Clinical characteristics and evolution of non-HIV-infected immunocompromised patients with an in-hospital diagnosis of tuberculosis*

Características clínicas e evolução de pacientes imunocomprometidos não HIV com diagnóstico intra-hospitalar de tuberculose

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Abstract

Objective: To investigate the characteristics of and risk factors for mortality among non-HIV-infected immunocompromised patients with an in-hospital diagnosis of tuberculosis. **Methods:** This was a two-year, retrospective cohort study of patients with an in-hospital diagnosis of tuberculosis. The predictive factors for mortality were evaluated. **Results:** During the study period, 337 hospitalized patients were diagnosed with tuberculosis, and 61 of those patients presented with immunosuppression that was unrelated to HIV infection. Extrapulmonary tuberculosis was found in 47.5% of cases. In the latter group, the in-hospital mortality rate was 21.3%, and the mortality rate after discharge was 18.8%. One-year survival was significantly higher among the immunocompetent patients than among the HIV patients (p = 0.008) and the non-HIV-infected immunocompromised patients (p = 0.015), although there was no such difference between the two latter groups (p = 0.848). Among the non-HIV-infected immunocompromised patients, the only factor statistically associated with mortality was the need for mechanical ventilation. Among the patients over 60 years of age, fibrosis/atelectasis on chest X-rays and dyspnea were more common, whereas fever and consolidations were less common. Fever was also less common among the patients with neoplasms. The time from admission to the initiation of treatment was significant longer in patients over 60 years of age, as well as in those with diabetes and those with end-stage renal disease. Weight loss was least common in patients with diabetes and in those using corticosteroids. **Conclusions:** The lower prevalence of classic symptoms, the occurrence of extrapulmonary tuberculosis, the delayed initiation of treatment, and the high mortality rate reflect the diagnostic and therapeutic challenges of tuberculosis in non-HIV-infected immunocompromised patients.

Keywords: Hospitalization; Immunosuppression; Risk factors; Tuberculosis/mortality; Immunocompromised host.

Resumo

Objetivo: Investigar as características de pacientes imunocomprometidos não HIV com diagnóstico intra-hospitalar de tuberculose e determinar os fatores de risco para mortalidade. **Métodos:** Durante um período de dois anos, foi realizado um estudo de coorte retrospectivo que incluiu os pacientes com diagnóstico de tuberculose após a internação. Os fatores preditores de mortalidade foram coletados. **Resultados:** Durante o período do estudo, 337 pacientes foram internados e diagnosticados com TB, e desses, 61 apresentavam imunossupressão não decorrente da infecção pelo HIV. A tuberculose extrapulmonar estava presente em 47,5% dos casos. Nesse grupo, a taxa de mortalidade intra-hospitalar foi de 21,3%, e a mortalidade após a alta foi de 18,8%. Os pacientes imunocompetentes tiveram sobrevida em um ano maior que os pacientes com HIV (p = 0,008) e que os imunocomprometidos não HIV (p = 0,015), mas não houve diferença na sobrevida entre esses dois últimos grupos (p = 0,848). Entre os pacientes imunocomprometidos não HIV, o único fator estatisticamente associado à mortalidade foi a necessidade de ventilação mecânica. Entre os maiores de 60 anos, dispneia e presença de fibrose/atelectasias na radiografia de tórax foram mais comuns, enquanto febre e consolidações foram menos frequentes nesse grupo. A febre também foi um sintoma encontrado menos comumente nos pacientes com neoplasias. O tempo até o início do tratamento foi significativamente maior nos pacientes maiores de 60 anos, nos diabéticos e nos pacientes renais crônicos. Nos pacientes diabéticos e naqueles usuários de corticosteroides, o emagrecimento foi um sintoma menos frequentemente relatado. **Conclusões:** A menor prevalência de sintomas clássicos, a ocorrência de tuberculose extrapulmonar, o atraso no início do tratamento e a alta taxa de mortalidade refletem o desafio diagnóstico e terapêutico da tuberculose em pacientes imunocomprometidos não HIV.

