (14). However, despite the high efficacy of COVID-19 vaccines, a small proportion of fully vaccinated people (i.e. who have received all recommended doses of an authorized COVID-19 vaccine) develop symptomatic or asymptomatic SARS-CoV-2 infections (15–17).

In light of this situation, the present study aimed to: describe factors associated with admission to intensive care units (ICUs) because of COVID-19 and death from COVID-19 in fully vaccinated patients hospitalized with severe COVID-19 (i.e. who had completed a two-dose or single-dose course); and assess the association between ICU admission and death from COVID-19 in this sample.

## METHODS

### Participants and data sources

The present retrospective study assessed cases of severe COVID-19 in fully vaccinated hospitalized patients in Brazil, using secondary data from the Influenza Epidemiological Surveillance Information System, Sivep-Gripe (Sistema de Informação de Vigilância Epidemiológica da Gripe) of the Ministry of Health. Data were collected by hospital teams using the Sivep-Gripe compulsory notification sheet for cases hospitalized with severe COVID-19. Of 5920 health facilities with hospitalized cases of confirmed COVID-19, 3388 had fully vaccinated patients and were included in the analytical sample. Severe COVID-19 was defined as flu-like illness (acute respiratory illness, exhibiting at least two of the following signs and symptoms: fever, chills, sore throat, headache, cough, runny nose, or loss of smell or taste) with dyspnea/respiratory discomfort or persistent pressure in the thorax or oxygen saturation less than 95% in ambient air, or blueness in the lips or face (18). Different serological tests were used to diagnose COVID-19. In case of differing results between laboratory methods, the value from reverse transcriptase polymerase chain reaction (RT-PCR) was used.

### Independent variables

The following variables were included: sex (female, male); age in completed years; self-reported skin color (white, black, other (yellow and indigenous), not reported); Brazilian macroregion (South, Southeast, Central-West, Northeast, North); comorbidities exhibited (asthma, diabetes mellitus, Down

syndrome, heart disease, hematological disease, hepatic disease, immunodeficiency disorder, lung disease, neurological disease, obesity, and renal disease); time between the second or single dose of the COVID-19 vaccine and the appearance of initial symptoms (in days); and time between onset of symptoms and hospitalization (in days). The comorbidities assessed were used to create the variable number of comorbidities.

Comorbidities were primarily measured by hospital teams by observing records in patients' charts. Sivep-Gripe's notification sheet contains the question "Do you have any risk factors/comorbidities? If yes, which ones? (Mark x)". This question is followed by a list of 12 comorbidities to be measured (18). After filling out the form, data are entered into the online information system. Because of the question's format in the notification sheet, individuals marked with "Yes" were considered to have a comorbidity, while those marked with "No" or for whom no answer was recorded were excluded.

### Exposure, outcomes, and effect modifiers

The variable ICU admission was considered as an exposure in the model assessing the association between ICU admission and death by COVID-19. The assessed outcomes were admission to an ICU and death from COVID-19. ICU admission was categorized as: yes, no, not recorded. The variable death from COVID-19 was categorized as: recovery, death, death from other causes, not recorded.

Age was found to be an effect modifier of COVID-19 outcomes in a previous study (7), and after testing we confirmed it was an effect modifier in the association between ICU admission and death by COVID-19. Age was also an effect modifier in the predictive models using ICU admission (age was as an effect modifier of obesity) and death from COVID-19 (age was as an effect modifier of obesity, diabetes mellitus, and renal disease) as outcomes. In addition, an exploratory analysis revealed that time between onset of symptoms and hospitalization (in days) also modified the effect of ICU admission on death from COVID-19. Thus, both age and time between onset of symptoms and hospitalization were included as effect modifiers in the association between ICU admission and death from COVID-19.

### Inclusion and exclusion criteria

The study sample consisted of patients 18 years or older in Brazil who were hospitalized with confirmed COVID-19 and who had already received the second dose or single dose (Johnson & Johnson/Janssen) of a COVID-19 vaccine before hospitalization. Patients had a recorded outcome of hospitalization (discharge or death) from February 12, 2021 to January 10, 2022.

Individuals (22 893) who received both doses of a two-dose COVID-19 vaccine or the single dose of a one-dose COVID-19 vaccine after infection were excluded, as were patients with no hospitalization outcome recorded by January 10, 2022 (6436 cases). We also excluded all cases where responses were not recorded for the variables: comorbidities, ICU admission, and death from COVID-19 (2825 cases), as well as cases recorded as death from causes other than COVID-19 (282 cases).

### Statistical analysis

Stata 14 software (Stata Corp., College Station, Texas, USA) was used for all analyses. Descriptive analyses of the independent variables and outcomes assessed were initially done and expressed as absolute and relative frequencies. Next, bivariate analyses between the independent and outcome variables were done with data expressed as 95% confidence intervals (95% CI). A Poisson regression model was used to estimate the crude and adjusted risk ratios (RR), with 95% CI. Finally, logistic regression analysis was used to verify the significance of effect modification.

Variables were included in the multivariate models through backward selection following a hierarchical conceptual model. In this model, the variables sex, age, self-reported skin color, and region were in the most distal level (indirectly affecting health), number of comorbidities or comorbidities were in the intermediate level, and the variables time between final dose of vaccine and onset of symptoms, time between onset of symptoms and hospitalization were in the proximal level (directly affecting health). Number of comorbidities and presence of comorbidities were included in the models one at a time, rather than together, as they are essentially the same variable. To control for confounding in the association between ICU admission and death from COVID-19, variables with a *p* value < 0.2 were kept in the model, while all variables with a *p* value > 0.2 were not included. A *p* value of < 0.01 was considered statistically significant because of the large sample size. A Wald test with

robust variance was used to estimate the *p* value of each variable included in the models.

