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SHORT COMMUNICATION

Tuberculosis infection in HIV *vs.* non-HIV patients

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Objectives

Tuberculosis (TB) is the most common opportunistic infection and cause of mortality among people living with HIV, and it is possible that it may also influence the evolution of the HIV infection. We assessed the differences between HIV-positive and -negative people infected with TB.

Methods

The present study is a cross-sectional retrospective study by electronic record revision. We included patients admitted to a tertiary hospital with a diagnosis of TB between 2011 and 2016, comparing those with HIV coinfection with non-HIV patients, according to demographic and clinical characteristics.

Results

This study included 591 patients, of whom 32% were HIV-coinfected. HIV-TB patients were younger, with a predominance of male gender. Considering TB risk factors, there was a higher prevalence of homelessness and intravenous drug use in the HIV group. In the non-HIV group, direct contact with other patients with TB and immunosuppression were more prevalent. Relative to TB characteristics, the HIV-coinfected group presents with a higher prevalence of disseminated disease and a higher occurrence of previous TB infection. Cancer was the most frequent cause of immunosuppression in the HIV group and the number testing positive for TB via microbiological culture was lower. Assessment of microbiological resistance and in-hospital mortality showed similar numbers in both groups.

Conclusions

There are few papers comparing clinical course of TB between HIV-infected and non-infected patients. Our study differs from others in the literature as we focused on a country with middling incidence of TB and further characterized the differences between HIV-infected and non-infected patients which can contribute to the management of these patients.

Keywords: clinical course, HIV infection, mortality, risk factors, treatment complications, tuberculosis

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Introduction

Tuberculosis (TB) remains a major global health problem. According to the Who Global Report, an estimated 10 million people were diagnosed with TB in 2019 [1]. It causes increased morbidity among millions of people each year and stands as the second leading cause of death from an infectious disease worldwide, after HIV [2]. Globally, there were 1.2 million TB deaths (range: 1.1–1.3 million) among HIV-negative people in 2019 and an additional 251 000 deaths among HIV-positive people [1]. Among all TB cases, 8.6% were people living with HIV. Geographically, those countries most severely affected by the two epidemics have low resources and weak health systems.

Airborne transmission of *Mycobacterium tuberculosis* is responsible for primary TB infection, which can evolve in immunocompetent, but more frequently in immunocompromised, hosts into TB. There has been an overall decrease in TB and HIV infection in recent decades [1,3];

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however, coinfection still remains an issue [4]. This is a reflection of increased risk of progression from latent to active TB in HIV patients, with a corresponding increase in mortality if not treated in a timely fashion for both TB and HIV [2,5]. However, a higher susceptibility to primary infection in HIV patients has also been demonstrated [4].

Currently we can accept that there is an increased susceptibility to disease once infection by *M. tuberculosis* has occurred, where it is comorbid with, for example, HIV infection, diabetes and chronic illness, or where people are taking immunosuppressive therapies, are malnourished or abusing alcohol or tobacco [6].

These variables should be taken into consideration when accounting for countries with higher *vs.* lower burden of TB.

Tuberculosis is the most common opportunistic infection and cause of mortality among people living with HIV, and it is possible that it may also influence the evolution of the HIV infection. Proinflammatory cytokine production by tuberculous granulomas has been associated with increased HIV viraemia, which might accelerate the course towards severe immunosuppression [7,8]. However, this remains controversial, and it has been suggested that poor prognosis may be related to previous HIV viral load [9]. Also antituberculous drugs, such as rifampicin, interfere with antiretroviral drugs, including protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs), which could lead to virological failure [7,8].

The higher morbidity and mortality rates of TB in HIV-infected individuals *vs.* non-infected patients is most likely due to a combination of factors related to the HIV coinfection itself. These include the rapid progression of disease due to the failure of immune responses to restrict the growth of *M. tuberculosis*, delayed diagnosis and treatment due to atypical presentation, delayed diagnosis of HIV infection, delayed start or lack of access to combination antiretroviral therapy (ART), and higher rates of multidrug-resistant TB (MDR-TB) leading to delayed initiation of effective therapy [2,10].

