

Acute tuberculosis in the intensive care unit

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Background/aim: The aim of this study was to determine mortality rates and to evaluate clinical features of patients with active tuberculosis (TB) requiring intensive care unit (ICU) admission.

Materials and methods: The medical records of active TB patients requiring ICU admission were retrospectively reviewed over a 5-year period.

Results: Sixteen patients with active TB admitted to the ICU were included in the study. Seven (43.8%) patients died in the ICU. The cause of mortality was septic shock in 5 patients and respiratory failure in 2 patients. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were higher in patients who died ($P = 0.012$ and 0.048 , respectively). Six of the 8 immunosuppressed patients and 1 of the 8 nonimmunosuppressed patients died ($P = 0.041$). The median mechanical ventilation (MV) duration was longer in patients who died (11 (5–45) days) than in patients who survived (4.5 (3–7) days) ($P = 0.036$). Seven of the 8 patients with nosocomial infection and/or coinfection died, while all of the patients without additional infection survived ($P = 0.01$).

Conclusion: Active TB patients admitted to the ICU had higher mortality rates, especially patients with immunosuppression, nosocomial infection, high APACHE II and SOFA scores, and patients receiving MV.

Key words: Acute disease, tuberculosis, intensive care, critical illness, sepsis

1. Introduction

Tuberculosis (TB) is a disease that can affect almost all organs of the body, particularly the lungs. Postprimary pulmonary TB is the most common type in adults, but the disease may present with different clinical and radiological features, especially in areas where tuberculosis is highly prevalent. TB is known as a chronic infectious disease, but it can mimic other infectious or noninfectious processes and may present acutely. The most common forms of TB presenting acutely are pulmonary, miliary, and meningeal (1). Pulmonary and miliary TB can lead to acute hypoxemic respiratory failure and, rarely, acute respiratory distress syndrome (2,3). Central nervous system TB, particularly meningoencephalitis, is the most severe form of extrapulmonary TB (4). This form of TB can cause impaired levels of consciousness including confusion, stupor, and coma. Delays in diagnosis and appropriate treatment may cause death in all these acute forms of TB.

Mortality rates of active TB patients with acute respiratory failure requiring mechanical ventilation (MV) range between 17.5% and 81% (2,5–8). The frequency

of intensive care unit (ICU) admission in patients with TB ranges between 1% and 3% (2,7,8). These patients often have pulmonary TB or miliary TB with serious comorbidities.

Several studies have attempted to identify clinical features of active TB requiring ICU admission (5,8–11). Most of them focused on pulmonary TB requiring mechanical ventilation. The aim of this study was to determine mortality rates and evaluate clinical features of newly diagnosed TB patients requiring ICU admission. We distinguished acute presentation of newly diagnosed TB from patients who had previous TB and/or who had already been receiving anti-TB medications for at least 30 days before admission.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the records of all patients admitted to the 9-bed medical ICU of a university hospital between 1 January 2009 and 1 January 2014 with a diagnosis of active TB. Only “new case of TB”

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patients were included (World Health Organization. Global tuberculosis report 2013, Geneva (2013)). Patients with clinical and radiological features of TB and positive cultures or positive acid-fast bacilli smears of biologic fluid specimens (sputum, bronchial aspirates, bronchoalveolar lavage, cerebrospinal, pleural, peritoneal fluids), and/or biopsy-proven caseating granuloma consistent with TB were included. Patients who had already been receiving anti-TB medications at least 30 days before ICU admission were excluded.

Clinical data were obtained from medical and radiological imaging records. These data included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Sequential Organ Failure Assessment (SOFA) scores, Glasgow Coma Scores (GCS), organs affected by TB, comorbidities, nosocomial infections and/or coinfections, medications, duration of mechanical ventilation, time from symptom onset to treatment, duration of hospital and ICU stay, radiographic findings of the lung, laboratory tests (blood chemistry and complete blood count), acid fast bacilli smear and culture results, and drug sensitivity of mycobacterium tuberculosis isolates. The study was approved by the Ethics Committee of Hacettepe University (no: 16969557-425).

2.2. Definitions

A new case of TB was defined as “a patient who has never taken medication for TB or has taken anti-TB drugs for less than 1 month”, based on World Health Organization definitions (World Health Organization. Global tuberculosis report 2013, Geneva (2013). http://www.who.int/tb/publications/global_report/en/index.html. Accessed: 23 October 2013.). TB cases were classified as pulmonary TB, extrapulmonary TB, and pulmonary plus extrapulmonary TB. Pulmonary TB was defined as a TB disease involving the lung parenchyma. Extrapulmonary TB was defined as TB of organs other than the lungs. Miliary tuberculosis was defined as TB with disseminated micronodules on the chest X-ray.

