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Characteristics of Active Tuberculosis Patients Requiring Intensive Care Monitoring and Factors Affecting Mortality

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Background: One to three percent of cases of acute tuberculosis (TB) require monitoring in the intensive care unit (ICU). The purpose of this study is to establish and determine the mortality rate and discuss the causes of high mortality in these cases, and to evaluate the clinical and laboratory findings of TB patients admitted to the pulmonary ICU.

Methods: The data of patients admitted to the ICU of Yedikule Chest Diseases and Chest Surgery Education and Research Hospital due to active TB were retrospectively evaluated. Demographic characteristics, medical history, and clinical and laboratory findings were evaluated.

Results: Thirty-five TB patients (27 males) with a median age of 47 years were included, of whom 20 died within 30 days (57%). The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were significantly higher, and albumin and PaO_2/FIO_2 levels were significantly lower, and shock, multiple organ failure, the need for invasive mechanical ventilation and drug resistance were more common in the patients who died. The mortality risk was 7.58 times higher in the patients requiring invasive mechanical ventilation. The SOFA score alone was a significant risk factor affecting survival.

Conclusion: The survival rate is low in cases of tuberculosis treated in an ICU. The predictors of mortality include the requirement of invasive mechanical ventilation and multiple organ failure. Another factor specific to TB patients is the presence of drug resistance, which should be taken seriously in countries where there is a high incidence of the disease. Finding new variables that can be established with new prospective studies may help to decrease the high mortality rate.

Keywords: Tuberculosis; Respiratory Insufficiency; Critical Care

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Introduction

Tuberculosis (TB) maintains its international prominence as a serious health problem and remains one of the most fatal contagious diseases. Unfortunately, it is still somewhat of a neglected disease. According to data from the World Health Organization, in 2013 TB occurred in nine million people globally, and 1.5 million people (360,000 of whom were human immunodeficiency virus [HIV]–positive) died of this disease[1]. Nevertheless, the prevalence of TB tends to decrease in many countries together with the developments in diagnosis and treatment. While the point prevalence rate of TB in Turkey was 38/100,000 in 2002, it had decreased to 24/100,000 by 2010. In 2009, the TB-related mortality rate in Turkey was reported to be 3.1% in all patients, 3.0% in newly diagnosed patients, and 3.3% in previously treated patients[2].

Although TB is a chronic disease, many unusual, acute TB manifestations have been identified[3]. Of the acute forms, miliary, meningeal, abdominal, and pulmonary TBs are the most acknowledged. The progress of acute TB is serious, with 1% to 3% of cases requiring treatment in intensive care units (ICU)[3]. It has been demonstrated that ICU admission is one of the factors that has an effect on mortality in pulmonary TB patients[4,5]. Pulmonary TB is the most prevalent among the acute forms requiring critical care and its in-hospital mortality has been reported to be 25%–33%. On the other hand, there are reports of the mortality rate increasing to 70% in those requiring mechanical ventilation[3].

To the best of our knowledge, there have been no studies in Turkey on TB cases requiring ICU admission due to respiratory failure. This is due to the fact that when ICU monitoring is required in TB cases, admission to an ICU poses a significant problem, as the disease is highly contagious and transmitted through inhalation. The aim of the present study was to evaluate the clinical and laboratory findings of TB patients who were admitted to the pulmonary ICU of Yedikule Chest Diseases and Chest Surgery Education and Research Hospital, which is one of the exceptional centers in Istanbul with a facility for monitoring and treating TB patients in the ICU, as well as to determine the mortality rate and factors affecting mortality. In the various studies conducted on this subject, the following factors, not necessarily specific to TB patients but associated with the presence of a critical disease, were found to negatively affect survival rates: delayed start of treatment in patients requiring intensive care follow-up for TB, widespread involvement or presence of miliary TB, multiple organ failure, albumin <20 g/L, HIV(+) disease, sepsis, presence of acute respiratory distress syndrome (ARDS), and high Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores. The main purpose of this study was to determine previously uncertain but specific factors, other than the acknowledged and standard ones, in TB patients requiring intensive care follow-up for this disease; the study also aimed to determine the factors that may be specific to Turkey.