Descritores: Hospitalização; Imunossupressão; Fatores de risco; Tuberculose/mortalidade; Hospedeiro imunocomprometido.

Introduction

In most countries, tuberculosis (TB) continues to be a major public health problem. It is estimated that one third of the world population is infected with *Mycobacterium tuberculosis*. Brazil ranks 14th among the 22 countries with the highest reported incidence of TB, with 48 cases/100,000 population in 2007.[1] Despite the availability of curative treatment, a significant proportion of TB patients continue to be hospitalized, and in-hospital mortality remains high, with estimates ranging from 2% to 12%.[2,3]

The presence of comorbidities, including HIV infection, and the delayed initiation of treatment have been considered causes of the high in-hospital mortality rates. In addition, hospitalized patients might be more susceptible to the adverse effects of anti-TB drugs, due to the concomitant use of multiple drugs and the presence of comorbidities.[2]

In individuals previously infected with Koch's bacillus, HIV infection is the major risk factor for developing TB, with a risk of 10% per year.[4] However, other causes of immunosuppression, due to diseases or drugs, have also been recognized as predisposing factors for developing TB. There is a high incidence of TB in patients with diabetes mellitus, chronic renal failure, or malignant tumors, as well as in those using immunosuppressive drugs or biological modifiers. In many clinical contexts, the use of immunosuppressants has become increasingly common, and the increased survival of immunocompromised patients has led to a greater number of cases of TB among such patients. In non-HIV-infected immunocompromised patients, TB can be as severe as it is in HIV-infected patients and is associated with high mortality.[5-10]

The objective of this study was to investigate the characteristics of and risk factors for mortality among non-HIV-infected immunocompromised patients with an in-hospital diagnosis of tuberculosis.

Methods

The study was carried out at the *Hospital de Clínicas de Porto Alegre*, which is a tertiary care hospital associated with the Federal University of Rio Grande do Sul, has 750 beds, and treats approximately 190 new TB cases a year. This was a two-year, retrospective cohort study of new TB cases. The study was approved by the local research ethics committee. The authors signed a data use agreement, guaranteeing the confidentiality of the patient information.

All new TB cases diagnosed after hospitalization were included in the study. Reported TB cases in which there was a subsequent change in diagnosis were excluded, as were cases of patients who started treatment before hospitalization. The patients were retrospectively identified based on data obtained from individual TB report forms in the *Sistema de Informação de Agravos de Notificação* (SINAN, Brazilian Case Registry Database), and patient charts were reviewed. At our hospital, computerized physician order entry of anti-TB drugs automatically generates the SINAN report form. Therefore, all of the patients who started treatment could be identified.

The diagnosis of pulmonary TB was based on meeting one or more of the following criteria[11]:
- detection by direct microscopy, with two positive sputum samples
- detection by direct microscopy, with one positive sputum sample and one positive sputum culture
- detection by direct microscopy, with one positive sputum sample and radiological findings consistent with TB positive sputum culture or
- clinical, epidemiological, and radiological findings consistent with TB, together with a favorable response to anti-TB drugs

The diagnosis of extrapulmonary TB was based on clinical data or on complementary test results, or a combination of the two, depending on the location of the infection. Treatment initiated based on clinical and radiological findings consistent with TB, in the absence of positive diagnostic test results, was defined as empirical treatment.

The review of the patient charts was performed by the investigators, who completed a standardized questionnaire including the following items: demographic data (age, gender, race, level of education); presence of comorbidities; smoking status; alcohol consumption; use of injection drugs, use of immunosuppressive drugs; history of TB; clinical

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form of TB; symptoms at admission; diagnostic methods; treatment regimen used; time from admission to the initiation of treatment; length of hospital stay; ICU admission; need for and duration of mechanical ventilation (MV); outcome of hospitalization (discharge or death); and outcome after discharge (cure, noncompliance, or death). Post-discharge data were obtained by reviewing patient charts, by searching the SINAN database, or by telephoning the outpatient health care facilities responsible for the patient.

