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Hematological profiles and mortality risk in critically ill and drug-resistant tuberculosis patients: insights from a longitudinal study

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Abstract

Background While tuberculosis (TB) remains a significant global health threat, data on mortality in critically ill TB patients and those with drug-resistant TB (DR-TB) is limited. This study explores hematological profiles of critically ill TB patients and those with DR-TB, investigating associations with in-hospital and short-term mortality.

Methods A longitudinal study of 269 patients with confirmed TB evaluated baseline blood cell counts and indices from medical records. We calculated in-hospital mortality and short-term prognosis, followed by analysis to identify predictors of mortality using hematological parameters.

Results One-third of TB patients were critically ill (35.32%) and required intensive care unit (ICU) admission, while 14.5% had DR-TB, more common in females and smokers. Critically ill patients were older and tended to be non-smokers. DR-TB patients exhibited elevated lymphocyte and monocyte counts but lower neutrophil count and blood indices. Critically ill DS-TB patients had lower hemoglobin (Hb) and platelet (PLT) but higher total leucocytes count (TLC) and mean platelet volume (MPV). In-hospital mortality rate was 29.37%, significantly higher in critically ill DS-TB patients (74.74%). In-hospital mortality was 14-fold higher in critically ill DS-TB patients, 11-fold higher in stable DR-TB patients, and 6-fold higher in patients with comorbidities. Decreased Hb, monocyte level, and neutrophil to lymphocyte ratio (NLR) were significantly associated with in-hospital mortality. Predictors of short-term mortality included critical illness and comorbidities. However, the effect of DR-TB on short-term mortality disappeared. Decreasing Hb and TLC, especially neutrophils were significantly linked to short-term mortality. The utility of Hb in discriminating in-hospital and short-term mortality was very good, with AUC values of 78% and 79%, respectively. Cutoff values of less than 10 mg/dL and 9.75 mg/dL showed sensitivity ranging from 71 to 80% and specificity ranging from 75 to 80%, respectively.

Conclusion This study provides valuable insights into patients with DR-TB and DS-TB with critically illness. We observed elevated lymphocyte and monocyte counts in DR-TB patients, as well as significant alterations in blood indices in critically ill patients. Importantly, the in-hospital mortality was notably higher in critically ill DS-TB patients, highlighting the importance of early recognition and aggressive management in this subgroup. Specifically, certain blood parameters such as hemoglobin, monocytes, neutrophils, and the NLR were associated with an increased

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risk of both in-hospital and short-term mortality. Furthermore, our findings underscore the prognostic significance of hematological parameters, particularly in resource-limited settings.

Keywords Critically ill TB patients, Drug-resistant tuberculosis, Blood cells, Blood indices, Mortality

Introduction

Tuberculosis (TB) remains a significant global health threat, particularly due to the rise of drug-resistant strains, especially Multidrug-resistant TB (MDR-TB) which presents formidable challenges [1, 2]. These strains complicate treatment, increase mortality risk, and disproportionately affect vulnerable populations like those with HIV [3]. Millions of cases occur annually, with India, Russia, and Pakistan leading the burden [4]. Risk factors include demographics, comorbidities like diabetes and HIV, and lifestyle factors like smoking and alcohol abuse [5]. Common symptoms are cough, fever, and weight loss [6]. In Egypt, TB ranks as the third most concerning communicable disease [7]. MDR-TB specifically refers to resistance against the key antibiotics Isoniazid and Rifampicin [8].

While uncommon in ICUs, TB patients may require admission due to respiratory or multiorgan failure, neurological complications, or decreased consciousness. Despite being treatable, these patients face high mortality (average 52.9%) and organ dysfunction, demanding a multifaceted approach. Scoring systems underestimate this mortality risk, highlighting the critical need for earlier TB detection and treatment initiation to improve outcomes. Regrettably, low-income countries with high TB burden face even higher mortality. Treatment presents its own challenges, including drug toxicity and potential absorption issues in critically ill patients, necessitating careful monitoring and potentially alternative regimens. Corticosteroids can be helpful in specific TB cases, but paradoxical reactions must be considered to avoid misinterpreting treatment failure [9, 10].

A complete blood count (CBC) is a standard test performed for all patients, regardless of infection type, that provides valuable information for treatment decisions. In TB, diverse hematological abnormalities are frequently observed. These include low hemoglobin levels (anemia), reduced lymphocyte counts and subsets, elevated neutrophil counts, and fluctuations in monocyte and platelet levels. In some cases, thrombocytosis (high platelet count) may also occur [11, 12]. Anemia is a common finding in TB patients and is associated with a poorer prognosis [13]. Iron deficiency anemia, a frequent type, weakens the immune response by hindering the body's ability to fight off foreign antigens [14]. The correlation between lymphocyte count and TB is a subject of debate. Some researchers report lymphopenia as a prominent feature, especially in severe disease [15], while others note lymphocytosis [16]. Neutrophils and macrophages play a critical role in the initial immune response (innate immunity) against TB by forming granulomas [17]. These white blood cells, along with the release of tumor necrosis factor-alpha (TNF-α), contribute to the destruction of Mycobacterium tuberculosis bacteria [17, 18]. Platelet count can also influence immune function. Chronic inflammation, like that seen in TB, can sometimes lead to a condition called reactive thrombocytosis [19]. CBC, C-reactive protein (CRP), and erythrocyte sedimentation rates (ESRs) are valuable tools for diagnosing, monitoring, and predicting the prognosis of TB patients [20–23]. Some studies suggest that ESR and CRP might be particularly sensitive markers for TB [23].

