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LETTER

TB in the intensive care unit in a low-endemic country

Dear Editor,

In low-endemic countries, TB is a rare cause of admission in intensive care units (ICUs), representing only 1–3% of admissions, and involving mainly lung TB with respiratory failure.[1,2] Mortality remains high, between 25% and 70%,[2–7] with several prognostic and risk factors such as poor SOFA (Sequential Organ Failure Assessment)[2,3,8] and APACHE (Acute Physiology and Chronic Health Evaluation) II scores,[2,4] also having miliary TB,[5] use of mechanical ventilation[5–7,9,10] or vasopressors,[5,7] shock, multiple organ failure[3,6,7,9,11] or having acute respiratory distress syndrome[9] and nosocomial over-infections.[5,7,9,12] Risk factors for ICU admission remain poorly characterised. Here, we aimed to describe the clinical features of patients diagnosed with TB admitted to the ICU of a TB reference hospital in a non-endemic country and to assess the risk factors associated with admission and mortality.

We performed a retrospective observational study on patients with a diagnosis of pulmonary TB (PTB), extra-pulmonary TB (EPTB) and miliary TB between January 2012 and June 2018. Miliary TB was defined as all forms of PTB and EPTB with typical radiological abnormalities, and/or blood or bone marrow cultures positive for *Mycobacterium tuberculosis*. Cases (i.e., ICU patients) were identified by combining all entries in the database on TB-diagnosed patients with the entries in the database on patients culture-positive for *M. tuberculosis*. Culture-negative cases who received at least one of the first-line TB drugs were identified via the pharmacy department. Timing of ICU admission was classified as "early admission" (≤4 days of hospitalisation) or "late admission" (>5 days), as previously reported.[12] TB treatment was considered inappropriate in case of delayed treatment or adequate treatment or prolonged interruption for any reason. A case-control study design was used to assess risk factors for admission to ICU by comparing demographics, comorbidities and risk factors, type of TB, susceptibility to drugs and mortality in ICU patients (cases) with patients who were hospitalised during the same period but not admitted to ICU (controls) for TB (Table). Each case was matched with two controls by sex (male/female); age (>40 years/≤40 years) and ethnic group (sub-Saharan African/not sub-Saharan African). A case-control comparison was performed using conditional logistic regression, both for univariable and multivariable analyses. Cases who survived were compared with those who died to identify factors related to mortality. Analyses were performed using SAS statistical software v9.4 (SAS Institute, Cary NC, USA). The Ethics Committee of the Centre Hospitalier Universitaire (CHU) Saint-Pierre (Brussels, Belgium) approved the study protocol (CE/18-12-26).

During the study period, 48 cases were admitted to the ICU out of a total of 1064 patients diagnosed with TB (incidence 4.5%); 73% were male and the median age was 46 years (interquartile range [IQR] 33–53.7). Demographic and microbiological data are reported in the Table. Twelve patients were HIV-positive, 75% of whom had a CD4 count of <200/μL, and only 25% were on treatment. Twenty-two patients (46%) had PTB associated with EPTB or miliary TB; 6 (13%) had EPTB alone, 4 of which were TB of the central nervous system (CNS). The *M. tuberculosis* strains isolated were pan-susceptible in 31 cases (65%), 5 cases were isoniazid-resistant (10%); 1 was multidrug-resistant and 2 were extensively drug-resistant. TB treatment was started in the ICU in 22 cases (46%), but was considered inappropriate for 5 cases (10%). The median delay between ICU admission and start of TB treatment was 2 days (IQR –15.5 to 6). The majority of the admissions ($n = 36$, 75%) occurred during the first 2 months of TB treatment; 28 (58%) were "early admissions". The median length of ICU stay was 4.5 days (IQR 3–8.5).

Thirty-four admissions (73%) were related to TB disease, involving respiratory insufficiency ($n = 13$, 27%); sepsis, multiple organ failure or shock ($n = 6$, 13%); complications associated with CNS TB ($n = 7$, 15%); TB-related surgery ($n = 4$, 8%) and complications associated with abdominal and pericardial TB ($n = 2$ each, 4%). During ICU stay, 19 cases (40%) received invasive ventilation, 7 (15%) received vasoconstrictor drugs and 22 (46%) standard antibiotics. Risk factors for ICU admission were being a recent migrant, having HIV infection and having mixed PTB and EPTB or miliary TB. In multivariable analysis, mixed PTB + EPTB or miliary TB was found to be the only independent risk factor (Table).