According to the literature, the risk of death in HIV-infected patients with TB is twice that in HIV-infected patients without TB with matched CD4 cell counts, with most deaths caused by progressive HIV infection, rather than TB [5].

Early detection of HIV-TB cases and prompt provision of ART and anti-TB treatment are key interventions to reduce mortality rates significantly.

The present study was therefore proposed to assess the differences between HIV-positive and -negative TB patients with regard to demographic characteristics, clinical features, diagnostic features, radiographic appearance and treatment outcome.

Methods

We performed a cross-sectional retrospective study including patients admitted to a tertiary hospital between 2011 and 2016 with a TB infection diagnosis. Inclusion criteria were age over 18 years old and an *International Classification of Diseases*, Ninth Revision (ICD-9) code for TB (010-018).

The electronic medical record for each eligible patient was reviewed to obtain demographic data, length of stay (LOS), comorbidities (according to the Charlson Index, excluding the HIV), ethnicity (white, African and Asian) and risk factors for TB (HIV infection, immunosuppression, direct contact with patient with TB, homeless status or resident in a healthcare facility, intravenous drug use and healthcare professional status). Tuberculosis was characterized according to site (lung, disseminated, etc.), previous infection, clinical (local and systemic symptoms), analytical (leucocyte values $> 11 \times 10^9$/L and $< 4.5 \times 10^9$/L, and C-reactive protein > 5 mg/mL, erythrocyte sedimentation rate > 16 mm/h and hyponatremia < 135 mmoL) and radiological features (any of the TB radiological presentations was considered), and microbiological isolate (and which) as dichotomous variables (presence/absence).

Patients were divided by their HIV status into two groups. Outcomes were in-hospital mortality, antibiotic complications and microbiologic resistance.

Data were analysed with mean and standard deviation (SD) if normally distributed, and median and interquartile range (IQR) if non-normally distributed. Student's *t*-test or Wilcoxon rank-sum test was performed for continuous variables, and χ^2 test for dichotomous variables. Multivariate logistic regression was done to account for confounding. To avoid model overfitting, the rule of 10 was observed. A P-value < 0.05 was considered to be significant. Analysis was conducted in Stata (release 14; StataCorp, College Station, TX, USA).

Results

A total of 591 patients were included, and of these 187 (32%) had HIV. Patients with HIV were slightly younger [43 (37–49) *vs.* 45 (33–61.5) years; $P = 0.06$), with a similar LOS [29 (16–46) *vs.* 27 (14–47) days; $P = 0.5$), Charlson index, when excluding HIV from its preponderance factors [1 (0–2) *vs.* 1 (0–4); $P = 0.08$], and ethnicity distribution (71% *vs.* 67% white, 26% *vs.* 25% African, and 2% *vs.* 7% Asian; $P = 0.06$). There was, however, a statistically significant difference in relation to gender, with a predominance of males in the HIV group (82% *vs.* 68%; $P = 0.001$) (Table 1).

Table 1 Demographic data and risk factors for tuberculosis (TB) infection: a total of 591 patients were included, of whom 187 (32%) had HIV

