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Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care

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ABSTRACT: Severe tuberculosis (TB) requiring intensive care unit (ICU) care is rare but commonly known to be of markedly bad prognosis. The present study aimed to describe this condition and to determine the mortality rate and risk factors associated with mortality.

Patients with confirmed TB admitted to ICU between 1990 and 2001 were retrospectively identified and enrolled. Clinical, radiological and bacteriological data at admission and during hospital stay were recorded. A multivariate analysis was performed to identify the predictive factors for mortality.

A total of 58 TB patients (12 females, mean age 48 yrs) admitted to ICU were included. Mean Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission was 13.1±5.6 and 22 of 58 (37.9%) patients required mechanical ventilation. The in-hospital mortality was 15 of 58 (25.9%); 13 (22.4%) patients died in the ICU. The mean survival of patients who died was 53.6 days (range 1–229), with 50% of the patients dying within the first 32 days. The factors independently associated with mortality were: acute renal failure, need for mechanical ventilation, chronic pancreatitis, sepsis, acute respiratory distress syndrome, and nosocomial pneumonia.

These data indicate a high mortality of patients with tuberculosis requiring intensive care unit care and identifies new independently associated risk factors.

KEYWORDS: Intensive care unit, mortality, risk factors, tuberculosis

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Tuberculosis (TB) is currently the most frequent cause of death due to an infection worldwide [1]. Since the initiation of intensive care units (ICUs) in the 1960s, many potentially life-threatening complications and critical illnesses could be efficiently treated. In this respect, the acute respiratory failure due to pulmonary infections is a common reason for admittance to the ICU. However, despite their high mortality rate, the TB-related critical conditions are rarely reported. The cases of TB requiring intensive care represent 1–3% of all patients with TB [2–4]. Hospital mortality has been reported to be ~60% for patients with respiratory failure due to pulmonary TB. By contrast, the mortality for patients with respiratory failure due to severe pneumonia is only ~25% [5].

The most common reasons for ICU admission of patients with TB are the development of acute respiratory distress syndrome (ARDS) [6, 7] and severe organ failure, such as renal failure [8, 9]. Several studies also reported a critical course in patients with miliary TB and in HIV-infected patients with TB [10–16], but patient numbers were relatively small, especially when reported from Europe.

In the present study, the authors aimed to describe the characteristics of TB patients requiring ICU care and to determine the in-hospital mortality rate and the predictive factors for mortality.

PATIENTS AND METHODS

Adult patients (>18 yrs) with TB that were admitted to the ICU of the Chest Hospital Heckeshorn, Berlin, Germany, between January 1990 and December 2001 were identified retrospectively. The diagnosis of TB was based on the following: 1) positive cultures of sputum, bronchial aspirates or bronchioalveolar lavage fluid; and/or 2) positive acid-fast bacilli smears; and/or 3) clinical and radiological findings.

The following data were obtained from the medical records: demographic characteristics (age, sex, origin), comorbidities, reasons for ICU admission, health status including Acute Physiology and Chronic Health Evaluation

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Score II and body mass index (BMI), symptoms, radiological appearance, bacteriological investigation (including results of susceptibility tests), laboratory investigations (total blood cell count, liver and renal function parameters, C-reactive protein, CD4 T-lymphocyte count), blood gas analysis, HIV status, anti-TB treatment, need and duration of mechanical ventilation, ICU complications (ventilator-associated pneumonia, ARDS, sepsis, tracheostomy), length of hospital/ICU stay, and mortality.

A BMI <20 kg·m^{-2} was defined as underweight. Chest radiographic patterns were classified according to the National TB and Respiratory Disease Association (NTRDA) [17], with stadium 1 defined as minimal infiltration without cavities, stadium 2 as moderate expansion of infiltrates, stadium 2a as occasional infiltrates uni- or bilateral without cavities, stadium 2b as compact infiltrates with expansion not more than one lung lobe and cavities with a diameter <4 cm, and stadium 3 as advanced stadium with any expansion (with or without cavities) and miliary forms. Microbiological investigations included TB smears and cultures with quantifications for smears and the amount of colony-forming units for cultures. Specimens were taken in a weekly/serial manner to calculate conversion times. The resistance towards anti-TB drugs was determined using critical concentrations in liquid media or Loewenstein–Jensen slants. Drug resistance was defined as either single or polydrug resistance to two or more anti-TB drugs. Multidrug resistance (MDR) defined resistance towards at least isoniazid (INH) and rifampicin (RMP). For the diagnosis of a hospital-acquired pneumonia (including ventilator-associated pneumonia), the American Thoracic Society (ATS) criteria were used [18]. ARDS, sepsis and renal failure were defined according to criteria described elsewhere [19–21].

