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Jean-Ralph Zahar
Elie Azoulay
Elise Klement
Arnaud De Lassence
Jean-Christophe Lucet
Bernard Regnier
Benoît Schlemmer
Jean-Pierre Bedos

Delayed treatment contributes to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure

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J.-R. Zahar (✉) · J.-C. Lucet · B. Regnier · J.-P. Bedos
Intensive Care Department,
Bichat Claude-Bernard Hospital,
University Paris 7, 46 rue Henri Huchard,
75018 Paris, France
E-mail: JRZahar@hotmail.com
Phone: +33-1-49 81 23 92

E. Azoulay · E. Klement · A. De Lassence · B. Schlemmer
Intensive Care Department,
Saint-Louis Hospital, University Paris 7,
1 avenue Claude Vellfaux, 75010 Paris,
France

Abstract *Objectives*: To clarify the patterns of pulmonary tuberculosis (TB) that should result in a high index of suspicion, to increase the chances of early therapy and to identify predictors of 30-day mortality.
Patients and methods: Retrospective, 7-year study in two medical intensive care units (ICUs). All patients admitted with pulmonary TB were enrolled. Clinical and laboratory data at admission and events within 48 h of admission were collected. Predictors of 30-day mortality were identified by univariate and multivariate analysis.
Results: The study included 99 patients with a median age of 41 years. Immunodeficiency was present in 60 patients, including 38 with AIDS. Fifty-nine patients had pulmonary TB alone, 22 also had extrapulmonary TB and 18 had miliary. All 99 patients were admitted for acute respiratory failure, some also with shock (20), neurologic disorders (18) or acute renal failure (10). Mechanical ventilation was needed in 50 patients; 22 patients met criteria for acute respiratory distress syndrome (ARDS). The 30-day mortality rate was 26.2 %. Four factors independently predicted mortality: a time from symptom onset to treatment of more than 1 month (OR, 3.49; CI, 1.20–10.20), the number of organ failures (OR, 3.15; CI, 1.76–5.76), a serum albumin level above 20 g/l (OR, 3.96; CI, 1.04–15.10), and a larger number of lobes involved on chest radiograph (OR, 1.83; CI, 1.12–2.98).
Conclusion: Delayed clinical suspicion and treatment of active pulmonary TB with respiratory failure may contribute to the persistently high mortality rates in ICU patients with these diseases.

Key words Pulmonary tuberculosis · Intensive care · Mortality · Prognosis · Suspicion · Diagnosis · Organ dysfunction · ARDS · Multiple organ failure · Serum albumin

Introduction

Despite the availability of effective chemotherapy, the incidence of pulmonary tuberculosis (TB) and of TB-related critical illness has increased dramatically over the last few decades [1, 2]. Moreover, mortality rates remain high in patients with active severe pulmonary TB requiring mechanical ventilation [3]. Delays in diagnosis and treatment have been recognized as causes of death due to pulmonary TB, and several studies have sought to reduce these delays by identifying factors that should lead to a high index of suspicion [4, 5, 6, 7]. Reasons for missing the diagnosis of TB have included failure to perform appropriate diagnostic investigations and misinterpretation of the radiologic or clinical manifestations of TB as indicating a malignancy, pneumonia or other conditions [8, 9, 10].

Many case reports of acute respiratory failure associated with pulmonary TB have been published [11, 12, 13, 14, 15, 16, 17, 18, 19]. The few studies of potential prognostic factors in ICU patients with TB found that mechanical ventilation, age, gender, malnutrition, im-

munodeficiency, delayed suspicion of TB, acute respiratory distress syndrome (ARDS) at admission and shock were associated with higher mortality [4, 5, 6, 7, 10, 20, 21, 22, 23]. However, these studies were restricted to specific patient subsets, such as HIV-positive or mechanically ventilated patients; they failed to distinguish between pulmonary and extrapulmonary TB and most were either descriptive or relied on only univariate tests. Moreover, all the published studies of patients admitted for active TB with acute respiratory failure included a total of only 103 patients [1, 3, 24].

We set two goals: (1) to clarify the patterns of pulmonary TB with the goal of helping physicians to determine when they should maintain a high index of suspicion for pulmonary TB and (2) to identify predictors of 30-day mortality. To achieve these goals, we conducted a 7-year, retrospective study of 99 patients admitted for severe active pulmonary TB.