Demographics	HIV	Non-HIV	Total	*P*-value
Age (years) [median (IQR)]	43 (37–49)	45 (33–61.5)	44 (35–56)	0.06
Gender (male)	154 (82%)	278 (68%)	432 (73%)	**0.001**
Length of stay (days) [median (IQR)]	28 (16–46)	27 (14–47)	27 (15–47)	0.5
Adapted Charlson Index [median (IQR)]	1 (0–2)	1 (0–4)	1 (0–3)	0.08
Ethnicity				
White	128 (71%)	263 (67%)	391 (69%)	0.06
African	47 (26%)	96 (25%)	143 (25%)	
Asian	4 (2%)	28 (7%)	32 (6%)	
Migrants	58 (31%)	147 (36%)	205 (35%)	0.2
Risk factors				
Homelessness	28 (15%)	21 (5%)	49 (8%)	**< 0.001**
Healthcare facility user	8 (4%)	7 (2%)	15 (2%)	0.07
Intravenous drug use	56 (30%)	33 (8%)	89 (15%)	**< 0.001**
Healthcare worker	2 (1%)	4 (1%)	6 (1%)	0.9
Direct contact	10 (5%)	54 (13%)	64 (11%)	**0.004**
Immunosuppression	25 (13%)	96 (24%)	121 (20%)	**0.004**
Immunosuppression cause				
Autoimmune disease	0 (0%)	5 (5%)	5 (4%)	**0.006**
Immunosuppressive drugs	0 (0%)	3 (3%)	3 (2%)	
Diabetes	9 (36%)	42 (44%)	51 (42%)	
Cancer	16 (64%)	25 (26%)	41 (34%)	
Haemodialysis status	0 (0%)	8 (8%)	8 (7%)	
Post-solid organ transplant status	0 (0%)	13 (14%)	13 (11%)	
Total [*N* (%)]	187 (32%)	404 (68%)	591	

Bold values are to highlight statistical significance.
IQR, interquartile range. Data are *n* (%) unless noted otherwise.

Considering TB risk factors, other than HIV, there was not a significant difference in both groups regarding the status of healthcare facility resident (4% *vs.* 2%; $P = 0.07$) and healthcare worker (1%, $P = 0.9$). There was higher prevalence of homelessness (15% *vs.* 5%; $P < 0.0001$) and intravenous drug use (30% *vs.* 8%; $P < 0.0001$) in the HIV group. On the other hand, direct contact with other patients with TB (5% *vs.* 13%; $P = 0.004$) and immunosuppression other than HIV (13% *vs.* 24%; $P = 0.004$) were more prevalent in the non-HIV group. The reason for immunosuppression was also different in the two groups ($P = 0.006$), with autoimmune disease (0% *vs.* 5%), immunosuppressive drugs (0% *vs.* 3%), diabetes (36% *vs.* 44%), hemodialysis status (0% *vs.* 8%) and post-solid organ transplant status (0% *vs.* 14%) being more frequent in the non-HIV group, and cancer (64% *vs.* 26%) more likely in the HIV group (Table 1).

As TB characteristics go, there was a statistically significant difference in TB site ($P < 0.0001$) with lower prevalence of lung (60% *vs.* 80%) and higher disseminated prevalence in HIV patients (27% *vs.* 7%) (Table 2). There was also a higher occurrence of previous TB infection (30% *vs.* 16%; $P < 0.0001$) in HIV patients. Clinically, both groups had similar features: systemic symptoms (85% *vs.* 86%; $P = 0.9$), analytical changes (81% *vs.* 79%; $P = 0.5$) and radiological changes (92% *vs.* 95%; $P = 0.3$). The exceptions were local symptoms which manifested less commonly (83% *vs.* 90%; $P = 0.02$) (Table 2).

Testing positive for TB via microbiological culture was less common in HIV patients (85% *vs.* 92%; $P = 0.005$), with no significant difference in relation to the microbiological sample type ($P = 0.4$) (Table 2).

As for the clinical outcomes, both groups had similar results with regard to microbiological resistance (10%; $P = 0.7$) and in-hospital mortality (6% *vs.* 7%; $P = 0.6$) (Table 2). However, there was a higher rate of treatment complications (20% *vs.* 13%; $P = 0.02$), which remained significant following confounder adjustment by logistic regression. The difference was also observed in the type of complications ($P = 0.04$), with a higher incidence of rash in HIV patients (21% *vs.* 2%) and liver toxicity (53% *vs.* 46%), and lower rates of gastrointestinal intolerance (3% *vs.* 10%), anaemia (0% *vs.* 4%) and polyneuropathy (0% *vs.* 2%) (Table 2).

Discussion

There are few papers comparing TB clinical course between HIV-infected and non-infected patients, most differences being in the country of origin of patients and the form of the TB (pulmonary *vs.* disseminated) [11].