Anti-TB treatment was categorised into three groups: 1) treatment with at least three first-line drugs including INH and RMP, 2) treatment with at least three first-line drugs including either INH or RMP, and 3) all other regimens.

STATISTICAL ANALYSIS

Data are expressed either as percentage for the group (categorical variables) or as mean±SD (continuous variables). Categorical variables were compared using Chi-squared or Fisher's exact test. The Mann–Whitney U-test was applied to compare continuous variables. Data were compared between survivors and patients who died during the hospital stay. A p-value <0.05 was considered as statistically significant. The Kaplan–Meier method was used to analyse survival. Factors significantly associated with survival were further analysed and ranked using a multivariate discriminate analysis.

RESULTS

Patient characteristics

A total of 58 patients with confirmed TB, which was 3% of all patients with suspected TB admitted to the hospital, were admitted to ICU within the study period. Of them, 15 (25.8%) died during ICU/hospital stay. The baseline characteristics of both survivors and deceased patients are shown in table 1.

TABLE 1 Patient characteristics including comparison of survivors and non-survivors

	Deceased		Survivors		Total		
	n	%	n	%	n	%	p-value#
Subjects	15	25.9	43	74.1	58		
Age yrs	56.5±11.5 (31–84)		44.7±17.7 (15–83)		47.8±17.0 (15–84)		0.05
Sex							NS
Female	3	25.0	9	75.0	12	20.7	
Male	11	84.6	2	15.3	13	22.4	
Origin							NS
German	12	26.1	34	73.9	46	79.3	
Foreign born	3	27.3	8	72.7	11	18.9	
BMI <20 kg·m^{-2}	5	16.7	25	83.3	30	51.7	<0.001
Comorbidities							
Diabetes	2	25.0	6	75.0	8	13.8	NS
Chronic pancreatitis	5	71.4	2	28.6	7	12.1	0.008
Chronic renal failure	2	40.0	3	60.0	5	8.6	NS
HIV infection	1	25.0	3	75.0	4	6.9	NS
Malignant diseases	0		1	100.0	1	1.7	NS
Liver damage	12	31.6	26	68.4	38	65.5	NS
TB reactivation	4	26.7	11	73.3	15	25.9	NS
Smoker	10	25.0	30	75.0	40	69.0	NS
Alcohol abuse	11	31.4	24	68.6	35	60.3	NS
COPD	4	66.7	2	33.3	6	10.3	0.03

Data are presented as mean±SD (range) unless otherwise indicated. NS: nonsignificant; BMI: body mass index; TB: tuberculosis; COPD: chronic obstructive pulmonary disease. #: p-value for comparisons between survivors and deceased.

DISEASE PRESENTATION

The most common symptoms (52 of 58, 89.6%) were fever, night sweat and consumption, with a mean duration from symptom onset to hospital admission of 4 weeks (range 1–26 weeks). Most of the patients (52 of 58, 89.6%) presented with dyspnoea, productive cough and/or haemoptysis. The duration of these symptoms from onset to admission differed from <1 week (10 patients), 1–4 weeks (30 patients), to >4 weeks (10 patients; table 2).

Acute respiratory failure due to TB was the primary cause for ICU admission in 47of 58 (81.1%) patients. Other reasons were exacerbated chronic obstructive pulmonary disease (COPD; n=2), acute gastrointestinal bleeding (n=2) and heart failure (n=2). One patient with HIV infection suffered severe respiratory insufficiency due to *Pneumocystis jiroveci* pneumonia. Other causes were diabetic coma, low levels of potassium, weaning problems after diagnostic thoracotomy, respiratory insufficiency after bronchoscopy, severe anaemia, delirium due to alcohol withdrawal and severe cachexia.