Materials and Methods

This study was conducted at the Yedikule Chest Diseases and Chest Surgery Education and Research Hospital in Istanbul. It is one of the several hospitals where severe, extensive, and difficult-to-treat cases from almost all regions of Turkey, and currently also from other countries such as the Turkic Republics, Syria and Iraq, are being treated. It is the only hospital in Istanbul in which patients with TB, who require intensive care follow-up, are admitted and treated due to respiratory failure. The data of the patients who were admitted to the ICU of our hospital from May 2010 through December 2013, due to active TB and respiratory failure, were retrospectively evaluated. The present study included patients who were acid-fast bacilli (AFB) positive, by the microscopic examination of at least one sputum sample, or those who were microbiologically proven to have TB based on the growth in culture. Patients with sequel TB and were admitted to the ICU due to an unrelated reason, were not included in the study. Drug susceptibility testing was performed on all culture-positive samples. In our center, the (BACTECTM MGITTM 960 SIRE Kit; Becton Dickinson, Sparks, MD, USA) method, which is culture based rapid methods MGIT 960 (Mycobacteria Growth Indicator Tube, Becton Dickinson) was used as the drug sensitivity test. The last concentrations in MGIT tubes were as follows: streptomycin, 1.0 μg/mL; isoniazid (INH), 0.1 μg/mL; rifampicin (RIF), 1.0 μg/mL; and ethambutol (ETB), 5.0 μg/mL. Rapid genotyping methods in which drug sensitivity can be determined in two to three days have not yet been performed at our center. According to the location, the diagnosis of extrapulmonary TB was based on clinical and/or complementary tests. Quadruple therapy, consisting of INH, RIF, ETB, and pyrazinamide, or quintuplet therapy with the addition of streptomycin (in cases reverted from treatment drops or recurrent cases) according to the clinical status, was initiated via the oral route or through a nasoduodenal catheter, as soon as AFB positivity was detected according to the national guidelines. In cases of drug resistance, treatment was resumed by selecting the appropriate major and minor drug combination.

Patient information was obtained from the medical records and computer system of our hospital. Chest radiographs were obtained during the admission procedure. Approval from the Hospital Local Ethics Committee was obtained for documentation and evaluation.

In addition to the demographic characteristics of the patients, the medical history, APACHE II and SOFA scores, clinical courses, and laboratory data, were evaluated. APACHE II and SOFA scores, along with partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FIO_2) values, were evalu-

ated when the cases were admitted to the ICU. These values were obtained from the medical reports of the patients. These parameters were evaluated daily and noted down on the medical reports of the patients admitted to the ICU of our hospital; they were therefore not recalculated retrospectively. A diagnosis of respiratory failure was made following the determination of an arterial oxygen pressure (PaO_2) level of less than 60 mm Hg, or arterial oxygen saturation (SaO_2) <90%, with or without the elevation of arterial partially arterial carbon dioxide ($PaCO_2$). ARDS classification was made in accordance with the 2012 Berlin definition[4]. The patients were ventilated in accordance with a Vt value of approximately 6 mL/kg, which was based on their estimated body weights in the presence of ARDS. For the diagnosis of organ failure, the Knaus criteria were used. Multiple organ failure (MOF) was defined as the failure of more than one organ[5].

Table 1. Characteristics of the study patients

Characteristic	No. (%)
Age, median (range), yr	47 (16–83)
Gender	29 (82.9)
Male	27 (77.1)
Female	8 (22.9)
History of smoking	29 (82.9)
History of previous tuberculosis	11 (31.4)
Presence of comorbid disease	13 (37.1)
Comorbidity	
Diabetes mellitus	8 (22.9)
Silicosis	2 (5.7)
Human immunodeficiency virus	1 (2.9)
Rheumatoid arthritis	1 (2.9)
Lung cancer	1 (2.9)
Vasculitis and alveolar hemorrhage	1 (2.9)
Substance addiction	1 (2.9)
Duration of symptoms, median (range), day	40 (2–365)
Presence of symptoms for longer than 1 month	24 (68.6)
Radiological involvement	
1 Lobe	4 (11.4)
2 Lobes	6 (17.1)
3 Lobes	4 (11.4)
≥4 Lobes	21 (60.0)
Presence of drug resistance	10 (28.6)
Single drug resistance	3 (8)
Poly-drug resistance	1 (3)
Multi-drug resistance	6 (17)

1. Statistical analysis

The IBM SPSS Statistics for Windows ver. 21 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Descriptive statistics were expressed as numbers and percentages for categorical variables and as median, minimum, and maximum for numerical variables. A chi-square test was used for two group comparisons of categorical variables. For numerical variables, the Mann-Whitney U-test was used in cases where the assumption of normal distribution was not met. The Cox regression analysis was performed to determine the risk factors associated with survival. A statistical significance level established as $p<0.05$.

Results

The present study included 35 TB patients monitored in the ICU and their characteristics are summarized in Table 1. Reasons for ICU admission and the clinical and laboratory findings of the TB patients in the ICU are presented in Table 2.

