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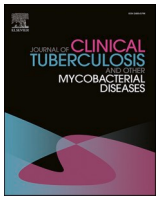

Hematochemical hallmarks as markers of pulmonary TB severity: A multicenter cross-sectional study

Francesco Di Gennaro [a,1], Giacomo Guido [a,1,*], Sergio Cotugno [a,1], Francesco Cavallin [b], Mariantonietta Pisaturo [c], Lorenzo Onorato [c], Federica Zimmerhofer [d], Luca Pipitò [d], Giuseppina De Iaco [a], Giuseppe Bruno [e], Massimo Fasano [f], Agostina Pontarelli [g], Annarita Botta [g], Tiziana Iacovazzi [f], Rossana Lattanzio [a], Virginia Di Bari [h], Gianfranco Panico [i], Raffaella Libertone [h], Caterina Monari [c], Alessia Musto [j], Mariangela Niglio [k], Federica De Gregorio [k], Gaetano Brindicci [a], Carmen Rita Santoro [a], Luigi Ronga [a], Roberta Papagni [a], Elda De Vita [a], Francesco Rosario Paolo Ieva [k], Loredana Alessio [c], Gina Gualano [h], Salvatore Minniti [j], Giovanni Battista Buccoliero [e], Sergio Lo Caputo [k], Sergio Carbonara [i], Antonio Cascio [d], Roberto Parrella [g], Fabrizio Palmieri [h], Nicola Coppola [c], Annalisa Saracino [a]

[a] *Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Jonian Area (DiMePreJ), Bari, Italy*
[b] *Independent Statistician, Solagna, Italy*
[c] *Department of Mental Health and Public Medicine, Section of Infectious Diseases, University of Campania Luigi Vanvitelli, Naples, Via L. Armanni 5, 80131 Naples, Italy*
[d] *Infectious and Tropical Disease Unit - Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G D'Alessandro", University of Palermo 90127 Palermo, Italy*
[e] *Infectious disease, Saint Giuseppe Moscati Hospital, Taranto, Italy*
[f] *UOC Malattie Infettive - ASL BA PO Della Murgia Altamura (BA), Italy*
[g] *Respiratory Infectious Disease Unit, AORN dei Colli, Cotugno Hospital, Naples, Italy*
[h] *Respiratory Infectious Diseases Unit, National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS, Rome, Italy*
[i] *UOC Malattie Infettive, Osp. V. Emanuele II, ASL BT, Bisceglie, BT, Italy*
[j] *UOC Malattie Infettive P.O. Perrino Brindisi, Italy*
[k] *Department of Medical and Surgical Sciences, Infectious Diseases Unit, University of Foggia, Foggia, Italy*

A R T I C L E I N F O

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A B S T R A C T

Background: Identifying accessible and reliable biomarkers for tuberculosis (TB) severity is crucial for improving patient management. This study evaluates hematological findings as potential indicators of TB severity in a large multicenter Italian cohort.

Methods: This retrospective, multicenter, cross-sectional study analyzed hematological parameters (hemoglobin, white blood cells, inflammatory indices, hepatorenal function, albuminuria) in 577 TB patients from 10 Italian centers (2018–2023). Severe TB was defined by at least two criteria: TIMIKA score > 60, sputum conversion time > 21 days, or need for oxygen supplementation. Statistical analyses included receiver operating characteristic curve (AUC) evaluation, calibration curves, and clinical utility.

Results: Of the patients, 30.3 % were classified as severe, 60.2 % as non-severe, and 9.5 % as uncertain. AUC values for predicting severe TB ranged from 0.51 to 0.56 across hematological variables. Anemia and elevated CRP demonstrated sensitivities of 0.71 and 0.74, respectively. Models using continuous or categorical hematological variables achieved AUCs of 0.61 and 0.65, showing poor calibration and limited clinical utility in the 30–60 % threshold range.

* Corresponding author.
[1] Equally contributed.