### Ethical considerations

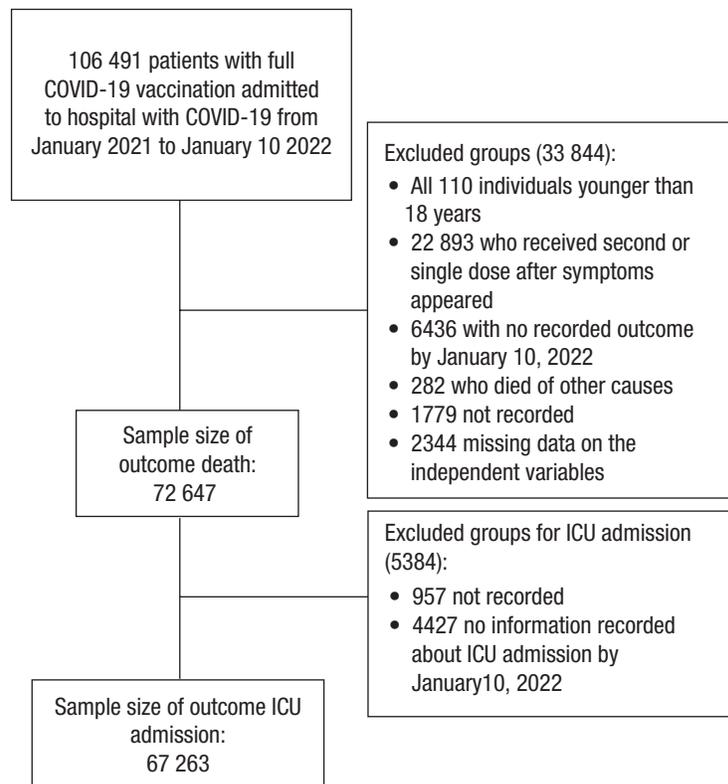
The secondary data from Sivep-Gripe are de-identified and publicly available on the OpenDataSUS website (19) maintained by the Ministry of Health. Thus, our study did not need approval from an ethics committee on research on human beings, as recommended by Resolution No. 510/2016 of the National Health Council. Aggregated data were used, with very little risk of identification of participants.

### RESULTS

The study sample consisted of 72 647 fully vaccinated patients hospitalized for severe COVID-19 from all Brazil; 67 263 were analyzed for ICU admission and 67 251 for the association between ICU admission and death from COVID-19 (Figure 1). Of the total sample, 51.54% were men and 67.27% were aged 70 years or older. The Southeast region had 57.44% of the cases; patients were predominantly White (55.43%) and 68.32% had at least one comorbidity. The percentages of patients admitted to the ICU and who died of COVID-19 were 43.20% and 43.35%, respectively (Table 1).

According to the adjusted analysis in Table 2, men had a 12% (RR = 1.12; 95% CI: 1.10–1.14) greater risk of being admitted to the ICU than women. In addition, patients aged 60–69 years

**FIGURE 1: Flow diagram of study sample**



COVID-19, coronavirus disease 2019; ICU, intensive care unit.  
**Source:** Prepared by authors from Brazil, Sivep-Gripe database (18).

**TABLE 1. Characteristics of fully vaccinated patients hospitalized for COVID-19 and proportion of deaths from COVID-19 and admission to an intensive care unit, Brazil, February 12, 2021 to January 10, 2022**

