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Characteristics and outcomes of in-hospital patients with Covid-19 and history of tuberculosis: a matched case-control from the Brazilian Covid-19 Registry

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Abstract

Background The Covid-19 pandemic caused a negative impact on other infectious diseases control, prevention, and treatment. Consequently, low and middle-income countries suffer from other endemic diseases, such as tuberculosis. This study was designed to compare Covid-19 manifestations and outcomes between patients with previously treated tuberculosis and controls without this condition.

Methods We performed a matched case-control study drawn from the Brazilian Covid-19 Registry data, including in-hospital patients aged 18 and over with laboratory-confirmed Covid-19 from March 1, 2020, to March 31, 2022. Cases were patients with a past history of tuberculosis. Controls were Covid-19 patients without a tuberculosis history. Patients were matched by hospital, sex, presence of HIV, and number of comorbidities, with a 1:4 ratio.

Results Of 13,636 patients with laboratory-confirmed diagnoses of Covid-19 enrolled in this study, 80 had a history of tuberculosis. Statistical differences in history of chronic pulmonary obstructive disease (15% vs. 3.2%), psychiatric disease (10% vs. 3.5%,), chronic kidney disease (11.2% vs. 2.8%), and solid-organ transplantation; (5% vs. 0.9%, $p < 0.05$ for all) were higher in patients with a past history of tuberculosis. Prior use of inhalatory medications (5% vs. 0.6%,), oral corticoids (8.8% vs. 1.9%), immunosuppressants (8.8% vs. 1.9%,) and the use of illicit drugs were more common in the case group (6.2% vs. 0.3% $p < 0.05$for all). There were no significant differences in in-hospital mortality, mechanical ventilation, need for dialysis, and ICU admission.

Conclusions Patients with a history of tuberculosis infection presented a higher frequency of use of illicit drugs, chronic pulmonary obstructive disease, psychiatric disease, chronic kidney disease, solid-organ transplantation, prior

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use of inhalatory medications, oral corticoids, and immunosuppressants. The outcomes were similar between cases and controls.

Keywords Covid-19, Tuberculosis, Hospitalization, Infectious diseases

Background

To reduce Covid-19 transmission and mortality rates, governments worldwide have strengthened the focus and expanded Covid-19 treatment in healthcare services [1, 2]. Over the last two years, vaccination has advanced all over the world and, with that, the Covid-19 death toll has diminished [2]. However, even with a significant reduction in mortality rates, Covid-19 incidence is still substantial, with thousands of new daily cases in low and middle-income countries [3].

Even though Covid-19 control has shown improvements, it is likely that the virus will continue to cause infections [4]. Most countries in South America, for example, are still suffering from the disease itself and its consequences, especially considering new covariants that led to new infection waves [5]. This disease has required extreme attention from governments and health professionals, and the focus on Covid-19 has caused a negative impact on the control and prevention of other infectious diseases, such as tuberculosis (TB) [6]. As TB is endemic to those countries, the coinfection scenario becomes more likely [6].

Tuberculosis can lead to severe lung disability and airflow impairment [7]. Host inflammatory response to *Mycobacterium tuberculosis* infection can cause pulmonary lesions. Furthermore, immune cells, cytokines, and chemokines can lead to granuloma formation and tissue necrosis, with subsequent cavitation and fibrosis [7].

In countries with higher TB rates, such as Brazil, SARS-CoV-2 infection in patients with a history of TB are a concern for health authorities and clinicians. Studies point out that patients with a previous history of TB have a higher incidence of lung impairment [7] and have up to a 2.5-fold chance of having chronic obstructive pulmonary disease (COPD) [8]. Furthermore, COPD leads to worse outcomes in Covid-19 [9] and a higher hospitalization rate [10].

