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HEALTH SCIENCES

Patients hospitalized with active tuberculosis and Covid-19 coinfection: A matched case-control from the Brazilian Covid-19 Registry

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Abstract: Although control of Covid-19 has improved, the virus continues to cause infections, such as tuberculosis, that is still endemic in many countries, representing a scenario of coinfection. To compare Covid-19 clinical manifestations and outcomes between patients with active tuberculosis infection and matched controls. This is a matched case-control study based on data from the Brazilian Covid-19 Registry, in hospitalized patients aged 18 or over with laboratory confirmed Covid-19 from March 1, 2020, to March 31, 2022. Cases were patients with tuberculosis and controls were Covid-19 patients without tuberculosis. From 13,636 Covid-19, 36 also had active tuberculosis (0.0026%). Pulmonary fibrosis (5.6% vs 0.0%), illicit drug abuse (30.6% vs 3.0%), alcoholism (33.3% vs 11.9%) and smoking (50.0% vs 9.7%) were more common among patients with tuberculosis. They also had a higher frequency of nausea and vomiting (25.0% vs 10.4%). There were no significant differences in in-hospital mortality, mechanical ventilation, need for dialysis and ICU stay. Patients with TB infection presented a higher frequency of pulmonary fibrosis, abuse of illicit drugs, alcoholism, current smoking, symptoms of nausea and vomiting. The outcomes were similar between them.

Key words: Covid-19, Hospitalization, Infectious diseases, Prognosis, Tuberculosis.

INTRODUCTION

Even with an important reduction in mortality rates, Covid-19 transmission is still high, with thousands of new daily cases in low and middle-income countries (WHO dashboard). Therefore, it is likely that the virus will continue to cause infections (Philips & William 2021). Most countries in South America, for example, are still suffering from Covid-19 infections, especially considering new covariants that led to new Covid-19 infection waves (Malta et al. 2021). Tuberculosis (TB) is also endemic to those countries, representing a possible scenario of coinfection (WHO 2022) and the focus on Covid-19 during the pandemic has shown a negative impact on its control and prevention (Coutinho et al. 2023).

The interaction between these two infections is still not completely understood. Two recent meta-analysis were conducted to investigate the topic. One of those included 43 studies and 236863 TB patients. Of those, only 406 were identified as inhospital patients. This metanalysis shown that patients with Covid-19 and active TB had a higher risk of mortality

(relative risk [RR] 1.93, 95% CI 1.56-2.39) and of developing serious illness (RR 1.46, 95% CI 1.05-2.02) than those without TB coinfection (Aggarwal et al. 2021). The authors hypothesize that the worse prognosis may be due to TB affecting both lung structure and immunity. When these patients are coinfected by the SARS-Cov-2 virus and develop Covid-19, it leads to an increase in IFN (Interferon), and this could cause a more severe disease manifestation. In addition, this high mortality could be explained by the profile of most patients: male, advanced age and who already have other comorbidities, such as a higher prevalence of HIV infection, which itself can cause worse prognosis (Aggarwal et al. 2021, Visca et al. 2021). The other metanalysis, which included 1294 TB patients and Covid-19 patients, but the authors compared these patients with patients without TB and HIV. Therefore, the higher mortality observed among patients with Covid-19 and TB, or Covid-19, TB and HIV, could have been explained not by TB itself, but the other comorbidities (Tamuzi et al. 2020).

Therefore, in order to explore this gap in knowledge and to investigate cases of Covid-19 and active TB coinfection taking into account other comorbidities and patient profile, this study aims to compare Covid-19 clinical manifestations and outcomes between patients with active pulmonary TB infection and matched controls.

MATERIALS AND METHODS

Study design

The present study is a part of the Brazilian Covid-19 registry, a retrospective multicentric cohort, described in detail elsewhere (Marcolino et al. 2021). It adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines (Lagrutta et al. 2021). It was approved by the Brazilian National Commission for Research Ethics (CAAE 30350820.5.1001.0008) and had internal approval of ethics boards from each participating hospital. Individual consent was waived due to the pandemic circumstances and analysis based only on unidentified patient data.

Consecutive adult patients (age ≥18 years-old) with laboratory confirmed Covid-19 according to the World Health Organization guidance (WHO COVID), who were admitted to one of the participating hospitals from March 1, 2020, to March 31, 2022 were included.

Records that state a past diagnosis of TB during the hospital stay or if it did not explicitly stated if the patient had TB or had a history of previous TB were excluded from the analysis.