Variable	n (%) (n = 72 647)	Proportion of deaths from COVID-19 (n = 72 647), % (95% CI)	Proportion of ICU admissions (n = 67 263), % (95% CI)
<b>Sex</b>			
Female	35 202 (48.46)	41.00 (40.48–41.51)	40.96 (40.43–41.50)
Male	37 445 (51.54)	45.57 (45.07–46.08)	45.30 (44.78–45.82)
<b>Age group, in years</b>			
18–39	2 396 (3.30)	9.93 (8.80–11.20)	31.91 (30.00–33.89)
40–59	7 261 (9.99)	19.64 (18.74–20.57)	37.70 (36.54–38.86)
60–69	14 123 (19.44)	36.31 (35.52–37.11)	44.90 (44.05–45.75)
≥ 70	48 867 (67.27)	50.55 (50.11–51.00)	44.08 (43.62–44.53)
<b>Region of residence</b>			
Southeast	41 726 (57.44)	44.18 (43.71–44.66)	43.50 (43.01–44.00)
South	17 819 (24.53)	42.44 (41.71–43.17)	40.05 (39.32–40.78)
Central-West	4 814 (6.63)	40.74 (39.35–42.13)	43.72 (42.25–45.20)
Northeast	6 271 (8.63)	46.12 (44.895–47.35)	53.48 (52.17–54.78)
North	2 017 (2.78)	32.03 (30.02–34.10)	33.58 (31.42–35.80)
<b>Skin color</b>			
White	40 268 (55.43)	44.87 (44.38–45.35)	41.28 (40.79–41.78)
Black	22 010 (30.30)	42.58 (41.93–43.24)	44.16 (43.47–44.85)
Other	807 (1.11)	41.76 (38.39–45.20)	41.87 (38.35–45.47)
Not recorded	9 562 (13.16)	38.90 (37.93–39.89)	49.50 (48.45–50.56)
<b>Number of comorbidities</b>			
0	23 109 (31.68)	35.29 (34.68–35.91)	36.97 (36.31–37.63)
1	24 728 (34.04)	43.10 (42.49–43.72)	42.66 (42.02–43.29)
2	17 726 (24.40)	48.86 (48.12–49.60)	47.57 (46.82–48.33)
3	5 776 (7.95)	55.99 (54.71–57.27)	52.69 (51.38–54.00)
≥ 4	1 308 (1.80)	60.09 (57.41–62.72)	54.92 (52.17–57.64)
<b>Time between full vaccination and onset of symptoms, in days</b>			
0–40	18 345 (25.25)	42.91 (42.20–43.63)	39.32 (38.59–40.06)
41–100	22 284 (30.67)	44.36 (43.71–45.01)	42.13 (41.46–42.81)
≥ 101	32 018 (44.07)	42.91 (42.37–43.45)	46.16 (45.59–46.73)
<b>Comorbidity</b>			
Heart disease	34 818 (47.93)	47.93 (47.40–48.45)	46.86 (46.32–47.40)
Diabetes mellitus	23 819 (32.79)	47.27 (46.64–47.91)	47.46 (46.80–48.11)
Down syndrome	140 (0.19)	41.43 (33.48–49.85)	38.35 (30.39–46.98)
Neurological disease	4 833 (6.65)	59.26 (57.87–60.64)	42.84 (41.42–44.27)
Renal disease	3 712 (5.11)	62.18 (60.60–63.72)	55.56 (53.93–57.19)
Asthma	1 865 (2.57)	37.75 (35.57–39.97)	42.07 (39.79–44.39)
Lung disease	4 045 (5.57)	57.48 (55.95–58.99)	49.40 (47.81–50.98)
Hematological disease	591 (0.81)	56.01 (51.96–59.97)	49.65 (45.54–53.77)
Immunodeficiency disorder	1 989 (2.74)	55.30 (53.11–57.48)	46.21 (43.98–48.46)
Hepatic disease	628 (0.86)	54.78 (50.85–58.64)	46.78 (42.82–50.78)
Obesity	6 603 (9.09)	45.45 (44.25–46.65)	52.77 (51.54–54.00)
<b>Time between onset of symptoms and hospital admission, in days</b>			
0–4	26 989 (37.15)	50.19 (49.59–50.78)	43.11 (42.49–43.73)
5–8	26 295 (36.20)	40.57 (39.97–41.16)	43.35 (42.73–43.97)
9–14	14 633 (20.14)	35.89 (35.12–36.67)	42.43 (41.61–43.26)
≥ 15	4 730 (6.51)	42.96 (41.55–44.3)	45.28 (43.82–46.75)
<b>Admission to intensive care unit (n = 67 263)</b>			
No	38 205 (56.80)	NA	56.80 (56.42–57.17)
Yes	29 058 (43.20)	NA	43.20 (42.83–43.58)
<b>Death from COVID-19</b>			
No	41 151 (56.65)	56.65 (56.28–57.01)	NA
Yes	31 496 (43.35)	43.35 (42.99–43.72)	NA

COVID-19, coronavirus disease 2019; NA, not applicable.

**Note:** Fully vaccinated patients had received a second dose of a two-dose vaccine or one dose of a single-dose vaccine before contracting COVID-19.**Source:** Prepared by the authors from the study results.

**TABLE 2. Factors associated with admission to an intensive care unit for severe COVID-19 in fully vaccinated patients, Brazil, February 12, 2021 to January 10, 2022**

Variable	Crude RR (95% CI)	p-value <sup>a</sup>	Adjusted RR <sup>b</sup> (95% CI)	p-value <sup>a</sup>
<b>Sex</b>		< 0.001		< 0.001
Female	Ref		Ref	
Male	1.10 (1.08–1.12)		1.12 (1.10–1.14)	
<b>Age group, in years</b>		< 0.001		< 0.001
18–39	Ref		Ref	
40–59	1.19 (1.11–1.27)		1.20 (1.11–1.30)	
60–69	1.41 (1.32–1.50)		1.35 (1.27–1.46)	
≥ 70	1.38 (1.30–1.46)		1.34 (1.24–1.44)	
<b>Region of residence</b>		< 0.001		< 0.001
North	Ref		Ref	
Northeast	1.58 (1.48–1.69)		1.54 (1.43–1.65)	
Central-West	1.29 (1.20–1.39)		1.28 (1.19–1.38)	
Southeast	1.29 (1.21–1.38)		1.24 (1.16–1.33)	
South	1.19 (1.11–1.27)		1.15 (1.07–1.23)	
<b>Skin color</b>		< 0.001		< 0.001
White	Ref		Ref	
Black	1.07 (1.05–1.09)		1.03 (1.01–1.06)	
Other	1.02 (0.94–1.11)		1.01 (0.93–1.10)	
Not recorded	1.21 (1.18–1.24)		1.17 (1.14–1.20)	
<b>Number of exhibited comorbidities</b>		< 0.001		< 0.001 <sup>c</sup>
0	Ref		Ref	
1	1.15 (1.13–1.18)		1.15 (1.12–1.17)	
2	1.28 (1.26–1.32)		1.28 (1.25–1.31)	
3	1.42 (1.37–1.46)		1.42 (1.37–1.46)	
4 or more	1.48 (1.40–1.56)		1.49 (1.41–1.57)	
<b>Time between full vaccination and onset of symptoms, in days</b>		< 0.001		< 0.001 <sup>c</sup>
0–40	Ref		Ref	
41–100	1.07 (1.05–1.10)		1.07 (1.04–1.10)	
≥ 101	1.18 (1.15–1.20)		1.18 (1.15–1.21)	
<b>Time between onset of symptoms and hospital admission, in days</b>		0.003		0.005
0–4	Ref		Ref	
5–8	1.01 (0.99–1.03)		1.01 (0.99–1.03)	
9–14	0.98 (0.96–1.01)		1.00 (0.98–1.03)	
≥ 15	1.05 (1.02–1.09)		1.06 (1.03–1.10)	
<b>Comorbidity<sup>d</sup></b>				
Renal disease	1.31 (1.27–1.35)	< 0.001	1.23 (1.19–1.27)	< 0.001
Heart disease	1.18 (1.16–1.20)	< 0.001	1.11 (1.09–1.13)	< 0.001
Lung disease	1.15 (1.11–1.19)	< 0.001	1.11 (1.08–1.15)	< 0.001
Diabetes mellitus	1.16 (1.14–1.18)	< 0.001	1.09 (1.07–1.11)	< 0.001
Hematological disease	1.15 (1.06–1.24)	0.001	1.08 (0.99–1.17)	0.091
Immunodeficiency disorder	1.07 (1.02–1.13)	0.008	1.07 (1.01–1.12)	0.012
Hepatic disease	1.09 (1.00–1.18)	0.049	1.02 (0.93–1.11)	0.698
Down syndrome	0.91 (0.74–1.12)	0.385	NI <sup>e</sup>	–
Asthma	0.97 (0.92–1.03)	0.347	NI <sup>e</sup>	–
Neurological disease	0.99 (0.95–1.02)	0.386	NI <sup>e</sup>	–
<b>Obesity by age category, in years</b>				
18–39	1.47 (1.47–1.90)	< 0.001	1.65 (1.45–1.86)	< 0.001
40–59	1.29 (1.20–1.39)	< 0.001	1.28 (1.19–1.38)	< 0.001
60–69	1.31 (1.25–1.37)	< 0.001	1.31 (1.25–1.37)	< 0.001
≥ 70	1.21 (1.17–1.26)	< 0.001	1.20 (1.16–1.24)	< 0.001