Even though knowledge about Covid-19 and possible coinfections has significantly grown, data regarding SARS-CoV 2 and its role in patients with a previous history of TB is still lacking, especially regarding patients that require hospitalization [11, 12]. This information may help clinicians identify possible patients at risk for Covid-19 severity and death. Therefore, this study aimed to compare Covid-19 manifestations and outcomes between patients with a previous history of TB and controls without this condition.

Methods

Study design and subjects

This study is a part of the multicentric cohort "Brazilian Covid-19 Registry", which included data from Covid-19 patients admitted in 39 Brazilian hospitals [13]. Consecutive patients aged 18 and over with Covid-19 admitted to the participating hospitals from March 1, 2020, to March 31, 2022, were included in the study. All patients presented a laboratory confirmation of Covid-19 according to the World Health Organization guidance [14].

This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guideline [15]. For this study, a matched analysis was conducted comparing patients with a history of TB treatment with controls without any history of TB. Active and previous TB diagnoses and treatment were retrieved by medical records. Records that state an active diagnosis of TB during the hospital stay or if it did not explicitly state a history of TB were excluded from the analysis.

This study was approved by the Brazilian National Commission for Research Ethics (CAAE 30350820.5.1001.0008) and had internal approval of ethics boards from each hospital. Individual informed consent was waived due to the severity of the situation, and we sought to de-identify the data collected. We state that this study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Data collection

The Brazilian Covid-19 Registry collected demographic, clinical, laboratory, and outcomes data from medical records by trained health professionals, and medical and nursing undergraduate students using the Research Electronic Data Capture (REDCap) tools [16, 17] hosted by the Telehealth Center, University Hospital, Universidade Federal de Minas Gerais [18].

Definitions and diagnosis

For the present study, Covid-19 was diagnosed by laboratory confirmation (RT-PCR or antigen test) of SARS-CoV 2 infection, according to the WHO recommendations [14]. As for TB, cases in Brazil are diagnosed by clinical presentation (weight loss, persistent cough for over three weeks, afternoon fever), as well as laboratory confirmation by molecular testing, smear microscopy, or bacterial culture [19].

Outcomes

Primary outcomes included: (i) invasive mechanical ventilation (IMV), (ii) intensive care unit admission, and (iii) in-hospital mortality. Dialysis, length of in-hospital stay and time spent in the ICU were analyzed as secondary outcomes.

Statistical analysis

To adjust for potential confounding variables, TB cases were matched to patients who had not underlying TB (controls) on the basis of propensity score. Propensity score model was estimated by logistic regression, and included age, sex, number of comorbidities, presence of HIV, and hospital. Patients from the control group were searched to find those who had the closest propensity score from the TB group with a 1:4 ratio, using the MatchIt package in R software. However, this process did not force the model to identify exactly four matched controls per case, as matches depend on availability within the database.

Categorical data was presented as absolute numbers and proportions, and continuous variables were expressed as medians and interquartile ranges. The Chi-square and Fisher Exact tests measured the association between cases and controls to compare the distribution of categorical variables, and the Wilcoxon–Mann–Whitney test for continuous variables in univariate analysis. Results were considered statistically significant if the p-value was <0.05. For primary outcomes, logistic regression was performed to identify any association. All statistical analysis was performed with R software (version 4.0.2).

Patient and public involvement

This was an urgent public health research study in response to a Public Health Emergency of International Concern. Patients or the public were not involved in the design, conduct, interpretation, or presentation of the results of this research.

Results

Of 13,636 patients with laboratory-confirmed diagnosis of Covid-19, 80 presented a previous diagnosis of tuberculosis, an incidence of 0.006 (IC: 0.004 to 0.007) among the study's population. In the matching processes, four patients with a history of TB patients did not have a match, resulting in 316 controls (Fig. 1).