Immunocompromised patients were defined as those over 60 years of age; those with diabetes (type 1 or type 2), chronic renal failure, or malignant tumors; transplant recipients; and those using prednisone or equivalent (at a dose $\geq$ 15 mg/day for 4 weeks), immunosuppressants (for 4 weeks or more), or biological modifiers, such as etanercept and infliximab.

Data were entered into a Microsoft Excel XP® database, after which they were processed and analyzed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). The study variables were analyzed descriptively. Quantitative data were presented as means and standard deviations or as medians and interquartile ranges (IQRs). Qualitative data were expressed as absolute values and percentages (of all cases), analyzed by the chi-square test, with Yates' correction or Fisher's exact test, as necessary. To compare quantitative data, we used ANOVA or the Kruskal-Wallis test, depending on the data distribution. Kaplan-Meier survival curves were used in order to analyze the groups of non-HIV-infected immunocompromised patients and HIV-infected patients, as well as the group of immunocompetent patients, in terms of the outcomes "in-hospital mortality" and "one-year mortality after diagnosis", and the log-rank test (Mantel-Cox test) was used for comparisons. All statistical tests used were two-tailed. The level of statistical significance was set at $p < 0.05$.

Results

During the study period, 337 hospitalized patients were diagnosed with TB. Of those, 26 were already being treated before hospitalization and were therefore excluded from the study. Of the remaining patients, 194 were HIV-infected, 61 presented with immunosuppression that

was unrelated to HIV infection, and 56 were considered immunocompetent.

Figure 1 shows the Kaplan-Meier survival curves for length of hospital stay in non-HIV-infected immunocompromised patients, HIV-infected patients, and immunocompetent patients. The in-hospital mortality rates for the non-HIV-infected immunocompromised patients, HIV-infected patients, and immunocompetent patients were 21.3% (13/61), 17.0% (33/194), and 7.1% (4/56), respectively. There was no statistically significant difference in survival among the groups ($p = 0.290$). Figure 2 shows the survival curves for the first year after diagnosis, by group. The one-year mortality rates after discharge for the non-HIV-infected immunocompromised patients, HIV-infected patients, and immunocompetent patients were 14.8% (9/61), 18.0% (35/194), and 8.9% (5/56), respectively. There was a statistically significant difference among the three groups ($p = 0.022$), and survival was higher among the immunocompetent patients than among the HIV-infected patients ($p = 0.008$) and the non-HIV-infected immunocompromised patients ($p = 0.015$). Survival did not differ between the
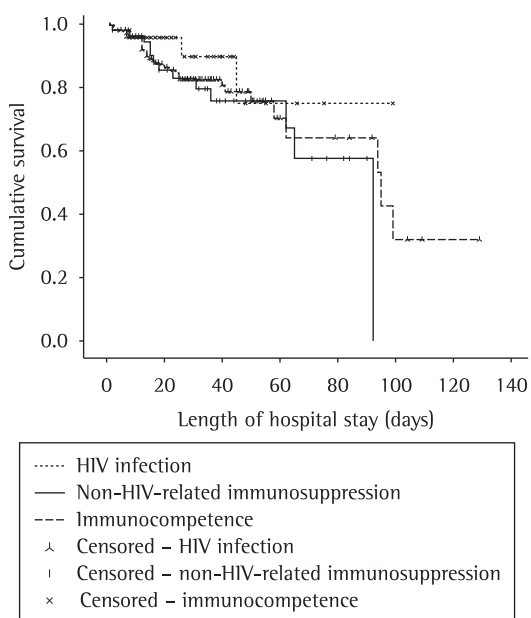

..... HIV infection
— Non-HIV-related immunosuppression
--- Immunocompetence
⋏ Censored – HIV infection
ı Censored – non-HIV-related immunosuppression
× Censored – immunocompetence