COVID-19, coronavirus disease 2019; RR, risk ratio; CI, confidence interval; Ref, reference category; NI, not included.

<sup>a</sup> Wald test with robust variance.

<sup>b</sup> Model adjusted for: sex, age, region, skin color, time between full vaccination and onset of symptoms, time between onset of symptoms and hospital admission, heart disease, diabetes mellitus, lung disease, immunodeficiency disorder, renal disease, and obesity.

<sup>c</sup> Test for linear trend.

<sup>d</sup> Reference category is not having a disease.

<sup>e</sup> Variable not included in the model because the p-value was more than 0.2 in the unadjusted analysis.

**Note:** Fully vaccinated patients had received a second dose of a two-dose vaccine or one dose of a one-dose vaccine before contracting COVID-19.

**Source:** Prepared by the authors from the study results.

had a 35% (RR = 1.35; 95% CI: 1.27–1.46) higher risk of being admitted to the ICU than the youngest age group. Among the five macroregions, patients from the North region, the reference category in our analysis, had the smallest risk of ICU admission for COVID-19 while patients from the Northeast region had the highest risk (RR = 1.54; 95% CI: 1.43–1.65). With regard to comorbidities, age was an effect modifier of the association between obesity and ICU admission for COVID-19 ( $p < 0.001$ ). Among all age groups, the greatest difference in risk of ICU admission between obese and non-obese patients was in the age group 18–39 years (RR = 1.65; 95% CI: 1.45–1.86). Patients whose COVID-19 symptoms began 101 days or more after being fully vaccinated against COVID-19 had an 18% (RR = 1.18; 95% CI: 1.15–1.21) greater risk of being admitted to the ICU than patients with a symptom onset of up to 40 days after full vaccination against COVID-19.

According to the adjusted analysis in Table 3, men were at 12% greater risk of death from COVID-19 than women (RR = 1.12; 95% CI: 1.10–1.14). In addition, the risk of death from COVID-19 increased with increasing age ( $p < 0.001$ ). For the

regional analysis, as with ICU admissions for COVID-19, the lowest risk was in the North region (reference category) and the highest was in the Northeast region (RR = 1.23; 95% CI: 1.15–1.31). The risk of death from COVID-19 increased as the number of comorbidities increased ( $p < 0.001$ ). Patients who were admitted to an ICU 9–14 days after the onset of COVID-19 symptoms had a 24% (RR = 0.76, 95% CI: 0.75–0.78) lower risk of dying of COVID-19 than those admitted 0–4 days after onset of symptoms. Age modified the effect of the comorbidities obesity ( $p < 0.001$ ), renal disease ( $p < 0.001$ ), and diabetes mellitus ( $p < 0.001$ ) on death from COVID-19. Furthermore, of all the age groups, patients aged 18–39 years with obesity (RR = 2.01; 95% CI: 1.54–2.63), diabetes mellitus (RR = 1.87; 95% CI: 1.38–2.53), and renal diseases (RR = 2.84; 95% CI: 1.87–4.30) had the largest differences in risk of death from COVID-19 compared with COVID-19 patients of the same age without these comorbidities.

Table 4 gives the analyses of the association between ICU admission and death from COVID-19 with age and time between onset of symptoms of COVID-19 and hospitalization

**TABLE 3. Factors associated with death from COVID-19 in fully vaccinated patients hospitalized with severe COVID-19, Brazil, February 12, 2021 to January 10, 2022**