Blood indices derived from differential blood cell counts offer a simple and cost-effective approach for diagnosing TB and evaluating disease progression, particularly in resource-limited settings. In one Ethiopian study, researchers found that the neutrophil-to-lymphocyte ratio (NLR) and ESR were significantly higher in TB patients. By combining NLR and ESR with specific cut-off values, they achieved 69% accuracy in distinguishing TB from bacterial community-acquired pneumonia [24]. Another recent case–control study assessed the association between impaired immune responses, indicated by high pre-treatment levels of NLR and monocyte-to-lymphocyte ratio (MLR), and delayed sputum conversion in new cases of pulmonary TB. Results showed that high pre-treatment MLR was significantly associated with an increased risk of delayed sputum conversion, highlighting its potential as a predictor of treatment outcomes in TB patients [25]. Additionally, a study examined the utility of NLR in predicting short-term prognosis in TB meningitis (TBM) patients without HIV infection. It found that higher NLR was significantly associated with increased risk of death within 28 days and correlated positively with TBM severity, suggesting its value in assessing short-term prognosis and disease severity in TBM patients [26].

While existing literature explores the role of blood cell counts in diagnosing and predicting TB severity and prognosis, a gap exists. No prior studies have examined the combined impact of DR-TB and critical illness on patients' hematological profiles. This study aims to

address this gap by investigating the hematological profiles of critically ill TB patients and those with DR-TB. We will explore potential associations between these profiles and in-hospital and short-term mortality.

Methods

Patients and study design

A longitudinal study was conducted at Abbassia Chest Hospital, a specialized tertiary hospital for chest diseases and tuberculosis, affiliated with the Egyptian Ministry of Health in Cairo. The study also included patients from the intensive care units (ICUs) within the Department of Chest Disease et al.-Zahraa University Hospital.

From May 2022 to December 2023, this study enrolled all confirmed tuberculosis cases. Confirmation was based on a combination of approaches: direct microscopic examination of sputum smears for acid-fast bacilli, microbiological culture and sensitivity tests for TB bacilli, and molecular diagnosis using GeneXpert methods [27]. Patients with associated genetic blood disease as hemophilia and thalassemia as well as hematological malignancies as leukemia, lymphoma and multiple myeloma were excluded from the study. Patients were then classified into three categories based on: [27] confirmation of drug resistance and [28–30] criteria for critical illness requiring ICU admission. The first group was drug sensitive TB patients (DS-TB), the second group was drug resistant TB (DR-TB), and the third group was critically ill TB patients that admitted in ICU.

Data collection and endpoints

1- Data collection included:

- Basic demographic information as age, sex, smoking status and comorbidities.
- Complete blood counts (CBC) with differential at the time of diagnosis.
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).
- Inflammatory markers: Inflammatory ratios were calculated using specialized formulas within the Excel spreadsheet. These ratios included: Neutrophil-to- Lymphocyte Ratio (NLR) = Neutrophil count/ Lymphocyte count, Neutrophil-to-Monocyte Ratio (NMR) = Neutrophil count/Monocyte count, Monocyte-to-Lymphocyte Ratio (MLR) = Monocyte count /Lymphocyte count, Platelet-to-Lymphocyte Ratio (PLR) = Platelet count/Lymphocyte count, Systemic Immune Response Index (SIRI) = (Neutrophil count x Monocyte count) / Lymphocyte count
- Liver and kidney function test

2- The end point of the study included:

- In-hospital mortality.
- Short term mortality after 90-days of follow up for discharged patients.

Ethics approval, IRB number and consent to participate

This study adhered to the ethical principles outlined in the Helsinki Declaration. Approval was obtained from the ethical committee of Al-Zahraa University Hospital, Faculty of Medicine for Girls, Al-Azhar University (No: 00012239: September 2022). All participants, or their legal guardians when necessary, provided informed consent. This ensured they fully understood the nature and purpose of the research and voluntarily agreed to participate.

Statistical analysis

We collected data in an Excel spreadsheet and analyzed it using SigmaPlot for Windows (version 12.5.0.38). The Shapiro–Wilk test assessed normality, with numerical data presented as mean and standard deviation (normal) or median and interquartile range (non-normal). Categorical data was shown as frequencies and percentages. Comparisons between two numerical groups used either the independent t-test (normal) or Mann–Whitney U test (non-normal), while the Chi-square test compared frequencies. Finally, a multiple logistic regression analysis with stepwise forward selection identified factors associated with both in-hospital and short-term mortality. All tests were two-sided, with a p-value less than 0.05 considered statistically significant.

Results

TB patients

In Table 1, the study included 269 patients with a confirmed diagnosis of TB infection. The median (IQR) age of the participants was 37 (27–55) years, and the majorities were males (71%). Over one-third of the patients were current smokers, with various comorbidities present in 39.03% and 40.89% of the cases, respectively. Chronic chest disease emerged as the most prevalent comorbidity, affecting 26.39% of patients, followed by diabetes mellitus (DM) at 14.87%. Regarding drug sensitivity for the first-line anti-tuberculous drugs, 85.5% of patients exhibited sensitivity, while 39 out of 269 patients (14.5%) had drug-resistant infections. All 39 drug-resistant patients showed resistance to both rifampicin and isoniazid (INH). Additionally, 11 of these patients exhibited resistance to ethambutol, and 15 exhibited resistance to pyrazinamide. Upon assessing the clinical stability of patients, it was observed that one-third of them were critically ill (35.32%) and required ICU admission.

