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Hospital readmission rates and factors due to COVID-19 reinfections: a registry-based cohort study in Brazil (2020–2022)

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Abstract

Background COVID-19 vaccination emerged as a key strategy to reduce disease severity and curb the pandemic's spread, proving crucial in preventing complications and hospitalizations. Despite its positive impact, hospital readmissions due to COVID-19 reinfections have been observed, influenced by emerging variants and individual clinical and demographic characteristics. Given the limited evidence on such readmissions, studies based on representative samples are essential to better understand the associated factors. This study aims to analyze the role of vaccination, identify clinical and demographic characteristics associated with readmissions due to COVID-19 reinfections, and estimate the annual readmission rate in Brazil from 2020 to 2022.

Methods This nationwide cohort study included hospitalized individuals reported in the National Influenza Surveillance System with confirmed COVID-19 or unspecified Severe Acute Respiratory Infection (SARI) diagnoses, encompassing approximately 1.9 million Brazilians from 2020 to 2022. Demographic and clinical variables from the first hospitalization and readmission were included, alongside a time-varying ecological vaccination variable. Fine and Gray's proportional subdistribution hazards model, accounting for death as a competing event, was used to assess predictors of hospital readmission. Results were expressed as hazard ratios (HR) with 95% confidence intervals.

Results The analysis indicated that the vaccination period following 80% first-dose coverage (from December 19, 2021, onward) showed a protective effect against readmission. After adjusting for multiple variables, this protective effect became evident, with a 13% reduction in the risk of readmission in the post-vaccination period compared to the pre-vaccination period (HR: 0.87; 95% CI: 0.85–0.89). In contrast, factors such as female sex, age 60 years or older, and the presence of comorbidities were associated with an increased risk of readmission.

Conclusion The findings reinforce the critical role of COVID-19 vaccination as a fundamental strategy for reducing reinfections and readmissions. Despite viral mutations, immunization stands out as a significant contributor to population protection.

Keywords Readmission, Associated factors, COVID-19, Reinfection

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Introduction

Severe acute respiratory infection (SARI) is a serious public health problem, requiring hospitalization and intensive care in many cases [1, 2]. SARI can be triggered by various respiratory diseases and is characterized by symptoms of a flu-like syndrome with dyspnea/respiratory distress or persistent chest pressure or O₂ saturation under 95% in ambient air or bluish color of the lips or face [3].

SARI became a global concern in 2020 due to the appearance of the novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing COVID-19 [4], whose clinical manifestations vary from mild to severe and even fatal [5]. In Brazil, 3,403,970 hospitalized SARI cases were reported from 2020 to 2022, of which 59.9%, 70.8%, and 42.9% were confirmed as COVID-19 in the years 2020, 2021, and 2022, respectively, while 36.4%, 22.6%, and 42.2% of the cases were classified as unspecified SARI [6, 7].

Although COVID-19 vaccination has emerged as one of the primary strategies to mitigate the impacts of the disease [8], the emergence of SARS-CoV-2 variants of concern (VOCs) has played an important role in the dynamics of the pandemic. These variants are not only highly transmissible but have shown the capacity to evade immune response, reducing vaccines' efficacy and contributing to a continuous cycle of reinfections, hospitalizations, and readmissions, thus exacerbating the pressure on health systems [9, 10].

Readmission due to COVID-19 reinfection has received little attention in the literature. Readmission is considered a multifactorial event that can be influenced by clinical factors such as comorbidities, demographic factors, including advanced age, male sex, and black race/color, and environmental factors such as smoking and physical inactivity [11]. In addition, emerging variants and vaccination may be determinant factors in this context [12].

Given the scarcity of scientific literature on readmission due to COVID-19 reinfection and associated factors, this study aims to estimate the annual readmission rate (2020–2022) study the role of vaccination and identify clinical and demographic characteristics of COVID-19 reinfection, establishing possible associations with subsequent admissions in this group of patients.

Materials and methods

Study design, population, and data source

This is a historical cohort study of individuals hospitalized and reported with a diagnosis of SARI in public and private hospitals throughout Brazil from 2020 to 2022.