Variable	Unadjusted RR (95% CI)	<i>p</i> value <sup>a</sup>	Adjusted RR <sup>b</sup> (95% CI)	<i>p</i> value <sup>a</sup>
<b>Sex</b>		< 0.001		< 0.001
Female	Ref		Ref	
Male	1.11 (1.09–1.12)		1.12 (1.10–1.14)	
<b>Age group, in years</b>		< 0.001		< 0.001 <sup>c</sup>
18–39	Ref		Ref	
40–59	1.97 (1.74–2.24)		2.01 (1.81–2.52)	
60–69	3.62 (3.21–4.08)		4.38 (3.74–5.12)	
≥ 70	5.04 (4.48–5.68)		6.36 (5.44–7.41)	
<b>Region of residence</b>		< 0.001		< 0.001
Northeast	1.44 (1.35–1.54)		1.23 (1.15–1.31)	
Southeast	1.37 (1.29–1.46)		1.14 (1.07–1.21)	
Central-West	1.26 (1.17–1.35)		1.14 (1.07–1.23)	
South	1.32 (1.24–1.40)		1.12 (1.05–1.19)	
North	Ref		Ref	
<b>Skin color</b>		< 0.001		< 0.001
White	Ref		Ref	
Black	0.95 (0.93–0.97)		0.98 (0.96–1.00)	
Other	0.93 (0.86–1.01)		0.99 (0.92–1.08)	
Not recorded	1.21 (1.18–1.24)		1.17 (1.14–1.20)	
<b>Number of comorbidities</b>		< 0.001		< 0.001
0	Ref		Ref	
1	1.22 (1.19–1.25)		1.14 (1.12–1.17)	
2	1.38 (1.35–1.41)		1.27 (1.24–1.30)	
3	1.58 (1.54–1.63)		1.44 (1.40–1.48)	
4 or more	1.70 (1.62–1.78)		1.52 (1.45–1.60)	
<b>Time between full vaccination and onset of symptoms, in days</b>		0.002		< 0.001 <sup>c</sup>
0–40	Ref		Ref	
41–100	1.03 (1.01–1.06)		0.97 (0.95–0.99)	
≥ 101	1.00 (0.98–1.02)		0.90 (0.89–0.92)	

(Continued)

**TABLE 3. (Continued)**

Variable	Unadjusted RR (95% CI)	p value <sup>a</sup>	Adjusted RR <sup>b</sup> (95% CI)	p value <sup>a</sup>
<i>Time between onset of symptoms and hospital admission, in days</i>				
0–4	Ref		Ref	
5–8	0.81 (0.79–0.82)	< 0.001	0.86 (0.84–0.87)	< 0.001
9–14	0.72 (0.70–0.73)		0.76 (0.75–0.78)	
≥ 15	0.85 (0.83–0.88)		0.85 (0.82–0.88)	
<i>Comorbidity<sup>d</sup></i>				
Immunodeficiency disorder	1.29 (1.24–1.35)	< 0.001	1.23 (1.18–1.28)	< 0.001
Neurological disease	1.40 (1.37–1.44)	< 0.001	1.23 (1.20–1.26)	< 0.001
Lung disease	1.35 (1.31–1.39)	< 0.001	1.18 (1.14–1.21)	< 0.001
Hematological disease	1.31 (1.22–1.40)	< 0.001	1.11 (1.03–1.20)	0.004
Hepatic disease	1.29 (1.21–1.38)	< 0.001	1.11 (1.03–1.19)	0.008
Heart disease	1.22 (1.20–1.24)	< 0.001	1.07 (1.05–1.09)	< 0.001
Asthma	0.87 (0.82–0.92)	< 0.001	0.88 (0.83–0.93)	0.001
Down syndrome <sup>e</sup>	0.96 (0.79–1.16)	0.345	NI	–
<i>Obesity by age group, in years</i>				
18–39	2.07 (1.60–2.68)	< 0.001	2.01 (1.54–2.63)	< 0.001
40–59	1.61 (1.45–1.79)	< 0.001	1.55 (1.39–1.73)	< 0.001
60–69	1.21 (1.14–1.28)	< 0.001	1.18 (1.11–1.26)	< 0.001
≥ 70	1.09 (1.05–1.12)	< 0.001	1.08 (1.05–1.12)	< 0.001
<i>Diabetes mellitus by age group, in years</i>				
18–39	2.40 (1.80–3.21)	< 0.001	1.87 (1.38–2.53)	< 0.001
40–59	1.54 (1.40–1.69)	< 0.001	1.36 (1.24–1.50)	< 0.001
60–69	1.15 (1.10–1.20)	< 0.001	1.11 (1.036– 1.15)	< 0.001
≥ 70	1.05 (1.03–1.07)	< 0.001	1.03 (1.01–1.05)	0.001
<i>Renal disease by age group, in years</i>				
18–39	3.05 (2.08–4.47 )	< 0.001	2.84 (1.87–4.30)	< 0.001
40–59	2.50 (2.18–2.85)	< 0.001	2.17 (1.89–2.49)	< 0.001
60–69	1.65 (1.55–1.76)	< 0.001	1.47 (1.37–1.57)	< 0.001
≥ 70	1.32 (1.28–1.36)	< 0.001	1.24 (1.21–1.28)	< 0.001

COVID-19, coronavirus disease 2019; RR, risk ratio; CI, confidence interval; Ref, reference category; NI, not included.

<sup>a</sup> Wald test with robust variance.

<sup>b</sup> Model adjusted for: sex, age, region, skin color, time between full vaccination and onset of symptoms, time between onset of symptoms and hospital admission, heart disease, diabetes mellitus, lung disease, hematological disease, hepatic disease, asthma, neurological disease, immunodeficiency disorder, renal disease, and obesity.

<sup>c</sup> Test for linear trend.

<sup>d</sup> Reference category is not having a disease.

<sup>e</sup> Variable not included in the model because the p-value was more than 0.2 in the unadjusted analysis.

**Note:** Fully vaccinated patients had received a second dose of a two-dose vaccine or one dose of a one-dose vaccine before contracting COVID-19.