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Conclusions: Hematological markers, while rapid and cost-effective, demonstrated limited discriminative ability for TB severity. Further studies are required to develop reliable predictive models, integrating additional clinical and molecular data.

1. Introduction

Tuberculosis (TB), with over 10 million new cases annually, remains one of the leading infectious diseases in terms of mortality. Despite significant global efforts, TB continues to challenge public health systems, particularly in both low- and middle-income countries and high income countries [1,2]. Progress in reducing TB-related fatalities has been limited, with a decrease of only 19 % from 2015 to 2022, far below the 75 % reduction target set by the 2025 milestone of the End TB Strategy1. This highlights the need for innovative strategies to complement traditional TB control measures. The World Health Organization (WHO) has relaunched an ambitious goal to "end the global TB epidemic" by 2035, aiming for a 90 % reduction in TB incidence and a 95 % reduction in TB-related deaths [3]. Achieving this objective requires a multifaceted approach that integrates biomedical advances, public health strategies, socioeconomic interventions, and robust research and innovation [3,4]. Emerging diagnostic methods, such as next-generation sequencing and the use of non-respiratory samples (e.g., stool), have demonstrated promise in improving TB diagnosis and resistance testing [5,6]. However, there remains a significant gap in understanding the role of hematochemical and biochemical markers in assessing TB severity and predicting outcomes. Hematochemical abnormalities, including anemia, leukocytosis, thrombocytosis, and hypoalbuminemia, are frequently observed in TB patients [10,11]. These markers, being simple and cost-effective, could serve as valuable tools for stratifying patients by disease severity, especially in resource-limited settings. Furthermore, recent studies suggest that these markers are more prevalent in TB patients than in the disease-free population, but their predictive value for TB severity remains unclear [7–9]. This study aimed to evaluate the potential role of hematological findings as indicators of TB disease severity in a large multicenter Italian cohort. Identifying accessible and reliable hematochemical markers could provide critical tools for early risk stratification and improving clinical outcomes in TB patients.

2. Patients and methods

This retrospective, multicenter, cross-sectional study investigated the ability of some hematological findings in identifying severe TB cases. The study was conducted in the Infectious and Tropical Disease Unit of several hospitals in Middle and Southern Italy. The participating centers were: "Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari" in Bari; "Ospedale Vittorio Emanuele II" in Bisceglie, Bari; "Ospedale della Murgia Fabio Perinei" in Altamura, Bari; "Ospedale Vanvitelli" in Napoli; "Ospedale Cotugno" in Napoli, "Ospedali Riuniti" in Palermo; "Ospedali Riuniti" in Foggia; "INMI Lazzaro Spallanzani" IRCCS in Roma; "Ospedale Santissima Annunziata" in Taranto; "Ospedale Perrino" in Brindisi. The local Ethics Committee approved the study (approval number 7401, 23/03/2024) and waived the requirement for written patient consent due to the retrospective nature and use of anonymized data.

All patients who were diagnosed with TB in the participating centers between 2018 and 2023 were eligible for inclusion in the study. The diagnosis of TB was made according to one of the following criteria: i) microbiological confirmation through microscopy, culture or molecular test; ii) TB-associated histological finding on biopsy; iii) clinical and radiological suspicion without microbiological confirmation.

Severe TB was defined as having at least two of the following conditions: i) TIMIKA score >60, ii) time of sputum conversion >21 days, or iii) need for oxygen supplementation.

All data were extracted from the hospital charts and collected in an anonymized database for the analysis. Data collection included demographics, clinical characteristics, and hematological profile at diagnosis.

All laboratory test results, TIMIKA scores [12], and other clinical variables were collected within the first 24–48 h of hospitalization, except for oxygen supplementation, which was recorded if administered at any point during the hospital stay.

Relevant hematological variables included hemoglobin, white blood count (WBC), percentage of lymphocytes (LYMPH%), neutrophilic percentage (NEUT%), platelet count, glycemia, eGFR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-Reactive Protein (CRP), Gamma-glutamyltransferase (GGT), albumin.