Patients and methods

We retrospectively reviewed the records of all patients admitted to the ICUs of two university hospitals between January 1, 1990, and January 1, 1997, with a diagnosis of acute respiratory failure related to active pulmonary TB. Only patients with microbiologically documented TB were included. All study patients presented with clinical and/or radiologic signs of TB and had either acid-fast bacilli upon direct light microscopy examination of at least one Ziehl-Neelsen-stained respiratory tract secretion sample or caseating granulomas with acid-fast bacilli by Ziehl-Neelsen's stain in histologic lung samples or positive culture.

The following data were abstracted from each medical record (Table 1): demographics (age, gender, ethnicity), comorbidities, chronic health status, [25] TB characteristics (recurrent pulmonary TB [with an interval > 6 months], weight loss during the last 3 months, time from symptom onset [weight loss, cough, sweating and fever] to treatment, chest radiograph patterns, other organs involved by TB, tools used for diagnosing TB), ICU admission parameters (reasons for admission, Knaus scale for organ dysfunction [26], SAPS II score [27]), routine laboratory tests (serum albumin, lymphocyte count, arterial blood gases on room air at admission or PaO_2/FIO_2 ratio in mechanically ventilated patients at admission), and whether mechanical ventilation was required at admission or within the first 48 h.

Immunodeficiency was defined as the presence of any of the following: leukocyte count below 1000/mm^3; underlying cancer or hematological disease; HIV infection with or without AIDS; steroid therapy (> 1 mg/kg per day) for at least 1 month; or chemotherapy within the last month. Disseminated TB was defined as active TB without a miliary pattern on the chest radiograph but with involvement of at least two extrapulmonary sites.[1] Radiographic patterns were classified as follows: alveolar, alveolar-interstitial or diffuse interstitial patterns; miliary; bronchopneumonia; pleural effusion; isolated apical cavity; and hilar or mediastinal lymphadenopathy; the number of lobes involved on radiograph was also recorded. ARDS was diagnosed based on Murray's criteria [28]. Shock was defined as a sustained (> 1 h) systolic blood pressure (SBP) decrease of at least 40 mmHg from baseline or as an SBP below 90 mmHg after adequate volume replacement or as a need for vasoconstricting agents.

Table 1 Characteristics of 99 ICU patients with active severe tuberculosis

	Number of patients (%) or median (25^{th}–75^{th} percentiles)
Male gender (%)	79 (79.8)
Age	41 (34–57)
Ethnic group	
Caucasian	52 (52.2)
North African	18 (18.2)
Black African	17 (17.1)
Asian	10 (10.1)
South American	2 (2)
Comorbidities	
Recurrent tuberculosis	20 (20.2)
Alcohol abuse	26 (26.3)
Homeless	13 (13.1)
Cirrhosis	5 (5)
Immunodeficiency	
AIDS	38 (38.4)
Hematological disease	16 (16)
Cancer	6 (6)
Steroids	5 (5)
Diagnostic of TB before ICU admission	69 (69.7)
Time from symptoms to treatment > 1 month (all patients)	34 (34.3)
Reasons for ICU admission other than acute respiratory failure	
Shock	20 (20.2)
Neurologic disorder	18 (18.2)
Acute renal failure	10 (10.1)
Concomitant infection	32 (32.3)
Organ failures (Knaus criteria)	
No organ failure[a]	28 (28.4)
1 Organ failure	37 (37.4)
2 Organ failures	26 (26.2)
≥ 3 Organ failures	8 (8)
Need for mechanical ventilation	50 (50.5)
ARDS	22 (22.2)
30-Day mortality	26 (26.3)

[a] According to Knaus criteria and despite clinical acute respiratory failure

In all 99 patients, the treatment included either enteral or parenteral administration of three or more first-line anti-TB drugs, namely isoniazid, rifampin, streptomycin, pyrazinamide and ethambutol. Because of the presence of respiratory failure, the 18 patients with miliary TB also received steroids, in a dosage of 1 mg/kg per day. Liver function tests were carried out before treatment initiation, then every 2 days; if values exceeding 5 times the upper limit of normal were found, the isoniazid and rifampin were stopped until the values returned to normal, after which both drugs were restarted in full dosage.

