A severity-of-illness score in patients with tuberculosis requiring intensive care

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Background. We previously retrospectively validated a 6-point severity-of-illness score aimed at identifying patients at risk of dying of tuberculosis (TB) in the intensive care unit (ICU). Parameters included septic shock, HIV infection with a CD4 count <200 cells/μL, renal dysfunction, a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (P/F) <200 mmHg, a chest radiograph demonstrating diffuse parenchymal infiltrates, and no TB treatment on admission.
Objectives. To prospectively validate the severity-of-illness scoring system in patients with TB requiring intensive care, and to refine and simplify the score in order to expand its clinical utility.
Methods. We performed a prospective observational study with a planned *post hoc* retrospective analysis**,** enrolling all adult patients with confirmed TB admitted to the medical ICU of a tertiary hospital in Cape Town, South Africa, from 1 February 2015 to 31 July 2018. The admission data of all adult patients with TB requiring admission to the ICU were used to calculate the 6-point severity-of-illness score and a refined 4-point score (based on the planned *post hoc* analysis). Descriptive statistics and χ^2 or Fisher's exact tests (where indicated) were performed on dichotomous categorical variables, and *t*-tests on continuous data. Patients were categorised as hospital survivors or non-survivors.
Results. Forty-one of 78 patients (52.6%) died. The 6-point scores of non-survivors were higher than those of survivors (mean (standard deviation (SD)) 3.5 (1.3) v. 2.7 (1.2); p=0.01). A score ≥3 v. <3 was associated with increased mortality (64.0% v. 32.1%; odds ratio (OR) 3.75; 95% confidence interval (CI) 1.25 - 10.01; p=0.01). *Post hoc*, a P/F ratio <200 mmHg and no TB treatment on admission failed to predict mortality, whereas any immunosuppression did. A revised 4-point score (septic shock, any immunosuppression, acute kidney injury and lack of lobar consolidation) demonstrated higher scores in non-survivors than survivors (mean (SD) 2.8 (1.1) v. 1.6 (1.1); p<0.001). A score ≥3 v. ≤2 was associated with increased mortality (78.4% v. 29.3%; OR 8.76; 95% CI 3.12 - 24.59; p<0.001).
Conclusions. The 6-point severity-of-illness score identified patients at increased risk of death. We were able to derive and retrospectively validate a simplified 4-point score with superior predictive power.

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Despite the presence of effective treatment, tuberculosis (TB) remains a significant challenge globally. In 2017, ~1.3 million deaths among HIV-negative people and a further 300 000 deaths among HIV-positive people were attributed to the disease worldwide.[1] The mortality rate in patients with active pulmonary TB requiring mechanical ventilation ranges from 26% to 83%.[2] Prognostic evaluation using severity-of-illness scores may be useful in developing strategies to improve outcome in the intensive care unit (ICU). However, the ideal prognostic score remains elusive. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score, frequently used to estimate the probability of hospital mortality for patients admitted to the ICU, is completed 24 hours following ICU admission and has not been validated in the emergency department.[3]

We previously retrospectively validated a 6-point severity-of-illness score aimed at identifying ICU patients at risk of dying of TB.[4] The parameters included septic shock, HIV infection with a CD4 count <200 cells/μL, renal dysfunction (creatinine >140 μmol/L (male) or >120 μmol/L (female)), arterial oxygen partial pressure to fractional inspired oxygen (P/F) ratio <200 mmHg, a chest radiograph demonstrating diffuse parenchymal infiltrates, and no TB treatment on admission.[4] The scores were significantly lower in survivors compared with non-survivors (mean (standard deviation (SD)) 2.27 (1.47) v. 3.58 (1.08); p<0.001). Moreover, a score of ≥3 was associated with significantly higher mortality than a score of <3 (64.6% v. 20.0%; odds ratio (OR) 7.29; 95% confidence interval (CI) 2.64 - 20.18; p<0.001).