Statistical analysis was carried out using R 4.4 (R Foundation for Statistical Computing, Vienna, Austria) [13]. Numerical data were summarized as median and interquartile range (IQR), while categorical data as absolute and relative frequency (percentage). The hematological variables had missing data and TB severity was labelled uncertain in some cases. We used multiple imputation to address these missing values, and the imputations were based on all variables in the database. The discrimination of severe TB cases was evaluated with the area under the receiver operating characteristic curve (AUC) for each hematological variable. We calculated the sensitivity when fixing specificity at 0.90 and specificity when fixing sensitivity at 0.90 to compare the hematological variables. The analysis also considered clinically relevant categories of the hematological variables, and calculated sensitivity and specificity for such prespecified thresholds. A model including the hematological variables as continuous variables and a model including the hematological variables as clinically relevant categories were also estimated. The discrimination of severe TB cases was evaluated with the AUC for each model, and sensitivity at 0.90 specificity and specificity at 0.90 sensitivity were calculated. The calibration of the models was evaluated with the calibration curves and the clinical utility was assessed by using decision curve analysis to decide which patients should be considered TB severe cases. The statistical significance was set at 5 %.

3. Results

The analysis included all 577 cases (426 males and 151 females; median age 41 years, IQR 26–63) who were diagnosed with pulmonary TB between 2018 and 2023. The assessment of TB severity classified 175 severe TB cases (30.3 %), 347 non-severe TB cases (60.2 %) and 55 TB cases with uncertain TB severity (9.5 %) due to missing information in the key variables for the classification (TIMIKA score, time of sputum conversion, need for oxygen supplementation). Demographics and clinical characteristics, and the hematological profile are summarized in Tables 1-2.

The AUC for the prediction of severe TB was low for all hematological variables (Fig. 1). When the specificity was fixed at 0.90, the sensitivity ranged from 0.09 (platelet count, PCR) to 0.16 (lymph %, glycemia) (Table 3). When the sensitivity was fixed at 0.90, the specificity ranged from 0.07 (glycemia, ALT) to 0.14 (hemoglobin, eGFR) (Table 3).

Table 4 shows the sensibility and specificity for clinically relevant categories of hematological variables predicting severe TB. Anemia and CRP > 5 mg/L were associated with reasonable sensitivity (suggesting few false negative results), but poor specificity (suggesting many false positive results). On the other hand, the categories of most hematological variables showed good specificity (suggesting few false positive

Table 1
Demographics and clinical characteristics. Data summarized as n (%) or median (IQR). [a] Adverse events included: hepatitis (n = 112), gastrointestinal (n = 9), cutaneous (n = 15), neuropathy (n = 7), visual impairment (n = 5), hearing impairment (n = 2), renal failure (n = 6), more than one symptom (n = 10), QT prolongation (n = 7) and generalized malaise (n = 2).

