J Bras Pneumol. 2018;44(2):118-124
http://dx.doi.org/10.1590/S1806-37562017000000316

Predictors of mortality among intensive care unit patients coinfected with tuberculosis and HIV

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Submitted: 2 September 2017.
Accepted: 14 January 2018.

Study carried out at the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, Manaus (AM) Brasil.

ABSTRACT

Objective: To identify factors predictive of mortality in patients admitted to the ICU with tuberculosis (TB)/HIV coinfection in the Manaus, Amazon Region. **Methods:** This was a retrospective cohort study of TB/HIV coinfected patients over 18 years of age who were admitted to an ICU in the city of Manaus, Brazil, between January of 2011 and December of 2014. Sociodemographic, clinical, and laboratory variables were assessed. To identify factors predictive of mortality, we employed a Cox proportional hazards model. **Results:** During the study period, 120 patients with TB/HIV coinfection were admitted to the ICU. The mean age was 37.0 ± 11.7 years. Of the 120 patients evaluated, 94 (78.3%) died and 62 (66.0%) of those deaths having occurred within the first week after admission. Data on invasive mechanical ventilation (IMV) and ARDS were available for 86 and 67 patients, respectively Of those 86, 75 (87.2%) underwent IMV, and, of those 67, 48 (71.6%) presented with ARDS. The factors found to be independently associated with mortality were IMV (p = 0.002), hypoalbuminemia (p = 0.013), and CD4 count < 200 cells/mm^3 (p = 0.002). **Conclusions:** A high early mortality rate was observed among TB/HIV coinfected ICU patients. The factors predictive of mortality in this population were IMV, hypoalbuminemia, and severe immunosuppression.

Keywords: Mycobacterium tuberculosis; Critical care; Respiration, artificial; Acquired immunodeficiency syndrome.

INTRODUCTION

Among communicable diseases, tuberculosis (TB) is the leading cause of death worldwide. In 2015, there were an estimated 10.4 million new TB cases and 1.8 million deaths worldwide, 400,000 of which occurred among HIV-infected individuals.[1] The reported incidence of TB in Brazil was 32.4 cases per 100,000 population in 2016, with 2.2 TB-related deaths per 100,000 population in 2015. Of the 66,796 new TB cases in Brazil in 2015, 6.8% were cases of TB/HIV coinfection. In 2016, the incidence of TB in Brazil was highest in the state of Amazonas, with 67.2 cases per 100,000 population and a mortality rate of 3.2 per 100,000 population. In the city of Manaus, which is the capital of the state of Amazonas and where 50% of the state population is concentrated, there were 93.2 cases per 100,000 population and 3.5 deaths per 100,000 population in 2016.[2]

Previous studies have shown that people living with HIV are 30 times more likely to develop infection with TB and progress to active disease than are individuals who do not have HIV, which increases the risk of latent TB reactivation up to 20-fold.[3] In TB/HIV coinfected individuals, the virus weakens the host immune response to *Mycobacterium tuberculosis* (*Mtb*), resulting in a more dramatic progression.[4]

Because of immunosuppression, TB is frequently paucibacillary in HIV-infected individuals, meaning that diagnosis and treatment are often delayed.[5] Admission to the ICU is required in 1-3% of cases, invasive mechanical ventilation (IMV) being required in 1.5%.[6] Patients coinfected with TB and HIV usually develop pulmonary lesions accompanied by intrapulmonary shunt and hypoxemic respiratory failure.[7]

Case-fatality rates are notoriously high in TB/HIV coinfected patients, ranging from 22.4% to 67%.[6,8-21] In patients coinfected with TB and HIV, death has been associated with the following: IMV; miliary (i.e., disseminated) TB; renal replacement therapy; use of vasoactive drugs; low Glasgow Coma Scale scores; high Simplified Acute Physiology Score II; high Acute

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Financial support: This study received financial support from the *Fundação de Amparo à Pesquisa do Estado do Amazonas* (FAPEAM, Foundation for the Support of Research in the State of Amazonas).