Objectives

To prospectively validate the severity-of-illness scoring system in patients with TB requiring intensive care, and secondarily to potentially refine and simplify the score in order to expand its clinical utility.

Methods

Study population and setting

All adult patients (aged ≥18 years) admitted to the medical ICU at Tygerberg Hospital, Cape Town, South Africa (SA), with the diagnosis of confirmed active TB were enrolled. Tygerberg Hospital, a 1 380-bed facility, is one of two referral centres in Cape Town rendering a tertiary service to a population of ~1.5 million

people. In 2018, the incidence rate of TB in SA was ~520/100 000 population.[1]

Study design

This prospective observational cohort study was conducted from 1 February 2015 to 31 July 2018 and was approved by the Stellenbosch University Health Research Ethics Committee (ref. no. N14/10/). Patients were considered to have active TB if at least two of the following criteria were met: (*i*) smear positive for acid-fast bacilli or Xpert MTB/RIF (Cepheid, SA) on sputum, tracheal aspirate, or any other clinical specimen; (*ii*) culture positive for *Mycobacterium tuberculosis* on sputum, tracheal aspirate or any other clinical specimen; (*iii*) histopathological identification of TB granuloma on biopsied tissues; (*iv*) strong clinical suspicion of active TB; (*v*) strong radiological evidence of active TB; and (*vi*) pleural fluid with a lymphocyte predominance (>75% lymphocytes and/or lymphocyte/neutrophil ratio >0.75) with adenosine deaminase >40 IU/L. A strong clinical suspicion of active TB required at least two of four constitutional symptoms (loss of weight with accompanying fever, night sweats, productive cough, and loss of appetite for >2 weeks) as well as known TB contact or a history of previous pulmonary TB. Positive cultures were identified as *M. tuberculosis* and tested for susceptibility to rifampicin and isoniazid using the MTBDRplus line probe assay (Hain LifeSciences, Germany). The study included patients with both drug-susceptible TB and drug-resistant TB (DR-TB).

Clinical data, laboratory tests, imaging and related investigations

Patient demographics, comorbid disease, the presence of septic shock, the degree of hypoxaemia utilising the P/F ratio and the presence of TB treatment were documented. Laboratory investigations included the white blood cell count, platelet count, serum haemoglobin, serum albumin, C-reactive protein, serum creatinine and alanine aminotransferase. Absolute CD4 counts were measured in HIV-positive patients. The admission chest radiograph of each patient was reviewed by two pulmonologists independently, who were blinded to the clinical data. The chest radiographs were classified as follows: (*i*) multilobar/diffuse involvement; (*ii*) lobar consolidation; (*iii*) cavitation; (*iv*) pleural effusion; (*v*) isolated lymphadenopathy; or (*vi*) normal. The APACHE II score was calculated after the first 24 hours in the ICU. The 6-point severity-of-illness score for each study participant was determined from data obtained on ICU admission.

Management and complications

All patients were managed according to local guidelines and received maximal supportive therapy. The standard combination anti-TB treatment regimen was used unless significant renal or hepatic impairment or confirmed drug resistance was present.[5] Standard diagnostic criteria for septic shock, renal failure and acute respiratory distress syndrome (ARDS) were employed.[6-8]

Statistical analysis

Data were analysed using SPSS 17.0 (IBM, USA). Descriptive statistics and χ^2 or Fisher's exact tests (where indicated) were performed on dichotomous categorical variables, and *t*-tests on continuous data. Patients were categorised as hospital survivors or non-survivors. Based on our previous study, we estimated that a sample size of ~80 patients was needed to validate the original 6-point severity-of-illness score.[4]

Post hoc analyses

A planned *post hoc* analysis was performed to assess the significance of various parameters used in the severity-of-illness score as well as other markers of mortality and potentially derive a simplified (and potentially more practical) score with equal or higher predictive power. The more recently described Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury[9] was used to define renal dysfunction in the revised severity-of-illness score.