**Source:** Prepared by the authors from the study results.

**TABLE 4. Association between admission to the intensive care unit and death from COVID-19 in fully vaccinated patients admitted for COVID-19, by modifying variables, Brazil, February 12, 2021 to January 10, 2022**

Modifying variables	Unadjusted RR (95% CI)	p-value <sup>a</sup>	Adjusted RR (95% CI) <sup>b</sup>	p-value <sup>a</sup>
<i>Age 18–39 years and time in days between onset of symptoms and hospital admission of:<sup>c</sup></i>				
0–4	5.01 (3.30–7.61)	< 0.001	5.48 (4.08–7.35)	< 0.001
5–8	10.72 (5.87–19.57)	< 0.001	7.23 (5.39–9.70)	< 0.001
9–13	7.37 (3.88–13.99)	< 0.001	8.49 (6.31–11.43)	< 0.001
≥ 14	10.13 (2.31–44.22)	0.002	7.40 (5.46–10.01)	< 0.001
<i>Age 40–59 years and time in days between onset of symptoms and hospital admission of:<sup>c</sup></i>				
0–4	3.49 (2.95–4.13)	< 0.001	3.69 (3.29–4.13)	< 0.001
5–8	5.21 (4.33–6.27)	< 0.001	4.87 (4.35–5.45)	< 0.001
9–13	7.08 (5.34–9.39)	< 0.001	5.72 (5.08–6.44)	< 0.001
≥ 14	2.83 (1.85–4.33)	< 0.001	4.98 (4.36–5.70)	< 0.001
<i>Age 60–69 years and time in days between onset of symptoms and hospital admission of:<sup>c</sup></i>				
0–4	2.53 (2.34–2.73)	< 0.001	2.71 (2.55–2.87)	< 0.001
5–8	3.67 (3.37–4.04)	< 0.001	3.57 (3.37–3.79)	< 0.001

(Continued)

TABLE 4. (Continued)

Modifying variables	Unadjusted RR (95% CI)	p-value <sup>a</sup>	Adjusted RR (95% CI) <sup>b</sup>	p-value <sup>a</sup>
9–13	5.11 (4.42–5.91)	< 0.001	4.20 (3.92–4.49)	< 0.001
≥ 14	3.60 (2.90–4.47)	< 0.001	3.65 (3.34–4.00)	< 0.001
<i>Age 70 years or older and time in days between onset of symptoms and hospital admission of:<sup>c</sup></i>				
0–4	1.77 (1.72–1.81)	< 0.001	1.77 (1.73–1.82)	< 0.001
5–8	2.31 (2.23–2.39)	< 0.001	2.34 (2.26–2.42)	< 0.001
9–13	2.65 (2.52–2.80)	< 0.001	2.75 (2.61–2.89)	< 0.001
≥ 14	2.44 (2.25–2.64)	< 0.001	2.39 (2.22–2.58)	< 0.001

COVID-19, coronavirus disease 2019; RR, risk ratio; CI, confidence interval.

<sup>a</sup> Wald test with robust variance.

<sup>b</sup> Adjusted for sex, skin color, region, obesity, heart disease, hematological disease, Down syndrome, hepatic disease, asthma, diabetes mellitus, neurological disease, lung disease, immunodeficiency disorders, renal disease, and time between full vaccination and onset of symptoms.

<sup>c</sup> The reference category is patients not admitted to intensive care units in the same categories of age and time between onset of symptoms and hospital admission.

**Note:** Fully vaccinated individuals had received a second dose of a two-dose vaccine or one dose of a one-dose vaccine before contracting COVID-19.

**Source:** Prepared by authors from the study results.

as effect modifiers. In the adjusted analysis, the highest risk of death from COVID-19 was in patients admitted to the ICU 9–13 days after the onset of symptoms for every age category – 18–39 years (RR = 8.49; 95% CI: 6.31–11.43); 40–59 years (RR = 5.72; 95% CI: 5.08–6.44); 60–69 years (RR = 4.20; 95% CI: 3.92–4.49); and 70 years or older (RR = 2.75; 95% CI: 2.61–2.89). The difference in risk of death from COVID-19 between patients admitted to an ICU and those not admitted to an ICU was highest in the youngest age group. We also estimated the risk of death in younger people with comorbidities and those without comorbidities, but the finding that younger people with comorbidities were at greatest risk of death was not statistically significant.

## DISCUSSION

The present study assessed factors associated with ICU admission and death from COVID-19, as well as the relationship between ICU admission and death from COVID-19 in patients hospitalized for the disease who had received both doses of a two-dose COVID-19 vaccine or one dose of a single-dose vaccine. Men and patients older than 60 years had a greater risk of admission to an ICU and of death from COVID-19. In addition, the more the number of comorbidities, the higher the risk of ICU admission and death from COVID-19. Studies have shown that men with COVID-19 have more severe symptoms than women and more men die of COVID-19 than women (20, 21), which corroborate our study's findings, and this was the case even in patients who had completed the COVID-19 vaccination series. A previous study found that the more severe COVID-19 outcomes in men may be partially caused by differences in inflammatory responses to viral infections between men and women and differences in inflammatory/immune status as they relate to cardiovascular comorbidities (e.g. obesity, hypertension, and age) (22). These different responses could be caused by higher expression of angiotensin-converting enzyme 2 (ACE2) – the entry receptor for SARS-CoV-2 – in men (23), which is associated with more severe illness and worse clinical manifestations of COVID-19 (21). At the same time, higher expression of 17β-estradiol in women may cause a reduction in ACE2 receptor expression and consequently reduce infectivity (24).

Of the five macroregions, the North showed the lowest risks for ICU admission and death from COVID-19 compared with other regions. The North is one of the country's poorest regions, where the highly contagious Gamma variant was detected (in Manaus, capital city of Amazonas state) (25). The North region

also had the lowest vaccination rate in Brazil as of June 23, 2021 (26). Thus, as we studied fully vaccinated patients, the severest cases and deaths from COVID-19 in the North region may be underrepresented in the study sample.