When comparing the clinical characteristics of those patients to matched controls, it was observed that chronic pulmonary obstructive disease (COPD) (15% vs. 3.2%, $p<0.001$), psychiatric disease (10% vs. 3.5%, $p=0.034$), and history of solid-organ transplantation (5% vs. 0.9%, $p=0.033$) were more frequent in study cases. Also, regular home use of inhalatory medications (5% vs. 0.6%, $p=0.017$), oral corticoids (8.8% vs. 1.9%, $p=0.006$), and immunosuppressants (8.8% vs. 1.9%, $p=0.006$) were more common in this group, as well as a higher frequency of illicit drug use when compared to controls(6.2% vs. 0.3% $p=0.002$). [Table 1]

When comparing the prevalence of symptoms presented at hospital admission, Covid-19 patients with and without a past diagnosis of TB had similar results, except for adynamia which was most frequent (35% vs. 22.2%, $p=0.025$) and myalgia the least common (21.2% vs. 33.9%, $p=0.042$) in cases [Table S1]. There was no difference in the use of antibiotics (42.5% vs. 44.4%, $p=0.857$), anticoagulants (85% vs. 88.8%, $p=0.456$), antifungals (6.2% vs. 3.5%, $p=0.337$) and corticoids (77.5% vs. 81.8%, $p=0.477$) medications during patient stay [Table S1].

Also, when comparing laboratory findings, values of C-reactive protein (CRP) at hospital admission were lower in patients with a previous history of TB (58 vs. 90, $p=0.005$) than in controls [Table S2].

No statistically significant differences were observed regarding patient outcomes between the groups, such as ICU admission (41.2% vs. 43.4%, $p=0.831$), mechanical ventilation requirement (28.7% vs. 36.7%, $p=0.483$), and death (23.8% vs. 24.8%, $p=0.966$). [Table 2]

After multivariate logistic regression, no statistically significant differences were observed regarding patient primary outcomes between the groups [Table 3].

Discussion

Among all patients admitted to this multicenter cohort that analyzed data from 37 Brazilian hospitals, the frequency of tuberculosis was low, with a ratio of 6:1000 individuals. Nevertheless, our records allowed the comparison of individuals with a previous history of TB and a control group. Our data revealed significant differences between both groups, including higher rates of COPD, psychiatric disorders, hypertension, previous solid organ transplants, and illicit drug use in the TB group. These are known risk factors for tuberculosis. It was also possible to observe a substantial difference between the use of medications such as immunosuppressants, and oral and inhalatory corticoids, which were were more prevalent in the TB group. We did not find significant differences in outcomes such as in-hospital mortality, IMV, dialysis, and ICU admission. This was further confirmed by multivariate regression, which did not demonstrate TB as an independent risk factor for severe outcomes.

There is still a great concern regarding Covid-19 and TB coinfections, especially in high-burden countries like Brazil. During the pandemic, TB prevention and treatment resources were diverted to focus on Covid-19 care in 2020 and 2021 [6]. A meta-analysis showed increased rates of treatment failure and death in several high-burden TB countries [20], resulting in a higher mortality rate