Immunodeficiency was defined when any of the following was present: human immunodeficiency virus (HIV) infection, underlying hematological cancer; steroid use (>1 mg/kg per day), or other immunosuppressive therapy for at least 1 month. Radiographic patterns were classified as cavity, miliary, consolidation, nodular, and pleural effusion. Sepsis syndromes were defined according to the latest survival sepsis guideline (12).

2.3. Statistical analysis

Data analysis was performed using SPSS 15.0 (Statistical Package for the Social Sciences, USA). Data were presented as number of cases, percentage, and median (minimum and maximum). Categorical comparisons were performed by chi-square test. The Mann-Whitney U test was applied to compare continuous variables. A P value <0.05 was considered statistically significant.

3. Results

During the 5-year period, 23 active TB patients were admitted to our intensive care unit. One patient died within 24 h after ICU admission, and 6 patients had already been receiving anti-TB drugs for more than 1 month. After these patients were excluded, 16 active TB patients were included in the study.

The characteristics and clinical features of all patients are shown in Table 1. The median age of the patients was 45 (24–74) years. Nine of the patients were male and 7 were female. The median APACHE II score was 21.5 (6–36) and the median SOFA score was 6 (1–12). Of the 16 patients, 3 had pulmonary, 3 had extrapulmonary, 4 had both pulmonary and extrapulmonary, and 6 had miliary TB. Extrapulmonary TB sites included meningoencephalitis (based on radiological features of TB meningoencephalitis and positive cultures or positive acid-fast bacilli smears of cerebrospinal fluid) in 4 patients, pleura in 1 patient (based on positive culture), the intestine in 1 (based on biopsy-proven caseating granuloma consistent with TB), and lymphadenopathy (based on biopsy-proven caseating granuloma consistent with TB and positive cultures or positive acid-fast bacilli smears) in 1 patient. Comorbidities were not present in 5 patients and 2 patients were positive for HIV infection. Eight (50%) patients had a history of immunosuppression due to drug or underlying disease. Ten (62.5%) patients received MV. Eight (50%) patients had nosocomial and/or coinfection including bacteremia, meningitis, and ventilator associated pneumonia. The primary cause for ICU admission was acute respiratory failure in 5 (31.3%), sepsis in 5 (31.3%), neurological deterioration in 5 (31.3%), and hemoptysis in 1 (6.3%). Anti-TB drugs were administered immediately after diagnosis of TB with a median 1 (0–20) day delay after ICU admission. Mycobacterium tuberculosis complex was isolated from all patients whose culture specimens were positive. Among all patients, the susceptibility tests showed rifampin resistance in 1 patient and isoniazid plus streptomycin resistance in 1 patient.

Seven (43.8%) patients died in the ICU. One patient died due to respiratory failure in hospital after being discharged from the ICU. The cause of mortality in the ICU was septic shock in 5 patients and respiratory failure in 2 patients. Two of the 4 TB meningitis with pulmonary tuberculosis patients died during the ICU stay. The median ICU stay for all patients was 10.5 (5–122) days. The median duration of hospitalization was 41 (6–122) days.

The patients who survived and did not survive in the ICU are compared in Table 2. APACHE II and SOFA scores were higher in patients who died (P = 0.012 and 0.048, respectively). At ICU admission the platelet and albumin levels were lower in patients who died (P = 0.050 and 0.017, respectively). Six of the immunosuppressed

Table 1. Clinical features of active TB patients admitted to the ICU.