ISSN 1806-3713

Physiology And Chronic Health Evaluation II (APACHE II) scores; high Sequential Organ Failure Assessment scores; lymphopenia; concomitant nontuberculous mycobacterial infection; organ failure; sepsis; and hypoalbuminemia.[8,11-13,16,18-21]

Only a few studies have assessed case-fatality rates in patients with severe TB,[6,10,12,15,17-21] and most had a small sample (of < 100 patients) and were retrospective in design. Prospective studies have focused on investigating ICU patients with TB (n = 83, 44 of whom were coinfected with HIV)[12] or predicting survival among HIV-infected patients (n = 125, 58 of whom were coinfected with TB).[19] There is a lack of studies investigating ICU patients with severe TB/HIV coinfection. In a retrospective study involving a small sample (of 12 patients), the reported mortality was 58.3%.[15]

Since 2004, strategies to minimize the impact of TB/HIV coinfection and improve the treatment of TB/HIV coinfected patients have been adopted, including improved integration between TB and HIV programs and early antiretroviral therapy (ART) to reduce the viral load in patients with a presumptive diagnosis of TB.[22] In the present study, we sought to describe the clinical features of a large cohort of severe TB/HIV coinfected patients admitted to the ICU of a referral hospital in the city of Manaus, Brazil, as well as to identify factors predictive of mortality in that population.

METHODS

This was a retrospective cohort study of TB/HIV coinfected patients admitted to the ICU of a referral hospital for infectious diseases in the city of Manaus, Brazil, between January of 2011 and December of 2014. The study was approved by the local research ethics committee in August of 2014 (Protocol no. CAAE 34073314.3.0000.0005).

HIV-infected patients who were 18 years of age or more and who were diagnosed with TB were included in the study. For a diagnosis of active TB, at least two of the following criteria had to be met[11]: a) two AFB-positive sputum smears; b) one positive *Mtb* culture; c) chest X-ray findings suggestive of TB; and d) postmortem histopathological findings of TB granuloma, caseous necrosis, or AFB. ARDS was defined as low PaO_2/FiO_2, recent appearance of bilateral pulmonary infiltrates, and no clinical evidence of left atrial hypertension.[23]

All of the HIV-infected patients who were included in the present study had serologically confirmed HIV infection, in accordance with the criteria established by the Brazilian National Ministry of Health.[24] The microbiology laboratory in which the tests were performed is quality-controlled within the World Health Organization (WHO) scheme for external quality assurance.

Patients who habitually smoked cigarettes were classified as smokers regardless of the number of cigarettes smoked per day. Alcoholism was defined as consumption of ≥ 60 g of pure alcohol on at least one single occasion at least monthly, in accordance with the WHO criteria.[25] Drug use was defined as use of ecstasy, cocaine, heroin, cannabis, or any combination of the four in the last 12 months.

Sociodemographic and clinical data were collected from the electronic medical records of the participating patients. Laboratory data regarding Xpert MTB/RIF test results, smear microscopy results, *Mtb* culture results, and autopsy findings were collected from the laboratory database. All chest X-rays were assessed with IMPAX digital imaging software, version 1.0 build 1.0389 (Agfa HealthCare, Mortsel, Belgium) and reviewed by the same radiologist, who was unaware of the clinical outcomes.

Age, gender, smoking status, alcohol use, illicit drug use, fever, cough, weight loss, diarrhea, dyspnea, opportunistic infections, and comorbidities were analyzed. Time to anti-TB treatment initiation, therapeutic regimen, ART, time to ICU discharge, and ICU clinical outcome (discharge to the ward or death) were also analyzed.

Glasgow Coma Scale and APACHE II scores were used in order to assess the level of consciousness and prognosis in the ICU. Laboratory parameters included hemoglobin levels, leukocyte count, lymphocyte count, platelet count, albumin levels, and CD4 count.

Patients were treated in accordance with the WHO guidelines recommending at least 6 months of rifampin/isoniazid/pyrazinamide/ethambutol for all clinical forms of TB if the patient has never undergone treatment or has undergone up to 30 days of treatment. In people living with HIV/AIDS with active TB, ART should be started 2-8 weeks after initiation of anti-TB treatment.[26,27]

Data on the study variables were imported into a spreadsheet and analyzed with the Stata statistical software package, version 9.0 (StataCorp LP, College Station, TX, USA) and the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Data were expressed as mean ± standard deviation or median (interquartile range). Normality was assessed by the Kolmogorov-Smirnov test. Patient survival was analyzed by the Kaplan-Meier method and the log-rank test. Variables with values of $p \leq 0.20$ in the univariate analysis were included in a Cox proportional hazards model adjusted for age and gender for survival analysis. The confidence interval was 95%, and values of $p < 0.05$ were considered significant.