At ICU admission or before, 46 of 58 (79.3%) patients with positive TB cultures during the course of the study were initially smear-positive from sputum, bronchial aspirates or

TABLE 2 Disease presentation

	Deceased		Survivors		Total		
	n	%	n	%	n	%	p-value#
Subjects n	15		43		58		
APACHE II	15.7±4.1 (10–22)		12.3±5.8 (5–28)		13.1±5.6 (5–28)		<0.05¶
Symptoms prior duration							NS
Fever							
<1 week	3	21.4	11	78.6	14	24.1	
2–4 weeks	7	29.2	17	70.8	24	41.4	
>4 weeks	0		8	100.0	8	13.8	
Cough, dyspnoea, haemoptysis							NS
<1 week	5	50.0	5	50.0	10	17.2	
2–4 weeks	6	23.1	20	76.9	26	44.8	
>4 weeks	1	10.0	9	90.0	10	17.2	
Radiological classification							NS
NTRDA 2a	0		3	100.0	3	5.2	
NTRDA 2b	2	15.4	11	84.6	13	22.4	
NTRDA 3	13	31.7	28	68.3	41	70.7	
Miliary TB	3	25.0	9	75.0	12	20.7	
Susceptibility tests							NS
Full susceptibility	13	27.1	35	72.9	48	82.8	
Single-drug resistance	0		4	100.0	4	6.9	
Polydrug resistance	0		1	100.0	1	1.7	
Multidrug resistance	0		2	100.0	2	3.5	
Nosocomial pathogens (isolated in respiratory secretions)	12	30.8	27	69.2	39	67.2	NS
MRSA	3	37.5	5	62.5	8	13.8	NS
Stenotrophomonas maltophilia	3	60.0	2	40.0	5	8.6	0.068
Pseudomonas aeruginosa	5	100.0	0		5	8.6	0.001
Acinetobacter spp.	1	33.3	2	66.6	3	5.2	NS
Anti-TB treatment							NS
No treatment	2	40.0	3	60.0	5	8.6	
Treatment I+	5	16.1	26	83.9	31	53.4	
Treatment II+	4	25.0	12	75.0	16	27.6	
Treatment III+	4	66.7	2	33.3	6	10.3	
ICU-related complications							
Nosocomial pneumonia	13	38.2	21	61.8	34	58.6	0.014
ARDS	5	71.4	2	28.6	7	12.1	0.008
Sepsis	9	52.9	8	47.1	17	29.3	0.001
Acute renal failure	7	100.0	0		7	12.1	0.000
Mechanical ventilation	11	50.0	11	50.0	22	37.9	0.002

Data are presented as mean±SD, unless otherwise indicated. APACHE: Acute Physiology and Chronic Health Evaluation; NS: nonsignificant; NTRDA: National Tuberculosis and Respiratory Disease Association; TB: tuberculosis; MRSA: methicillin-resistant *Staphylococcus aureus*; ICU: intensive care unit; ARDS: acute respiratory distress syndrome. #: Fishers' exact test; ¶: Mann–Whitney U-test; +: Treatment I is treatment with at least three first line drugs including isoniazid (INH) and rifampicin (RMP), treatment II is treatment with at least three first-line drugs including either INH or RMP, and treatment III is all other regimens.

bronchoalveolar lavge. In all patients, the TB involved the lung parenchyma. Additional pleural involvement was present in 13 of 58 (22.4%) patients and lymph node involvement in four of 58 (6.9%) patients. Extrapulmonary sites of TB were present in 11/58 (19.0%) patients: urogenital (n=7), bone marrow (n=2), and gastrointestinal and meningeal in one patient each. Miliary TB was diagnosed by chest radiograph in 12 cases. Among the 58 patients with *Mycobacterium tuberculosis*, the susceptibility tests showed single-drug resistance in four cases, polydrug resistance in one patient and MDR in two cases.

More than two-thirds (40 of 58, 69.0%) of the patients presented severe alterations according stadium 3 NTRDA with extensive bilateral infiltrates (table 2). Cavities were found in 29 of 58 (50.0%) patients. All HIV-infected patients (n=4) presented a miliary TB.

At ICU admission an elevated white blood cell count was present in 29 of 58 (50%) patients and/or hypersegmentation in 22 of 58 (37.9%) cases. C-reactive protein was elevated in 55 of 58 (94.8%) patients. Anaemia was frequent (35 of 58, 60.3% patients), as well as impaired liver function (39 of 58, 67.2% patients). A partial respiratory insufficiency was observed in 34 of 58 (58.6%) patients. Out of these patients, 17 had an alveolar oxygen partial pressure of <40 mmHg. Hypercapnia was recorded in eight of 58 (13.8%) patients.

All patients were treated immediately after diagnosis and initially according to the guidelines of the ATS and the German Respiratory Society [22] (table 2). Treatment modifications were due to side-effects of the anti-TB treatment: hepatotoxicity (n=35), exanthema (n=7) and ototoxicity (n=14). A withdrawal of ethambutol was necessary in one case due to neuritis of nervus optici.

Corticosteroids were given in 40 of 58 (68.9%) patients for ARDS (n=7), severe COPD (n=2) and severe inflammation related to TB (n=31).