In the statistical analysis the results are reported as medians and 25^{th} and 75^{th} percentiles or as proportions. Categorical variables were compared using the chi-square test and continuous variables using Wilcoxon's rank sum test for unpaired data. Regression splines were used to obtain a non-parametric estimate of the cut-

off of continuous covariates influencing the risk of mortality. Multivariate analysis was performed using stepwise forward logistic regression with 30-day mortality as the outcome variable of interest. Odds ratios and their 95% confidence intervals were calculated. Log rank tests have been computed for the comparison of the survival curves. Statistical tests were performed using SPSS software (SPSS version 8.1, SPSS, Chicago, Ill.). A p value of less than 0.05 was considered significant.

Results

Patient characteristics

During the study period, 99 patients were admitted to one of the two study ICUs for acute respiratory failure related to active pulmonary TB. Twenty (20.2%) patients had recurrent TB. According to the criteria of MacCabe and Jackson, 56 (56.6%) patients had no or a non-fatal underlying condition, 38 (38.4%) had ultimately fatal underlying conditions and 5 (5.1%) had rapidly fatal underlying conditions. Weight loss in the past 3 months was present in 70 (70.7%) patients, with a median of 6 kg (0–25), temperature at admission was 38.5 (37.5–39.4) and 12 patients reported not having fever before anti-TB treatment. Cough was reported in all our patients and sweats in 89 (89.8%) patients.

Characteristics of the acute disease

At ICU admission, 22 (22.2%) patients had already been on treatment for TB since a median delay of 6 days (2–28). In 47 (47.5%) patients, TB treatment was instituted within 24 h from ICU admission. In the remaining 30 (30.3%) patients, the median time from ICU admission to TB diagnosis was 20 days (3–39), and the median time from ICU admission to anti-TB treatment initiation was 5 days (1–10); in 22 (22.2%) patients, anti-TB treatment was started in the ICU before confirmation of the diagnosis was obtained. The median time from symptom onset to treatment initiation was 26 days (14–46); in 34 (34.3%) patients, this time exceeded 1 month. All patients had acute respiratory failure at ICU admission, with or without shock ($n = 20$; 20.2%), neurologic disorders ($n = 18$ including 10 with coma; 18.2%) or acute renal failure ($n = 10$; 10.1%).

According to the Knaus scale, 71 (71.7%) patients had one or more organ failures and 28 (28.3%) did not; 37 (37.4%) had one organ failure and 34 (34.3%) had two organ failures or more. Mechanical ventilation was needed at admission in 35 (35.4%) patients and within 48 h in 15 (15.2%) additional patients; ARDS criteria were met in 22 (22.2%) patients. A concomitant non-tuberculous infection was diagnosed at admission in 32 patients, of whom 26 had a bacterial infection (pneumonia, $n = 13$; septicemia, $n = 7$; urinary tract infection, $n = 5$; pyogenic liver abscess and endocarditis, $n = 1$) and 6 an AIDS-related opportunistic infection (*Pneumocystis carinii* pneumonia, $n = 4$; cerebral toxoplasmosis, $n = 2$). In addition to the 20 patients with shock at ICU admission, 5 patients developed shock within 48 h of ICU admission.

None of the *Mycobacterium tuberculosis* strains exhibited multiple drug resistance. Hepatic cytolysis attributed to combination isoniazid and rifampin therapy occurred on seven occasions and led to temporary withdrawal of the two medications.

Table 2 shows that isolated pleuropulmonary TB was the most common pattern, with 59 (59.6%) cases. Another organ was involved by TB in 40 (40.4%) patients, including 19 disseminated TB, 10 meningitis, 3 liver TB, 3 urinary tract TB, 3 pericardial TB and 2 hematological TB (granulomatous involvement of bone marrow). Although miliary was present in only 18 (18.2%) patients, more than half our patients had involvement of more than one lung lobe (Table 3); in contrast, 10 (10.1%) patients had a normal chest radiograph at admission.

Serum albumin was 25 g/l (22–28); 15 (15.1%) patients had a serum albumin level of less than 20 g/l. The

Table 2 Organs affected by tuberculosis *(TB)* in 99 ICU patients

	Number of patients (%)
Pleuropulmonary TB	59 (59.7)
Disseminated TB	19 (19.2)
Pulmonary TB plus TB at one extrapulmonary site	
TB meningitis	10 (10.1)
Liver TB	3 (3)
Urinary tract TB	3 (3)
Pericardial TB	3 (3)
Hematological TB	2 (2)

