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Tuberculosis infection in the elderly versus in the young adult

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Objective. Tuberculosis (TB) is an infectious disease in which the clinical course is influenced by age-related changes in the respiratory and immune systems.
Methods. Cross sectional retrospective analysis of patients admitted with the diagnosis of tuberculosis between 2011 and 2016, comparing patients with ages under and above 65 years old.
Results. Inclusion of 591 patients, 16% of the individuals being over 65 years. Predominance of male gender, with white race preponderance in the elderly group (84%). Disease site at presentation was predominantly lung (74%), followed by disseminated disease (14%). As expected, the mortality registered was higher in the older population (20 *vs* 4%).
Conclusions. TB remains a less frequent infection in the elderly. The infection characteristics are similar in both groups however with a more atypical presentation in the elderly.

Key words: tuberculosis, risk factors, mortality, elderly

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INTRODUCTION

Tuberculosis (TB) is an infectious-contagious disease, whose etiological agent is *Mycobacterium tuberculosis* [1]. This infection can result in either the elimination of infection or the persistence of the pathogen. When the pathogen persists, a dynamic relationship is thought to exist between the host and *M. tuberculosis*, resulting in a continuous spectrum between TB infection and disease [2].
Even though a cure has been found, TB is still the leading cause of death from a single infectious agent worldwide since 2007, affecting susceptible individuals, including the geriatric population, and is considered a global health emergency by the World Health Organization [3,4]. However, there has been a large drop in TB notification from 2016-2021, result from the COVID-19 pandemic [5]. The elderly (defined as individuals over 65 years) are a particularly vulnerable population because they have especially high risk for reactivation of latent TB and more susceptible to new TB infection, higher mortality rates and adverse reactions (such as liver toxicity, cutaneous reactions, but also, hematological complications) [2,4,6,7]. This results from interaction of existing co-morbidities, compromised nutrition,

polypharmacy, decreased renal and hepatic drugs clearance, living conditions and access to health care facilities, alongside physiological changes with weaken protective barriers, impaired microbial clearance mechanisms, together with changes in immune function (immunosenescence) [8].

Evidence also suggests that time from symptom onset to treatment in patients with pulmonary TB is significantly longer in those over 65 years compared with those aged 18-64 years [9,10]. Clinicians should have a high index of suspicion for TB to confirm the diagnosis because elderly individuals present fewer of the classical symptoms of TB (such as fever, night sweats, or hemoptysis), less specific radiological changes and more comorbidities than in younger patients [11-13]. On the other hand, elderly may exhibit atypical and subtle clinical manifestations such as loss of appetite, functional decline, and low-grade fever or weight loss [9-14]. UK surveillance data show that the proportion of TB patients who experienced a delay of more than 4 months from symptom onset to starting treatment increases with age, from 24.9% in those aged 15-44 years to 38.6% among those aged over 65 years old (2).

Scarce studies explore the differences between older and younger TB patients therefore we proposed to evaluate the differences between younger and elderly population regarding demographic, clinical and diagnostic characteristics, radiographic appearance, and treatment outcome.

METHODS

We performed a cross-sectional retrospective study by chart review of patients with Tuberculosis (TB) infection admitted to a single tertiary-care center between 2011 and 2016. Eligible patients were 18 years or older and identified using an ICD-9 code for Tuberculosis (010-18).

The electronic medical record for each eligible patient was reviewed to obtain demographic data, length of stay, comorbidities (according to the Charlson Index), race (white, African and Asian) and risk factors for TB (HIV infection, direct contact with patient with TB, homeless status or resident in a health care facility, intravenous drug use and health care professional status, or immunosuppression). TB was characterized according to site (lung, disseminated, etc), previous infection and clinical (local and systemic symptoms), analytical (leucocytes values higher than 11x10 ^{9}/L and below 4,5x10 ^{9}/L, and C-reactive protein (CRP)> 5 mg/mL, erythrocyte sedimentation rate (ESR) > 16 mm/h and hyponatremia < 135 mmoL) and radiological features (any of the TB radiological presentations was considered), microbiological isolate (and which), as dichotomous variables (presence/absence).