The characteristics of the patients who died (n=20) and

Table 2. ICU parameters

Parameter	No. (%)
Reasons for ICU admission	
Respiratory failure	20 (57.1)
Sepsis	7 (20.0)
Massive hemoptysis secondary to TB	3 (8.6)
Extrapulmonary TB*	3 (8.6)
Lung cancer and pneumonia	1 (2.9)
Alveolar hemorrhage together with vasculitis	1 (2.9)
APACHE II score, median (range)	18 (7–32)
SOFA score, median (range)	6 (1–14)
Need for IMV	24 (68.6)
Need for NIMV	23 (65.7)
PaO_2/FIO_2, median (range)	181 (59–376)
Additional bacterial growth	26 (74.3)
Presence of shock	19 (54.3)
Multiple organ failure	17 (48.6)
Acute renal insufficiency	13 (37.1)
30-Day mortality	20 (57.1)
Hospital mortality	22 (62.9)

*Two patients with meningitis and one patient with pericarditis.
ICU: intensive care unit; TB: tuberculosis; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; PaO_2/FIO_2: partial pressure of oxygen/fraction of inspired oxygen.

Table 3. Characteristics of the patients who died and those who survived

Characteristic	Survived (n=15)	Died (n=20)	p-value
Age, yr	39 (16–60)	51.5 (20–83)	0.059
Sex			
Male	10 (66.7)	17 (85.0)	0.246
Female	5 (33.3)	3 (15.0)	
History of smoking	12 (80.0)	17 (85.0)	1.000
History of previous TB	2 (13.3)	9 (45.0)	0.069
Presence of DM	2 (13.3)	6 (30.0)	0.419
Duration of symptoms, day	40 (2–180)	40 (7–365)	0.780
Drug resistance	1 (6.7)	9 (45.0)	0.022
Scores			
APACHE II	14 (7–21)	22 (16–32)	<0.001
SOFA	2.5 (1–7)	9 (2–14)	<0.001
Need for IMV	6 (40.0)	18 (90.0)	0.003
Need for NIMV	13 (86.7)	10 (50.0)	0.034
PaO_2/FiO_2	202 (84–376)	144 (59–298)	0.017
Blood pH	7.43 (7.08–7.52)	7.21 (7.08–7.48)	0.019
WBC, $\times10^3/\mu L$	7.2 (4.7–42.9)	12.4 (2–28.6)	0.386
Hematocrit, %	30.4 (21.5–45)	29.2 (22–39)	0.172
Albumin, g/dL	3.1 (1.7–3.8)	2.4 (1–3.1)	0.002
ALT, U/L	35 (8–107)	19.5 (7–146)	0.766
AST, U/L	59 (11–158)	41.5 (10–380)	0.726
Sodium, mmol/L	133 (122–140)	133.5 (120–151)	0.569
Potassium, mmol/L	4.4 (3.5–5.1)	4.3 (2.7–5.9)	0.358
Creatinine, mg/dL	0.7 (0.2–1.3)	0.6 (0.2–3.1)	0.856
C-reactive protein, mg/L	50 (1.5–273)	22.6 (4.2–187)	0.806
Additional bacterial growth	11 (73.3)	15 (75.0)	1.000
Presence of shock	2 (18.2)	17 (89.5)	<0.001
Multiple organ failure	2 (13.3)	14 (70.0)	0.001
Acute renal insufficiency	3 (20.0)	10 (50.0)	0.069

Values are presented as median (range) or number (%).
TB: tuberculosis; DM: diabetes mellitus; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; PaO_2/FIO_2: partial pressure of oxygen/fraction of inspired oxygen; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

survived (n=15) over a period of 30 days were compared (Table 3). The APACHE II and SOFA scores were significantly higher, and albumin, blood pH, and PaO_2/FIO_2 levels were significantly lower in those patients who died than in those who survived. Shock, MOF, the need for invasive mechanical ventilation (IMV), and drug resistance, were more common in the patients who died. Drug resistance was determined in 10 patients (28%) who were included in the study, 1/3 of resistance cases had single drug resistance, and seven patients had multidrug resistance (Table 4). The presence of drug resistance was previously known in only four patients, and suitable treatments for drug resistance were started. Although one of these cases was one of cases with quadruple drug resistance, the patient was the only case that lived, and resistance patterns in the rest of cases could be learned later due to the methods used. The rate of the use of non-IMV support was higher in the patients who survived. Directly following the diagnosis of TB, all the patients were administered anti-TB treatment; hepatotoxicity developed in six of the 20 patients (30%) that died, and anti-TB drugs were discontinued in two cases

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Table 4. Resistance patterns of cases with determined drug resistance

Resistance pattern	No. of cases
SM	1
INH	1
RIF	1
INH, RIF	1
INH, RIF, SM	2
INH, SM, ETB	1
INH, RIF, ETB, SM	3

SM: streptomycin; INH: isoniazid; RIF: rifampicin; ETB: ethambutol.

due to hepatotoxicity. Hepatotoxicity developed in only two of the survivors (13%).