RESULTS

Between January of 2011 and December of 2014, 858 patients were admitted to the ICU. Of those, 141 (16.4%) were diagnosed with TB, 131 (92.9%) being coinfected with HIV. A total of 120 patients were included in the study and underwent further analysis.

The mean age of the patients was 37.0 ± 11.7 years, and 70.0% were male. Alcohol consumption, smoking, and illicit drug use were identified in 48.9%, 36.7%, and 25.4%, respectively. As can be seen in Table 1,

the most commonly reported signs and symptoms were weight loss (94.1%), dyspnea (86.4%), and cough (82.9%).

Pulmonary TB was found in 47.0%, and disseminated TB was found in 39.0%. The primary reason for ICU admission was acute respiratory failure (in 80.0%). Data on IMV and ARDS were available for 86 and 67 patients respectively. Of those 86, 75 (87.2%) underwent IMV, and, of those 67, 48 (71.6%) presented with ARDS. The median APACHE II score was 18 (interquartile range, 5-35). Comorbidities were found in 83 (69.2%) of the 120 patients evaluated: neurotoxoplasmosis, in 21.7%; pneumocystis pneumonia, in 15.8%; acute kidney injury, in 13.3%; pneumonia, in 10.8%; and histoplasmosis, in 7.5%.

A total of 80 patients underwent bacteriological screening for TB. Of those, 16 (13.3%) had positive smear results/positive culture results and 8 (6.6%) had negative smear results/positive culture results. Of the 99 patients who underwent chest X-rays or CT scans, 26 had findings suggestive of TB. Autopsy findings were consistent with TB in 5 of the 10 patients in whom an autopsy was performed.

The median length of ICU stay was 5 days (interquartile range, 3-10.5 days). Information on TB treatment initiation was available for 107 patients. Of those, 90 (84.1%) had been receiving anti-TB treatment before ICU admission (for at least 1 month in 33.6%). Of the 120 patients evaluated, 94 (78.3%) died. Of those 94 deaths, 62 (66.0%) occurred within the first week after admission.

In the univariate analysis, mortality was found to be associated with illicit drug use, diarrhea, low CD4 count, hypoalbuminemia, and IMV (Table 1). As can be seen in Figure 1, the Kaplan-Meier method and the log-rank test showed that mortality was associated with low CD4 count ($p = 0.008$), hypoalbuminemia ($p = 0.001$), and IMV ($p < 0.001$).

All of the variables showing $p \leq 0.20$ in the univariate analysis were included in a Cox proportional hazards model adjusted for age and gender. The factors found to be independently associated with mortality were IMV (hazard ratio [HR] = 0.10; 95% CI: 0.02-0.45; $p = 0.002$), hypoalbuminemia (HR = 0.47; 95% CI: 0.26-0.85; $p = 0.013$), and low CD4 count (< 200 cells/mm^3; HR = 0.26; 95% CI: 0.08-0.87; $p = 0.02$; Table 1).

DISCUSSION

The objective of the present study was to describe the clinical features of a large cohort of severe TB/HIV coinfected individuals admitted to the ICU of a referral hospital in the Brazilian Amazon, as well as to identify factors predictive of mortality in that population. We found a mortality rate of 78.3% in the study population, most of the deaths having occurred within the first week after admission. The factors found to be independently associated with mortality were IMV, hypoalbuminemia, and low CD4 count.

The case-fatality rate observed in our cohort was higher than those reported by Balkema et al. (57%)[12] and Silva et al. (65%)[6] in South Africa and Brazil, respectively, as well as being higher than those reported by Zahar et al. (26.7%),[18] Lanoix et al. (28%),[17] and Valade et al. (42%)[10] in France. However, none of these cohorts were designed for studying TB/HIV coinfected patients in the ICU; such patients were primarily evaluated in a subanalysis of larger studies. In addition, as previously mentioned, TB is usually paucibacillary in HIV-infected individuals, and diagnosis remains a challenge. Of the 120 patients in our sample, only 24 (20.0%) had a microbiological diagnosis of TB. Therefore, the case-fatality rate found in the present study can be attributed, at least in part, to histoplasmosis and other fungal diseases (which are generally underdiagnosed), as well as to noninfectious diseases that mimic TB. It is also of note that 89.0% of those patients had been receiving treatment. It is possible that some patients were diagnosed late, meaning that treatment was also delayed. Given the severity of the clinical conditions, it is possible that the doses of the anti-TB drugs used were lower than required, that adherence was suboptimal, or both. Therefore, the directly observed treatment strategy should be revised.