Table 3 Radiographic patterns in our 99 patients with active severe tuberculosis

	Number of patients (%)
Normal chest radiograph	10 (10.1)
Radiographic patterns	
Alveolar	12 (12.1)
Alveolar-interstitial	13 (13.1)
Diffuse interstitial	17 (17.2)
Miliary	18 (18.2)
Bronchopneumonia	7 (7.1)
Pleural effusion	9 (9.1)
Isolated apical cavity	11 (11.1)
Isolated hilar lymphadenopathy	2 (2)
Number of lobes involved	
1	35 (35.4)
2	27 (27.3)
3	10 (10.1)
4	17 (17.2)

Table 4 Univariate predictors of 30-day mortality

	Survivors	Decedents	Odds ratio	95 % CI	*p* value
	n = 73 (%)	*n* = 26 (%)			
Underlying fatal condition	30 (41)	13 (50)	1.46	0.61–3.64	0.43
Immunodeficiency	44 (60.3)	16 (61.5)	1.37	0.21–16	0.98
Recurrent tuberculosis	14 (19.1)	6 (23)	1.31	0.46–3.70	0.61
Time from symptoms to treatment > 1 month	22 (30.1)	12 (46.1)	1.37	1.08–6.4	0.03
TB treatment before ICU admission	50 (68.5)	19 (73)	0.65	0.23–1.85	0.42
Lymphocyte count < 1000/mm^3	41 (56.1)	22 (84.6)	0.99	0.97–1.01	0.01
Serum albumin < 20 g/l	6 (8.2)	9 (34.6)	4.2	1.43–14	0.01
PaO_2/FIO_2 ratio	240 ± 134	188 ± 112	0.99	0.99–1.00	0.06
Number of lobes involved (chest radiograph)	1.7 ± 1.2	2.4 ± 1.2	1.49	1.04–2.1	0.02
SAPS II	29.8 ± 15.1	44.7 ± 21.2	1.04	1.01–1.07	< 0.001
More than one organ failure (Knaus criteria)	14 (19.1)	20 (76.9)	10.50	3.72–29.5	< 0.0001
Mechanical ventilation	26 (35.6)	24 (92.3)	21.7	4.74–99.1	< 0.001
ARDS	10 (13.6)	12 (46.1)	5.40	1.86–13.9	0.001
Shock	10 (13.6)	15 (57.7)	8.59	3.08–23.9	0.0001
Concomitant non-tuberculous infection	18 (24.6)	14 (53.8)	1.8	1.01–6.67	0.04

Table 5 Multivariate analysis: independent predictors of 30-day mortality

	Odds-ratio	95 % CI	*p* value
Number of organ failures	3.11	(1.45–6.65)	0.003
Number of lobes involved on chest radiograph	1.83	(1.12–2.98)	0.01
Serum albumin < 20 g/l	3.73	(1.09–15.31)	0.04
Time from symptoms to treatment > 1 month	3.73	(1.06–13)	0.02

lymphocyte count was 750/mm^3 (381–1305), PaO_2 on room air at admission was 58 mmHg (33–71) in spontaneously breathing patients, and the PaO_2/FIO_2 ratio was 204 mmHg (119–318) in intubated patients. In most patients (85), TB was diagnosed based on studies of sputum, tracheal aspirates or bronchoalveolar lavage fluid specimens, which were positive upon direct microscopic examination in 62 (62.6 %) patients and upon culturing in 23 (23.2 %) patients. In the remaining 14 patients (14.1 %), the diagnosis of TB was provided by histologic examination of a transbronchial biopsy specimen.

The median length of ICU stay was 11 days (range, 5–23). Twenty-six (26.3 %) patients died within 30 days of ICU admission.

Factors predicting 30-day mortality

Ten parameters were associated with 30-day mortality in the univariate analysis: a time from symptom onset to treatment initiation of more than 1 month, a lymphocyte count below 1000/mm^3, a serum albumin level below 20 g/l, the number of lobes involved on chest radiograph, the SAPS II score at admission, the number of organ failures, whether mechanical ventilation was needed within 48 h of admission, whether ARDS occurred, whether shock occurred within 48 h of admission and whether a concomitant non-tuberculous infection was present (Tables 4 and 5). Of these ten parameters, only four were independent predictors of 30-day mortality (Fig. 1), namely the number of organ failures (OR, 3.11 per failing organ; CI, 1.45–6.65), the number of lobes involved on chest radiograph (OR, 1.83 per lobe involved; CI, 1.12–2.98), a serum albumin level below 20 g/l (OR, 3.73; CI, 1.09–15.31), and a time from symptom onset to treatment initiation of more than 1 month (OR, 3.73; CI, 1.06–13.00; Fig. 2 and Fig. 3).