Results

Study population characteristics

During the study period, a total of 78 TB patients (mean (standard deviation (SD)) age 36.1 (14.4) years, *n*=40 males) were admitted to the medical ICU, all of whom were included in the study. The majority of the patients (*n*=76; 97%) had active pulmonary TB. Eleven of these patients had disseminated disease. Two patients had evidence of extrapulmonary TB exclusively. Extrapulmonary involvement in all patients, including those with concomitant pulmonary involvement, included pleural (*n*=16), pericardial (*n*=4) and neurological (*n*=5) disease, TB lymphadenitis (*n*=2) and abdominal TB (*n*=5). Seventeen patients (21.8%) were on TB treatment at the time of admission. Twenty-four patients (30.8%) were HIV-infected, of whom 17 had a CD4 count <200 cells/μL. Other forms of immunocompromised states included diabetes mellitus (*n*=10) and treatment with immunosuppressive drugs (*n*=3).

The mean (range) duration of ICU admission was 7.4 (1 - 22) days. The most common indication for admission directly related to TB was acute respiratory failure (*n*=51; 65.4%). ARDS was present in 5 survivors and 6 non-survivors in this group of patients. Other indications included a decreased level of consciousness (*n*=7), upper airway obstruction (*n*=1) and cardiac tamponade (*n*=1). Eighteen patients were admitted for concomitant disease unrelated to TB.

Tracheal aspirates were obtained from all patients with presumed pulmonary TB, and the diagnosis was supported by a positive Xpert MTB/RIF in all but 6 patients. Three patients were rifampicin resistant (DR-TB). The diagnosis of TB in the absence of direct microbiological proof or a positive Xpert MTB/RIF was based on a high clinical probability, combined with radiological evidence alone (*n* =2), radiological and pleural fluid analysis (*n*=2), radiological and cerebrospinal fluid (CSF) fluid analysis (*n*=1) and CSF analysis alone (*n*=1).

Twenty-one patients died in the ICU (ICU mortality 26.9%) and a further 20 patients died in hospital following ICU discharge (in-hospital mortality 52.5%).

Predictors of mortality and the performance of the 6-point score

The clinical, radiological and laboratory data of survivors and non-survivors are summarised in Tables 1 - 3. Of note is the fact that other forms of immunosuppression were strongly associated with increased mortality, as was renal impairment. Septic shock was a strong predictor of mortality (OR 5.21; 95% CI 1.97 - 9.33). Patients with lobar consolidation had an increased likelihood of survival. Thrombocytopenia and hypolbuminaemia were associated with increased mortality, as was high serum creatinine. The 6-point severity of illness score predicted mortality (Table 4). A score of ≥3 was associated with a higher mortality rate than a score of <3 (*p*=0.007 and OR 3.75; 95% CI 1.41 - 10.01).

Post hoc analyses

In view of the lack of a significant association with mortality of both P/F <200 mmHg and absence of TB treatment on admission, in conjunction with the strong association with other (non-HIV) immunocompromised states and the more recently described KDIGO guidelines for acute kidney injury, we proposed a refined score,

Table 1. Population characteristics, survivors v. non-survivors

Parameter	All (*N*=78)	Survivors (*N*=37)	Non-survivors (*N*=41)	OR (95% CI)	*p*-value
Sex (female), *n*	38	19	19	0.82 (0.34 - 1.99)	0.64
Age (years), mean (SD)	36.1 (14.4)	33.0 (11.8)	38.8 (16.1)	NA	0.07
APACHE II, mean (SD)	23.8 (8.0)	21.2 (7.4)	26.3 (7.8)	NA	0.01
Extrapulmonary TB, *n*	13	4	9	2.32 (0.65 - 8.30)	0.19
HIV positive, *n*	24	11	13	1.10 (0.42 - 2.88)	1
HIV with CD4 <200 cells/μL, *n*	17	7	10	1.38 (0.47 - 4.11)	0.56
Other immunosuppression, *n*	13	1	12	14.8 (1.83 - 121.38)	0.002
TB treatment on ICU admission, *n*	17	11	6	0.41 (0.13 - 1.24)	0.18

OR = odds ratio; CI = confidence interval; SD = standard deviation; NA = not available; APACHE II = Acute Physiology and Chronic Health Evaluation II; TB = tuberculosis; ICU = intensive care unit.