Table 1 Demographic and clinical criteria of TB patients

Factors	Total ($n=269$)	
Age (median, IQR)	37	(27–55)
Sex (n, %)		
Female	78	29
Male	191	71
Smoking status (n, %)		
Smoker	105	39.03
Ex-smoker	42	15.61
Non-smoker	122	45.35
Comorbidity (n, %)		
Total comorbidity	110	40.89
DM	40	14.87
IHD	17	6.32
HTN	20	7.43
CRD	9	3.35
CLD	13	4.83
CCD	71	26.39
Comorbidity No		
One	64	23.79
Two and more	46	17.1
Drug sensitivity type (n, %)		
Sensitive	230	85.5
DR	39	14.5
• R + INH	39	14.5
• R + INH + E	11	4.08
• R + INH + Z	15	5.57
Host- clinical stability (n, %)		
Stable	174	64.68
Critically ill	95	35.32

N number, *IQR* inter quartile range, *DM* diabetes mellitus, *IHD* ischemic heart disease, *HTN* hypertension, *CRD* chronic renal disease, *CLD* chronic liver disease, *CCD* chronic chest disease, *DR* drug resistant, *R* Rifampicin, *INH* Isoniazid, *E* Ethambutol, *Z* Pyrazinamide, the numerical data presented as median and IQR and categorical data as number and percentage

Impact of DR-TB infection on hematological features of patients

The flowchart (Fig. 1) illustrated the classification of the study. About 39 were identified as having drug-resistant infections (DR-TB). Table 2 reveals that patients with DR-TB infection were more frequently female (46.15%) compared to 22.22% in the drug sensitive and clinically stable (DS-TB) group ($p=0.003$) and were current smokers at a higher rate (51.2% vs. 32.59% in the sensitive group, $p=0.001$).

The hematological features of patients with DR-TB infection showed a significant elevation in lymphocyte and monocyte counts ($p=0.002$ and <0.001, respectively). However, the neutrophil count was significantly lower ($p=0.01$). Regarding blood indices, NLR, NMR, and PLR were significantly lower, while MLR was significantly higher ($p<0.05$ for all). Additionally, liver enzyme levels were significantly elevated in DR-TB patients ($p<0.05$).

Hematological features of patients with critically ill TB disease

In the provided flowchart (Fig. 1), it is observed that the total number of critically ill patients was 95, all of whom were sensitive to the first anti-tuberculous class (DS-TB). Table 3 highlighted the characteristics of critically ill patients, revealing that they were significantly older ($p=0.03$) and tended to be non-smokers (56.84%, $p=0.001$). The prevalence of comorbidities was higher than in stable patients, regardless of whether the number of comorbidities was one or two and more ($p=0.001$).

The hematological features of critically ill patients with DS-TB infection indicated significantly lower levels of Hb and PLT, $p=0.001$. However, the TLC and MPV were significantly higher ($p=0.001$). The differential blood cell

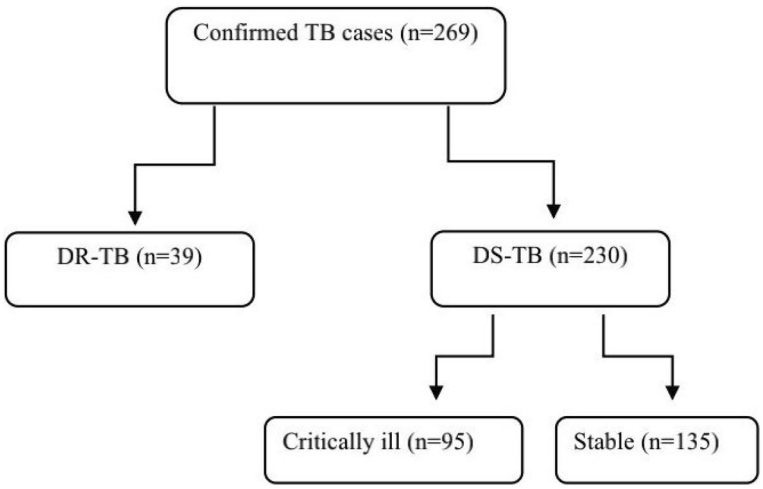

Fig. 1 Flow chart of the TB patients

Table 2 Characteristics of patients with drug resistant TB infection

Factors	DR ($n=39$)		Sensitive ($n=135$)		p
Age (median, IQR)	27	(18–35)	26	(18–34)	0.57
Sex (n, %)					
Female	18	46.15	30	22.22	**0.003**[*]
Male	21	53.85	105	77.78	
Smoking status (n, %)					
Smoker	20	51.28	44	32.59	**0.001**[*]
Ex-smoker	0	0	42	31.11	
Non-smoker	19	48.72	49	36.3	
Comorbidity (n, %)					
Total comorbidity	9	23.08	24	17.78	0.47
DM	7	17.95	16	11.85	0.32
IHD	1	2.56	7	5.19	0.49
HTN	1	2.56	8	5.93	0.36
CLD	2	5.13	0	0	**0.04**
Comorbidity No					
One	7	17.95	18	13.33	0.47
Two and more	2	5.13	6	4.44	
Blood investigation					
Hb (median, IQR)	11.2	(10–13.2)	11.8	(10.5–13)	0.93
TLC (median, IQR)	10.7	(7.8–10.7)	10.3	(7.3–10.3)	0.51
PLT (median, IQR)	343	(255–458)	332	(268–332)	0.33
MPV (median, IQR)	8	(7.5–8.6)	8.4	(7.5–8.9)	0.31
Neutrophil (median, IQR)	3.96	(2.5–5.8)	5	(3.4–6.9)	**0.01**[†]
Lymphocyte (median, IQR)	4.28	(3–5.1)	2.8	(1.8–4.6)	**0.002**[†]
Monocyte (median, IQR)	0.74	(0.5–1.2)	0.43	(0.2–0.7)	**< 0.001**[†]
N:L-Ratio (median, IQR)	1.25	(0.7–1.3)	1.67	(0.9–3.1)	**< 0.001**[†]
N:M-ratio (median, IQR)	5	(3.3–5)	10.3	6.7–20.8)	**< 0.001**[†]
M:L-Ratio (median, IQR)	0.25	(0.2–0.3)	0.12	(0.1–0.2)	**0.003**[†]
P:L-Ratio (median, IQR)	87.4	(65–135)	113.7	(71–194)	**0.02**[†]
SIRI (median, IQR)	0.82	(0.4–1.4)	0.65	(0.3–1.2)	0.31
ESR-1 h (median, IQR)	43	(24–77)	44	(19–70)	0.91
ESR-2 h (median, IQR)	95	(65–135)	90	(66–108)	0.32
AST (median, IQR)	19	(15–26)	12	(11–13)	**< 0.001**[†]
ALT (median, IQR)	18	(13–24)	13	(10–16)	**0.003**[†]
Urea (median, IQR)	23	(19–34)	22	(17–30)	0.21
Creatinine (median, IQR)	0.7	(0.6–0.9)	0.6	(0.5–0.8)	0.14