Patients were then categorized by their age into two different age groups: elderly (≥ 65 years old) or young (under 65 years old). Assessed outcomes were in-hospital mortality, antimicrobial side effects and microbiologic resistance.

Data were analyzed with mean and standard deviation (SD) if normally distributed and with median and Interquartile range (IQR), if non-normally distributed. Student t-test or Wilcoxon Rank-Sum test was performed for continuous variables, and chi square test for dichotomous variables. Multivariate logistic regression was done to account for confounding. To avoid model overfitting, the rule of ten was observed. A p-value of < 0.05 was considered to be significant. Analysis was conducted in Stata (StataCorp. Stata statistical software: release 14. College Station, TX: StataCorp LP).

RESULTS

A total of 591 patients were included, out of those 96 (16%) were older than 65 years old. Median age for the elderly group was 73 (69-79.5) comparing to a median of 41 (33-50) in the younger group. On both groups, there was a predominance in the male gender, even though it was statistically more significant in the younger group (75 *vs* 65%, p-value = 0.04). Patients' race was also different according to age group: in the elderly white was the most prevalent (84%), comparing to African (2%) and Asian (0%) (p-value = 0.003) (Tab. I).

Considering risk factors for TB infection, the most frequent is HIV infection (31%), followed by immunosuppression (20.5%), IV drug use (15%) and homelessness status (8%). All these risk factors had differences between the two age groups, with HIV, IV drug use and homelessness status being more prevalent in the young (36 *vs* 8%, p-value < 0.0001; 18 *vs* 0%, p-value < 0.0001 and 9 *vs* 3%, p-value = 0.04, respectively). Immunosuppression, however, was more frequent in the elderly (15 *vs* 50%, p-value < 0.0001). Regarding the causes of immunosuppression: diabetes mellitus (45 *vs* 38%), cancer (30 *vs* 40%), solid organ transplantation (15 *vs* 4%), hemodialysis status (7 *vs* 6%), autoimmune disease (1 *vs* 8%) and the use of immunosuppressive drugs (1 *vs* 4%). The differences were not statistically significant (p-value = 0.1) (Tab. I).

Clinically, TB infection was globally similar between the groups. Previous infection (22 *vs* 15%, p-value = 0.2), infection site on the lung (75 *vs* 71%, p-value = 0.4), presence of systemic symptoms (87 *vs* 80%, p-value = 0.09), laboratory changes (80 *vs* 78%, p-value = 0.7), and radiological changes (94% both groups,

Table I. Demographic data and risk factors. Total of 591 patients included of which 16% were elder. Median age 73 (69-79.5) *vs* 41 (33-50) in the young group. Predominance of male gender, and difference in race preponderance according to age group: in the elderly white was the most prevalent (84%). The most frequent was HIV infection (31%), followed by immunosuppression (20.5%), IV drug use (15%) and homelessness status (8%). HIV, IV drug use and homelessness status are more prevalent in the young and immunosuppression in the elderly.