The retrospective analysis included hospitalizations for confirmed SARS-CoV-2 SARI and unspecified SARI in individuals aged 18 years or older. Individuals who did

not die or experience the outcome within 90 days were also retained in the database.

Administrative data from the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) database were submitted initially to a deduplication process, performed by a non-deterministic linkage of the database with itself with an algorithm previously validated in Python language [13]. A time window of 90 days or more was used, as recommended by Technical Note no. 52/2020 of the Brazilian Ministry of Health [14] for differentiation between duplication and new SARI cases, considering the period from onset of symptoms for the first hospitalization to the appearance of new symptoms for the second admission. All data were anonymized before analysis by the other authors.

Variables and definitions

Variables used from the SIVEP-Gripe database included demographic and clinical information from the first admission such as patient's age (in years), age bracket (18–29 years; 30–59 years; 60 or older), sex (male, female), race/color (white; black, which included black + brown; others, including Asian-descendant + indigenous + missing), comorbidities, final classification (unspecified SARI; SARI from COVID-19; missing), Intensive Care Unit (ICU) admission (yes; no; missing), outcome (cure; death; death from other causes; missing).

Comorbidities were analyzed according to the number of conditions present in the SIVEP-Gripe database, including Down syndrome, cardiac, pulmonary, renal, hepatic, autoimmune, neurological, and hematological diseases, and diabetes, among others. This variable was categorized into four groups (none, 1, 2, and 3 or more comorbidities). Vaccination was defined in three periods: "period before vaccination", from 26 February 2020 to 31 January 2021; "period during vaccination", from 31 January 2021 to 19 December 2021; and "period after vaccination", from 19 December 2021 to 31 December 2022, based on the milestones in the administration of the COVID-19 vaccine. The periods were established according to the month of the first reported case (February 2020), the start of nationwide vaccination in Brazil (January 2021), and the month when Brazil reached 80% coverage of the first dose (December 2021), as determined by Technical Note of the FIOCRUZ COVID-19 Observatory [15].

Outcome of interest

Outcome was defined as time until the first episode of readmission. Initial date was defined as the date of the first symptoms recorded in the first hospitalization reported to the SIVEP-Gripe database with a diagnosis of SARS-CoV-2 confirmed and unspecified SARI plus 90 days. The end date was the date of the first symptoms

in the individual who was readmitted or administrative censure (end of study), whichever occurred first. Deaths were treated as competitive events.

The follow-up of hospitalized individuals started on the 91st day after the first hospital admission. The first 90 days are excluded from the risk period to prevent an immortal time bias, i.e., a period during which the event cannot occur [16].

Statistical analysis

Descriptive analysis was performed by comparing the group of non-readmitted individuals with the group of readmitted individuals, using Kruskal-Wallis tests for continuous variables, characterized by their medians and interquartile range (IQR). For categorical variables, Pearson's chi-square tests were used to compare proportions. Readmission rates were calculated as the ratio between the number of readmissions in the year and the sum of person-years for the same period, multiplied by 100.

Fine and Gray's proportional subdistribution hazards model was used to assess the effect of vaccination coverage periods and other covariates on the risk of hospital readmission, accounting for death as a competing event [17]. For individuals who died on the same day as symptom onset, the event date was postponed by one day to allow proper inclusion in the model. Since the dataset contained time-varying covariates, the data were restructured according to the subdistribution hazard function, with individual-specific weights that varied dynamically as competing events occurred [18].

The results were reported as hazard ratios (HR) with respective 95% confidence intervals (95% CI). Schoenfeld's residual test was used to ascertain the proportional hazards assumption.

All analyses were performed in the R software, version 4.2.3 [19]. The survival [20, 21] and mstate [22, 23] packages were used for survival analyses.

Results

A total of 1,947,783 hospitalized patients in Brazil from 2020 to 2022 were selected according to the inclusion criteria. Readmission rates per person-time were 2.15/100, 2.10/100, and 1.34/100 for reinfection from SARS-CoV-2 confirmed and unspecified SARI in 2020, 2021, and 2022, respectively. Table 1 presents demographic and clinical data related to cases of admission and readmission.

