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LETTER TO THE EDITOR

Impact of the COVID-19 pandemic on in-hospital diagnosis of tuberculosis in non-HIV patients

Dear editor,

The coronavirus disease 2019 (COVID-19) pandemic brought unprecedented consequences for everyday activities, damaging economies and severely affecting healthcare systems.[1] A modelling analysis commissioned by the STOP TB Partnership has indicated that the COVID-19 pandemic has deeply affected the efforts on tuberculosis (TB) prevention, case detection and management. Reductions in TB diagnoses during the pandemic have been reported worldwide which has been attributed to a reduction in admissions due to lockdown, as well as to the abundance of public health measures directed against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the expense of other respiratory infectious diseases.[2]

In Portugal, the first COVID-19 case was recorded on the 2nd March 2020. We retrospectively reviewed adult hospitalised patients with TB, not associated with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) disease, in our tertiary hospital, and compared those admitted between March 2018 and June 2019 (pre-pandemic) with those admitted from March 2020 to June 2021 (pandemic). Chi-square test was used to compare categorical variables. Independent-samples t-test was used to evaluate differences in continuous variables with normal distribution and Mann-Whitney U tests were applied to evaluate differences in continuous variables with skewed distribution. Patient data were entirely anonymized and authorized by the Responsible for Access to Information (RAI) of Centro Hospitalar Universitário de São João. The registration protocol complies with the ethical guidelines of the Declaration of Helsinki and it was approved by the Ethics and Health Committee of Centro Hospitalar Universitário de São João.

We analysed a total of 100 cases (58 from pre-pandemic period and 42 from pandemic period) and the 42 cases linked with the time of pandemic reflected 72.4% of the admissions comparing to the homologous pre-pandemic one. There were fewer admissions in the first three months of the pandemic (18 in the pre-pandemic vs 7 in the pandemic, $p = 0.101$), coinciding with a mandatory household lockdown period and in line with reports disclosing partial disruptions in TB case detection and treatment during the same three months.[3]

Patients were significantly older in the pandemic group (54.5 years vs 63.0 years, $p = 0.015$), (Table 1). In both groups, most were male (75.9% in the pre-pandemic vs 78.6% in the pandemic sets, $p = 0.250$) and had smoking history (62.1% vs 61.9%, $p = 0.987$). Pre-existing lung disease was present in 32.8% ($n = 19$) and 38.1% ($n = 16$) of the patients ($p = 0.992$), with chronic obstructive lung disease (COPD) being the most frequent among those - 36.8% and 43.8%. Previous TB diagnosis was found in 6.9%, $n = 4$ and 9.5%, $n = 4$ of the cases in each group ($p = 0.805$). A variety of immunosuppression status was present in 46.6% ($n = 27$) of the patients in the pre-pandemic group vs 16.7% ($n = 7$) in the pandemic, a difference that was statistically significant ($p = 0.002$).

Disseminated tuberculosis was identified in 20.7% ($n = 12$; pre-pandemic group) and 31.0% ($n = 13$; pandemic group) of cases ($p = 0.324$). However, a significant increase in disseminated tuberculosis in immunocompetent patients was seen in the pandemic group - $n = 11$, 84.6% vs $n = 4$, 33% ($p = 0.009$) - affecting mainly bone, liver and genitourinary system. Exclusive pulmonary tuberculosis was found in 51.7% ($n = 30$) and 47.6% ($n = 20$) of patients ($p = 0.421$), respectively. Despite no difference in cavitating pulmonary disease ($p = 0.239$), bilateral lesions were more frequent in the pandemic period - $n = 12$, 60% vs $n = 9$, 30% ($p = 0.035$) - as was previously reported.[4] Concerning patients with negative sputum smears at presentation ($n = 32$ vs $n = 17$), and patients with numerous (>50/field) bacilli ($n = 7$ vs $n = 12$), the differences found across the two populations did not however achieve a statistically significant difference ($p = 0.055$). The length of stay was longer (median, 19.5 days [IQR 9.75-51.00] vs. 40.5 days [IQR 13.25-67.25]) in the pandemic period.