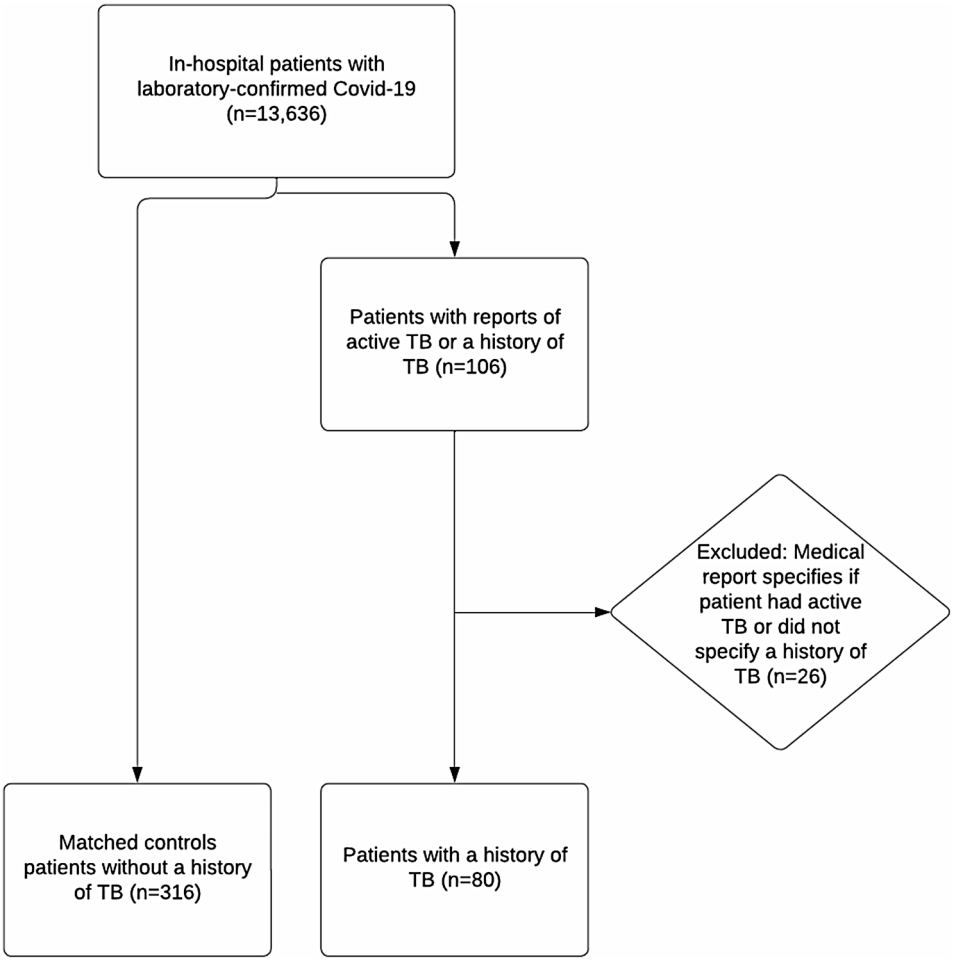

Fig. 1 Flowchart of Covid-19 Patients included in the study. TB: tuberculosis

than expected. This scenario may reflect a rise in undiagnosed and untreated TB patients, potentially leading to a great burden of Covid-19 and TB coinfections, as well as Covid-19 in patients with sequelae from previous TB.

The coinfection of acute TB and Covid-19 has been assessed in several studies. A meta-analysis showed patients with active TB and Covid-19 had a higher chance of severe Covid; need for hospitalization and mortality [21]. However, the impact of a history of TB on Covid-19 severity was unclear. The present study contributes to filling this gap, suggesting that patients with a history of TB do not experience a worse prognosis.

Previous studies suggest that TB is frequently associated with pulmonary comorbidities leading to lung impairments. These conditions may exacerbate the severity of respiratory diseases like Covid-19 [22]. For instance, inflammation triggered by the immune response to Mycobacterium tuberculosis can cause lung damage resulting in COPD, which supports our finding of a higher incidence of COPD among patients with a TB history compared to controls (15.0% vs. 3.2%, $p<0.001$) [7].

However, despite the higher rate of COPD patients in the TB group, both groups reported similar rates of dyspnea (58.8% vs. 65.2%, $p=0.347$) and cough (62.5% vs. 53.8%, $p=0.203$) in the acute phase of Covid-19.