Figure 1 – Kaplan-Meier survival curves for length of hospital stay in 61 non-HIV-infected immunocompromised patients, 194 HIV-infected patients, and 56 immunocompetent patients ($p = 0.290$).
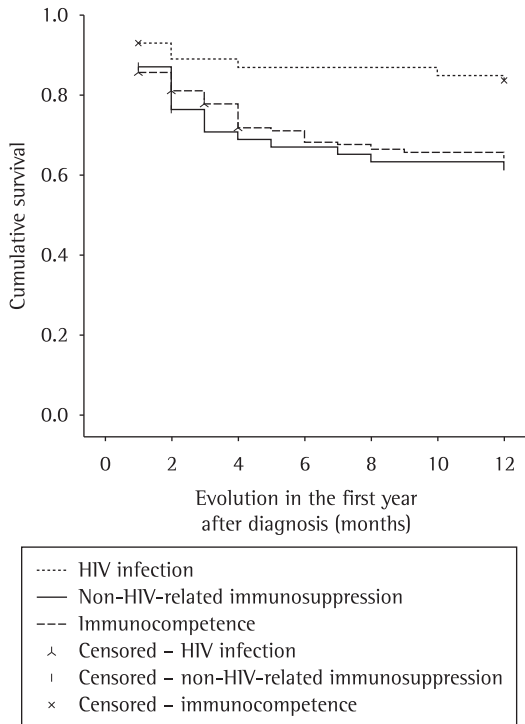
Figure 2 – Kaplan-Meier survival curves for overall evolution in the first year after diagnosis for 61 non-HIV-infected immunocompromised patients, 194 HIV-infected patients, and 56 immunocompetent patients. *Survival in immunocompetent patients was statistically different from survival in HIV-infected patients and in non-HIV-infected immunocompromised patients.

non-HIV-infected immunocompromised patients and the HIV-infected patients (p = 0.848).

Of the patients with immunosuppression that was unrelated to HIV infection, 37 were over 60 years of age, 19 had diabetes, 15 were using corticosteroids, 8 were being treated with other immunosuppressants, 7 had chronic renal failure, 7 were transplant recipients, and 7 had neoplasia. Some patients had more than one form of immunosuppression. The principal characteristics of the patients are shown in Table 1.

Extrapulmonary TB was the most common form (seen in 47.5%), followed by pulmonary TB alone (in 45.9%). Seventeen patients (27.9%) had pulmonary and extrapulmonary TB. The most common presentations of extrapulmonary TB were as follows: pleural (n = 13); bone (n = 6), peritoneal (n = 4); meningeal (n = 3); disseminated (n = 3); lymph node (n = 2); and pericardial (n = 2). Fifty-two patients (85.2%)

had at least one symptom at admission, the most common being fever (41%), weight loss (36.1%), and cough (34.4%). The most common radiological pattern was pleural effusion, which was observed in 17 patients (27.9%), and cavitation was found in only 6 patients (9.8%).

The median time to the initiation of treatment was 8 days (IQR: 4-14 days). In 12 patients (19.7%), treatment was empirical; in the group of HIV-infected patients and in the group of immunocompetent patients, treatment was empirical in 22.7% and 21.4% of cases, respectively. The drugs most commonly used—in 54 patients (88.5%)—were rifampin, isoniazid, and pyrazinamide. Hepatotoxicity during hospitalization occurred in only 4 patients (6.6%). Tem patients (17.2%) required ICU admission and MV. Thirteen patients died during hospitalization (mortality rate = 21.3%). After discharge, 9 patients (18.8%) died, 38 (79.2%) were cured, and 1 (2.1%) abandoned treatment.

Table 2 shows the characteristics of the surviving and nonsurviving patients. The only factor statistically associated with mortality was the need for MV (p < 0.0001).

Dyspnea was more common among the patients over 60 years of age than among of those below 60—11 patients (26.2%) vs. 36 patients (13.5%)—and the difference was statistically significant (p = 0.033; Table 3). Fever was reported in 16 (38.1%) of the patients over 60 years of age—vs. 176 (65.4%) of those below 60—and in 5 (35.7%) of the patients with neoplasia—vs. 187 (63.0%) of those without—the difference between significant in both cases (p = 0.001 and p = 0.040, respectively). The types of neoplasia found in our study were as follows: lung cancer (in 2 patients); cancer of the prostate, esophagus, tongue, and floor of the mouth (in 1 patient each); and chronic myelomonocytic leukemia (in 1 patient).