Patient no.	Age (years)	Sex	APACHE II	Form of TB	Co-morbidity	Immuno-suppression	Nasocomial Infection or co-infection	Reason for ICU admission	Time from symptoms to treatment (days)	Treatment delay in ICU (days)	Anti-TB drug resistance*	Radiological interpretation	Outcomes in ICU
1	40	male	17	Extrapulmonary (CNS)	No	No	No	Neurological deterioration	30	0	No	Leptomeningeal (meningoenzephalitis)	Discharged
2	49	male	21	Extrapulmonary (CNS)	No	No	No	Neurological deterioration	10	0	No	Leptomeningeal (meningoenzephalitis)	Discharged
3	43	male	18	Pulmonary	CRF amyloidosis	Yes	Acinetobacter spp. (VAP)	Sepsis	45	0	NA	Left lower lobe cavity	Exitus
4	30	female	6	Pulmonary	TOF (underwent operation)	No	No	Hemoptysis	45	1	NA	Right upper lobe cavity and nodular	Discharged
5	39	male	18	Miliary	HIV+	Yes	No	Respiratory Failure	30	0	No	Disseminated nodular	Discharged
6	24	female	9	Pulmonary+ extrapulmonary (intestine)	No	No	No	Sepsis	7	4	NA	Nodular	Discharged
7	58	female	23	Miliary	ALL	Yes	Klebsiella (bacteremia)	Sepsis	45	15	NA	Multiple micro-nodular	Exitus
8	49	male	36	Miliary	HIV+	Yes	Pseudomonas (VAP)	Sepsis	50	0	INH+SM	Disseminated nodular	Exitus
9	28	female	22	Miliary	No	No	Acinetobacter (VAP)	Respiratory failure	25	0	No	Disseminated nodular	Discharged
10	26	female	29	Pulmonary + extrapulmonary (CNS)	No	Yes	Candida (meningitis)	Neurological deterioration	90	3	No	Left upper lobe posterior consolidation Multiple cerebral, cerebellar lesion Leptomeningeal	Exitus
11	47	female	22	Miliary	RA	Yes	Acinetobacter (VAP)	Sepsis	24	0	RIF	Disseminated bilateral nodular	Exitus
12	29	male	27	Pulmonary+ extrapulmonary (CNS)	Behçet's disease	Yes	Cryptococcus (meningitis)	Neurological deterioration	10	3	No	Cerebral enfarct-edema Left upper lobe nodule cavity	Exitus
13	62	female	29	Pulmonary	Renal transplant	Yes	St.malophililia (VAP)	Respiratory failure	40	4	NA	Bilateral upper and lower lobe consolidation	Exitus
14	56	male	16	Pleural	Diabetes mellitus	No	No	Respiratory failure	45	20	No	Bilateral pleural effusion Focal consolidation	Discharged
15	74	male	29	Pulmonary + extrapulmonary (lymphadenopathy)	Hypertension, Heart failure COPD	No	No	Respiratory failure	72	2	No	Bilateral nodular infiltration, cavity, Lymphadenopathy	Discharged
16	61	male	15	Miliary	Heart failure	No	No	Neurological deterioration	7	1	No	Bilateral nodular	Discharged

* Anti-TB drug resistance of patients whose diagnoses were based on biopsy proven granuloma consistent with TB and the results that were not found in medical records are shown as not available (NA).
Abbreviations: ALL: Acute lymphoblastic leukemia, CNS: Central nervous system, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, CSF: Cerebrospinal fluid, HIV: Human immunodeficiency virus, INH: Isoniazid, NA: Not available, RA: Rheumatoid arthritis, RIF: Rifampicin, SM: Streptomycin, St. malophililia: Stenotrophomonas maltophilia, TOF: Tetralogy of Fallot, VAP: Ventilator associated pneumonia

Table 2. Comparison of patients who survived and did not survive.

	Total n = 16	Nonsurvivor n = 7	Survivor n = 9	P value
Age	45 (24–74)	47 (26–62)	40 (24–74)	0.832
Sex (male/female)	9/7	3/4	6/3	0.615
APACHE II	21.5 (6–36)	27 (18–36)	17 (6–29)	0.012
SOFA	6 (1–12)	9 (4–12)	4 (1–9)	0.048
GCS	11 (3–15)	11 (3–15)	12 (6–15)	0.389
Hemoglobin (g/dL)	10.6 (8.0–15.6)	9.1 (8.0–12.2)	12.1 (8.3–15.6)	0.071
Leukocytes (/ μ L) $\times 10^3$	7.85 (0.3–16)	4.1 (0.3–16)	8.3 (4.9–13.4)	0.421
Platelets (/ μ L) $\times 10^3$	158,5 (26–398)	101 (26–216)	236 (76–398)	0.050
Albumin (g/dL)	2.55 (1.22–4.40)	1.90 (1.22–2.81)	3.20 (1.69–4.40)	0.017
Hypoalbuminemia (<3.0 g/dL) yes/no (%)	9/7 (56)	7/0 (100)	2/7 (22)	0.003
C-reactive protein (mg/L)	7.01 (0.8–42)	13.5 (2.16–42)	5.25 (0.8–16.5)	0.153
Erythrocyte sedimentation rate (mm/h)	27 (3–78)	42.5 (5–78)	19 (3–71)	0.317
Immunosuppression yes/no (%)	8/8 (50)	6/1 (85)	2/7 (22)	0.041
Nosocomial infections yes/no (%)	8/8 (50)	7/0 (100)	1/8 (11)	0.010
Invasive mechanical ventilation yes/no (%)	10/6 (62.5)	7/0 (100)	3/6 (33)	0.011
Noninvasive mechanical ventilation n (%)	2 (12.5)	0 (0)	2 (22)	
Duration on mechanical ventilation (day)	7 (3–45)	11 (5–45)	4.5 (3–7)	0.036
Acid resistant staining and/or TB culture +/- (%)	13/3 (75)	6/1 (85)	7/2 (77)	0.600
Time from symptoms to treatment (day)	35 (7–90)	45 (10–90)	30 (7–72)	0.240
Treatment delay in ICU (day)	1 (0–20)	3 (0–15)	1 (0–20)	0.658
Length of stay in ICU (day)	10.5 (5–122)	14 (6–50)	9 (5–122)	0.491
Length of stay in hospital (day)	41 (6–122)	42 (6–60)	40 (17–122)	0.277