There was a slight predominance of males (53%) among non-readmitted individuals, while sex proportions were the same (50%) in the readmitted, with a median of 57 years of age (IQR 43–70) among the non-readmitted and 69 years (IQR 56–80) in the readmitted; 70% of the readmitted were in the 60 years or older group, compared to 44% of the non-readmitted, suggesting greater propensity to readmission with advancing age.

The variable Race/color indicated a predominance of the "white" category in both groups. As for comorbidities, among the readmitted, the proportion of patients without comorbidities was lower (21%), while the proportion of those with comorbidities increased.

The final classification of SARI cases also revealed differences between the groups: most of the cases of initial admission were categorized as SARS-CoV-2 confirmed SARI (69%), while among readmissions there was a predominance of unspecified SARI (61%).

ICU admission was more frequent among non-readmitted patients. Hospitalization outcome was very different between groups: even though most patients recovered, the proportion was higher for readmission (88%) than first admission (87%) and deaths by any cause were much lower for the latter (0.1%) than the former (0.1%).

The estimates presented in Table 2 show the association between vaccine coverage and readmission. After adjusting for multiple variables, the protective effect of vaccination became evident, with a 13% reduction in the risk of readmission during the post-vaccination period compared to the pre-vaccination period.

Female sex was associated with slightly higher risk of readmission compared to male sex (4%). Likewise, advanced age (60 years or older) proved to be a significant risk factor for readmission, with a 143% increase.

As for race/color, black individuals showed lower risk of readmission (4%). The presence of comorbidities was associated with a significant risk of readmission, with an upward risk gradient as the number of comorbidities increased.

Regarding ICU admission, individuals that were not admitted to the ICU during the initial hospitalization showed higher risk of readmission (2%).

Discussion

This study, based on a large administrative cohort of hospitalized patients in Brazil, demonstrated that the vaccination era had a significant protective effect against readmissions due to COVID-19 reinfection. Factors such as female sex, advanced age, and presence of comorbidities were associated with greater risk of readmission. These findings highlight that although the clinical and demographic characteristics were relevant, the true protective effect evidenced over time emerged from population-wide vaccination.

The existing literature, is concentrated on readmissions due to various factors and in short time frames, which limits direct comparisons with the current study. However, the results align with and extend prior evidence linking the vaccination era to reduced risks of hospitalization and severe COVID-19 outcomes. Dos Santos et al. [24] estimated that the vaccination era in Brazil

Table 1 Characteristics of admissions and readmissions with the 90-day time criterion, Brazil, 2020–2022

Characteristics	Total N = 1.947.783 ^a	Readmission		p-value ^b
		No N = 1.893.861 ^a	Yes N = 53.922 ^a	
Sex				<0.001
Male	1.038.639 (53%)	1.011.812 (53%)	26.827 (50%)	
Female	909.144 (47%)	882.049 (47%)	27.095 (50%)	
Age				<0.001
N	1.947.783	1.893.861	53.922	
Median (IQR)	57 (43. 71)	57 (43. 70)	69 (56. 80)	
Age group (years)				<0.001
18–29	126.411 (7%)	124.540 (7%)	1.871 (3%)	
30–59	943.246 (48%)	928.832 (49%)	14.414 (27%)	
60 or older	878.126 (45%)	840.489 (44%)	37.637 (70%)	
Race/color				<0.001
White	817.305 (42%)	793.429 (42%)	23.876 (44%)	
Black	730.958 (38%)	711.222 (38%)	19.736 (37%)	
Other	399.520 (20%)	389.210 (20%)	10.310 (19%)	
Comorbidities				<0.001
None	790.699 (41%)	779.129 (41%)	11.570 (21%)	
One	799.834 (41%)	774.920 (41%)	24.914 (46%)	
Two	261.758 (13%)	250.199 (13%)	11.559 (21%)	
Three or more	95.492 (5%)	89.613 (5%)	5.879 (12%)	
Final classification				<0.001
Unspecified SARI	535.086 (27%)	502.457 (27%)	32.629 (61%)	
SARS-CoV-2 confirmed SARI	1.326.053 (68%)	1.306.654 (69%)	19.399 (36%)	
Missing	86.644 (5%)	84.750 (4%)	1.894 (3%)	
ICU admission				<0.001
Yes	419.612 (22%)	407.305 (22%)	12.307 (23%)	
No	1.292.834 (66%)	1.257.100 (66%)	35.734 (66%)	
Missing	235.337 (12%)	229.456 (12%)	5.881 (11%)	
Hospitalization Outcome				<0.001
Cure	1.695.658 (87%)	1.648.140 (87%)	47.518 (88%)	
Death	1.989 (0.1%)	1.237 (0.1%)	752 (1.9%)	
Death from other causes	601 (0.1%)	533 (0.1%)	68 (0.1%)	
Missing	249.535 (12.9%)	243.951 (12.8%)	5.584 (10%)	