Fibrotic/atelectatic changes were signifi-cantly more common in patients over 60 years of age—7 patients (16.7%) vs. 16 patients (5.9%)—(p = 0.023). Conversely, in this same group of patients, consolidation seen on chest X-rays was less common than in the group of patients under 60 years of age—2 patients (4.8%) vs. 50 patients (18.6%)—(p = 0.026). The median time to the initiation of treatment was 8 days (IQR: 4.0-13.8 days) in those over 60 years of age

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Table 1 - Characteristics of the 61 non-HIV-infected immunocompromised patients.

Characteristic	n (%)[a]
Male gender	24 (39.3)
Age, years[b]	61.3 ± 18.7
White race	50 (82.0)
Current smoking	9 (17.3)
History of TB	8 (13.1)
Pulmonary TB alone	28 (45.9)
Extrapulmonary TB alone	29 (47.5)
Pulmonary + extrapulmonary TB	4 (6.6)
Cough	21 (34.4)
Fever	25 (41.0)
Weight loss	22 (36.1)
Cavitation	6 (9.8)
Pleural effusion	17 (27.9)
Positive tuberculin skin test result	17 (56.7)
Time to initiation of treatment, days[c]	8 (4-14)
Need for mechanical ventilation	10 (17.2)
In-hospital mortality	13 (21.3)
Mortality after discharge	9 (18.8)
Cure	38 (79.2)
Noncompliance	1 (2.1)

TB: tuberculosis. [a]Except where otherwise indicated. [b]Values expressed as mean ± SD. [c]Values expressed as median (interquartile range).

and 5 days (IQR: 2-11 days) in the other patients (p = 0.021). The initiation of treatment was also delayed in patients with diabetes and in those with chronic renal failure—10 days (IQR: 7-17 days) vs. 5 days (IQR: 2-11 days; p = 0.005) and 12 days (IQR: 8.0-15.5 days) vs. 5 days (IQR: 2-11 days; p = 0.018), respectively. Noncompliance with treatment after discharge was significantly lower in patients over 60 years of age than in the remaining immunocompromised patients—1 patient (3.0%) vs. 44 patients (19.3%)—(p = 0.021).

In patients with diabetes and in those using corticosteroids, weight loss was less common than in the other immunocompromised patients without these characteristics—5 patients (25.0%) vs. 147 patients (50.5%; p = 0.027) and 4 (22.0%) vs. 148 (50.5%; p = 0.020), respectively. The presence of at least one symptom was confirmed in 13 (72.2%) of the patients who used corticosteroids and in 269 (92.4%) of those who did not (p = 0.014). Other immunosuppressants used were cyclosporine (in 6 patients), mycophenolate (in 6), and tacrolimus (in 1). These immunosuppressants were used in the treatment of 7 kidney transplant recipients

and 1 patient with ulcerative colitis. Pleural effusion was more common in patients using other immunosuppressants—4 patients (50.5%) vs. 55 patients (18.2%)—and the difference was significant (p = 0.045).

The overall length of hospital stay was longer in the immunocompromised patients with diabetes and in those with chronic renal failure than in the other immunocompromised patients—38.5 days (IQR: 13.0-59.8) vs. 19.0 days (IQR: 12.0-35.3; p = 0.036) and 43.5 days (IQR: 20-53) vs. 19.5 days (IQR: 12-37; p = 0.033), respectively. All of the transplant recipients who started TB treatment during the study period were the recipients of kidney transplants. There were no statistically significant differences between the transplant recipients and the other patients.

Discussion

In this retrospective study, we describe the characteristics of non-HIV-infected immunocompromised patients who were diagnosed with TB during hospitalization. Extrapulmonary TB was as common as was pulmonary TB (47.5% vs. 45.9%). We found the in-hospital mortality rate to be high (21.3%) in these patients, with no statistically significant difference when compared with the HIV-infected patients or even with the immunocompetent patients. After discharge, a significantly high number of patients died (18.8%). In the first year after TB diagnosis, survival was higher among the immunocompetent patients than among the HIV-infected patients and the non-HIV-infected immunocompromised patients, there being no such difference between the two latter groups. The noncompliance rate was low (2.1%), and the cure rate after treatment was 79.2%.