N number, *IQR* inter quartile range, *DM* diabetes mellitus, *IHD* ischemic heart disease, *HTN* hypertension, *CRD* chronic renal disease, *CLD* chronic liver disease, *CCD* chronic chest disease, *DR* drug resistant, *Hb* hemoglobin, *TLC* total leukocyte count, *PLT* platelets, *MPV* mean platelet volume, *N:L-ratio* neutrophil to lymphocyte ratio, *N:M-ratio* neutrophil to monocyte ratio, *M:L-ratio* monocyte to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, the numerical data presented as median and IQR and categorical data as number and percentage

[†] Mann Whitney test

[*] Chi square test, $p<0.05$ considered significant

Table 3 Characteristics of critically ill patients with drug sensitive TB infection

Factors	Sensitive TB-Infection				p
	Critically ill ($n=95$)		Stable ($n=135$)		
Age (median, IQR)	42	(28–59)	26	(18–34)	**0.03**[†]
Sex (n, %)					
Female	30	31.58	30	22.22	0.11
Male	65	68.42	105	77.78	
Smoking status (n, %)					
Smoker	41	43.16	44	32.59	**0.001**[*]
Ex-smoker	0	0	42	31.11	
Non-smoker	54	56.84	49	36.3	
Comorbidity (n, %)					
Total comorbidity	77	81.05	24	17.78	**0.001**[*]
DM	17	17.89	16	11.85	0.19
IHD	9	9.47	7	5.19	0.21
HTN	11	11.58	8	5.93	0.12
CRD	9	9.47	0	0	**0.001**[*]
CLD	11	11.58	0	0	**0.001**[*]
CCD	71	74.74	0	0	**0.001**[*]
Comorbidity No					
One	39	41.05	18	13.33	**0.001**[*]
Two and more	38	40	6	4.44	
Blood investigation					
Hb (median, IQR)	8.9	(7.5–11.1)	11.8	(10.5–13)	**0.001**[†]
TLC (median, IQR)	11	(7.7–15.4	10.3	(7.3–10.3)	0.13
PLT (median, IQR)	190	(120–321)	332	(268–332)	**0.001**[†]
MPV (median, IQR)	9.1	(8.3–9.8)	8.4	(7.5–8.9)	**0.001**[†]
Neutrophil (median, IQR)	0.78	(0.5–4.6)	5	(3.4–6.9)	**0.001**[†]
Lymphocyte (median, IQR)	4.55	(3.2–6)	2.8	(1.8–4.6)	**0.001**[†]
Monocyte (median, IQR)	2.81	(1.4–4.4)	0.428	(0.2–0.7)	**0.001**[†]
N:L-Ratio (median, IQR)	0.12	(0.1–1.3)	1.667	(0.9–3.1)	**0.001**[†]
N:M-ratio (median, IQR)	0.31	(0.2–4)	10.3	(6.7–20.8)	**0.001**[†]
M:L-Ratio (median, IQR)	0.8	(0.3–0.9)	0.12	(0.1–0.2)	**0.001**[†]
PLR (median, IQR)	45	(22.4–88.5)	113.7	(71–194)	**0.001**[†]
SIRI (median, IQR)	0.62	(0.4–1.5)	0.649	(0.3–1.2)	0.36
ESR-1 (median, IQR)	69	(45–79)	44	(19–70)	**0.001**[†]
ESR-2 (median, IQR)	113	(100–130)	90	(66–108)	**0.001**[†]
AST (median, IQR)	45	(30–79)	12	(11–13)	**0.001**[†]
ALT (median, IQR)	31	(20–55)	13	(10–16)	**0.001**[†]
Urea (median, IQR)	40	(25–60)	22	(17–30)	**0.001**[†]
Creatinine (median, IQR)	1	(0.7–1.5)	0.6	(0.5–0.8)	**0.001**[†]

N number, *IQR* inter quartile range, *DM* diabetes mellitus, *IHD* ischemic heart disease, *HTN* hypertension, *CRD* chronic renal disease, *CLD* chronic liver disease, *CCD* chronic chest disease, *DR* drug resistant, *Hb* hemoglobin, *TLC* total leukocyte count, *PLT* platelets, *MPV* mean platelet volume, *N:L-ratio* neutrophil to lymphocyte ratio, *N:M-ratio* neutrophil to monocyte ratio, *M:L-ratio* monocyte to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, the numerical data presented as median and IQR and categorical data as number and percentage

[†] Mann Whitney test

[*] Chi square test, $p<0.05$ considered significant

count revealed a significant elevation in lymphocytes and monocytes and a decrease in neutrophilis, $p=0.001$. Blood indices, including NLR, NMR, and PLR, were significantly lower, while MLR was significantly higher, $p=0.001$. Furthermore, liver enzymes (AST and ALT) and kidney function markers (urea and creatinine) were significantly elevated in addition to ESR in critically ill DS-TB patients than stable one, $p=0.001$.

Hospital stay, in-hospital mortality, and short-term outcomes in TB patients

The median length of stay (LOS) in the hospital for all TB patients was 6 days and IQR about (5–7 days). The DR-TB group reported the longest period, with a median LOS of 25 days (IQR: 23–27), while both stable and critically ill patients in the DS-TB groups had more modest durations, with median LOS of 6 days and ranges of 5–6 and 3–8 days, respectively (Supplementary Table 1).