^an (%)^bPearson's chi-square test; Kruskal-Wallis test

prevented approximately 74% of severe cases and 82% of COVID-19 deaths. Similarly, in Chile, Brault et al. [25] reported significant reductions attributed to vaccination: 26% in confirmed cases, 66% in hospitalizations, 70% in ICU admissions, and 67% in deaths. It is important to note that these impacts occurred alongside broader pandemic shifts, including natural immunity from prior infections [26, 27] and improvements in therapeutic strategies and clinical care [28, 29]. In our study, the relative protection observed against readmission may also be associated with the fact that, during the analyzed period, vaccination coverage was still expanding and a considerable proportion of individuals had received only one dose or had not yet received a booster (vaccines available in Brazil included CoronaVac, AstraZeneca, Pfizer, Janssen, and later bivalent Comirnaty® formulations).

In addition, vaccines played an important role in reducing the use of health services, including medicines, appointments, imaging tests, and ICU and general admissions [30]. However, the persistence of serious clinical events, even with increase in vaccination coverage, challenges the idea that the expansion of immunization alone guarantees an effective reduction in COVID-19 severity. This suggests that multiple factors may influence the clinical course and outcomes of COVID-19 [31].

New variants with different levels of transmissibility and severity also play a considerable role. While the literature suggests that the Gamma, Delta, and Omicron variants are associated with increased risk of severe outcomes [10, 32–34], the findings from the complementary analyses indicate that VOCs have a protective effect against readmissions (Supplementary Material 1). This

Table 2 Cox model for competitive events according to time-dependent variable and other covariates related to risk of readmission due to SARS-CoV-2 reinfection, Brazil, 2020–2022

Variables	HR ^a	CI ^b
Sex (REF = male)		
Female	1.04	1.03–1.06
Age group (REF = 18–29 years)		
30–59 years	0.99	0.95–1.04
60 years or older	2.43	2.32–2.54
Race/color (REF = white)		
Black	0.96	0.94–0.97
Others	0.84	0.83–0.86
Comorbidities (REF = none)		
One	1.67	1.63–1.71
Two	2.34	2.27–2.40
Three or more	3.23	3.13–3.33
ICU admission (REF = yes)		
No	1.02	1.00–1.04
Missing	1.05	1.02–1.08
Vaccination period (REF = period before vaccination)		
Period during vaccination	1.01	0.98–1.04
Period after vaccination	0.87	0.85–0.89

^aHazard Ratio^bConfidence Interval

appears to suggest that the effect of vaccination prevailed over time, surpassing the impact of these viral strains.

Besides variants, other clinical and demographic factors also significantly influenced the results and needed to be used to control confounding in our models. For example, advanced age emerged as a significant risk factor for readmission due to COVID-19. Individuals 60 years or older presented greater risk of readmission, in line with findings by Sandoval et al. [12], who identified 24% greater risk of readmission in individuals in the 50–69-year age group and an even greater risk (44% higher) for those 70 years or older. This association can be explained by the higher prevalence of comorbidities in the elderly, in addition to age-related immunodepression, which compromises the body's capacity to fight infection.

Women displayed greater risk of readmission when compared to men. Although this finding contrasts with part of the literature that associates greater risk with men, factors such as biological differences in the immune response [35–37], health behaviors, occupational exposures [38, 39], and sociocultural influences [40] may explain this discrepancy. These findings warrant further investigation to better understand their underlying mechanisms.