Variables	All patients (n = 577)	Non-severe TB (n = 347)	Severe TB (n = 175)	Uncertain TB severity (n = 55)
Age (years)	41 (26–63)	45 (27–66)	36 (24–51)	48 (25–55)
Males	426 (73.8)	244 (70.3)	139 (79.4)	43 (78.2)
Natives	257 (44.5)	198 (57.1)	38 (21.7)	21 (38.2)
Migrants	320 (55.5)	149 (42.9)	137 (78.3)	34 (61.8)
BMI:				
Underweight	252/537 (46.9)	147/323 (45.5)	90/162 (55.6)	36/52 (29.7)
Normal weigh	255/537 (47.5)	156/323 (48.3)	64/162 (39.5)	79/52 (65.3)
Overweight/obese	30/537 (5.6)	20/323 (6.2)	8/162 (4.9)	6/52 (5.0)
Workers	260 (45.1)	179 (51.6)	57 (32.6)	24 (45.1)
Educational level:				
None	37 (6.4)	22 (6.4)	15 (8.6)	0 (0.0)
Primary school	189 (32.8)	132 (38.0)	47 (26.9)	10 (18.2)
Secondary school	105 (18.2)	66 (19.0)	19 (10.9)	20 (36.4)
University	12 (2.1)	9 (2.6)	1 (0.5)	2 (23.6)
Not declared	234 (40.5)	118 (34.0)	93 (53.1)	23 (41.8)
Smoking habits	147 (25.5)	80 (23.1)	51 (29.1)	16 (29.1)
Alcohol drinking	47 (8.1)	19 (5.5)	24 (13.7)	4 (7.3)
Diabetes	81 (14.0)	44 (12.7)	32 (18.3)	5 (9.1)
Hypertension	79 (13.7)	51 (14.7)	21 (12.0)	7 (12.7)
COPD/bronchiectasis	44 (7.7)	34 (9.8)	8 (4.6)	2 (3.6)
Chronic renal disease	24 (4.2)	14 84.0)	7 (4.0)	3 (5.5)
Liver disease	26 (4.5)	19 (5.5)	5 (2.9)	2 (3.6)
PLHIV	6 (1.0)	3 (0.9)	3 (1.7)	0 (0.0)
Cancer	9 (1.6)	9 (2.6)	0 (0.0)	0 (0.0)
Previous TB	15 (2.6)	10 (2.9)	5 (2.9)	0 (0.0)
Cough	299 (51.8)	184 (53.0)	87 (49.7)	28 (50.9)
Chronic cough (≥8 weeks)	183 (31.7)	133 (38.3)	32 (18.3)	18 (32.7)
Fever	128 (22.2)	54 (15.6)	52 (29.7)	22 (40.0)
Weight loss	121 (21.0)	60 (17.3)	46 (26.3)	15 (27.3)
Night sweats	57 (9.9)	39 (11.2)	10 (5.7)	8 (14.5)
Chest pain	99 (17.2)	63 (18.2)	29 (16.6)	7 (12.7)
Dyspnea	42 (7.3)	16 (4.6)	22 (12.6)	4 (7.3)
Hemoptysis	52 (9.0)	27 (7.8)	20 (11.4)	5 (9.1)
Diagnosis:				
Presumptive TB	108 (18.7)	65 (18.7)	28 (16.0)	15 (27.3)
Confirmed TB	463 (80.3)	277 (79.8)	146 (83.4)	40 (72.3)
Histological	6 (1.0)	5 (1.5)	1 (0.6)	0 (0.0)
Adverse events [a]	173 (30.0)	108 (31.19	56 (32.0)	9 (16.4)

results) but poor sensitivity (suggesting many false negative results).

The model including the hematological variables as continuous variables had an AUC of 0.61 (95 % confidence interval 0.56 to 0.66), a sensitivity of 0.19 (95 % confidence interval 0.12 to 0.26) when the specificity was fixed at 0.90, and a specificity of 0.20 (95 % confidence interval 0.15 to 0.24) when the sensitivity was fixed at 0.90. The model including the hematological variables as clinically relevant categories had an AUC of 0.65 (95 % confidence interval 0.62 to 0.69), a sensitivity of 0.24 (95 % confidence interval 0.15 to 0.33) when the specificity was fixed at 0.90, and a specificity of 0.14 (95 % confidence interval 0.00 to 0.31) when the sensitivity was fixed at 0.90.

In both models, lower risk estimates were overestimated and higher risk estimates were underestimated (Fig. 2A). Both models showed some clinical utility to select severe TB cases in the 30–60 % threshold range, with the model including categorical hematological variables providing the largest benefit (Fig. 2B).

Overall, mortality rate was 5/175 (2.8 %) in severe TB patients, 7/347 (2.0 %) in non-severe TB patients, and 2/55 (3.6 %) in those with uncertain TB severity. Complete treatment was achieved in 89/175 (33.7 %) severe TB patients, 239/347 (68.9 %) non-severe TB patients, and 30/55 (54.5 %) patients with uncertain TB severity. Full information about prognosis is reported in Supplementary Table S1.