Data are presented as number of cases (%) and median (minimum–maximum).

patients and 1 of the nonimmunosuppressed patients died ($P = 0.041$). Seven of the 8 patients with nosocomial and/or coinfection died. Conversely, all of the patients without nosocomial infection and/or coinfection survived ($P = 0.01$). Seven (62.5%) of the 10 patients who underwent invasive MV died ($P = 0.011$). The median MV duration was 11 (5–45) days in patients who died and 4.5 (3–7) days in patients who survived ($P = 0.036$). The median time from symptom onset to treatment was 45 (10–90) days in patients who died and 30 (7–72) days in patients who survived. The median duration from ICU admission until initiation of treatment was 3 (0–15) days in patients who died and 1 (0–20) day in patients who survived.

4. Discussion

In this study, the clinical features of 16 newly diagnosed active TB patients admitted to our ICU were evaluated. Although TB is a treatable and curable disease, the mortality rate in active TB patients requiring ICU admission is high. The mortality rate of active TB patients with acute respiratory failure requiring mechanical ventilation (MV) ranges between 17.5% and 81% (2,5–8). It is more than twice that of respiratory failure due to community-acquired pneumonia (13). Another acute form of TB is meningitis, which is the most severe form of extrapulmonary TB. Its mortality rate ranges between 17% and 27% in Turkey (14,15). Two of the 4 TB meningoencephalitis patients that

had pulmonary tuberculosis died during ICU stay in our study.

Frame et al. (5) reported a mortality rate of 67% for 43 active TB patients requiring ICU admission. The mortality rate was 81% in the patients with acute respiratory failure in this study. Erbes et al. (8) found a mortality rate of 22.4% for 58 TB patients requiring ICU admission, and the number of patients who underwent MV was 22 (37.9%). Ten (62.5%) patients received MV in our study. Seven (43.8%) of these patients died in the ICU. The median MV duration was longer in patients who died (11 (5–45) days) than in patients who survived (1.5 (0–7) days).

Zahar et al. (10) found a 30-day mortality rate of 26.2% for 99 TB patients with acute respiratory failure. The HIV infection rate was 38.4% in these 99 TB patients with acute respiratory failure. A time from symptom onset to treatment of more than 1 month, the number of organ failures, serum albumin level above 20 g/L, and the number of lobes involved on chest X-ray were found as predictors of mortality. Our study is a single center study with very small sample size. Thus, it is limited in detecting the independent factors associated with mortality. However, lower platelet and albumin levels and higher SOFA scores were observed in the patients who died compared with the patients who survived in our study.

Sepsis, nosocomial pneumonia, and a requirement of MV were associated with mortality in patients with active tuberculosis (8). Four of the 7 patients who died had severe pneumonia among our patients. Ryu et al. (11) found a 30-day mortality rate of 59% for active TB patients requiring ICU admission. Destroyed lung, APACHE II score above 20, and sepsis were found as predictors of mortality in that study (11). In our study, APACHE II score for the patients who died was significantly higher than for the patients who survived (median 27 (18–36) and 17 (6–29), respectively).

Diseases or drugs that cause immunosuppression are among the factors that increase mortality in patients with active tuberculosis requiring ICU admission (9). In our study, 8 patients had immunosuppression due to drugs or diseases. Six of these patients died.

TB can, rarely, lead to sepsis or septic shock, which is known as Landouzy septicemia (1,16,17). This process is usually seen in immunocompromised patients, but may be seen in immunocompetent patients (1,16,17). However, other causal microorganisms must be excluded for the diagnosis of TB-associated sepsis or septic shock. In our study, other non-TB microorganisms were isolated from blood and other body fluids in patients with septic shock.

Delayed treatment is another important factor that contributes to mortality in active TB patients with acute respiratory failure (10). Levy et al. (18) found 3–4 days of treatment delay in hospital and a mortality rate of 33% for TB patients with acute respiratory failure. The median delay of anti-TB treatment was detected as 1 (0–20) day in TB patients admitted to our ICU in this study. The median time from symptom onset to treatment was 35 (7–90) days. However, treatment delay in ICU and the time from symptom onset to treatment was not found to be associated with mortality in our study with a small sample size.

In conclusion, active TB patients admitted to the ICU have higher mortality rates, especially patients with immunosuppression, nosocomial and/or co-infection, high APACHE II and SOFA scores, and patients receiving mechanical ventilation. The mortality rate of patients admitted to the ICU with acute presentation of TB was higher than that of patients with chronic presentation of the disease. Diagnostic tests should be conducted without delay and treatment should be initiated early in patients who are suspected of having tuberculosis.

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