The in-hospital mortality rate among TB patients was 29.37%; 79 out of 269 cases. A significantly higher mortality rate was observed in critically ill patients with DS-TB infection, with 71 out of 95 cases (74.74%). In contrast, one patient died in the stable DS-TB group, and seven patients died in the stable DR-TB group (Supplementary Table 1).

Examining short-term mortality (within 90 days after hospital discharge), it was observed that, during the follow-up period, 10 patients died. The majority of these deaths were associated with the critically ill DS-TB group, accounting for 7 out of 10 deaths. Only one patient from the stable DS-TB group and two patients from the DR-TB group died during this period (Supplementary Table 1).

Predictors of in-hospital and short-term mortality

In Table 4, the likelihood of in-hospital mortality in TB patients increased 14-fold in critically ill patients, even with DS-TB infection, 11-fold in patients with DR-TB infection, even if they were stable, and 6-fold with associated comorbidity (OR = 13.76, 10.57, and 5.95, respectively; $p=0.001$ for all). Additionally, when considering hematological parameters, we observed that a decrease in Hb level, monocyte level, and NLR were significantly associated with in-hospital mortality (OR = 0.8, 0.74, and 0.42, respectively; $p=0.02$, 0.02, and 0.04, respectively).

Table 4 Predictors of in-hospital mortality of TB patients

Factors	CE	OR	95% CI	P^*
Hb	-0.23	0.80	(0.6579,0.9693)	**0.02**
Monocyte	-0.31	0.74	(0.5646,0.9599)	**0.02**
NLR	-0.88	0.42	(0.1495,1.1611)	**0.04**
PLR	0.001	1.00	(0.9939,1.0015)	0.30
Comorbidity (Yes)	1.78	5.95	(2.0572,17.1926)	**0.001**
Critically ill (Yes)	4.93	13.76	(11.4548,15.2867)	**0.001**
DR-TB (Yes)	3.02	10.56	(2.2844,18.0954)	**0.001**

CE coefficient, *OR* odd ratio, *CI* confidence interval, *Hb* hemoglobin, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *DR-TB* drug resistant TB infection

* the test of significant: multiple logistic regression analysis with stepwise forward selection, $p<0.05$ considered significant, the sign before coefficient denoting the direction of relationship

The utility of Hb, NLR, and monocyte count in discriminating patients with in-hospital mortality was very good, with AUC values of 78%, 79%, and 85%, respectively, $p<0.001$ (Fig. 2). Additionally, the sensitivity and specificity of the cutoff value for Hb less than 10 mg/dL were 71% and 75%, respectively. The cutoff value for NLR less than 0.23 showed a sensitivity and specificity of 61% and 94%, respectively, while the cutoff value for monocytes greater than 1.08 had a sensitivity of 82% and a specificity of 83% (Table 5).

Furthermore, Table 6 presents the predictors of short-term mortality (90-day follow-up). Critically ill patients still had a three-fold increased likelihood of short-term mortality, and the presence of associated comorbidity increased the likelihood of mortality two-fold (OR = 2.99 and 2.17, respectively; $p=0.03$ and 0.04, respectively). However, unlike in-hospital mortality, the effect of DR-TB infection on short-term mortality disappeared ($p=0.13$).

Moreover, when considering hematological parameters, decreasing Hb had the same effect as in-hospital mortality, increasing the likelihood of short-term mortality. Conversely, decreasing TLC, especially neutrophilis, was more significantly linked to short-term mortality but not in-hospital mortality (OR = 0.65, 0.75, and 0.45, respectively; $p=0.03$, 0.01, and 0.04, respectively).

The utility of Hb, TLC, and neutrophil count in discriminating patients with short-term mortality was very good and excellent, with AUC values of 79%, 70%, and 91%, respectively, $p<0.001$, 0.01 and <0.001, respectively (Fig. 3). Additionally, the sensitivity and specificity of the cutoff value for Hb less than 9.75 mg/dL were 80% and 83%, respectively. The cutoff value for TLC less than 8.45 showed a sensitivity and specificity of 70% and 71%, respectively, while the cutoff value for neutrophil less than 1.59 had a sensitivity of 70% and a specificity of 92% (Table 7).

Discussion

While the global burden of MDR-TB showed concerning increases from 1990 to 1999, especially in low-income areas, recent years have seen encouraging declines. However, MDR-TB remains a significant challenge requiring effective control strategies [31]. Middle Eastern countries face unique challenges in controlling TB due to