Demographic data	< 65 years old	≥ 65 years old	Total	P-value
Age (median; IQR)	41 (33-50)	73 (69-79.5)	44 (35-56)	< 0.0001
Gender (male)	75% (370)	65% (62)	73% (432)	0.04
Length of stay (median; IQR)	27 (16-48)	25.5 (12.5-43.5)	27 (15-47)	0.4
Charlson Index (median; IQR)	2 (0-6)	6 (4-8)	3 (0-6)	< 0.0001
Race				0.003
White	67% (318)	84% (75)	69% (391)	
African	27% (131)	2% (2)	25% (143)	
Asian	6% (30)	0% (0)	6% (32)	
Total (N)	84% (495)	16% (96)	100% (591)	
Riskfactors	< 65 years old	≥ 65 years old	Total	P-value
HIV	36% (179)	8% (8)	31% (187)	< 0.0001
Homelessness	9% (46)	3% (3)	8% (49)	0.04
Health care facility user	2.6% (13)	2% (2)	2.5% (15)	0.7
IV drugs user	18% (89)	0% (0)	15% (89)	< 0.0001
Health care worker	1% (6)	0% (0)	1% (6)	0.3
Direct contact	12% (59)	5% (5)	11% (64)	0.05
Immunosuppresion	15% (74)	50% (47)	20.5% (121)	< 0.0001
Immunosuppresion cause				0.1
Autoimmune disease	1% (1)	8% (4)	4% (5)	
Use of immunosuppressive drugs	1% (1)	4% (2)	2.5% (3)	
Diabetes mellitus	45% (33)	38% (18)	42% (51)	
Active cancer	30% (22)	40% (19)	34% (41)	
Hemodialysis	7% (5)	6% (3)	7% (8)	
Solid organ transplant	15% (11)	4% (2)	11% (13)	

p-value = 0.9) (Tab. II). Statistically significant differences were observed in the presence of local symptoms (90 *vs* 78%, p-value = 0.002) and in the specimen positivity (91 *vs* 81%, p-value = 0.003) (Tab. II). Sputum was the most used microbiological sample, yielding a higher percentage of positive results in the younger group (79 *vs* 53%, p-value < 0.0001). In the older group bronchoalveolar fluid allowed to diagnose pulmonary TB more often (22 *vs* 5%).

Considered outcomes were microbiological resistance, treatment complications and in-admission mortality. Treatment complications were similar in the two groups (15 *vs* 18%, p-value = 0.5), (Tab. II) and were mostly due to liver toxicity (74 *vs* 67%) and rash (12 *vs* 33%). There was a slightly higher incidence of microbiological resistance in the young, however this was not statistically significant (11 *vs* 4%, p-value = 0.056).

Mortality was largely different between the 2 groups (2 *vs* 20%), with a OR of 5.8. When adding demographic data on the multivariate analysis, mortality remained different between the groups, however, with the addition of the risk factors this difference lost significance (p-value = 0.09, OR 2.3) (GOF p-value = 0.09, AUROC 0.9) (Tab. II).

CONCLUSIONS

Tuberculosis infection remains less frequent in the elderly (16%) and lessens the male predominance observed in the younger (65%). There is also a difference in race between the two groups, with a bigger importance on African and Asian cases in the young (27% and 6%), related to migrant populations. Comorbidities

Table II. Clinical characteristics of infection. TB infection was similar between the young and elderly regarding previous infection, infection localized on the lung, presence of systemic symptoms, and laboratory and radiological changes. However, younger patients had higher incidence of local symptoms and specimen positivity. Microbiological resistance, treatment complications and mortality were assessed. Although resistance was higher in the younger (11 *vs* 4%), it was not statistically significant. Mortality was higher in the elderly (4 *vs* 20%). Univariate analysis shows an OR of 5.8 for old age, 1.2 for comorbidities and 4.2 for immunosuppression. Following multivariate analysis only the Charlson index remains determinant for mortality (OR 1.3). Good model performance (GOF p-value = 0.09, AUROC 0.9).