The Cox regression model, which was created to determine the factors that influence survival, consisted of gender, the presence of diabetes mellitus, the need for mechanical ventilation, additional bacterial growth, smoking, history of TB, and drug resistance. It was determined that the risk of mortality was 7.58 times higher in those patients who were in need of IMV (odds ratio [OR], 7.58; confidence interval [CI], 6.873–8.167). The analysis performed to determine whether the SOFA score influenced survival, revealed that the SOFA score alone was a significant factor (OR, 1.375; CI, 1.179–1.605). It was determined that an increase of one unit in the SOFA score increased the risk of mortality 1.375 times.

Discussion

Respiratory failure is not a common condition in TB. The frequency of respiratory failure in patients with active pulmonary TB has been reported between 1.5% and 5.0%[6-8]. The etiological factor has been determined to be TB in 4.9% of cases presented with ARDS[9]. Studies from various countries have reported different mortality rates in TB patients monitored in ICUs, and the rates are usually high. Data from similar studies on this subject are summarized in Table 4. Based on the previously mentioned studies, mortality rates range from 20% to 70%. In the present study, the 30-day mortality rate was 57.1%. One of the reasons for the different results obtained in these various studies might be the heterogeneity of the patient groups. Factors leading to the heterogeneity of the study groups include different age ranges, the presence of immunosuppressed or HIV-positive patients, the inclusion of all TB patients in the ICU, or TB patients requiring mechanical ventilation, and the conducting of studies in areas where TB is either rare or endemic.

Studies have also investigated factors associated with mortality in TB patients requiring intensive care. In many studies, univariate analyses, in terms of age and gender, have revealed no difference between patients who died and survived[10-20]. In the present study, as well, age and gender were not found to be associated with mortality. Moreover, the lack of difference between the patients who died and survived, in terms of their history of smoking, was consistent with the literature[12,15,16]. Although studies have reported no relationship between the duration of symptoms and mortality[14], as was reported in the present study, there is also research reporting that the presence of symptoms for longer than 1 month, is associated with mortality due to TB[18]. It has been found that among the comorbidities, diabetes[12-14,16,21], and HIV infection[10-12,17,21] are not associated with mortality. In the present study, there was only one HIV-positive patient, and no difference was found between the patients who died and survived in terms of the presence of diabetes mellitus. Although there are studies reporting that MOF is more prevalent in patients who died[13,14,18], in this aspect there are also studies reporting no difference between patients who died and survived[17,21]. In the present study, the rate of MOF was significantly higher in the patients who died than in those who survived (70% vs. 13.3%, p=0.001). The development of shock in patients is one of the risk factors that increases mortality[18]. In the present study, the presence of shock was significantly more common in the patients who died than in those who survived (89.5% vs. 18.2%, p<0.001). Nevertheless, there are also studies reporting no difference between patients who died and survived in terms of the presence of shock[15-17,21].

Studies have found no difference between patients who died and survived in terms of drug resistance[10,12,14]. We found that drug resistance was significantly more common in those who died than in those who survived (45% vs. 6.7%, p=0.022). This discrepancy between our results and the literature might be attributed to the difference in TB endemicity and drug resistance rates across countries. According to the 2010 data from Turkey, resistance was determined to at least one drug in 19.5% (n=975) of 4,965 patients (4,734 pulmonary+231 extrapulmonary TB) who underwent drug susceptibility testing[2]. Turkey is one of the countries in which the rates of major and minor drug resistances are high, and it is clear that such types of cases will be seen more in the future due to regional wars and migration. The main difference in our findings was the markedly higher drug resistance in the patients that died. Low-burden countries still experience high death rates due to severe TB[10]. Similarly, in situations where drug resistance rates are high, survival expectation will be lower due to the presence of more severe and widespread forms of TB. This is the first study that demonstrated that in cases of drug resistance, which was one of the TB-specific factors, mortality was significantly increased in patients in the ICUs. Since rapid tests, which can report the results in two or three days were absent in the study center, we believe that the mortality rate increased because the drug resistance pattern was unknown in

the majority of patients at admission to the ICU or during anti-TB treatment planning; therefore, ineffective treatments were administered. Furthermore, as hepatotoxicity risk increased, there were enteral absorption disorders, and lower albumin levels in ICU patients caused lower drug resistance levels than expected. Moreover, it was impossible to use INH and RIF in patients with multidrug resistance, which would decrease the efficacy of the regimen[8]. In addition, it is also very important that these patients are admitted to the ICUs and followed up in the ICU. The patients' should stay in negative pressure isolation rooms, rather than in corridors and other rooms. For this reason, ICUs should be properly isolated, continuously checked, and monitored using engineering techniques.