Presence of comorbidities also significantly increased the risk of readmission due to COVID-19. This association can be explained by physiological factors such as the exacerbated inflammatory response to the infection mediated by the angiotensin-converting enzyme 2 (ACE2) and genetic deficiencies, which increase the

susceptibility to complications [41]. In addition, the pandemic and social isolation measures may have induced lifestyle changes such as physical inactivity [42, 43] and inadequate diet [44], potentially triggering the development of new comorbidities or aggravating existing ones and leading to the emergence of new health conditions.

ICU admission during the first SARS-CoV-2 infection is frequently associated with more severe cases [45] and greater risk of death [46, 47]. Although the present analysis identified a statistical relationship between ICU admission and readmission, the high mortality rate in this group suggests the presence of a survival bias, that is, part of the patients did not survive long enough to be readmitted.

As for race/color, the data showed a lower risk of readmission among black individuals, also contrasting with previous studies that indicate this population's greater vulnerability to COVID-19 due to the higher prevalence of comorbidities and barriers to healthcare access [41, 48–50]. This discrepancy may be related to the data's quality. The "missing" category in the hospitalization outcome was more frequent among black individuals, and black individuals experienced higher odds of death when compared to whites in a logistic regression model (data not shown). These findings suggest that the observed effect for readmission may have been underestimated, since the high mortality among black individuals reduces the number of individuals that could be readmitted.

This study has some methodological limitations. The lack of control for VOCs in the vaccine model was a consequence of the need to include it as an ecological variable, used as a proxy for the vaccination coverage setting, which does not capture the effect of individual-level protection. In addition, the joint analysis of admissions and readmissions may not capture important differences, since the two events may be associated with different risk factors. The inclusion of cases of unspecified SARI together with confirmed COVID-19 cases was a necessary decision, reflecting the limitations of laboratory diagnosis during the pandemic. The lack of information on lifestyle, socioeconomic status, and access to health services are factors that may have influenced the results. As a partial proxy for social determinants, we used the variable race/color, although we recognize its limitations in capturing the complexity of socioeconomic and structural inequalities. It is also important to consider bias in the completion and recording of case report forms, which depend on health workers' practice and may vary in quality and consistency. To minimize potential immortal time bias, the analysis only considered the risk period beginning on day 91 following the first hospitalization. We also acknowledge the presence of residual confounding, since not all relevant variables could be included in the model.

Despite these potential problems, we were able to control for several variables, and the strength of association combined with the large sample and treating deaths as competing events in our models should have minimized their impact on our results. Other strengths include the evaluation of risk of readmission due to COVID-19 reinfection for the first time in Brazil over the course of three years; and the use of information from a database widely acknowledged by Brazil's national epidemiological surveillance system, thereby ensuring the scope and representativeness of the data on the Brazilian population.

Conclusion

The study showed a very positive impact of the vaccination era on hospital readmission due to COVID-19 reinfection, despite the circulation of VOCs associated with more severe disease. The evidence can also provide a basis for orienting public health policies, channeling efforts to vulnerable groups and suggesting the strengthening and continuous importance of vaccination as an essential strategy, not only as an initial preventive measure, but also in the mitigation of future variants and possibly in the reduction of reinfection and readmission rates.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12889-025-25330-3>.

Supplementary Material 1.

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Authors' contributions

RKAN, LSB, DAMV, MFCG, LMFC, and AGP conceived and designed the study. RKAN, MFCG, and AGP contributed to the study implementation and data management. RKAN and AGP conducted the analysis and drafted the manuscript. RKAN, LSB, DAMV, MFCG, LMFC, and AGP reviewed the manuscript. All authors discussed the results and contributed to the final version of the manuscript.

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Data availability

The data that support the findings of this study are available from the Influenza Epidemiological Surveillance System (SIVEP-Gripe) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from the Brazilian Ministry of Health.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Brazil (ENSP/FIOCRUZ; CAAE: 74953523.5.0000.5240).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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