4. Discussion

The focus of this study was to identify potential predictors of TB severity among hematological markers routinely used in standard care. Our findings revealed that markers such as anemia, leukocytosis, thrombocytosis, lymphopenia, and hypoalbuminemia were prevalent in patients with severe TB. However, these markers demonstrated limited discriminative ability. Among them, only anemia and elevated CRP levels showed reasonable sensitivity, suggesting a reduced likelihood of false negatives, but their poor specificity resulted in a higher rate of false positives.

A potential explanation for these findings is the chronic inflammation caused by *M. tuberculosis*, a mechanism well-documented in other infectious diseases [14,15]. Chronic inflammation triggers the activation of cytokines, such as interleukin-6 and tumor necrosis factor-alpha, which contribute to anemia through hepcidin-mediated iron sequestration and inhibition of erythropoiesis [16]. In TB, anemia of chronic disease may be exacerbated by malabsorption, micronutrient deficiencies (e.g., folate and vitamin B12), and direct iron sequestration by *M. tuberculosis* [17,18]. Additionally, hemoptysis and malnutrition may further aggravate anemia in affected patients [19].

CRP, a widely recognized marker of systemic inflammation, has been increasingly studied as a prognostic factor in TB [20,21]. Elevated CRP levels have been linked to more extensive lung involvement, delayed sputum culture conversion, and poorer clinical outcomes [18,19]. In our cohort, CRP levels > 5 mg/L demonstrated reasonable sensitivity, reflecting the intensity of the inflammatory response to *M. tuberculosis*. However, CRP's low specificity limits its utility as a standalone marker, as it can be elevated in various other inflammatory conditions.

Several studies have evaluated the role of hematological markers in predicting TB severity. For instance, anemia and hypoalbuminemia have

Table 2
Hematological profile: numerical values and relevant categories. Data summarized as n (%) or median (IQR). Data not available in [a]10, [b]45, [c]104, [d]85, [e]43, [f]112, [g]91, [h]52, [i]56, [j]55, [k]169, [i]95 patients.