Table 2. Clinical characteristics, survivors v. non-survivors

Parameter	All (*N*=78), *n*	Survivors (*N*=37), *n*	Non-survivors (*N*=41), *n*	OR (95% CI)	*p*-value
Septic shock,*	37	10	27	5.21 (1.97-13.75)	<0.01
Renal impairment,†	28	8	20	3.48 (1.28-9.33)	0.02
ARDS	11	5	6	0.91 (0.25 - 3.28)	1
P/F ratio <200 mmHg	34	19	15	0.55 (0.22 - 1.35)	0.28
Radiology					
Multilobar involvement‡	69	31	38	2.45 (0.57 - 10.61)	0.29
Lobar consolidation	7	6	1	0.13 (0.01 - 1.13)	0.05
Cavitation	19	12	7	0.43 (0.15 - 1.25)	0.19
Pleural effusion	16	5	11	2.35 (0.73 - 7.55)	0.17
Isolated lymphadenopathy	0	0	0	NA	NA
Normal	2	0	2	NA	NA

OR = odds ratio; CI = confidence interval; ARDS = acute respiratory distress syndrome; P/F ratio = arterial partial oxygen pressure to inspired fractional oxygen concentration ratio; NA = not available.
*Systolic blood pressure <90 mmHg, 40 mmHg drop from baseline; lactate >4 mmol/L.
†Creatinine >140 μmol/L (male) or >120 μmol/L (female).
‡Includes diffuse interstitial infiltrates, miliary tuberculosis and multilobar consolidation.

Table 3. Laboratory data, survivors v. non-survivors

Parameter	Reference	All (*N*=78), mean (SD)	Survivors (*n*=37), mean (SD)	Non-survivors (*n*=41), mean (SD)	*p*-value
CD4 count (cells/μL)	600 - 1 500	160 (181)	176 (134)	145 (221)	0.68
P/F ratio (mmHg)	>300	216 (100)	220 (109)	229 (91)	0.79
White cell count (× 10^9/L)	4.0 - 11.0	14.1 (7.6)	14.5 (6.3)	13.7 (8.7)	0.67
Platelet count (× 10^9/L)	150 - 400	254 (147)	284 (120)	226 (164)	0.03
Haemoglobin (g/dL)	12.0 - 15.0	10.2 (8.5)	9.3 (2.1)	11.0 (11.5)	0.38
Serum albumin (g/L)	35 - 50	23.7 (6.8)	26.6 (7.0)	21.3 (5.7)	0.001
C-reactive protein (mg/L)	<5	177 (101)	161 (97)	191 (104)	0.20
Creatinine (μmol/L)	<90	217 (464)	125 (188)	227 (236)	0.04
ALT (U/L)	5 - 40	112 (323)	99 (374)	122 (281)	0.76

SD = standard deviation; P/F ratio = arterial partial oxygen pressure to inspired fractional oxygen concentration ratio; ALT = alanine transaminase.

utilising 4 parameters: (*i*) septic shock; (*ii*) any immunocompromised state; (*iii*) acute kidney injury; and (*iv*) chest radiography not compatible with lobar consolidation. We subsequently retrospectively applied the 4-point score to the current cohort's admission data and found even higher discrimination (Table 5, Fig. 1). The 4-point scores of non-survivors were significantly higher than those of survivors (mean (SD) 2.8 (1.1) v. 1.6 (1.1); $p<0.001$). A score ≥3 v. ≤2 was associated with significantly increased mortality (78.4% v. 29.3%; OR 8.76; 95% CI 3.12 - 24.59; $p<0.001$).