In our study, the presence of comorbidities and age were both associated with ICU admission and death from COVID-19. Obesity as a risk factor for ICU admission in our fully vaccinated patients with confirmed severe COVID-19 was most evident in the younger age group (18–39 years), which had the largest differences between obese and non-obese patients. Similarly, obesity, diabetes mellitus, and renal diseases were more important as risk factors for death from COVID-19 in younger patients than in their older counterparts. Obesity and kidney disease were both reported as risk factors for ICU admission and death from COVID-19 in a review evaluating the risk of in-hospital mortality from COVID-19 among hospitalized patients with confirmed COVID-19 (27). The review also found that having any comorbidity increased the risk of in-hospital death from COVID-19 (27). Obesity is known to increase the risk of respiratory failure through mechanical and inflammatory mechanisms (28). Furthermore, people with obesity also tend to have higher concentrations of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6), which affect immunity and could aggravate inflammatory processes in the airways of patients with severe COVID-19 (29). Among the possible reasons for the association between underlying kidney conditions and worse COVID-19 outcomes are innate immune changes caused by uremia that hamper leukocyte function and, in turn, bactericidal and antimicrobial ability (30, 31). Other studies have also demonstrated the risk of death from COVID-19 in patients with diabetes mellitus (27, 32). A potential mechanism for this association is increased expression of ACE2 in the lungs and other tissues of patients with type 2 diabetes mellitus (33). This upregulation is associated with chronic inflammation, endothelial cell activation, and insulin resistance, which aggravate the inflammatory response and lead to dysfunction of the alveolar-capillary barrier (34).

In our evaluation of ICU admission and death as a result of COVID-19 as outcomes, time between onset of symptoms was weakly associated with ICU admission for COVID-19, but significantly associated with death from COVID-19. Specifically, for any age group, patients admitted to an ICU for COVID-19 whose symptoms appeared 0–4 days before hospitalization had the greatest risk of death. This may be because patients

admitted for COVID-19 a few days after the appearance of initial symptoms could have more severe disease.

Age also increased the risk of admission to an ICU and death from COVID-19. These results mirrored those of studies performed with unvaccinated adults in the United States, Italy, and Brazil before vaccine rollout in those countries (32–34), reinforcing the importance of targeting older age groups in the COVID-19 pandemic response efforts.

As regards the relationship between ICU admission and death, we found that the biggest difference in risk of dying of COVID-19 was between patients aged 18–39 years with severe COVID-19 admitted to the ICU and the same age group with severe COVID-19 who were not admitted to an ICU. In addition, younger patients admitted to the ICU for COVID-19 whose symptoms began 9–13 days before ICU admission had a higher risk of death from COVID-19 than those not admitted to an ICU. This finding suggests that the time delay in admission to the ICU after the onset of symptoms is important for patient survival.

In our study, 43% of fully vaccinated patients hospitalized for severe COVID-19 in Brazil died. Brazil has the second highest number of deaths from COVID-19 worldwide (12), which is linked to the collapse of the country's health system (35). This may explain the finding of larger differences in the risk of death between younger patients admitted to the ICU and those not admitted than between older patients admitted and not admitted to an ICU, as in extremely low-resource situations younger patients may have been given priority in ICU admission over older patients with a lower likelihood of survival, which could underestimate the risk of death in older patients admitted to the ICU.

It is also worth noting that the prevalence of obesity in our sample was higher in younger patients than in elderly patients (15.29% in patients 18–39 years; 7.16% in patients 70 years and older), just as there was a higher proportion of younger patients (18–39 years) with obesity admitted to the ICU than younger patients without obesity (48.31% and 28.95%, respectively). This may have also contributed to the larger differences in risk of death from COVID-19 among younger patients admitted to the ICU.

Our study's results are similar to those conducted in unvaccinated populations. However, the greatest differences lie in our finding that in the fully vaccinated patients hospitalized for severe COVID-19, young adults with comorbidities were particularly vulnerable to ICU admission and death from COVID-19, and young adults admitted to an ICU were at greater risk of death from COVID-19. We encourage the general population to continue to take public health precautions, such as the use of masks, handwashing, and social distancing, very seriously as COVID-19 continues to pose serious problems even for those who have received full COVID-19 vaccination. Nevertheless, further studies are needed to elucidate the mechanisms and structural factors that cause fully vaccinated young adults hospitalized for severe COVID-19 in Brazil to have higher risks of ICU admission and death from COVID-19.

Among this study's strengths is the use of all hospitalized cases of severe COVID-19 in fully vaccinated patients in Brazil, using a reliable national surveillance systems (34), Sivep-Gripe. In addition, ours is one of the few studies that have evaluated: age and time between onset of symptoms and hospitalization as effect modifiers of the association between

ICU admission for and death from COVID-19; risk factors for ICU admission and death from COVID-19 in fully vaccinated patients; and the association between ICU admission and death from COVID-19 in fully vaccinated patients hospitalized for severe COVID-19.

This study also had some limitations. Information was not available in the database on the different SARS-CoV-2 variants, some of which can evade the protection offered by COVID-19 vaccines and behave differently from one another and in different countries (36). This leaves open the possibility of residual confounding in the findings, in addition to other potential confounding variables not studied. In addition, few data were available on socioeconomic position of the patients, such as level of schooling, and data were missing on skin color for a number of patients. Finally, because we used secondary data, some may have been collected or entered incorrectly, possibly creating information bias.

## CONCLUSION

This study found that, among fully vaccinated Brazilians hospitalized for severe COVID-19, the risk of ICU admission and death from COVID-19 was highest in older patients. Nonetheless, young adults hospitalized for severe COVID-19 with and without comorbidities showed the largest differences in risk of ICU admission and of death from COVID-19 among all age groups, just as younger adults admitted and not admitted to an ICU showed the largest differences in risk of dying from COVID-19. These findings are important for COVID-19 health education efforts, which must be revitalized to better communicate the need for all age groups to continue to socially distance, wear masks and practice personal hygiene, even after vaccination. Furthermore, better health policies that aim to improve care for patients admitted to ICUs are needed to avoid more years of life lost to COVID-19.