In recent decades, non-HIV-infected immunocompromised patients have accounted for most TB cases. Impairment of cellular immunity by the use of immunosuppressants to treat patients with neoplasia or organ transplant recipients can make these patients particularly susceptible to developing TB. In addition, TB can have an unusual clinical presentation, making diagnosis more difficult in these patients. In agreement with our findings, previous studies have reported high mortality rates in non-HIV-infected immunocompromised patients.[5-10]

Table 2 – Characteristics of the surviving and nonsurviving non-HIV-infected immunocompromised patients with TB.

Characteristic	Survivors (n = 48)	Nonsurvivors (n = 13)	p
Age, years[a]	61.9 ± 17.1	59.1 ± 24.3	0.630
Male gender, n (%)	16 (33.3)	8 (61.5)	0.065
White race, n (%)	41 (85.4)	9 (69.2)	0.226
Current smoking, n (%)	7 (17.1)	2 (18.2)	0.999
Age > 60 years, n (%)	29 (60.4)	8 (61.5)	0.999
Diabetes mellitus, n (%)	15 (31.3)	4 (30.8)	0.999
Neoplasia, n (%)	5 (10.4)	2 (15.4)	0.634
Chronic renal failure, n (%)	6 (12.5)	1 (7.7)	0.999
Renal transplantation, n (%)	6 (12.5)	1 (7.7)	0.999
Use of corticosteroids, n (%)	11 (22.9)	4 (30.8)	0.718
Use of immunosuppressants, n (%)	6 (12.5)	2 (15.4)	0.999
Pulmonary TB alone, n (%)	21 (43.8)	7 (53.8)	0.517
Extrapulmonary TB alone, n (%)	25 (52.1)	4 (30.8)	0.172
Pulmonary + extrapulmonary TB, n (%)	2 (4.2)	2 (15.4)	0.196
Cough, n (%)	15 (31.3)	6 (46.2)	0.341
Fever, n (%)	20 (41.7)	5 (38.5)	0.835
Dyspnea, n (%)	11 (22.9)	2 (15.4)	0.715
Cavitation, n (%)	4 (8.3)	2 (15.4)	0.599
Consolidation, n (%)	5 (10.4)	1 (7.7)	0.999
Pleural effusion, n (%)	15 (31.3)	2 (15.4)	0.319
Miliary pattern, n (%)	3 (6.3)	2 (15.4)	0.287
Reticulonodular infiltrate, n (%)	8 (16.7)	4 (30.8)	0.263
Positive tuberculin skin test result, n (%)	16 (64.0)	1 (20.0)	0.138
Need for mechanical ventilation, n (%)	1 (2.2)	9 (69.2)	< 0.0001

TB: tuberculosis. [a]Values expressed as mean ± SD.

One of the physiological systems most affected by aging is the immune system. The clinical expression of so-called immunosenescence depends on the presence of comorbidities and exposures to other environmental factors or infections. It results from limited T-cell clonal expansion and involution of the thymus, with consequent T-cell dysfunction. In some regions, the designation of the group at the highest risk for developing active TB has shifted to the elderly.[12] In our study, we found a higher prevalence of dyspnea in patients over 60 years of age, a finding that has been reported in another study[13] and might be due to age-related changes in pulmonary function.[14] Fibrotic/atelectatic changes on chest X-rays were also more common among the patients over 60 years of age, which suggests that many of them had a history of TB. However, we do not have consistent data regarding the history of TB in these cases. Pulmonary consolidation was found in a smaller number of patients over 60 years of age, although many studies have suggested a higher prevalence of atypical imaging findings.[15-17] Fever was also less common, which is in agreement with a meta-analysis,[13] probably due to the fact that aging affects the pyrogenic response.[18] In addition, an interesting finding in this group of patients was a lower noncompliance rate, a finding previously reported.[19]

The time to the initiation of treatment was significant longer in patients with diabetes, in those with chronic renal failure, and in those over 60 years of age. Delayed diagnosis in elderly patients can occur due to the atypical presentation of the disease, and possibly also because TB is rarely considered as a working diagnosis in this age group.[20] In our study, the elderly patients showed an unusual clinical profile (dyspnea was more common, whereas fever and weight loss were less common, in comparison with the other patients), which might have contributed to the delayed initiation of treatment. Similarly, in

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Table 3 – Principal characteristics of the non-HIV-infected patients, by type of immunosuppression.