Data collection

Data was collected through medical records by trained health professionals, and medical and nursing undergraduate students using the Research Electronic Data Capture (REDCap) tools (Harris et al. 2009, 2019), hosted at the Telehealth Center of the University Hospital of the Universidade Federal de Minas Gerais (Telehealth Center). Patients' demographic and clinical characteristics, clinical evaluation at hospital presentation, laboratory data, therapeutic interventions and outcomes were collected from the patient's records. All data underwent an automatic verification periodically in order to identify possible inconsistencies, which were sent back to each center for correction, to ensure data quality.

Outcomes

The primary outcomes for the present analysis were need for invasive mechanical ventilation, need for dialysis and in-hospital mortality. Secondary outcomes included intensive care unit (ICU) admission, time spent in the ICU and in-hospital stay.

Statistical analysis

For the present analysis, patients with TB in its active form were matched to controls according to a propensity score in a 1:4 proportion by to age, sex, number of comorbidities, previously diagnosed HIV infection and hospital of admission. Selection of cases and controls are presented in figure 1.

The statistical analysis was performed with R software (version 4.0.2, R Foundation, Vienna, Austria) using the MatchIt package. Data was presented in continuous and categorical variables. Association between cases and controls in continuous variables were measured by the Wilcoxon-Mann–Whitney test. Meanwhile in categorical data it was used Chi-square and Fisher Exact tests. Results were considered statistically significant if the p-value was inferior to 0.05.

RESULTS

From 13,802 patients with laboratory-confirmed diagnosis of Covid-19, 39 were diagnosed with TB, a frequency incidence of 0.0028 (CI: 0.0020 to 0.0039) when compared to the study group. These patients were admitted in 13 hospitals, from 7 cities from 3 Brazilian states.

After pairing, we analyzed 36 patients with active TB and its controls. When comparing patients with active TB to controls, there was no statistical difference between the prevalence of comorbidities, except for pulmonary fibrosis, which was more prevalent in patients with active TB (5.6% vs 0.0%, p=0.044) [Table I]. Unhealthy life habits, such as abuse of illicit drugs (30.6% vs 3.0%, p<0.001), alcoholism (33.3% vs 11.9%, p=0.002) and current smoking (50.0% vs 9.7%, p<0.001) were more frequent in patients with active TB than in controls, as shown in Supplementary Material - Table SI. There were no statistically significant differences in medications in use at home between the groups. [Table SI].

When evaluating Covid-19 symptoms presented at hospital admission, nausea was more frequently reported in patients with active TB than in controls (25.0% vs 10.4%, p=0.031). However, there were no statistically significant differences in other symptoms between patients with TB and controls. [Table SI]

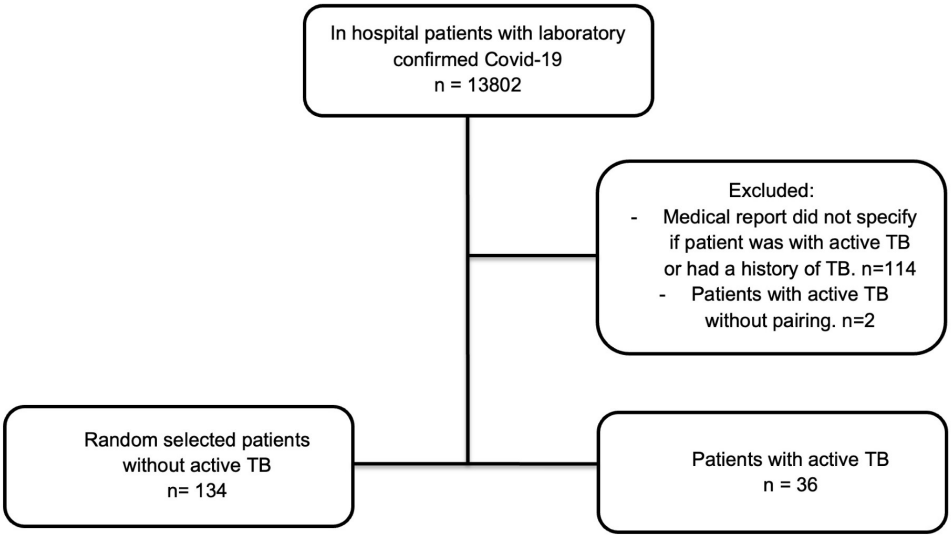

Figure 1. Stages of selection of cases and controls.