Twenty-two patients (37.9%) received mechanical ventilation. Patients ventilated for longer than 10 days were tracheotomised (n=15). The mean duration of mechanical ventilation was 26 days (range 1–101 days).

ICU-related complications

ICU-related complications are shown in table 2. Nosocomial respiratory infections alongside the TB were common during the course of ICU stay (39 of 58, 67.2% patients). Most of the patients (34 of 58, 58.6%) developed a nosocomial pneumonia; 10 of the 34 (29.4%) cases had a ventilator-associated pneumonia. In 15 of the 34 (44.1%) patients, the following pathogens were isolated from the lower respiratory secretions: methicillin-resistant *Staphylococcus aureus* (MRSA; n=8 patients), *Pseudomonas aeruginosa* (n=5), *Stenotrophomonas maltophilia* (n=5) and *Acinetobacter spp.* (n=3). Most MRSA patients were mechanically ventilated over a long period and were treated with multiple antibiotic regimens.

Other complications during ICU stay were: ARDS (seven of 58, 12.1%), pneumothorax (eight of 58, 13.8%), which most often occurred during mechanical ventilation (n=5), acute renal failure (seven of 58, 12.1%), sepsis (15 of 58, 25.8%) and multiple organ failure (two of 58, 3.4%; table 2).

Outcome and risk factors for mortality

The overall in-hospital mortality was 15 of 58 (25.9%); 13 of 58 (22.4%) patients died during their ICU stay. The mean in-hospital survival of patients who died was 53.6 days (range 1–229) with 50% of the patients dying within the first 32 days and 75% of the patients dying within the first 75 days (fig. 1). The duration of the hospital stay was 87.1 days (range 3–340), and the duration of ICU care 21.6 days (range 3–119). Due to death, the duration of hospital stay was shorter in the nonsurvivor group, with 53.6 days (range 3–229 days) compared with survivors; however, ICU stay was longer, with 31.2 days (range 3–119 days) in patients who died compared with survivors.

Twenty-five of the survival patients failed to follow up after discharge, and nine of 24 (37.5%) evaluable patients died within 1–124 months (median 13 months).

Factors found to be associated with in-hospital mortality in the univariate analysis (younger age, underweight, chronic pancreatitis, COPD, nosocomial infections, ARDS, development of renal failure, severe respiratory failure with need for mechanical ventilation) were included in the multivariate disciminant analysis. Table 3 shows the factors independently associated with in-hospital mortality.

DISCUSSION

This retrospective analysis of 58 TB patients requiring intensive care found an in-hospital mortality rate of 25.9%,

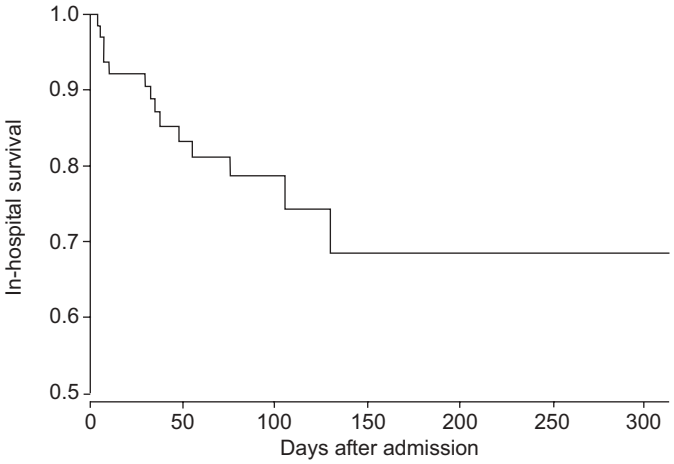

FIGURE 1. In-hospital survival using Kaplan–Meier (n=58).

TABLE 3 Predictive factors for in-hospital mortality

Ranking	Factor	p-value
1	Acute renal failure	0.001
2	Mechanical ventilation	0.002
3	Chronic pancreatitis	0.001
4	Sepsis	0.001
5	ARDS	0.008
6	Nosocomial pneumonia	0.002

ARDS: acute respiratory distress syndrome.

which was associated with a number of independent risk factors, such as acute renal failure, ARDS, nosocomial infections and the need for mechanical ventilation.