Characteristic	Age > 60 years		Diabetes mellitus		Neoplasia		Chronic renal failure		Renal transplantation		Corticosteroids		Other immunosuppressants	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Age, years[b]	72.6 ± 8.7	37.2 ± 12.7	56.3 ± 14.2	41.0 ± 17.0	50.4 ± 17.7	41.6 ± 17.1	56.6 ± 14.5	41.6 ± 17.2	41.3 ± 13.5	42.0 ± 17.3	42.8 ± 18.1	41.9 ± 17.2	39.0 ± 14.1	42.1 ± 17.3
Male gender	16 (38.1)	93 (34.6)	9 (45.0)	100 (34.4)	4 (28.6)	105 (35.4)	0 (0)	109 (36.0)	0 (0)	109 (35.9)	10 (55.6)	99 (33.8)	1 (12.5)	108 (35.6)
Fever	16 (38.1)*	176 (65.4)	9 (45.0)	183 (62.9)	5 (35.7)*	187 (63.0)	6 (75.0)	186 (61.4)	6 (85.7)	186 (61.2)	10 (55.6)	182 (62.1)	6 (75.0)	186 (61.4)
Dyspnea	11 (26.2)*	36 (13.5)	4 (20.0)	43 (14.9)	4 (28.6)	43 (14.6)	3 (37.5)	44 (14.6)	0 (0)	47 (15.6)	0 (0)	47 (16.2)	0 (0)	47 (15.6)
Weight loss	20 (47.6)	22 (52.4)	5 (25.0)*	147 (50.5)	5 (35.7)	147 (49.5)	3 (37.5)	149 (49.2)	2 (28.6)	150 (49.3)	4 (22.2)*	148 (50.5)	2 (25.0)	150 (49.5)
One or more symptoms	36 (85.7)	246 (92.1)	16 (80.0)	266 (92.0)	12 (85.7)	270 (91.5)	6 (75.0)	276 (91.7)	6 (85.7)	276 (91.4)	13 (72.2)	269 (92.4)	6 (75.0)	276 (91.7)
Cavitation	4 (9.5)	31 (11.5)	1 (5.0)	34 (11.7)	4 (28.6)	31 (10.4)	0 (0)	35 (11.6)	0 (0)	35 (11.5)	1 (5.6)	34 (11.6)	0 (0)	35 (11.6)
Fibrosis/atelectasis	7 (16.7)*	16 (5.9)	0 (0)	23 (7.9)	3 (21.4)	20 (6.7)	1 (12.5)	22 (7.3)	1 (14.3)	22 (7.2)	1 (5.6)	22 (7.5)	1 (12.5)	22 (7.3)
Consolidations	2 (4.8)*	50 (18.6)	3 (15.0)	49 (16.8)	1 (7.1)	51 (17.2)	2 (25.0)	50 (16.5)	2 (28.6)	50 (16.4)	3 (16.7)	49 (16.7)	2 (25.0)	50 (16.5)
Pleural effusion	11 (26.2)	48 (17.8)	4 (20.0)	55 (18.9)	3 (21.4)	56 (18.9)	2 (25.0)	57 (18.8)	3 (42.9)	56 (18.4)	6 (33.3)	53 (18.1)	4 (50.0)*	55 (18.2)
Time to initiation of treatment, days[c]	8 (4-13.8)*	5 (2-11)	38.5 (13-59.8)*	19 (12-35.3)	13 (2-31)	5.5 (2-11)	43.5 (20-53)*	19.5 (12-37)	8 (6-24)	5 (2-12)	8 (4.5-12.5)	5 (2-12)	7.5 (5.3-21)	5 (2-12)
Need for MV	6 (15.0)	42 (16.2)	4 (21.1)	44 (15.7)	2 (14.3)	46 (16.1)	1 (14.3)	47 (16.1)	1 (16.7)	47 (16.0)	5 (29.4)	43 (15.2)	2 (28.6)	46 (15.8)
Cure	21 (87.5)	136 (71.2)	13 (92.9)	144 (71.6)	5 (71.4)	152 (72.4)	3 (75.0)	154 (73.0)	5 (100.0)	152 (72.4)	10 (100.0)	147 (71.7)	5 (100.0)	152 (72.4)
Treatment noncompliance	1 (3.0)*	44 (19.3)	1 (6.3)	44 (18.0)	1 (10.0)	44 (17.5)	0 (0)	45 (17.7)	0 (0)	45 (17.6)	0 (0)	45 (18.1)	0 (0)	45 (17.6)