Discussion

This retrospective study sought to identify predictors of 30-day mortality in 99 ICU patients with acute respiratory failure related to severe active pulmonary TB. We found that a higher number of organ failures, a higher number of lobes involved on chest radiograph, a serum albumin level below 20 g/l and a time from symptom onset to treatment initiation longer than 1 month were independently associated with a higher 30-day mortality rate.

Our 26.2 % mortality rate is low compared to previous reports. This difference may be due to the fact that earlier studies included only mechanically ventilated patients [1], only patients with AIDS [23, 29], a higher proportion of patients with shock [10, 23] or a higher proportion of patients with TB as a contributory reason for ICU admission rather than as the main reason [30].

Pulmonary TB with respiratory failure still carries a high mortality rate despite the availability of effective

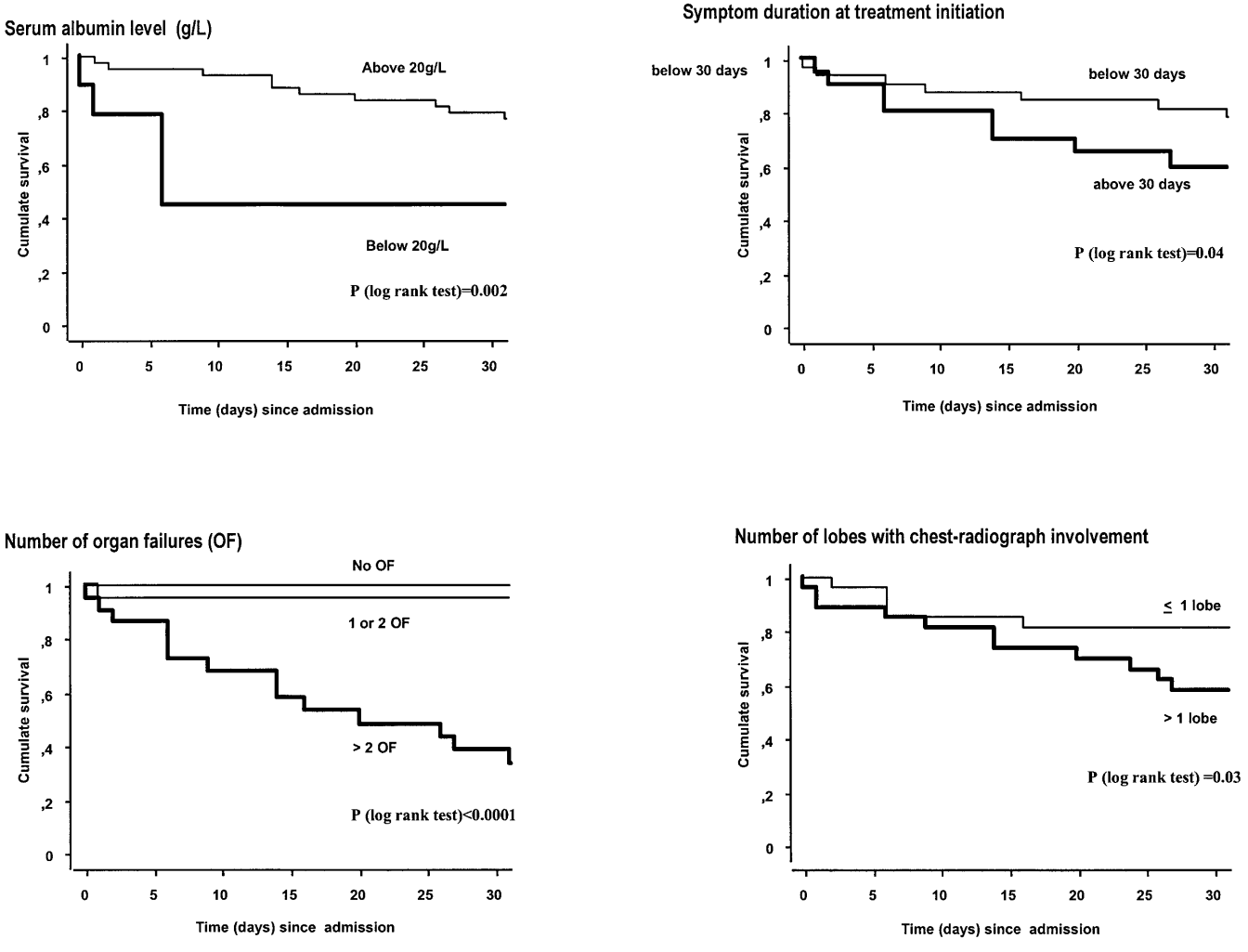

Fig. 1 Survival curves according to the independent predictors of 30-day mortality