Discussion

In this prospective study, we found that the proposed 6-point severity-of-illness score accurately identified critically ill patients at increased risk of dying of TB. A score of ≥3 was associated with a higher mortality rate, with an OR of 3.75 ($p=0.007$). Moreover, we were able to refine and simplify the score. The refined score had even higher predictive power: a score of ≥3 v. ≤2 was strongly associated with increased mortality (78.4% v. 29.3%; OR 8.76; $p<0.001$).

Table 4. Mortality rates according to the 6-point severity-of-illness score

Score	All (*N*=78), *n*	Survivors (*N*=37), *n*	Non-survivors (*N*=41), *n*	Mortality, %
≤2	28	19	9	32.1
3	16	6	10	62.5
≥4	32	12	22	68.8
<3	28	19	9	32.1
≥3	50	18	32	64.0

Table 5. Mortality rates according to the revised 4-point severity-of-illness score

Score	All (*N*=78), *n*	Survivors (*N*=37), *n*	Non-survivors (*N*=41), *n*	Mortality, %
≤1	23	18	5	21.7
2	18	11	7	38.9
3	25	6	19	76.0
4	12	2	10	83.3
≤2	41	29	12	29.3
≥3	37	8	29	78.4

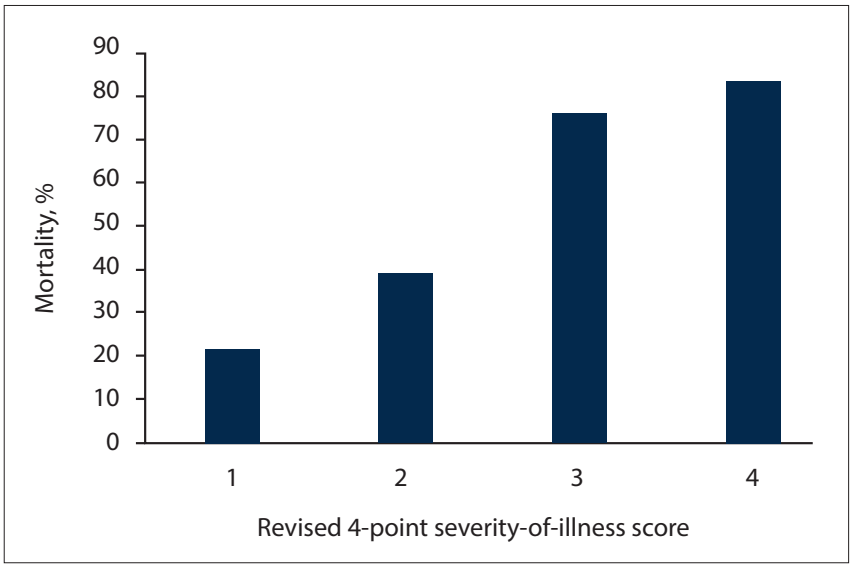

Fig. 1. Mortality rates according to the revised 4-point severity-of-illness score.

The need for mechanical ventilation in critically ill patients with TB is associated with increased mortality and prolonged ICU and hospital stays.[10] Tatar *et al.*[11] reported a mortality rate of 80.5% in 36 of 40 patients requiring mechanical ventilation in an ICU in Turkey, while in India, an ICU mortality rate of 44% was observed in 57 mechanically ventilated patients.[10] We previously reported ICU mortality and hospital mortality of 44% and 59%, respectively.[2] The lower ICU (27%) and in-hospital mortality rate (52.5%) observed in the present study may in part be attributed to the recent introduction of the Xpert MTB/RIF as a rapid diagnostic test in the ICU, reducing the delay to diagnosis and treatment, which is a well-known risk factor for TB mortality.[12]