Furthermore, understanding the role of comorbidities like COPD in the prognosis of patients with both TB and Covid-19 may be crucial for improving care. Previous studies have shown that patients with COPD and Covid-19 have a higher risk of developing severe pneumonia, potentially due to increased availability of angiotensin-converting enzyme 2 (ACE2) receptors in the small airways [23], which may which facilitate SARS-CoV-2 entry [24]. Another mechanism that explains the greater propensity to develop severe cases of pneumonia is the tissue damage caused by the disease itself, which results in poor underlying lung reserves [24]. However, ACE2 receptors appear to be more abundant in older male individuals [25], which in itself may be a risk factor for developing severe forms of Covid-19 [26]. This study did not show

Table 1 Comparison between patients with treated TB and controls

	Treated TB N = 80[1]	Controls N = 316[1]	*p*-value
Women	49 (61.3%)	189 (59.8%)	0.915[2]
Age (years)	58.5 (46.8, 69.0)	59.0 (45.8, 69.0)	0.999[3]
Comorbidities			
Hypertension	28 (35.0%)	152 (48.1%)	**0.048**[2]
Diabetes mellitus	16 (20.0%)	76 (24.1%)	0.536[2]
COPD	12 (15.0%)	10 (3.2%)	**< 0.001**[2]
Chronic kidney disease	9 (11.2%)	9 (2.8%)	**0.004**[2]
Psychiatric disease	8 (10.0%)	11 (3.5%)	**0.034**[2]
Obesity	6 (7.5%)	47 (14.9%)	0.122[2]
Heart failure	6 (7.5%)	11 (3.5%)	0.125[2]
Asthma	5 (6.2%)	19 (6.0%)	0.999[2]
Transplant	4 (5.0%)	3 (0.9%)	**0.033**[2]
Stroke	4 (5.0%)	10 (3.2%)	0.495[2]
HIV infection	4 (5.0%)	10 (3.2%)	0.495[2]
Coronary artery disease	3 (3.8%)	15 (4.7%)	0.999[2]
Rheumatological disease	3 (3.8%)	4 (1.3%)	0.150[2]
Cancer	3 (3.8%)	10 (3.2%)	0.731[2]
Atrial fibrillation/flutter	2 (2.5%)	7 (2.2%)	0.999[2]
Medications in use at home			
Oral anticoagulant	1 (1.2%)	12 (3.8%)	0.480[2]
Inhalatory corticoid	4 (5.0%)	2 (0.6%)	**0.017**[2]
Oral corticoid	7 (8.8%)	6 (1.9%)	**0.006**[2]
Immunosuppressants	7 (8.8%)	6 (1.9%)	**0.006**[2]
Toxic habits			
Alcoholism*	9 (11.2%)	17 (5.4%)	0.101[2]
Illicit drugs	5 (6.2%)	1 (0.3%)	**0.002**[2]
Current smoking	9 (11.2%)	19 (6.0%)	0.165[2]

[1]n (%); Median (IQR); [2]Pearson's Chi-squared testFisher's exact test. [3]Wilcoxon rank sum test; *Alcoholism: patients diagnosis stated in medical records

COPD: chronic obstructive pulmonary disease

Table 2 Outcomes comparison between patients with treated TB and controls

	Treated TB N = 80[1]	Controls N = 316[1]	*p*-value
In-hospital stay (days)	13.0 (6.0, 22.2)	9.0 (5.0, 19.0)	0.064[3]
ICU admission	33 (41.2%)	137 (43.4%)	0.831[2]
Time spent in the ICU (days)	12.0 (5.0, 17.0)	10.0 (5.0, 18.0)	0.853[3]
Mechanical ventilation requirement	23 (28.7%)	106 (33.7%)	0.483[2]
Time with mechanical ventilation	9.0 (6.0, 14.0)	13.0 (6.0, 20.2)	0.107[3]
Dialysis	10 (12.5%)	39 (12.4%)	0.999[2]
Septic shock	8 (10.0%)	57 (18.0%)	0.118[2]
Acute heart failure	4 (5.0%)	6 (1.9%)	0.122[2]
In-hospital death	19 (23.8%)	78 (24.8%)	0.966[2]

[1]n (%); Median (IQR) [2]Pearson's Chi-squared testFisher's exact test. [3]Wilcoxon rank sum test. ICU: intensive care unit

Table 3 Outcomes comparison between patients with treated TB and controls after multivariate logistic regression