As previously stated by Visca et al., COVID-19 may occur at any time during a patient's TB journey and may cause a spectrum of host immunological responses. Nevertheless, more evidence is needed to understand the potential of COVID-19 to modify TB severity or to promote reactivation of TB infection.[5] We detected 3 cases of COVID-19 and tuberculosis co-infection, all male with no previous TB diagnosis. One had exclusive pulmonary tuberculosis and was immunocompromised due to chemotherapy, the other two patients had pleural and disseminated tuberculosis and no co-morbidities. No deaths were recorded.

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Table 1 Patients' characteristics and clinical presentations. Data are presented as frequencies and percentages for categorical variables and as medians and interquartile ranges (IQR) for continuous variables.

	March 2018-June 2019 (*n* = 58)	March 2020-June 2021(*n* = 42)	*p*-value
Age (years)	54.5 (41.75-67.50)	63.0 (47.75-77.00)	0.015
Male, *n* (%)	44 (75.9)	33 (78.6)	0.250
Smoking habits, *n* (%)			
Previous or active	36 (62.1)	26 (61.9)	0.987
Non-smokers	20 (34.5)	16 (38.1)	0.847
Passive	2 (3.4)	0	0.224
Previous or active drug abuse, *n* (%)	5 (8.6)	4 (9.5)	0.367
Previous pulmonary tuberculosis, *n* (%)	4 (6.9)	4 (9.5)	0.805
Pre-existing lung disease, *n* (%)	19 (32.8)	16 (38.1)	0.992
Chronic obstructive lung disease	7 (36.8)	7 (43.8)	
Non-cystic fibrosis bronchiectasis	3 (15.8)	4 (25.0)	
Silicosis	3 (15.8)	3 (18.7)	
Asthma	2 (10.5)	2 (12.5)	
Hypersensitivity pneumonitis	2 (10.5)	0	
Alpha-1 antitrypsin deficiency	1 (5.3)	0	
Cystic lung disease	1 (5.3)	0	
Immunocompromised status, *n* (%)	27 (46.6)	7 (16.7)	0.002
Chronic alcoholism	12 (44.5)	3 (42.9)	
High dose steroids	6 (22.2)	2 (28.5)	
Hematologic malignancy	5 (18.5)	2 (28.5)	
Monoclonal antibody treatment	4 (14.8)	0	
Pulmonary tuberculosis, *n* (%)	49 (84.5)	38 (90.5)	0.379
Restricted to lungs	30 (51.7)	20 (47.6)	0.421
Disseminated	12 (20.7)	13 (31.0)	0.324
Pleuropulmonary	7 (12.1)	5 (11.9)	0.601
Extrapulmonary tuberculosis, *n* (%)	9 (15.5)	4 (9.5)	0.379

For McQuaid et al., two of the main concerns of the COVID-19 pandemic on TB would be a greater impact on patients with drug-resistant TB and a net increase in deaths in all scenarios with some level of health service disruption.[6] According to our data, during the pandemic period, 95.2% (*n* = 40) of the cases were drug-sensitive and mortality was lower (12.1%, *n* = 7, vs. 4.8%, *n* = 2) but no statistical difference was found (*p* = 0.208).

In our study, less immunocompromised patients hospitalized with TB were seen in the pandemic period. Particular care with social distancing, self-quarantine and the thorough use of facial masks by these patients might have had an impact in this finding. In the pandemic setting there was: (i) a clear increase in extended pulmonary forms, (ii) a significant rise of disseminated tuberculosis cases in immunocompetent patients and (iii) a tendency to find a greater proportion of numerous bacilli on smears, indicating that people might have tolerated longer symptomatic periods before seeking medical aid, as they were reluctant to go to the hospital, leading to diagnostic delay and to an increased risk of TB transmission in households and communities. Rodrigues et al. reached the same conclusion, finding delays in the diagnosis of tuberculosis in the outpatient tuberculosis centres (OTBC), even though they had been open during the pandemic.[7] In our population, COVID-19 did not impact in a rise of drug-resistant cases or higher mortality, but more data are needed in the following years.

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