therapy [2]. Numerous reports have suggested that delayed treatment initiation may reduce survival in patients with active TB [4, 5, 6, 7, 31]. The four independent predictors of mortality identified in our study support this possibility. Thus, a symptom duration longer than 1 month at treatment initiation obviously reflects delayed treatment [4], a low serum albumin level is associated with active infection or terminal illness [24, 32], a higher number of organ failures reflects the propensity for uncontrolled, untreated infection to cause multiple organ dysfunction [33] and a higher number of involved pulmonary lobes denotes the spread of untreated TB [5]. Numerous studies have found that most patients whose pulmonary TB diagnosis was performed at death were hospitalized prior to death and that in 50% of these patients the hospital stay duration prior to death was at least 2 weeks [6, 7, 34].

In our study, although 22 of the 30 non-treated patients were put on anti-TB drugs in the ICU as soon as TB was suspected, i.e., without waiting for confirmatory test results, death occurred within 30 days of ICU admission in more than one-third of the 34 patients with a pretreatment symptom duration longer than 1 month (Fig. 3). As reported by others [1, 35] and despite established guidelines, both the physicians who provided care prior to ICU admission (77 (77.7%) of the 99 patients) and the ICU physicians (8 (26.6%) of the 30 patients not on anti-TB therapy at ICU admission failed to consider TB. Treatment delays may be dependent on the experience and practice patterns of individual clinicians, which are probably modifiable with education [7].

A conspicuous finding from our study is that many patients had atypical chest radiographs at admission including 10 (10%) without any abnormalities at all. This may explain a number of missed diagnoses [4, 5]. Atypical chest radiographs have been reported by others [13, 36], particularly in patients with immunodeficiency, which was present in half our study population and in