	Treated TB N = 80[1]	Controls N = 316[1]	OR	95% CI	*p*-value
ICU admission	33 (41.2%)	137 (43.4%)	0.94	0.54–1.6	0.808[2]
Mechanical ventilation requirement	23 (28.7%)	106 (33.7%)	0.74	0.4–1.32	0.305[2]
In-hospital death	19 (23.8%)	78 (24.8%)	0.75	0.38–1.43	0.402[2]

[1]n (%); [2]Adjusted by sex, age, hypertension, diabetes, COPD, CKD, obesity, heart failure, asthma, previous transplant, stroke, HIV diagnosis, arterial disease, rheumatic disease, Cancer, atrial fibrillation, alcoholism, and current smoking status. ICU: intensive care unit

a difference in outcomes of case and control groups, as far as the acute phase is concerned. We have no information about the severity of COPD, which could have been relevant.

It should be noted that patients in the case group also had higher rates of solid organ transplants (5.0% vs. 0.9%, $p=0.033$). Tuberculosis is one of the most frequent complications of solid organ transplantation [27, 28], mainly because the prevalence of latent TB is high in Brazil [29].

The reports of hypertension were smaller in patients with a history of TB when compared with controls (35% vs. 48%, $p=0.048$). A meta-analysis points out that there is no correlation between hypertension in TB and non-TB patients, studies have shown a higher and lower frequency of TB [30]. Hypertension is a risk factor for mortality in TB patients [31], however, it was not found as an independent risk factor for Covid mortality [32]. In this study, we found no difference in admission systolic blood pressure levels between groups (128 vs. 123 mm/Hg, $p=0.823$).

Previous solid organ transplants were more common among cases than controls, likely due to the elevated risk of TB in transplant patients who are immunosuppressed [33]. Population-based studies indicate that transplant patients have a 3.9-fold increased risk of developing TB compared to non-transplant patients [33]. The prolonged use of immunosuppressive medication may heighten susceptibility to TB infections among solid organ transplant recipients, particularly in TB-endemic regions such as Brazil, explaining the higher incidence of solid organs transplants in patients with a history of TB.

The baseline rate of psychiatric conditions was also higher among cases compared to controls (10% vs. 3.5%, $p=0.034$). There is growing evidence of an association between TB and various psychiatric conditions, though the exact mechanisms and causative factors remain complex. Studies show a higher prevalence of psychiatric disorders, including depression, anxiety, bipolar disorder, schizophrenia, and substance use disorders, among TB patients [34–38]. This may lead to delays or missed diagnosis of TB [32]. Additionally, TB's chronic nature, the

extended treatment duration, and associated stigma may exacerbate mental health conditions, which can hinder adherence to TB treatment, consequently affecting disease outcomes [35].

In addition, mental health disorders are associated with behaviors or lifestyle factors that may increase the risk of TB transmission, including substance use disorder, especially alcohol and tobacco, and social determinants such as poverty, improper hygiene, poor nutrition or unstable housing [34, 35, 39]. Some authors also hypothesize mental health disorders, such as depression and chronic stress, may downregulate immunological response which makes individuals more susceptible to TB infection and its progression [38]. Likewise, TB infections can lead to chronic inflammation, which is increasingly linked to psychiatric conditions. Therefore, other researchers suggest that TB-related inflammation might contribute to mental health issues.

Furthermore, certain anti-TB medications, for example, isoniazid, have known psychiatric side effects. The drug can lead to mood changes and psychosis. This can further complicate mental health in TB patients who are already vulnerable due to socioeconomic determinants. It is very important to identify these side effects, as replacement with other anti-tuberculosis treatments has been shown to reverse psychiatric symptoms [40].