In Brazil, 25% of patients have a low CD4 count at diagnosis of HIV infection.[28] In the state of Amazonas, as many as 30% have a mean count of 282 cells/mm^3 at diagnosis.[28] Most (79.0%) of the deaths among the patients included in the present study occurred in those with a CD4 count of < 200 cells/mm^3 at ICU admission, a finding that is consistent with those of other studies.[12,29] This is probably due to delayed HIV diagnosis and advanced AIDS. In highly immunosuppressed individuals requiring critical care, it is best to "hit hard and hit early" with active bactericidal agents in order to stop TB progression and save time in the ICU. Another issue that merits further investigation is whether there is a need to wait 2 weeks before initiating ART or whether ART should be initiated earlier. In HIV-infected patients, a low CD4 count is known to be associated with early ICU admission and increased case-fatality rates.[30,31]

Belperio & Rhew reported the prevalence and outcomes of anemia in HIV-infected individuals,[32] in whom anemia is commonly caused by disseminated TB.[33] Although low hemoglobin levels are common among HIV-infected patients and have previously been described as constituting an important predictor of mortality in such patients,[32] we found no association between anemia and mortality in our cohort. However, anemia is a common sign of TB and HIV infection, being present not only in critically ill patients in the ICU but also in recently diagnosed patients in an outpatient setting. Therefore, it might have no impact on ICU prognosis.[33]

In the present study, acute respiratory failure was the main reason for ICU admission (in 80.0% of the patients) and a variable that was associated with high mortality rates among our patients. These results