At hospital admission, patients with active TB presented lower hemoglobin (11.3 vs 13.4 p=0.002), and sodium values 135 vs 137.4, p=0.027) and higher heart rate (90.5 vs 82.0 p=0.07) when compared to controls. Also, alanine transaminase (ALT) was found lower in case group (20.5 vs 45.0, p<0.001), and bicarbonate values were higher in cases (25.8 vs 23.5, p=0.020), when compared to controls [Table SII]. With regards to clinical outcomes, no difference was observed regarding need for ICU admission (20.0% vs 30.3% p=0.228), requirement of invasive mechanical ventilation (5.7% vs 19.5% p=0.051) and in-hospital death (8.6% vs 13.5% p=0.572) when comparing patients with TB and Covid-19 co-infection and controls. [Table II and Table SIII]

DISCUSSION

Despite the fact that the frequency of patients with co-infection of Covid-19 and active TB was small, our records allowed the comparison of individuals with TB infection with Covid-19 and their respective control group of patients with only Covid-19. We observed higher frequency of pulmonary fibrosis and toxic habits (illicit drugs, smoking and alcoholism), as well as a higher frequency of nausea and vomiting in the TB group, when compared to matched controls. which was also higher in the case group, and heart rate that was lower in the patients with active TB. In terms of laboratory tests, we also had higher hemoglobin, sodium and glutamic-pyruvic transaminase (GPT) values in controls, and higher bicarbonate values in cases with co-infection. There were no major differences in mortality or in the need for IMV.

Infection by *Mycobacterium tuberculosis,* known as Koch's bacillus, induces an inflammatory response, type 4 hypersensitivity reaction, that can contain an infection or generate a severe inflammatory reaction later on (Ravimohan et al. 2018, Lopes et al. 2006). In this case, there is activation of numerous chemokines and cytokines that induce the formation of granulomas, necrosis and pulmonary cavitation (Ravimohan et al. 2018, Lopes et al. 2006). However, the bacillus is capable of producing catalase peroxidase, inhibiting macrophage apoptosis and stimulating the production of IL-10, inducing the latency of the infection (Moutinho 2011). Over time granuloma formation occurs, through this process, the patient's symptoms are usually insidious, with a dry cough, low and evening fever and night sweats due to the intense inflammatory process that affects the patient (Ravimohan et al. 2018, Lopes et al. 2006, Moutinho 2011). Other symptoms such as anorexia, weight loss and adynamia chest pain due, respiratory difficulty, dyspnea, chronic dry cough and worsening weight loss (Ravimohan et al. 2018, Moutinho 2011) are also common in chronic infection. At that moment, the individual may have nonspecific symptoms, such as fever and cough, which are commonly self-resolving (Ravimohan et al. 2018, Moutinho 2011), that may have a similar presentation to Covid-19, such as fever and cough, and is an infection that also mainly affects the lungs.

The presence of undesirable outcomes in part of the tuberculosis patients hospitalized with Covid-19 draws attention to an important fact: around the globe, clinicians working in tuberculosis care were reassigned to work on the burden of Covid-19 cases during the pandemic, causing a negative impact on tuberculosis programmes due to the shortage of professionals. (Visca et al. 2021) This may have caused the migration of most of the health service actions to contain the overwhelming wake of the pandemic public calamity. In 2020, the World Health Organization (WHO) estimated that nearly 10 million people developed tuberculosis, but only 5.8 million cases were diagnosed and reported.

Table I. Comparison between patients with active TB and controls.

Characteristics	Active TB N = 36[1]	Controls N = 134[1]	p-value[2]
Age (years)	46.0 (39.8, 61.2)	48.0 (36.0, 55.0)	0.770
Women	29 (80.3%)	109 (81.3%)	0.915
Comorbidities			
Hypertension	7 (19.4%)	26 (19.4%)	0.996
Heart failure	0 (0.0%)	4 (3.0%)	0.580
Coronary artery disease	0 (0.0%)	2 (1.5%)	0.999
Asthma	4 (11.1%)	4 (3.0%)	0.063
Pulmonary fibrosis	2 (5.6%)	0 (0.0%)	**0.044**
COPD	1 (2.8%)	1 (0.7%)	0.380
Diabetes mellitus	6 (16.7%)	8 (6.0%)	0.079
Obesity	1 (2.8%)	8 (6.0%)	0.686
HIV infection	8 (22.2%)	18 (13.4%)	0.193
Psychiatric disease	4 (11.1%)	9 (6.7%)	0.477
Chronic kidney disease	2 (5.6%)	3 (2.2%)	0.286
Cancer	3 (8.3%)	5 (3.7%)	0.368
Number of comorbidities			
0	23 (63.9%)	97 (72.4%)	
1	7 (19.4%)	20 (14.9%)	
2	5 (13.9%)	13 (9.7%)	
3	0 (0.0%)	3 (2.2%)	
4	1 (2.8%)	1 (0.7%)	
Clinical assessment at admission			
SF ratio	452.4 (395.8, 461.9)	400.0 (296.9, 457.1)	0.070
Respiratory rate	21.0 (19.0, 28.0)	20.0 (18.0, 24.0)	0.420
Heart rate	90.5 (80.5, 102.8)	82.0 (74.0, 92.0)	0.007
Glasgow coma score <15	1 (2.8%)	5 (3.7%)	0.999
Systolic blood pressure			
≥ 90 (mm Hg)	28 (96.6%)	108 (97.3%)	
< 90 (mm Hg)	1 (3.4%)	3 (2.7%)	0.609
Diastolic blood pressure			
> 60 (mm Hg)	21 (72.4%)	88 (79.3%)	
≤ 60 (mm Hg)	8 (27.6%)	23 (20.7%)	0.572
Laboratory parameters			
Hemoglobin (g/L)	11.3 (9.0, 13.2)	13.4 (11.8, 14.8)	0.002