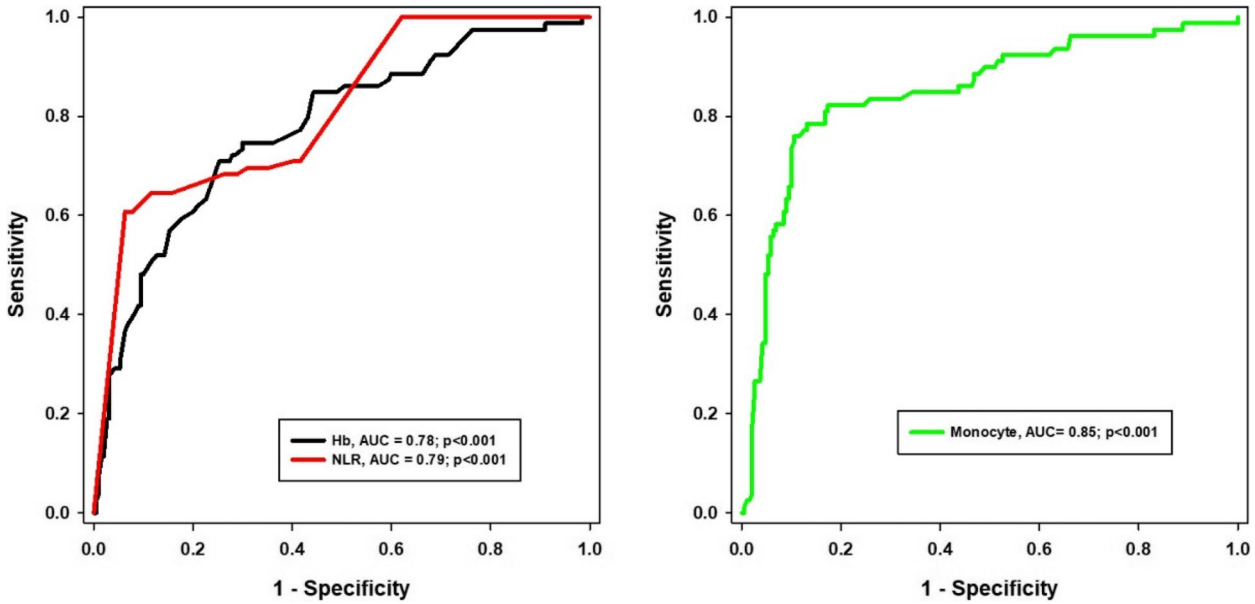

Fig. 2 ROC curve of Hb, Monocyte and NLR for in-hospital mortality. AUC: area under curve, Hb: hemoglobin, TLC: Total leukocytic count, $p < 0.05$ considered significant

Table 5 Utility of Hb, monocyte and NLR in detecting in-hospital mortality

Factors	Cutoff	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV
HB	< 10.05	71%	0.5958 to 0.8057	75%	0.6794 to 0.8075	74%	72%
NLR	< 0.23	61%	0.4913 to 0.7156	94%	0.8923 to 0.9669	91%	70%
Monocyte	> 1.08	82%	0.7206 to 0.8996	83%	0.7648 to 0.8773	83%	82%

CI confidence interval, *Hb* hemoglobin, *PPV* positive predictive value, *NPV* negative predictive value, *NLR* neutrophil to lymphocyte ratio

Table 6 Predictors of short-term mortality (90-days follow up)

Factors	CE	OR	95% CI	*P**
Hb	-0.42	0.65	(0.4163,1.0286)	**0.03**
TLC	-0.29	0.75	(0.5691,0.9875)	**0.01**
Neutrophil	-0.80	0.45	(0.1684,1.1942)	**0.04**
F-Sex	1.91	6.73	(0.7543,26.0688)	**0.04**
Comorbidity (Yes)	2.16	8.68	(0.9248,81.4347)	**0.04**
Critically ill (Yes)	2.99	19.96	(1.0550,377.7089)	**0.03**
DR-TB (Yes)	2.37	1.70	(0.4480,5.8172)	0.13

CE coefficient, *OR* odd ratio, *CI* confidence interval, *Hb* hemoglobin, *TLC* total leucocytes count, *DR-TB* drug resistant TB infection

* the test of significant: multiple logistic regression analysis with stepwise forward selection, $p < 0.05$ considered significant, the sign before coefficient denoting the direction of relationship

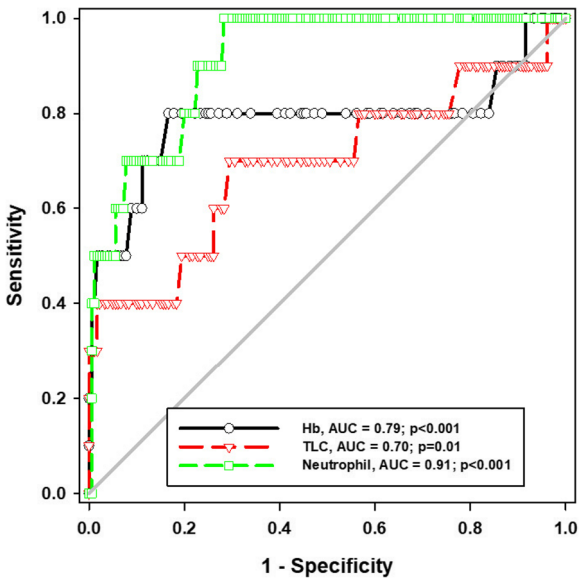

Fig. 3 ROC curve of Hb, TLC and neutrophil for short-term mortality

factors like war and refugee populations [32]. Egypt, with an estimated 13,000 TB cases annually, exemplifies these difficulties [33]. Despite high treatment success rates for regular TB, MDR-TB cases (both new and previously treated) have a much lower success rate; around

Table 7 Utility of Hb, TLC and neutrophil in detecting short-term mortality

Factors	Cutoff	Sensitivity	95% CI	Specificity	95% CI	PV +	PV -
HB	< 9.75	80%	0.4439 to 0.9748	83%	0.7707 to 0.8846	51%	95%
TLC	< 8.45	70%	0.3475 to 0.9333	71%	0.6332 to 0.7710	34%	91%
Neutrophil	< 1.59	70%	0.3475 to 0.9333	92%	0.8729 to 0.9568	66%	93%

CI confidence interval, *Hb* hemoglobin, *PPV* positive predictive value, *NPV* negative predictive value, *TLC* Total leukocytic count