TB infection characteristics	< 65 years old	> 65 years old	Total	P-value
TB site				0.4
Lung	75% (371)	71% (68)	74% (437)	
Other	25% (126)	29% (27)	26% (153)	
Previous infection	22% (94)	15% (13)	21% (107)	0.2
Systemic symptoms	87% (428)	80% (77)	86% (505)	0.09
Local symptoms	90% (442)	78% (75)	88% (517)	0.002
Laboratory changes	80% (390)	78% (73)	79% (463)	0.7
Imagiological changes	94% (465)	94% (89)	94% (554)	0.9
Specimen positivity	91% (451)	81% (78)	90% (529)	0.003
Outcomes	< 65 years old	> 65 years old	Total	P-value
Resistance	11% (54)	4% (4)	10% (58)	0.056
Treatment complications	15% (73)	18% (17)	15% (90)	0.5
Mortality	4% (20)	20% (19)	6,6% (39)	< 0.0001

Mortality	Univariate		Multivariate	
	Odds ratio (CI 95%)	P-value	Odds ratio (CI 95%)	P-value
> 65 years old	5.8 (3-11)	< 0.0001	2.3 (0.9-6)	0.09
Male gender	0.9 (0.4-1.9)	0.85	0.8 (0.4-1.8)	0.6
Charlson index	1.2 (1.1-1.3)	< 0.0001	1.3 (1-1.5)	0.004
Race	1.5 (0.9-2.5)	0.064	1.2 (0.7-2)	0.4
HIV	0.8 (0.4-1.7)	0.6	0.4 (0.09-1.2)	0.1
IV drug user	1 (0.4-2.5)	0.9	1.5 (0.5-4.3)	0.5
Immunosuppression	4.2 (2.2-8)	< 0.0001	1.4 (0.6-3.2)	0.5

are more prevalent in the elderly group as expected [4]. As for the risk factors, HIV, IV drug use and homelessness are the most important for the young, contrasting with immunosuppression, mostly from diabetes mellitus and cancer in the elderly, which suggest a different infection pathway. Infection characteristics remain very similar between the groups. We had expected less lung TB in the elderly, with a higher percentage of atypical locations, and we emphasize higher non-significant percentage of lymph node TB in the elderly (3 *vs* 6%) [2]. Data regarding previous infection are, however, higher in the young (22 *vs* 15%), which we believe is related to recall bias (elderly patients may not remember infection as young, and younger patients also have medical records to register the infection). The elderly had fewer local symptoms and so their clinical presentation was often more atypical, comparing to the young [6]. Contributing to harder diagnosis was also a lower sensitivity in microbiological diagnostic (91 *vs* 81%), but also the type of specimen, which often required invasive interventions (for example sputum specimen were less frequent in the elderly 79 *vs* 53%, but bronco-alveolar lavage was more frequent 5 *vs* 22%) [2,4,6].

Considering the outcomes, we had expected for the elderly patients to have higher risk of treatment complications such as liver toxicity, due to polypharmacy, but this was not observed [4]. Our hypothesis is that considering the younger group risk factors of HIV and IV drug use, with frequent liver disease (21 *vs* 15%), their risk was increased. Microbiological resistance was expected to be higher in the young group due to differences in the infection history (migrants, HIV and IV drug users with higher risk), however this was not statistically significant. Mortality was largely different between groups with a OR of 5.8. Multivariate analysis revealed that Charlson index remained the major determinant in mortality (OR 1.3, p-value = 0.004).

Our work has some important limitations. For starters, despite the big sample size, however only a small percentage of cases (16%) were of elderly, which limited statistical analysis, namely multivariate analysis. The retrospective nature of our work compromised data

collection due to missing data, but also to the lack of detail of such data (for example many variables were dichotomous because detailed information was lacking, such as risk factors, previous infection, and type of radiological changes).

To conclude, TB infection presents itself differently in elderly patients and we should expect an increase in incidence with the population ageing. Therefore, healthcare workers should be alert for this condition and the particularities of its management and public health policies should be more embracing to include the elderly.

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Conflict of interest

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Author contributions

IRF, HG: Study design; IRF, JBF, SD, RVA, DDB, MT: Data collection; IRF: Data analysis; IRF, JBF, SD: Manuscript writing; SGC, FL, AMA, HG, AP: Manuscript revision.

Ethical consideration

Considering the retrospective nature of the project, the need to submit to the center Ethics Committee was waivered.

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