Table I. Continuation.

Characteristics	Active TB N = 36[1]	Controls N = 134[1]	p-value[2]
Platelet count (109/L)	244,000.0 (198,000.0, 414,750.0)	221,000.0 (173,000.0, 284,500.0)	0.057
Neutrophils	7,152.0 (3,407.8, 10,580.2)	5,976.0 (4,300.5, 9,330.0)	0.507
Lymphocytes	1,237.0 (658.5, 1,870.5)	968.0 (576.0, 1,518.8)	0.374
Lactate (mmol/L)	1.4 (1.0, 1.9)	1.2 (1.0, 1.7)	0.891
C-reactive protein (mg/L)	84.8 (49.8, 147.3)	85.0 (34.4, 144.4)	0.812
Urea	29.0 (20.0, 42.0)	34.0 (27.0, 46.9)	0.089
Creatinine (mg/dL)	0.8 (0.6, 1.2)	0.9 (0.7, 1.1)	0.062
Sodium (mmol/L)	135.0 (134.0, 138.0)	137.4 (135.2, 140.0)	0.009
Bicarbonate (mEq/L)	25.8 (23.7, 27.4)	23.5 (22.2, 25.1)	0.020
pH	7.4 (7.4, 7.5)	7.4 (7.4, 7.5)	0.909
pO2 (mmHg)	68.5 (58.1, 94.0)	73.0 (61.2, 81.0)	0.933
pCO2 (mmHg)	38.0 (34.0, 40.0)	35.8 (31.9, 38.3)	0.293

[1]n (%); Median (IQR) [2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.
TB: Tuberculosis; COPD - Chronic obstructive pulmonary disease; SF ratio: SpO2/FiO2 ratio.

That year also saw an estimated 1.5 million TB related-deaths worldwide, being the first year-on-year increase in TB deaths since 2005, mainly because of reduced access to care (WHO 2022). Likewise, services associated with tuberculosis were also impacted, and, according to the WHO, in 2020 there was a reduction of 18% in new cases diagnosed when compared to 2019, at the same time that the number of deaths increased (WHO 2022). Therefore, in high burden TB countries, TB and Covid-19 co-infection can be a problem, with lower rates of TB diagnosis due to the focus on Covid-19, as well as the possible similarity between disease presentations. Besides that, a co-infection can result in worse outcomes, such as higher ICU admission or even increased mortality (WHO 2020).

When compared to controls, patients with an active form of TB had similar outcomes. Although these facts go against the previously mentioned meta-analyses (Aggarwal et al. 2021, Visca et al. 2021, Wang et al. 2021), these findings can be explained by the small number of patients with active TB (n=36, incidence of 0.0026). Another hypothesis would be that an early intervention was performed in patients with both infections, since 46.2% of these patients were considered low risk by the ABC2-SPH risk score, associated with lower values of sodium and glutamic-pyruvic transaminase.

It was observed that patients with active tuberculosis had a higher percentage of illicit drug use, alcoholism and tobacco use when compared to individuals in the control group. The use of illicit drugs, especially injectable drugs, is an important risk factor in the global epidemiology of TB (Silva et al. 2018). Evidence shows that the psychological and immunosuppressive effects of illicit substances associated with psychosocial factors increase the chance of these patients remaining in the infectious stage and increase the time to achieve negative culture (Silva et al. 2018). In addition, alcoholism and the use of illicit drugs can cause discontinuation of TB treatment and its subsequent ineffectiveness (Silva et al. 2018).