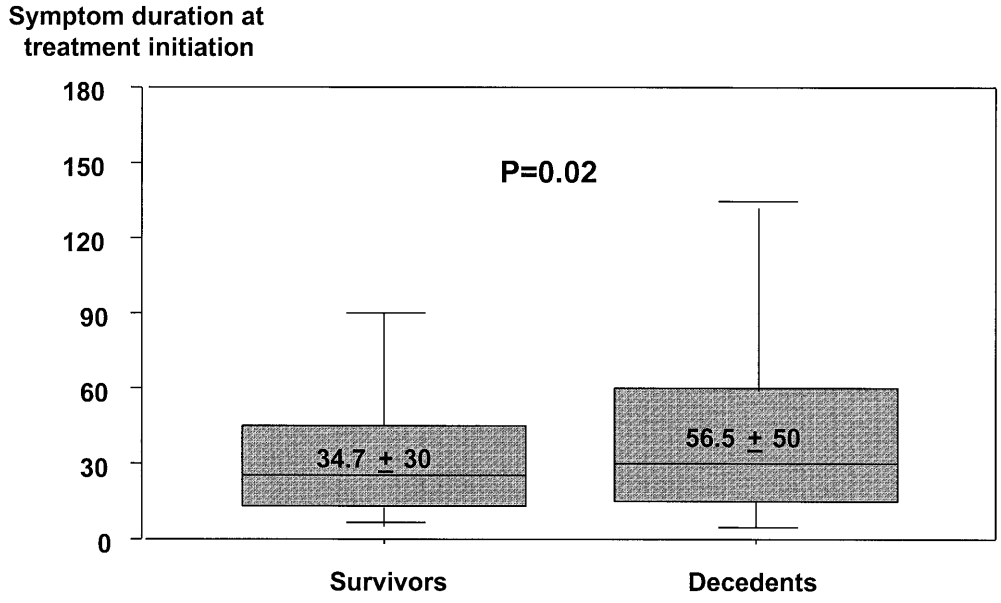

Fig. 2 Comparison of the symptom duration in survivors and decedents

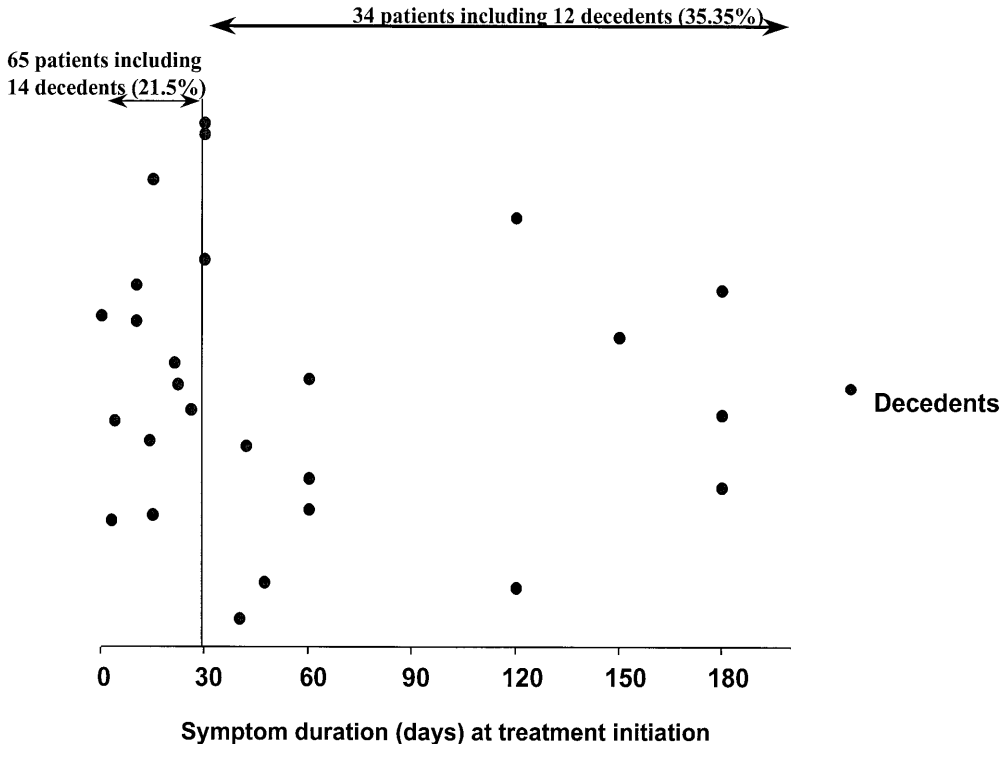

Fig. 3 Distribution of symptom duration at treatment initiation (X axis) in ICU patients with active pulmonary tuberculosis and respiratory failure: each point represents a non-survivor

six of the ten patients with a normal chest radiograph at admission. It follows that physicians should constantly be on the alert for pulmonary TB in immunocompromised patients, even in the absence of pulmonary symptoms or chest radiograph changes.

Strikingly, in contrast with previous reports, we found that parameters such as comorbidities, AIDS or the PaO_2/FIO_2 ratio failed to predict 30-day mortality [10, 21]. Nevertheless, these parameters are included in, or related to, SAPS II score, lymphopenia or ARDS. Moreover, associated infections did not correlate independently with mortality, serum albumin at admission, number of lobes with chest radiograph involvement or number of organ failures.

The number of organ failures was strongly and independently associated with 30-day mortality in our patients with pulmonary TB, whereas the SAPS II score at admission was not. An association between the APACHE II score and mortality in patients with TB requiring mechanical ventilation has been reported [1]. However, one study suggested that the APACHE II score consistently underestimated mortality, particularly in patients without comorbidities and despite obvious and significant destructive lung changes [37].

Intensive care unit patients with severe pulmonary TB remain at high risk of death, at least in part because of delays in suspecting and treating TB before and after ICU admission. We believe that our study provides clinicians with epidemiological information capable of helping them maintain a high index of suspicion when appropriate. Despite the potential toxicity of empirical TB treatment and because delayed treatment can result in death of the patient and of other individuals contaminated by nosocomial spread [38, 39], we recommend that ICU patients with weight loss, cough, sweating and fever without evidence of documented infection be promptly given an effective combination of anti-TB medications before the results of diagnostic tests are available. In immunocompromised patients, even those without characteristic pulmonary infiltrates, TB should be considered routinely and the index of suspicion should be particularly high if the symptoms started several days before admission, even if these symptoms could be ascribed to the underlying condition. Our results also suggest that primary care physicians and intensivists should be encouraged to use screening measures more widely.

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