Illicit drug use was also higher at baseline in patients with a history of TB. Illicit drugs are a risk for TB infection [34], the use of illicit drugs facilitates close physical contact and also is higher in the homeless population, a group also at risk for TB [41]. The use of powder or crack cocaine can lead to pulmonary edema, pneumonia, alveolar hemorrhage, and other lung damage. This damage, associated with the cocaine effect reducing alveolar macrophage response and proinflammatory responses facilitates the infection from *M. tuberculosis* [42]. The relationship between illicit drugs and Covid-19 was pointed out by Wang et al. (2021), substance abuse was related to an increase in hospitalization and death rates in Covid-19 patients. However, there was no difference between these outcomes in our groups [43].

Besides psychiatric diseases and illicit drug use, chronic kidney disease (CKD) also presented a higher frequency in our case group at baseline, compared with controls (11.2% vs. 2.8% $p=0.004$). Chronic kidney disease leads to malnutrition, oxidative stress, and inflammation, which impairs cell-mediated immunity. This state of immunosuppression can result in the reactivation of latent tuberculosis infections and even new TB infections. Consequently, TB incidence is higher in CKD patients than in non-CKD [44].

Furthermore, CKD is found as a risk factor for Covid hospitalization, severity, and mortality [45]. Data published by the Brazilian Covid-19 Registry shows that elevated blood urea nitrogen at admission is a risk for death in COVID patients [46] and higher creatinine levels at admission lead to greater chances for renal replacement therapy [47]. This evidence reinforces that kidney impairment is a risk factor for COVID severity, however, little is known of the physiopathology of CKD and COVID severity [45]. Since CKD is a risk factor for TB infection, we advise that the population at risk for CKD should have priority in vaccination and boosts shots against COVID and clinicians have to better screen these patients for the presence or a history of TB and other infections [47].

Patients with a history of TB had significantly higher home use of inhaled corticosteroids and oral corticosteroids than the control group at baseline. The higher rate of inhaled and oral corticosteroid use may explain better outcomes than those expected since the use of specific corticosteroids can lead to better outcomes such as a lower rate of need for ventilatory support [48, 49]. In-hospital use of corticosteroids did not differ between groups (77.5 vs. 81.8, $p=0.477$). However, further studies are necessary to support that home use of corticosteroids can contribute to better outcomes in patients with a previous diagnosis of TB.

For this study, a few limitations were observed. First, all of our patients were retrieved through medical data, which resulted in a low number of patients with a history of TB. Second, this study was retrospective, which can lead to report bias from the medical records. In order to lessen the burden of this potential bias, data collected was audited for possible errors.

Conclusion

In this study, patients with a previous TB infection presented a higher frequency of illicit CKD, COPD, psychiatric disease, solid organ transplants, and drug abuse when compared to controls. Furthermore, cases presented a higher home use of oral and inhalatory corticosteroids and immunosuppressants than controls. Covid-19 clinical presentation was similar between groups, except for adynamia, which was more prevalent in patients with treated TB, and myalgia, which was more frequently reported by controls. No statistically significant differences were observed between the groups regarding ICU admission, hospital length of stay, time spent in the ICU, dialysis, need for mechanical ventilation, and in-hospital death.

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization, RLRC. and RC.; methodology, RLRC; DP; VC, RC and MM; software, MM; validation, MM; formal analysis, RLRC, MC and MM.; investigation FC; GN; KR; LM; MC; MJ; MC; NB; NO; and RA; resources, RLRC and MM; data curation, FC; GN; KR; LM; MC; MJ; MC; NB; NO; RA and MC; writing—original draft preparation, RLRC; DP; VC; and RC.; writ-ing—review and editing, RLRC; DP; VC; VA; RC; MC and MM; visualization, RLRC; supervision, RLRC and RC.; project administration, MM; funding acquisition, RLRC and MM.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Brazilian National Commission for Research Ethics (CAAE 30350820.5.1001.0008) and had internal approval of ethics boards from each hospital. Individual informed consent was waived due to the severity of the situation, and we de-identify the data collected.

Consent for publication
All authors approved the manuscript before submission.

Competing interests
The authors declare no competing interests.

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