Another factor that can potentially affect mortality is difficulty with the enteral administration of drugs. However, with this cohort, no difficulty was encountered with drug administration. In all cases, the drugs were administered through a nasoduodenal catheter. Drug administration was suspended in cases with an elevation in liver function tests of more than 5 times the normal levels, and was resumed after the tests had returned to normal levels.

There are reports of elevations in the Simplified Acute Physiology Score (SAPS) II[10,11,18], SOFA score[10,16], and APACHE II score[12,13] being associated with mortality. APACHE II and SOFA scores were found to be associated with mortality, which is to be expected. In terms of the APACHE II score, some studies have reported no difference between those patients who died or survived[14-17,21]. The need for IMV has been indicated as significantly higher in the patients who died than in those who survived[10-12,18]. In the present study, also, the need for IMV was significantly higher in the patients who died than in those who survived (90% vs. 40%, p=0.003). In contrast, the use of non-IMV in the patients who developed respiratory failure was more prevalent in those who survived than in those who died (86.7% vs. 50%, p=0.034).

Among the complete blood count and biochemical parameters evaluated in the present study, albumin concentrations differed between the patients who died and survived (median, 2.4 g/dL and 3.1 g/dL, respectively; p=0.002). In addition to the studies reporting that a serum albumin level <2.0 g/dL is associated with death due to TB[18], there are also studies reporting no difference in terms of albumin levels[10,15,21]. Consistent with the literature[11,21], no difference was determined between the patients who died or survived, in terms of serum creatinine levels in the present study. In some studies, low PaO_2/FIO_2 has been found to be associated with death due to TB[11,18], whereas some studies have found no difference between the patients who died and survived in terms of PaO_2/FIO_2 values[13,15,16]. In the present study, PaO_2/FIO_2 values were significantly lower in the patients who died than in those who survived (median, 144 vs. 202; p=0.017). On the other hand, ventilation strategies require a dynamic approach, which is regulated according to effective secretion control, the close monitorization of blood gases, and the hemodynamic variables. It is obvious that the main approach should be the prevention of a high tidal volume and increased airway pressures.

In previous studies, many parameters have been found to be significant in the multivariate regression analysis performed to determine the risk factors affecting mortality. These parameters used to predict mortality include the onset of symptoms 1 month before, a serum albumin level <2.0 g/dL, the high number of the lobes involved[18], MOF[13,14,18], miliary TB, vasopressor requirement[11], mechanical ventilation[11,12], acute renal insufficiency, chronic pancreatitis, ARDS[12], sepsis[12,19], nosocomial pneumonia[12,13,17], high SAPS II[10], high APACHE II scores (≥20)[19], and high SOFA scores[14]. In the present study, the need for IMV and a high SOFA score were identified as risk factors for mortality. However, both of these parameters are not specific to TB patients, and they are the expected factors for all patient groups requiring intensive care follow-up. The most important finding in the present study is the negative effect of drug resistance on the survival rate. Although our study had a relatively small sample size, it is significant because it emphasized the effects of rapidly reached drug resistance results, and starting appropriate treatment regimen in time on mortality. This primarily indicated the significance of rapid diagnosis using genotypic drug susceptibility test, especially in patients being treated in ICUs, while planning diagnosis and treatment of anti-TB more appropriately and rapidly.

In conclusion, as was emphasized by the results of the present study, the mortality rate is high in TB patients who require intensive care. The main factors affecting mortality include the requirement of IMV and MOF. In this cohort, drug resistance was also found to be one of the factors affecting mortality. Prospective studies will aid in the detection of new parameters and ventilation strategies that can be used in decreasing the mortality in TB cases that are followed-up in ICUs. Even in countries where the TB disease load is lower, mortality is relatively higher in severe and widespread cases of TB, especially in those requiring intensive care follow-up, when compared with other disease groups. Therefore, it is wise to conclude that in countries like Turkey, where the disease load and resistance rates are high, mortality would be much higher in the presence of drug resistance.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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