Others studies reported mortality rates up to 90% in patients suffering from miliary TB and ARDS [10, 23]. Patients who died were significantly older than the survivors but the average age of all patients included was relatively low. The incidence of TB in Germany shows two peaks in age distribution; the first peak ranges 40–50 yrs of age, while the second is >70 yrs [24]. The first peak is commonly interpreted as a newly acquired TB infection and the second as TB reactivation. The findings of the present study, with a mean age of 48 yrs in ICU-treated TB patients, suggest that newly acquired TB infections may present a more severe cause of the disease. However, the average age of patients in other studies ranged between 41 [9] and 59 yrs [2]. A further sex-related finding was that severe TB affected more often male patients, which is in agreement with other studies. In this respect, the proportion of female patient ranges from 13% (present study) to 45% [15].

The vast majority of the current study's patients presented with severe radiographic alterations or miliary TB. According the NTRDA classification, two-thirds of the patients in the present study had extensive bilateral infiltrates and cavitary lesions. The outcome of these patients was worse than that of patients with fewer radiographic alterations. Radiographic findings contributing to mortality were of pneumonic pattern and consolidation. By contrast, cavitary, interstitial or nodular patterns occurred in similar percentages in both survivors and nonsurvivors, which is in agreement with earlier studies [5, 6, 9, 25].

Factors contributing to mortality in the present study included organ failure, and circumstantial evidence of alcohol abuse or nosocomial infections. Similar factors influencing the course of most severe TB were reported by other studies. FRAME *et al*. [2] reported an in-hospital mortality rate of 67% for patients with TB requiring intensive care; ~70% of the patients in this study developed acute respiratory failure and the mortality rate increased to 83%; factors identified as contributing to respiratory failure were Gram-negative pneumonia and/or sepsis, COPD, prior anti-TB medication with non-compliance and malignancy. With a 1.5% incidence of acute respiratory failure in patients hospitalised with pulmonary TB, LEVY *et al*. [6] described 15 patients with a need for ICU care, with 11 of 15 being mechanically ventilated; the in-hospital mortality was 33%. PENNER *et al*. [5] described 13 TB patients with respiratory failure requiring mechanical ventilation, of whom eight developed ARDS; the in-hospital mortality was 69%.

Comorbidity is a further factor associated with mortality. In the present study, a history of chronic pancreatitis was identified as an independent risk factor, which is most often related to chronic alcohol abuse. However, a history of alcohol abuse (37 patients) and/or liver function impairment (39 patients) did not influence mortality rates in the present study.

It was demonstrated that decompensation or development of renal failure as a complication during intensive care highly influenced the outcome. RAO *et al*. [15] found that end-stage renal failure requiring dialysis was a further comorbidity factor predicting mortality. PIQUERAS *et al*. [10] described acute renal failure in seven of nine patients, with no patients surviving. In the study of PENNER *et al*. [5], seven of 13 TB patients developed multiorgan failure and six of them died. However, other studies did not find a correlation between mortality and acute renal failure [2, 9, 26].

Treatment has been also been considered to be an important factor affecting patients' outcome [5, 27, 28]. It was found that a higher mortality is present in patients who did not receive an optimal treatment with a triple combination including INH and RMP. Most often, causes other than TB resistance led to the withdrawal of INH and RMP, with impaired liver function being a major reason; however, other causes have been also described [29]. The MDR rate in the present study reached 3.5%, which is slightly increased in comparison with the MDR rate of 1.4% reported in Germany for the year 1999 [24]. Moreover, critically ill patients are more likely to develop organ dysfunction, which represents a further cause for changes in the treatment regimen.

Although the duration from exhibition of first symptoms to treatment onset was earlier outlined as a crucial factor to mortality [30], patients in the present study with a longer history of symptoms such as fever or haemoptysis did not show a significantly worse outcome.

Since the emergence of AIDS, TB and HIV infection have been intimately connected. The presentation of TB is generally known to be related to the degree of immunosuppression, and TB dissemination and extrapulmonary localisation are reported to be more frequent in patients with HIV infection [31]. Only 7% of the present study's patients were infected with HIV, but the HIV status did not influence the mortality. However, this percentage shows a considerable increase of the coinfection rate in the present study's institution compared with a rate of 2% reported in 1995 [32].

A further factor positively related to mortality was the development of a nosocomial infection during ICU stay. Pneumonia and sepsis were most frequently found in the present study. An early report also suggests a significant impact of nosocomial infections on the mortality of critically ill TB patients [33].

In conclusion, the present study found a high mortality rate in tuberculosis patients requiring intensive care unit care. Interestingly, some of the predictive factors for mortality, such as nosocomial infections, were actually related to the intensive care procedures. These findings suggest that a better preventive approach of these patients, which are prone to prolonged mechanical ventilation and frequent nosocomial infections, may improve the outcome.

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