63% [34]. Studies in Cairo report an MDR-TB prevalence of around 16%, highlighting the seriousness of the issue [34–36]. Supporting this concern, in this study 14.5% of our cohort had DR-TB infection, and they were clinically stable. However, in Chinese study [37], among 166 patients, 73.5% showed resistance to first-line drugs, with 58.4% being MDR-TB. The prevalence of DR-TB varies due to several factors. Varied study populations, such as our inclusive approach versus the Chinese study's focus on patients with multiple treatment episodes, influence prevalence by affecting exposure to drug-resistant strains. Sampling bias may also play a role, with our study capturing a more diverse sample, potentially leading to different findings. Geographic disparities in TB epidemiology, treatment protocols, and access to diagnostic tools contribute, with China's challenges in TB control and high drug resistance rates in some regions impacting prevalence. Differences in diagnostic methods, like the Chinese study's use of potentially more sensitive techniques, also affect reported prevalence. Nevertheless, it was observed that one-third of our DS-TB cohort (35.32%) were critically ill and required admission to ICU. This finding aligns with a South African study where approximately 83 TB patients required mechanical ventilation in an ICU setting over a one-and-a-half-year period [38]. The current study revealed interesting disparities in patient characteristics between DR-TB and DS-TB patients. Females and current smokers were more prevalent in the DR-TB group. Conversely, the DS-TB group, particularly critically ill patients, skewed older and tended to be non-smokers. Additionally, the prevalence of comorbidities was significantly higher in the DS-TB group, regardless of the number. These findings contrast with an Indonesian study [39] where males with pre-existing diabetes mellitus (DM) dominated the DR-TB subgroup. Age and gender did not differ significantly between previously treated and newly diagnosed cases in that study. Furthermore, our results diverge from another recent study [40] which reported no difference in gender or smoking history between DR-TB and DS-TB patients. However, both our study and *Varol* et al. [40], concurred on the higher prevalence of comorbidities in TB patients, irrespective of drug resistance, highlighting their importance in TB management. Moreover, while some consistencies exist, like the increased prevalence of comorbidities, our findings emphasize the significant variability in TB epidemiology across diverse populations and settings.

In contrast to the expected dominance of neutrophils in bacterial infections, DR-TB patients exhibited a unique immune response. We observed significantly decreased neutrophils alongside elevated lymphocyte and monocyte counts. This suggests a potential shift towards adaptive immunity, which mediated by lymphocytes, and antigen presentation by monocytes in DR-TB, possibly reflecting a chronic or dysregulated immune response compared to the typical neutrophil-driven response seen in TB. Neutrophils, acting as frontline defenders, initially engulf and eliminate Mycobacterium tuberculosis, but their prolonged response can lead to inflammation and tissue damage [41–43]. Conversely, monocytes/macrophages play a crucial role in removing apoptotic/necrotic neutrophils, thereby regulating inflammation and promoting tissue repair [44–47]. This neutrophil-macrophage cooperation underscores the importance of a balanced immune response in combating TB [41]. Moreover, our results align with previous studies indicating altered lymphocyte subsets in TB patients, suggesting their potential utility as treatment monitoring indicators [48, 49]. However, further research is warranted to explore additional immune function markers for improved TB diagnosis and management.

Furthermore, this cellular trend was reflected in blood indices, hence we found that NLR, NMR, and PLR being significantly lower, while MLR was significantly higher in DR-TB. While some aspects of these findings align with previous research [50–53], such as elevated lymphocytes and monocytes in DR-TB, and lower NLR, NMR, and PLR suggesting a dampened inflammatory response, there are also some discrepancies. Unlike some studies [52, 53] reporting neutropenia in TB patients, DR-TB here exhibited a decrease, but not complete absence of neutrophils. However, in comparing TB patients with healthy individuals, a Nigerian study found pulmonary TB patients have lower red blood cell counts and higher inflammation markers [54]. In the same line, another study compared blood parameters in 70 tuberculosis patients and 70 healthy controls [55], and found that patients with TB had lower red blood cell counts

(hemoglobin, PCV) and lower blood indices. Conversely, they had higher white blood cell counts (WBC, neutrophils), platelet counts, and ESR compared to healthy individuals. The aforementioned findings align with our suggestion that measuring these blood parameters can offer a straightforward and cost-effective method for diagnosing and monitoring TB, especially in resource-limited settings. A recent meta-analysis supported that the newly diagnosed TB patients frequently have anemia alongside with elevated ESR and sometimes TLC, which make awareness of these common blood abnormalities valuable for physician in both diagnosing TB and managing the course of the disease [56].

While most studies focus on pulmonary TB patients in the ICU, common reasons for admission include acute respiratory failure and the onset of multi-organ failure [9]. High rates of acute respiratory distress syndrome (ARDS) are observed [57], although post mortem studies indicate that tuberculous bronchopneumonia may resemble ARDS [58, 59]. Additionally, neurological deterioration from tuberculosis meningitis (TBM) can necessitate ICU care [5]. To address this knowledge gap, our study investigated a previously unexplored area; the hematological profiles of critically ill TB patients. This is particularly significant because this patient group likely faces higher mortality rates and requires prompt intervention and specialized treatment. As expected, our findings revealed distinct blood cell characteristics in critically ill TB patients compared to those with stable disease. Hemoglobin (Hb) and platelet (PLT) levels were significantly lower, while total leukocyte count (TLC) and mean platelet volume (MPV) were significantly higher. Differential blood cell analysis mirrored these findings, showing a significant increase in lymphocytes and monocytes accompanied by a decrease in neutrophils. Blood indices also followed a similar pattern, with NLR, NMR, and PLR being significantly lower, while MLR was significantly higher. Anemia was prevalent (over 60%) in TB patients at a Brazilian referral center [60], correlating with severe disease forms like meningeal and disseminated TB. The impact of anemia on disease course has been discussed in Shanghai study [61], anemic TB patients showed poorer improvement in lung injury, including cavity closure and fluid resolution, during treatment. They also exhibited higher levels of inflammatory markers like complement 4 (C4) and C-reactive protein (CRP) at treatment onset, with worsening trends in lymphocytes and increasing levels of monocytes and basophils during treatment. These findings suggest that anemia associated inflammatory changes indicating poorer prognosis [60, 61]. Additionally, another study found higher level of platelet distribution width (PDW), mean platelet volume (MPV), and plateletcrit in active TB patients compared to controls [62]. These levels decreased with treatment. Interestingly, these changes weren't simply due to inflammation, as pneumonia patients, which had lower levels. The study suggests these platelet changes might be specific to tuberculosis. A supportive data found that higher PLT count in TB patients interact with immune cells and worsening tissue damage [19].