Besides that, patients with an active form of TB also presented a higher frequency of

Table II. Outcomes comparison between patients with active TB and controls.

	Active TB N = 36[1]	Controls N = 134[1]	p-value[2]
In-hospital stay (days)	12.0 (6.8, 23.0)	9.0 (4.0, 16.0)	0.063
ICU admission	7 (20.0%)	40 (30.3%)	0.228
Time spent in hospital before ICU admission (days)	1.0 (0.0, 3.5)	1.0 (0.0, 3.0)	0.118
Time spent in the ICU (days)	7.0 (6.0, 9.5)	9.0 (5.0, 19.0)	0.453
Invasive mechanical ventilation	2 (5.7%)	26 (19.5%)	0.051
Time with mechanical ventilation	12.0 (11.0, 13.0)	10.0 (7.0, 23.0)	0.999
Dialysis	0 (0.0%)	5 (3.8%)	0.585
Septic shock	1 (2.8%)	9 (6.7%)	0.691
In-hospital death	3 (8.6%)	18 (13.5%)	0.572

[1]n (%); Median (IQR) [2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test. TB: Tuberculosis; ICU - Intensive Care Unit.

pulmonary fibrosis than controls. Regarding the previous clinical conditions of the patients, it is known that the lungs of patients with tuberculosis can present granulomas, mediated by cicotics, chemokines and matrix metalloproteinases to contain the proliferation of *Mycobacterium tuberculosis* (Ravimohan et al. 2018). This exacerbated inflammatory response generates tissue necrosis, forming cavitations, followed by an aberrant tissue response that initiates the process of fibrosis in the cavitations, which explain the high prevalence of fibrosis in patients with active TB when compared to the control group (Ravimohan et al. 2018). Furthermore, in a Korean cohort, patients with interstitial lung disease (ILD) were more likely to develop severe Covid-19 than those without ILD.

Another point to be discussed was the higher prevalence of nausea and vomiting in patients with active TB. Knowing that these manifestations are common in patients with Covid-19 and active TB, medications to prevent them can be given to patients in advance, preventing the exacerbation of these symptoms generating more well-being to the patient. In addition, for those patients diagnosed with Covid-19, the presence of nausea and vomiting can also be indicative of Covid-19 and TB coinfection. This information may help clinicians make an earlier diagnosis of TB in those patients who have previously been diagnosed with Covid-19, but further studies are needed to confirm this association, since the n in the study was small (n=36).

Mild anemia was observed in those patients with the co-infection. This finding can be attributed to the anemia of chronic disease that can develop in patients with high levels of circulating chemokines and inflammatory cytokines, as well as in patients with TB and Covid-19 simultaneously (Ravimohan et al. 2018, Silva et al. 2018). It is known that in this type of anemia there is a decrease in the survival of red blood cells, inadequate medullary response to anemia and iron metabolism disturbance, but without generating clinical manifestations or physiological damage to the patient (Silva et al. 2018). Therefore, the presence of anemia of chronic disease in these patients can be used to monitor the level of inflammation they are experiencing, because with the reduction of cytokines and chemokines, this anemia tends to

improve and restore normal levels of red blood cells and hemoglobin (Silva et al. 2018).

This study had some limitations. First all data was retrieved from medical records, this could be the reason of the low number of patients with active TB. Furthermore, our patients with TB records had the diagnosis prior or in hospital admission and there was no registry of systematic TB testing in patients, so more co-infections could be present and were not accountable. In addition, there could be report bias from the medical records in data collection. In order to lessen the burden of this potential bias, data collected was audited for possible errors.

CONCLUSIONS

Patients with an active TB infection and Covid-19 presented a higher frequency of illicit drug use; smoking; alcoholism; pulmonary fibrosis; nausea and vomiting as signs and symptoms; and lower heart rate. Furthermore, the active TB group presented lower hemoglobin, sodium and GPT, but presented higher PTTA and bicarbonate values. There was no difference between the need for MV, dialysis, ICU admission and in-hospital mortality.

Contrary to the literature, we did not find worse outcomes in the active TB group, but this may be related to the lack of TB screening in patients with Covid-19. Moreover, as previously mentioned, the cohort analyzed was made up of only 36 people, which makes a faithful representation of reality difficult. However, data from this study may help to understand Covid-19 and TB co-infection in hospitalized patients, mainly with regard to previous comorbidities and signs and symptoms.

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SUPPLEMENTARY MATERIAL

Tables SI-SIII.

How to cite

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