Factors significantly associated with mortality in the present study included a higher APACHE II score, hypolbuminaemia and thrombocytopenia, concurring with previous studies.[2,10,11,13] Moreover, Tatar *et al.*[11] and Ryu *et al.*[14] identified an APACHE II score of >18 and >20, respectively, as being predictive of death. The mean APACHE II score of 23.8 (21.2% for survivors v. 26.3% for non-survivors) in our study highlights the high disease acuity in our cohort, a finding consistent with other studies with predominantly mechanically ventilated patients.[2,11]

The association between renal failure and TB-related mortality remains conflicting.[17,18] We identified renal failure to be predictive of mortality in accordance with some, but not all, studies.[2,15,16] In contrast to previous reports, we did not find a significant correlation with multilobar involvement on the chest radiograph and mortality.[17,18] The vast majority of our patients had multilobar involvement on admission, which may explain this observation. However, the presence of lobar consolidation was found to be negatively associated with mortality. Additionally, we confirmed the lack of association between radiographic evidence of cavitation and mortality, as previously described.[4] Septic shock was a strong predictor of mortality in our study. This is not surprising, considering the high mortality related to both mycobacterial and non-mycobacterial septic shock. Kethireddy *et al.*[19] reported a 79% mortality rate in patients with mycobacterial septic shock compared with those with non-mycobacterial septic shock (49.7%) in a multinational study.[19] Duro *et al.*[20] reported a significant association between severe sepsis/septic shock and mortality (p=0.049; OR 8.5 (95% CI 0.931 - 77.598)) in 39 patients in Portugal.

Our study highlights the presence of any form of immunosuppression as a significant predictor of mortality. A contributing explanation for the poor outcomes observed in these patients may be the atypical radiographic presentation of TB, potentially resulting in delayed diagnosis and commencement of anti-TB treatment. Approximately one-third of our patients were co-infected with HIV, a factor that did not contribute to mortality. This is in line with recent literature, possibly reflecting improving standards of care in this population.[20,21] The lack of association between mortality and HIV infection in our study may additionally be explained by the fact that our non-HIV patients had a similar level of disease acuity and a high mortality rate. Although poorer outcomes have been reported in HIV-infected patients with a low CD4 count in critical illness,[22] TB itself may significantly reduce the CD4 count, with subsequent recovery after treatment.[23]

TB-related ARDS was not significantly associated with mortality in the present study, in keeping with our previous report.[2] Additionally, we found no association between a P/F ratio <200 mmHg and in-hospital mortality. This finding is in concordance with several studies that have shown that the P/F ratio is not an independent predictor of mortality at the onset of ARDS.[24,25] A plausible explanation may be that the P/F ratio is a highly variable parameter, depending on the fraction of inspired oxygen and ventilator strategy utilised. Standardisation of ventilation strategies may improve its discriminatory power.[25] Early initiation of empirical TB treatment, in view of the high burden of TB

in our country, combined with earlier diagnosis utilising nucleic acid testing, may explain the lack of a significant association between the presence of TB treatment on admission and mortality in our cohort.

Study strengths and limitations

Our study has certain strengths. Unlike most current TB studies, which are retrospective, we prospectively enrolled a large number of patients in a single centre over a relatively short period of time, ensuring a consistent standard of care and limiting the impact of changes in critical care practice that occur over years. The simplicity and lack of a complex weighted scoring system of the revised 4-point score may lend itself to its use at all levels of care to develop strategies to improve outcome in the ICU. Future prospective research is needed to properly validate the revised 4-point score.

Our study may have some limitations. Resource constraints may have led to a selection bias towards patients with perceived better outcomes being preferentially admitted to the ICU. Delays in admission to the ICU, from the emergency department and other hospitals, may have resulted in delays in appropriate diagnosis and treatment and contributed to deteriorating clinical parameters.

Conclusions

The 6-point severity-of-illness score identified critically ill patients at increased risk of dying of TB. Moreover, we were able to derive and retrospectively validate a simplified 4-point score with superior predictive power, which may be particularly useful in a high-incidence and resource-limited setting.

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