MV: mechanical ventilation. [a]Except where otherwise indicated. [b]Values expressed as mean ± SD. [c]Values expressed as median (interquartile range). *$p < 0.05$ vs. patients without the respective type of immunosuppression.

patients with chronic renal failure, nonspecific symptoms and a common extrapulmonary presentation can be risk factors for delayed diagnosis.[21] One group of authors also described the atypical presentation of pulmonary TB in patients with diabetes.[22] Among the patients with diabetes included in our study, a history of weight loss was less common. However, there was not a higher prevalence of other unusual clinical and radiological changes in this group.

Patients with malignant tumors are immunocompromised due to the local or systemic effects of the disease itself, as well as to the treatment regimens, which can impair the immune system. Among cancer patients, those with hematologic malignancies have the highest incidence of TB. Among patients with solid tumors, the highest incidence of TB is those with head and neck tumors,[23] as suggested in the present study. The diagnosis of TB in patients with cancer can be particularly difficult due to overlap of symptoms, such as in cases of lymphoma, or even to attenuation of the classic clinical symptoms of TB.[6] In our sample, fever was less common among the patients with neoplasia than among the other patients.

In the present study, extrapulmonary TB was more common than was pulmonary TB, and pleural effusion on chest X-rays was more common in patients using nonsteroidal immunosuppressants. The high incidence of TB in kidney transplant recipients is associated with the use of immunosuppressants, such patients already being immunocompromised by chronic renal failure and uremia.[24,25] Among immunocompromised patients, the most common radiological pattern is primary TB, with adenopathy, consolidation, and pleural effusion.[26] In case studies of different types of transplantation, TB is described in its disseminated, extrapulmonary, or miliary form in approximately 45% of cases.[10,27]

In our study, the presence of at least one symptom was less prevalent in patients using corticosteroids, as was a history of weight loss. It is well known that corticosteroid use leads to a six times higher risk of TB, and the fact that corticosteroids mask clinical symptoms makes diagnosis difficult.[10] In addition, corticosteroids promote weight gain,[28] which might have contributed to the lower occurrence of weight loss in our sample. Other studies have shown

that atypical manifestations of TB, such as the absence of symptoms, are associated with delayed diagnosis and higher mortality.[2,29] In our study, only 34.4% of the immunocompromised patients reported cough at hospital admission. Taking into account the fact that most physicians see cough as a necessary condition to consider the possibility of TB, this diagnosis might not be readily recognized, causing delayed initiation of treatment and higher mortality.

This study has some methodological limitations. Its retrospective design does not allow the assessment of some potential risk factors for mortality. In addition, the reduced sample size in each immunosuppression group might have increased the likelihood of obtaining false-negative results. Furthermore, the study included only hospitalized patients, and the cases of TB were therefore probably more severe. However, despite these limitations, the study achieved its objective of showing the peculiarities of TB in non-HIV-infected immunocompromised patients, and the information gathered here is relevant for the diagnostic evaluation of this specific subgroup of patients in a hospital context.

In conclusion, we described the characteristics of hospitalized non-HIV-infected immunocompromised patients. The lower prevalence of classic symptoms, the occurrence of extrapulmonary TB, the delayed initiation of treatment, and the high mortality rate reflect the challenges of diagnosing and treating tuberculosis in such patients.

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