Parameters	All patients (n = 577)	Non-severe TB (n = 347)	Severe TB (n = 175)	Uncertain TB severity (n = 55)
Hemoglobin, g/dL [a]	12.4 (10.9–13.4)	12.4 (10.8–13.4)	12.2 (10.9–13.0)	12.3 (10.9–13.4)
Anemia (hemoglobin < 13 g/dL in males, <12 g/dL in females)	319/567 (56.3)	169/342 (49.4)	121/171 (70.8)	29/54 (53.7)
WBC, x10^3/uL [b]	7620 (5830–10770)	7600 (5700–10100)	8500 (6200–11480)	6765 (5030–8832)
WBC:				
<4 x 10^3/uL	55/532 (10.3)	31/325 (9.5)	16/161 (10.1)	8/48 (16.7)
4–11 x 10^3/uL	358/532 (67.3)	230/325 (70.8)	94/161 (59.1)	34/48 (70.8)
>11 x 10^3/uL	119/532 (22.4)	64/325 (19.7)	49/161 (30.8)	6/48 (12.5)
lymph % [c]	19.0 (13.2–27.6)	19.9 (13.7–28.2)	16.4 (12.1–26.7)	20.0 (11.0–26.1)
neut % [d]	69.0 (57.9–77.6)	68.1 (56.6–76.0)	71.6 (60.4–79.7)	66.8 (59.2 (79.1)
Platelet count, x10^3/uL [e]	308 (209–457)	286 (200–440)	333 (231–475)	307 (211–472)
Platelet count:				
<150 x 10^3/uL	74/534 (13.9)	51/327 (15.6)	16/157 (10.2)	7/50 (14.0)
150–500 x 10^3/uL	358/534 (67.0)	214/327 (65.4)	110/157 (70.1)	34/50 (68.0)
>500 x 10^3/uL	102/534 (19.1)	62/327 (19.0)	31/157 (19.7)	9/50 (18.0)
Glycemia mg/dL [f]	81 (76–91)	82 (76–90)	80 (75–91)	81 (74–93)
Glycemia:	29/465 (6.2)	14/275 (5.1)	9 (8.7)	2/41 (4.9)
<60 mg/dL	403/465 (86.7)	243/275 (88.4)	124/149 (83.2)	36/41 (87.8)
60–125 mg/dL > 125 mg/dL	33/465 (7.1)	18/275 (6.5)	12/149 (8.1)	3/41 (7.3)
eGFR, mL/min [g]	100 (78–122)	99 (76–122)	102 (88–122)	100 (100–118)
eGFR:	157/486 (32.3)	106/295 (35.6)	44/151 (29.2)	8/40 (20.0)
<90 mL/min	199/486 (40.9)	107/295 (36.3)	68/151 (45.0)	24/40 (60.0)
90–120 mL/min > 120 mL/min	130/486 (26.8)	83/295 (28.1)	39/151 (25.8)	8/40 (20.0)
eGFR < 50 mL/min	44/486 (9.0)	32/295 (10.8)	9/151 (6.0)	3/40 (7.5)
AST, U/L [h]	25 (16–34)	25 (15–34)	26 (17–36)	22 (16–30)
AST:	10/537 (1.8)	26 (2.4)	2 (0.0)	2/49 (4.1)
<9 U/L (women) or < 10 U/L (men)	402/537 (74.9)	245/326 (75.2)	119/162 (73.5)	38/49 (77.5)
9–36 U/L (women) or 10–34 U/L (men) > 36 U/L (women) or >34 U/L (men)	125/537 (23.3)	73/326 (22.4)	43/162 (26.5)	9/49 (18.4)
ALT, U/L [i]	23 (15–34)	23 (16–34)	21 (15–34)	19 (14–31)
ALT:	10/521 (1.9)	18 (1.3)	57 (1.9)	3/46 (6.5)
<9 U/L (women and men)	415/521 (79.7)	57/318 (89.8)	3/157 (78.3)	35/46 (76.1)
9–36 U/L (women) or 9–43 U/L (men) > 36 U/L (women) or > 43 U/L (men)	196/521 (18.4)	0.57/318 (17.9)	57 (19.7)	8/46 (17.4)
Gamma GT, U/L [j]	27 (20–61)	24 (20–60)	31 (20–61)	27 (18–74)
Gamma GT:	14/532 (2.6)	0 (3.3)	58 (1.9)	0/44 (0.0)
<7 U/L (women) or < 11 U/L (men)	440/532 (82.7)	270/330 (81.8)		39/44 (88.6)
7–32 U/L (women) or 11–150 U/L (men) > 32 U/L (women) or > 150 U/L (men)	78/532 (14.7)	49/330 (14.9)	131/158 (82.9)	5/125 (11.4)
			0.24/158 (15.2)	
Albumin, g/dL [k]	3.6 (3.0–4.1)	3.7 (3.0–4.2)	3.4 (3.0–4.0)	3.8 (3.2–4.1)
Albumin < 2.5 g/dL	36/408 (8.8)	20/251 (8.0)	14/122 (11.5)	2/35 (5.7)
CRP, mg/L [i]	26 (4–74)	26 (4–74)	27 (5–81)	15 (4–56)
CRP > 5 mg/L	357/482 (74.1)	216/291 (74.2)	108/144 (75.0)	33/47 (70.2)