The mortality rate was 33% (16/48) in cases compared to 5% (5/96) in controls. Causes of death included respiratory failure (8/16), shock or multiple organ failure (5/16), complications associated with CNS TB (2/16) and liver failure on DRESS (drug rash with eosinophilia and systemic symptoms) syndrome (1/16). Of the 16 patients who died, 5 (31%) died

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?1 **Table** Case control analysis assessing risk factors for intensive care unit admission following TB diagnosis

Variable	Cases ($n = 48$) *n* (%)	Controls ($n = 96$) *n* (%)	Univariable OR	Univariable 95%CI	Univariable *P* value	Multivariable OR	Multivariable 95%CI	Multivariable *P* value
Homelessness	8 (17)	12 (13)	1.4	0.454–4.25	0.657			
Recent arrived migrants*	7 (15)	2 (2)	12.5	1.576–571.746	0.009	4.5	0.47–222.97	0.290
Alcohol abuse	13 (27)	23 (24)	1.2	0.467–3.025	0.819			
Diabetes	5 (10)	11 (11)	0.9	0.248–2.838	1			
Tobacco smokers	18 (35)	51 (53)	0.4	0.174–1.079	0.077	0.5	0.20–1.49	0.300
HBsAg	6 (13)	5 (5)	2.4	0.610–9.941	0.244			
Cancer	5 (10)	7 (7)	1.5	0.336–7.027	0.722			
Liver cirrhosis	4 (8)	8 (8)	1	0.220–3.733	1			
History of TB	7 (15)	12 (13)	1.1	0.373–3.548	0.914			
Other immunodeficiencies	6 (13)	6 (6)	2.3	0.536–11.885	0.312			
HIV*	12 (25)	7 (7)	3.7	1.301–12.348	0.011	1.9	0.54–7.79	0.381
PTB	21 (44)	67 (70)	0.2	0.085–0.619	0.001			
PTB+EPTB/miliary TB*	26 (54)	20 (21)	5.7	2.204–17.413	<0.0001	3.9	1.36–12.92	0.008
EPTB	7 (15)	9 (9)	1.6	0.482–5.735	0.500			
INH-resistant TB	5 (10)	6/76 (8)†	1.3	0.227–7.528	0.986			
Negative cultures	10 (21)	23 (24)	0.8	0.345–1.979	0.856			

* Statistically significant.
† Data for 20 patients missing.
OR = odds ratio; CI = confidence interval; HBsAg = hepatitis B surface antigen; PTB = pulmonary TB; EPTB = extrapulmonary TB; INH = isoniazid.

within the first 5 days of treatment and 9 (56%) in the first month. Risk factors independently associated with mortality were homelessness (odds ratio [OR] 9, 95% confidence interval [CI 1.559–51.949), alcohol abuse (OR 5.4, 95% CI 1.375–21.204), liver cirrhosis (not applicable), inadequate TB treatment (OR 10.3, 95%CI 1.046–102.08), use of mechanical ventilation (OR 4.5, 95%CI 1.731–12.109), vasoconstrictor drug use (OR 3.5, 95%CI 1.894–6.519) and use of standard antibiotics (OR 3.5, 95%CI 1.332–9.435).

During the 7-year study period, incidence of ICU admission was 4.5%, which is higher than previously reported.[1,2] This could be explained by the at-risk population referred to the CHU Saint-Pierre, such as recent migrants, the homeless and HIV patients, all known to be at high risk of late access to health care.[13] Moreover, the CHU Saint-Pierre is a reference centre for TB management in the Brussels Capital Region, which has one of the highest incidence rates for TB in Europe.[13] As reported in other studies,[10,12] acute respiratory failure was the main cause of TB-related ICU admissions, while the other causes were mainly associated with disseminated TB.[4] This is coherent with our high prevalence of EPTB/miliary TB compared to other studies.[5,7,9]

The only factor that was independently associated with ICU admission was having mixed PTB + EPTB or miliary TB. Incidence of EPTB can be high (40–63%)[3,11,12] in ICU patients with TB, and EPTB seems to be more frequent in migrants, especially if HIV-positive.[14] Despite rapid initiation of treatment, a high mortality rate of 33% was observed, especially in the first 30 days of treatment, in line with the existing literature.[2–7] Risk factors for mortality also included inadequate and delayed TB treatment. This is coherent with other studies that showed that delayed adequate treatment was more frequent in deceased patients.[11,15]

The main limitations of our study were the small number of patients and the retrospective design, which limited our ability to record common measures such as APACHE II or SOFA scores. The main strengths were the heterogeneity of the population and the assessment of multiple risk factors for ICU admission, which have not been explored before.

In conclusion, mixed PTB + EPTB or miliary TB is the most serious form of TB, leading to severe complications and subsequent ICU admission. In these patients, mortality is high and often premature despite early treatment initiation. Homeless people with alcohol abuse and cirrhosis appear to be a risk population for death, which may be due to delayed access to health care. Established risk factors could help in the rapid triage of patients who need ICU admission, thereby improving therapeutic management and outcome.

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