Table 2 Tuberculosis (TB) infection characteristics. There was a statistically significant difference in TB site with lower prevalence of lung as well as local symptoms, which manifested less commonly in the HIV group and frequency of microbiological positivity

TB infection	HIV	Non-HIV	Total	*P*-value
TB site				
Lung	113 (60%)	324 (80%)	437 (74%)	**< 0.0001**
Other	74 (40%)	80 (20%)	154 (26%)	
Previous infection	49 (30%)	58 (16%)	107 (21%)	**< 0.0001**
Systemic symptoms	159 (85%)	346 (86%)	505 (86%)	0.9
Local symptoms	155 (83%)	362 (90%)	517 (88%)	**0.02**
Laboratory changes	149 (81%)	314 (79%)	463 (79%)	0.5
Radiological changes	172 (92%)	382 (95%)	554 (94%)	0.3
Specimen positivity	158 (85%)	371 (92%)	529 (90%)	**0.005**
Outcomes				
Microbiological resistance	17 (10%)	41 (10%)	58 (10%)	0.7
Treatment complications	38 (20%)	52 (13%)	90 (15%)	**0.02**
Liver toxicity	20 (53%)	24 (46%)	44 (49%)	
Gastrointestinal intolerance	1 (3%)	3 (10%)	4 (4%)	
Anemia	0 (0%)	2 (4%)	2 (2%)	
Rash	8 (21%)	1 (2%)	9 (10%)	
Polyneuropathy	0 (0%)	1 (2%)	1 (1%)	
In-hospital mortality	11 (6%)	28 (7%)	39 (7%)	0.6

Data are *n* (%).

Our study differs in that we focused on a country with a middling incidence of TB (*vs.* low incidence in the cited paper), and further characterized the differences between HIV-infected and non-infected patients.

First, there was a significant difference in regard to gender, with a higher prevalence of males among HIV patients. Despite a slightly higher prevalence of Asian ethnicity in non-HIV patients, this was not significant. Another major difference had to do with risk factors, in which we observed that certain risk factors (homelessness and IV drug use) were more associated with HIV-infected patients, while others (contact with other TB-infected patients and immunosuppression) were more prevalent in non-HIV patients. Cancer as a cause of immunosuppression was more frequent in the HIV patients, as opposed to other causes of immunosuppression which were more frequent in non-HIV patients. However, there was a high prevalence of diabetes in the HIV population as well. Previous infection with TB was similarly more frequent in HIV patients.

As for clinical features of TB, we also encountered some important differences (see also Fenner *et al.* [11]), such as disseminated TB being more prevalent in HIV patients. However, in contrast to their results, pulmonary TB was less common in HIV patients. Similarly, clinically, local symptoms were common in non-HIV patients, and sputum microbiological positivity was higher in this group.

Correspondingly, in conflict with previous studies, we did not find a significant difference in mortality in the two groups, or in microbiological resistance. Further to this latter finding, we hypothesize it might have something to do with the higher frequency of Asians in the non-HIV group. It could also be related to clinicians' higher degree of suspicion with regard to TB, which would lead to earlier diagnosis and therefore treatment.

Interestingly, the treatment complication rate was higher among HIV patients – in particular, rash, which is often benign and does not compromise treatment. This could be related to other drugs these patients are on, such as ART or prophylaxis (e.g. cotrimoxazole).

There were some limitations to our study. First, it was retrospective and there are some important missing data. Also, there was loss of follow-up after discharge, because patients were then followed at a different institution. This limited our ability to draw correct inferences about the outcomes and also to make assessments about treatment completion. We also believe that further characterization of the HIV population could have provided greater understanding of certain results. In addition, our hospital reference area has a varied population, with high percentages of the elderly and also of migrants (particularly Asian, but also African) and homeless people, which could lead to bias in our results.

We believe we have highlighted some important differences in the features of HIV-infected and non-infected TB patients, which could contribute to their management. We also believe that using data from a country with a medium incidence of TB, with both native and imported cases, adds value to our findings.

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Author contributions

IRF and HG designed the project. IRdF, RVA, DDB and MT collected the data. IRdF carried out the data analysis. IRdF, JBF and SD wrote the manuscript, and SGC, FL, AMA, HG and AP revised it.

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