**Author contributions.** GMH conceived and designed the study, analyzed the data, and wrote the manuscript. PCGV contributed to the study design and data acquisition, and wrote and reviewed the paper. NJ contributed to data analysis and interpretation, and wrote and reviewed the paper. DGPL contributed to analysis and interpretation, and wrote and reviewed the paper. All authors reviewed and approved the final version.

**Acknowledgements.** This study was sponsored in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES). We thank all health professionals in Brazil's public health system for their work in the country's response to the COVID-19 pandemic, and for their collection of primary epidemiological surveillance data.

**Conflicts of interest.** DGPL is a short-term consultant for Pan American Health Organization-WHO country office in Guyana engaged in projects unrelated to the present study. Other authors declare no conflicts of interest.

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Manuscript received on 19 August 2022. Revised version accepted for publication on 24 August 2022.

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## Factores de riesgo para el ingreso en la unidad de cuidados intensivos y la muerte debido a la COVID-19 en pacientes con el esquema completo de vacunación hospitalizados por COVID-19 grave en Brasil, 2021-2022

### RESUMEN

**Objetivos.** Evaluar los factores asociados con el ingreso en la unidad de cuidados intensivos (UCI) y la muerte por la enfermedad del coronavirus del 2019 (COVID-19) en pacientes con el esquema completo de vacunación que presentan un cuadro grave de COVID-19, así como la relación entre el ingreso en la UCI y la muerte por esta enfermedad en Brasil.

**Métodos.** Se realizó en Brasil un estudio retrospectivo de pacientes hospitalizados con COVID-19 del 12 de febrero del 2021 al 10 de enero del 2022 que habían recibido el esquema completo de vacunación contra la COVID-19 antes de ser hospitalizados. Los resultados fueron el ingreso en la UCI debido a la COVID-19 y la muerte por esta enfermedad. Las variables evaluadas fueron sexo, edad, color de piel autodenunciado, macrorregión, comorbilidades, período entre el esquema completo de vacunación y la aparición de los síntomas y período entre el inicio de los síntomas y la hospitalización. Se utilizó un modelo de regresión de Poisson para estimar los cocientes de riesgo crudo y ajustado.

**Resultados.** De los 74 991 pacientes hospitalizados con un cuadro grave de COVID-19, 67,28% tenía 70 años o más y 68,32% tenía al menos una comorbilidad. Los varones, los pacientes de 60 a 69 años y los pacientes de 18 a 39 años con obesidad presentaron el mayor riesgo de ingreso en la UCI. Los pacientes de 18 a 39 años con obesidad, diabetes o enfermedades renales presentaban el mayor riesgo de muerte por esta enfermedad. Cuando la edad y el período entre el inicio de los síntomas y la hospitalización se consideraron modificadores del efecto, los pacientes ingresados en la UCI entre 9 y 13 días después del inicio de los síntomas en cada categoría de edad presentaron el mayor riesgo de muerte debido a la COVID-19.

**Conclusión.** Aunque los pacientes de mayor edad presentaron el mayor riesgo de ingreso en la UCI y muerte debido a la COVID-19, la diferencia en el riesgo de morir por esta enfermedad entre pacientes ingresados en la UCI y pacientes no ingresados fue más elevada en adultos jóvenes.

**Palabras clave** COVID-19; vacunación; unidades de cuidados intensivos; mortalidad; Brasil.

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## Fatores de risco para admissão em unidade de terapia intensiva e óbito pelo coronavírus em pacientes totalmente vacinados, internados por COVID-19 grave no Brasil, 2021-2022

### RESUMO

**Objetivos.** Avaliar fatores associados à admissão em unidade de tratamento intensivo (UTI) e óbito por doença do coronavírus 2019 em pacientes com COVID-19 grave, totalmente vacinados, no Brasil, bem como a relação entre a entrada na UTI e a morte por COVID-19.

**Métodos.** Estudo retrospectivo de pacientes hospitalizados com COVID-19, de 12 de fevereiro de 2021 a 10 de janeiro de 2022, em todo o Brasil, que tinham o esquema vacinal completo contra a COVID-19 antes da hospitalização. Os desfechos foram a admissão em UTI devido à COVID-19 e a morte em decorrência da doença. As variáveis avaliadas foram sexo, idade, cor da pele autodeclarada, macrorregião, comorbidades, tempo entre a vacinação completa e o início dos sintomas, e tempo entre o início dos sintomas e a internação. Para estimar os coeficientes de risco bruto e ajustado foi usado um modelo de regressão de Poisson.

**Resultados.** Dos 74.991 pacientes internados com quadro de COVID-19 grave, 67,28% tinham  $\geq 70$  anos e 68,32% apresentavam pelo menos uma comorbidade. Os homens, pacientes entre 60-69 anos e pacientes entre 18-39 anos com obesidade tinham o maior risco de internação na UTI. Os pacientes de 18-39 anos de idade com obesidade, diabetes ou doenças renais apresentavam o maior risco de morte por COVID-19. Quando a idade e o intervalo entre o início dos sintomas e a hospitalização foram considerados modificadores de efeito, os pacientes admitidos em UTI entre 9 e 13 dias após o início dos sintomas em cada categoria de idade tinham o maior risco de morte devido à COVID-19.

**Conclusão.** Embora os pacientes mais velhos tivessem maior risco de admissão na UTI e morte por COVID-19, a diferença no risco de óbito pelo coronavírus entre os pacientes admitidos em uma UTI e aqueles não admitidos foi maior para os adultos jovens.

**Palavras-chave** COVID-19; vacinação; unidades de terapia intensiva; mortalidade; Brasil.

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