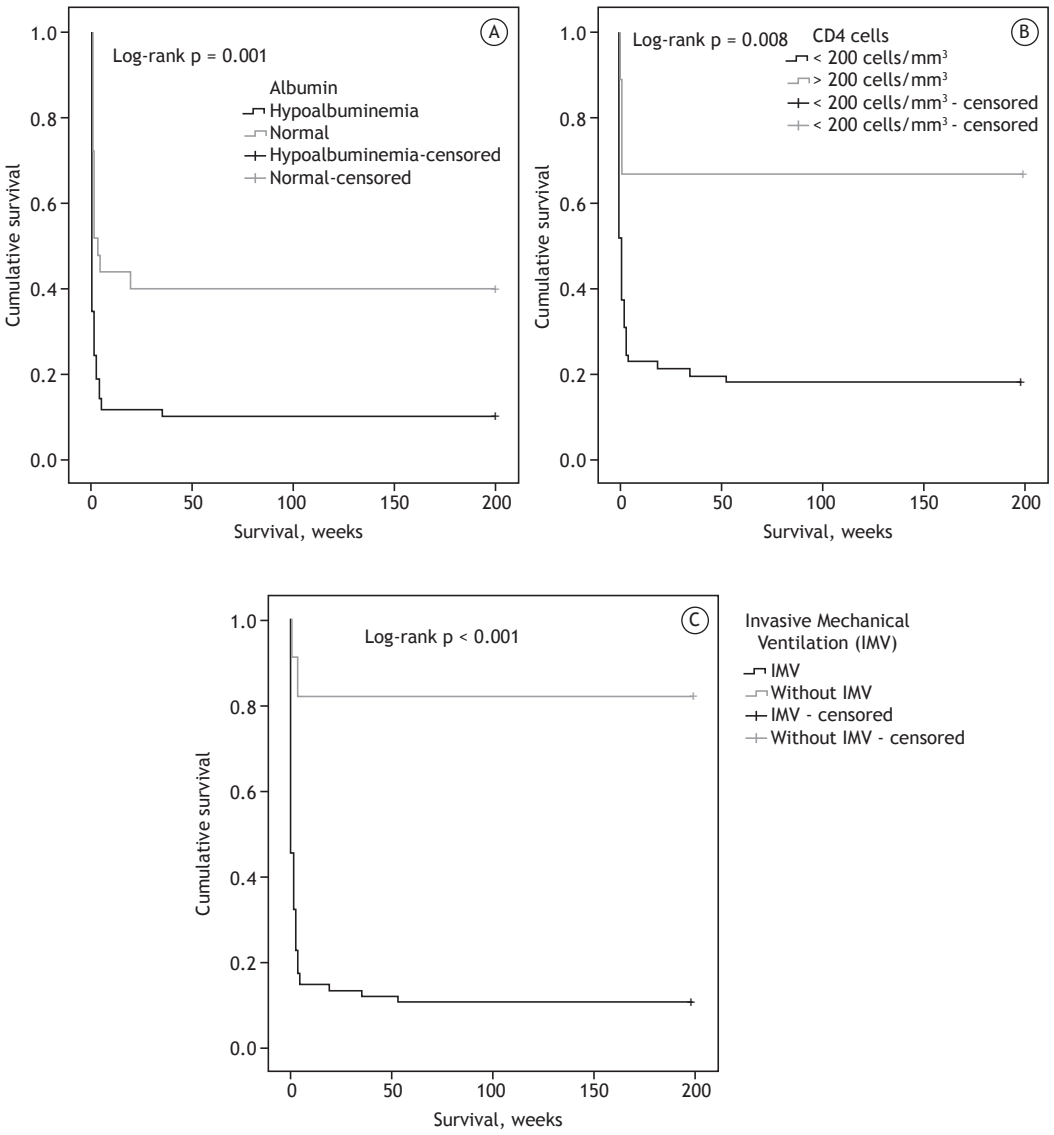

Figure 1. Kaplan-Meier curves for survival among TB/HIV coinfected patients in the ICU. In A, albumin levels; in B, CD4 cell count; and in C, invasive mechanical ventilation.

are similar to those of studies analyzing patients undergoing IMV.[6,12,13]

Potential factors responsible for low rates of bacteriological confirmation include the lack of quality assurance schemes[34] and the empirical approach to TB treatment in the ICU. Suboptimal diagnostic quality can hinder differential diagnosis as well. In the present study, the rate of bacteriological confirmation among patients facing high case-fatality rates was found to be low (i.e., 27.5%). Despite evidence of increased mortality among patients without microbiological confirmation because of HIV-related immunosuppression,[35] we found no significant differences in mortality rates between TB cases with and without microbiological confirmation.

Few studies have examined treatment adequacy and patient adherence.[5] It is of note that although 75.0% of our patients were started on TB treatment before ICU admission, the mean time from admission to treatment in most studies is 1.6-5 days.[9,10,12] The high prevalence of TB/HIV coinfection in Brazil pushes health professionals to the edge. There are currently few ART regimens that can be prescribed in combination with anti-TB drugs; new regimens based on different drugs might make it easier to combine the two in the future.

ICU patients with severe TB pose a major challenge in TB diagnosis (microbiological confirmation of TB) and treatment (poor absorption of anti-TB drugs; organ dysfunction; and apparent deterioration of TB during appropriate treatment, i.e., paradoxical reactions).[7] The potential role of malabsorption of anti-TB drugs in severe cases and the potential utility of therapeutic drug monitoring have been poorly studied and deserve more attention.[36,37] To our knowledge, this is the first

Table 1. Demographic, clinical, and laboratory characteristics of TB/HIV coinfected ICU patients who either survived or died in the 2011-2014 period.[a]