While only a small percentage (3.4%) of hospitalized TB patients require ICU admission, their prognosis is significantly worse compared to other severe pneumonia cases [63]. This is reflected in the high mortality rate of 60% for critically ill TB patients, compared to 25% for other severe pneumonia patients. These critically ill TB patients are often immunocompromised and have severe disseminated or miliary TB forms [9, 63]. This trend was further highlighted in our study, where we found an overall in-hospital mortality rate of 29.37% (79 out of 269 cases) among TB patients. Notably, the mortality rate was significantly higher in critically ill patients with DS-TB infection, reaching a staggering 74.74% (71 out of 95 cases). In contrast, only one patient died in the stable DS-TB group, and seven died in the stable DR-TB group. Furthermore, the majority of short-term deaths (within 90 days of discharge) were from the critically ill DS-TB group, accounting for 7 out of 10 deaths. Similarly, critically ill patients and those with drug-resistant TB (DR-TB) were 14 and 11 times more likely to die in the hospital, respectively, with comorbidities further increasing the risk by 6-fold. Notably, while DR-TB wasn't a factor in short-term mortality (within 90 days), critically ill patients still faced a tripled risk, and specific blood markers like low hemoglobin and decreased white blood cells (especially neutrophils) emerged as stronger predictors compared to in-hospital mortality. These findings underscore the critical need for early identification and aggressive treatment of critically ill TB patients, while also suggesting potential use of blood markers to assess mortality risk. Comparatively, in Zahedan, Iran, among the TB registered patients, 10.5% died during TB treatment [64]. Factors significantly associated with death included anemia, positive sputum smear, smoking, drug hepatitis, diabetes mellitus, drug use, and history of previous TB treatment. However, it did not specifically mention the impact of critical illness or drug-resistant TB on mortality risk as in our study. Moreover, our study provides additional insights into the role of specific blood markers and short-term mortality risk, which could potentially aid in risk assessment and management strategies for TB patients. Unlike the current study, results from Tanzania found that factors like hospital care and facility-based treatment increased mortality risk [65]. Their findings highlight the need for improved TB referral systems, diagnostics, and earlier treatment initiation, particularly in primary care settings, which were

not addressed in our study. On comparing with older study [66], this study and a previous one identify critical illness as a major risk factor for death in tuberculosis patients; yet, our study delves deeper by providing specific mortality rates and highlighting new risk factors, in addition to showing drug resistance (DR-TB) and comorbidities significantly increase mortality risk, and for short-term deaths specific blood markers like low hemoglobin and neutrophils emerge as stronger predictors than those identified in the previous study. We found that, Hb level was the most important predictor for both in-hospital and short-term mortality, demonstrating very good utility in discriminating these outcomes, with AUC values of 78% and 79%, respectively ($p < 0.001$). The cutoff values of less than 10 mg/dL and 9.75 mg/dL provided sensitivity ranging from 71 to 80% and specificity from 75 to 83%, respectively. While Isanaka et al. found that anemia is highly prevalent among TB patients and significantly increases the risk of mortality [67], their study did not focus on MDR and critically ill subgroups of the TB cohort. Anemia, whether due to iron deficiency or related to an infectious state, is linked to poor prognosis in TB patients. This may be because iron is essential for proper immune function, and its deficiency can impair cell-mediated immunity by reducing T-cell numbers, proliferative response, and macrophage activity, compromising the body's ability to control infections [68]. Iron status also affects the type of immune response by influencing cytokine profiles, with iron deficiency promoting a Th2-dominant response linked to clinical TB and HIV progression [69]. Additionally, anemia of inflammation involves the redistribution of iron, where iron is sequestered in macrophages, potentially aiding M. tuberculosis growth and inhibiting cellular defenses. This iron loading can shift the immune response from Th1 to Th2, reduce macrophage cytotoxic activity, and prevent effective defense mechanisms against TB [70]. High iron levels have also been linked to increased TB risk and mortality, as well as accelerated HIV disease progression, due to enhanced production of reactive oxygen species, increased viral replication, and growth of pathogens [71].

Strength and limitations

Despite offering a comprehensive analysis of laboratory and clinical features in various tuberculosis patient groups, particularly critically ill patients, the study has limitations. Firstly, the single-center design restricts the generalizability of findings to other populations and healthcare settings. Secondly, the moderate sample size necessitates larger studies to solidify some associations, especially regarding short-term mortality. Finally, the focus on specific blood parameters may have overlooked other potential prognostic factors or confounding variables that could influence tuberculosis outcomes.

Conclusion

This longitudinal study revealed critical illness and drug resistance as major contributors to mortality in tuberculosis patients. Notably, critically ill patients with drug-sensitive TB (DS-TB) exhibited the highest mortality rates, both during hospitalization and in the short term. Interestingly, specific blood markers, such as low hemoglobin and decreased white blood cells (particularly neutrophils), proved to be stronger predictors of short-term mortality compared to in-hospital mortality. These findings emphasize the crucial role of early identification and aggressive management for critically ill TB patients, regardless of their drug sensitivity. Additionally, the results underscore the value of incorporating blood parameters into the diagnostic and prognostic evaluation of TB, particularly in settings with limited resources.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
A.Ali, E.M. Moazen, S.B. Elsawy and K.S.M.Salama worked on data collection, A.Ali and Liang Wu analyzed and interpreted the results. All authors were significant contributors to writing up the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval has been obtained from ethical committee office, Al-Zahraa University Hospital, Faculty of Medicine for Girls, Al-Azhar University (No: 00012239: September 2022).

Consent for publication
Not applicable.

Competing interests
The authors have no conflicts of interest.

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