Characteristic	Total sample (N = 120)	Patients who survived (n = 26)	Patients who died (n = 94)	OR (95% CI)	p	HR (95% CI)	p
Age, years		34.3 ± 12.0	37.7 ± 11.54	-	0.393	-	-
Male gender	84 (70.0)	18 (21.4)	66 (78.6)	1.04 (0.40-2.68)	0.884	-	-
Alcoholism	44/90 (48.9)	13 (29.6)	31 (70.5)	0.42 (0.15-1.20)	0.167	1.32 (0.81-2.16)	0.264
Smoking	33/90 (36.7)	10 (30.6)	23 (69.7)	0.48 (0.17-1.34)	0.254	-	-
Drug use	17/67 (25.4)	8 (47.1)	9 (52.9)	0.18 (0.05-0.63)	0.012	0.50 (0.23-1.06)	0.074
Comorbidities	83 (69.2)	19 (22.9)	64 (77.1)	0.78 (0.29-2.07)	0.804	-	-
Cough	73/88 (82.9)	16 (21.9)	57 (78.1)	0.25 (0.03-2.08)	0.284	-	-
Fever	31/109 (28.4)	6 (19.4)	25 (80.1)	1.07 (0.37-3.06)	0.897	-	-
Weight loss	80/85 (94.1)	13 (16.3)	67 (83.8)	1.28 (0.13-12.4)	1.000	-	-
Diarrhea	37/84 (44.0)	2 (5.4)	35 (94.6)	5.34 (1.10-25.8)	0.034	1.34 (0.83-2.17)	0.220
Dyspnea	89/103 (86.4)	15 (16.9)	74 (83.3)	2.74 (0.80-9.33)	0.140	1.57 (0.78-3.16)	0.199
Clinical form of TB	120			-	0.938	-	-
Pulmonary	57 (47.5)	13 (22.8)	44 (77.2)	0.88 (0.36-2.09)	0.946	-	-
Disseminated	47 (39.2)	10 (21.3)	37 (78.7)	1.03 (0.42-2.53)	0.885	-	-
Extrapulmonary	16 (13.3)	3 (18.8)	13 (81.3)	1.23 (0.32-4.69)	1.000	-	-
TB treatment initiation[b]	107			-	0.232	-	-
< 30 days before ICU admission	54 (50.5)	11 (20.3)	43 (79.6)	-	-	-	-
≥ 30 days before ICU admission	36 (33.6)	10 (27.8)	26 (72.2)	-	-	-	-
After ICU admission	17 (15.9)	4 (23.5)	13 (76.5)	-	-	-	-
CD4 count	71			7.53 (1.65-34.28)	< 0.009	0.29 (0.09-0.94)	0.04
< 200 cells/mm^3	62 (87.3)	13 (21)	49 (79)	-	-	-	-
≥ 200 cells/mm^3	9 (12.7)	6 (66.7)	3 (33.3)	-	-	-	-
Hemoglobin level	83	18 (21.6)	65 (78)	0.70 (0.22-2.21)	0.747	-	-
Males (8-13 g/dL)	55 (66.3)	13 (23.6)	42 (76.4)	-	-	-	-
Females (7-12 g/dL)	28 (33.7)	5 (17.9)	23 (82.1)	-	-	-	-
Lymphocyte count	114			-	0.081	0.73 (0.46-1.14)	0.175
Lymphocytosis	4 (3.5)	0 (0.0)	4 (100.0)	-	-	-	-
Lymphocytopenia	84 (73.7)	14 (16.7)	70 (83.3)	-	-	-	-
Normal	26 (22.8)	9 (34.6)	17 (65.4)	-	-	-	-
Albumin level	94			5.99 (2.03-17.64)	0.001	0.48 (0.26-0.88)	0.018
Hypoalbuminemia	69 (73.4)	8 (11.6)	61 (88.4)	-	-	-	-
Normal	25 (26.6)	11 (44.0)	14 (56.0)	-	-	-	-
APACHE II score	96			-	0.362	-	-
1-15	37 (38.4)	6 (16.2)	31 (83.8)	-	-	-	-
16-30	51 (53.1)	14 (27.5)	37 (72.5)	-	-	-	-
31-45	8 (8.3)	1 (12.5)	7 (87.5)	-	-	-	-
IMV	75/86 (87.2)	10 (13.3)	65 (86.7)	29.25 (5.50-155.4)	0.000	0.12 (0.03-0.51)	0.004
ARDS	67			0.80 (0.22-2.88)	1.00	-	-
Yes	48 (71.6)	12 (25.0)	36 (75.0)	-	-		
No	19 (28.4)	4 (21.1)	15 (79.0)	-	-		

TB: tuberculosis; HR: hazard ratio; APACHE II: Acute Physiology and Chronic Health Evaluation II; and IMV: invasive mechanical ventilation. [a]Values expressed as n, n (%), or mean ± SD, except where otherwise indicated. [b]Information on TB treatment initiation was unavailable for 13 patients.

study to evaluate TB/HIV coinfected ICU patients in the Amazon region, being the largest of its kind. Information on how to improve TB/HIV coinfection management in the ICU is still anecdotal, and important issues (such as uncertainty regarding severity classification, mortality scores, vulnerable populations, and effective treatment) have yet to be resolved.

Our study has several limitations. First, all data were obtained retrospectively by reviewing patient medical records and were probably not as complete or accurate as are data that are collected prospectively. Second, although our cohort is the largest available sample of TB/HIV coinfected patients in the ICU, its power was too low to allow subanalyses to be undertaken. Despite these limitations, our results provide important implications for similar demographic areas and clinical settings. In addition, our study poses questions on how to approach TB/HIV coinfected patients and how to predict their prognosis while providing timely interventions.

The high mortality rate found in the present study underlines how difficult it is to manage TB in the ICU. Pre-ICU interventions (including early diagnosis and effective treatment) can have a major impact on TB/HIV mortality in the ICU, as well as improving the quality of TB control.

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