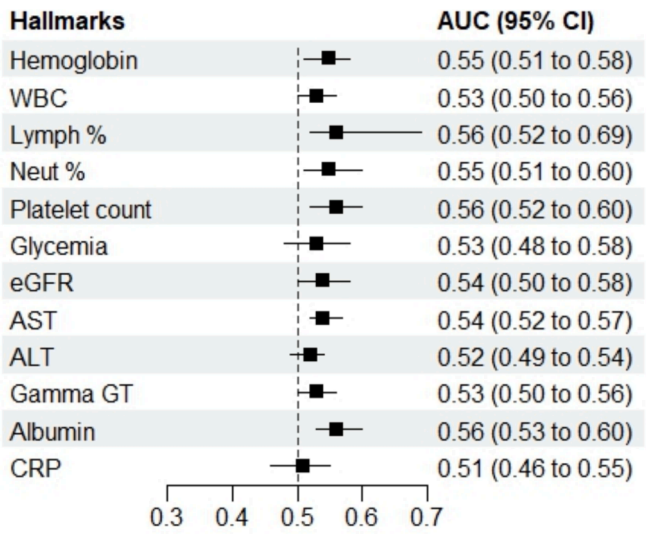

Fig. 1. Summary forest plot with the area under the receiver operating characteristic curve (AUC) with 95 % confidence interval (CI) for each hematological variable.

been identified as independent predictors of mortality in TB patients, while leukocytosis and thrombocytosis are considered indicators of systemic inflammation, particularly in advanced disease stages [20,21]. Despite their potential, integrating these markers into predictive models for TB severity has had limited success [22]. A recent *meta*-analysis highlighted that while markers such as elevated ESR, leukocytosis, and anemia improved sensitivity in identifying TB patients, they lacked sufficient specificity to reliably guide clinical decision-making [23]. These findings align with our observation that combining multiple markers did not significantly enhance the discriminative ability of our risk model.

Severe TB in this study was defined as having at least two of the following conditions: i) TIMIKA score > 60, ii) time of sputum conversion > 21 days, or iii) need for oxygen supplementation. These criteria were selected for their clinical significance and based on a consensus among the authors. A TIMIKA score > 60 reflects extensive disease burden, as it indicates the presence of multiple pulmonary cavities and/or involvement of several lung lobes. Delayed sputum conversion (>21 days) suggests prolonged infectivity and a slower response to therapy, requiring closer monitoring compared to the standard 14-day conversion time in non-severe cases. Finally, the need for oxygen supplementation indicates respiratory failure, a serious complication of advanced TB that is frequently associated with poorer prognoses and increased mortality. Robust evidence underscores the association of these criteria with TB severity. Higher TIMIKA scores have been linked to more extensive pulmonary damage, greater bacterial load, and worse clinical outcomes [24–26]. Similarly, delayed sputum conversion has been consistently associated with severe disease, extended treatment duration, and adverse outcomes [27,28]. Moreover, respiratory insufficiency necessitating oxygen therapy is widely recognized as a hallmark of advanced TB and a strong predictor of mortality risk [29,30]. Together, these criteria provide a clinically relevant framework for identifying patients with severe TB and guiding appropriate management strategies.

The combination of hematological hallmarks in risk models offered limited improvement in predictive performance, providing some clinical

Table 3
Sensitivity (at 90 % specificity) and specificity (at 90% sensitivity) for each hematological variable.

Variables	At 0.90 specificity:		At 0.90 sensitivity:	
	Sensitivity (95 % confidence interval)	Threshold	Specificity (95 % confidence interval)	Threshold
Hemoglobin	0.10 (0.09 to 0.12)	9.7 g/dL	0.14 (0.09 to 0.19)	13.5 g/dL
WBC count	0.10 (0.06 to 0.14)	13,959 x 10^3/uL	0.08 (0.05 to 0.10)	3584 x10^3/uL
Lymph %	0.16 (0.13 to 0.19)	10.2 %	0.12 (0.07 to 0.17)	38.2 %
Neut %	0.13 (0.08 to 0.18)	85.5 %	0.11 (0.07 to 0.14)	47.5 %
Platelet count	0.09 (0.06 to 0.12)	600 x 10^3/ uL	0.13 (0.03 to 0.24)	142 x 10^3/ uL
Glycemia	0.16 (0.05 to 0.27)	67 mg/dL	0.07 (0.04 to 0.10)	122 mg/ dL
eGFR	0.13 (0.11 to 0.15)	134 mL/ min	0.14 (0.07 to 0.22)	54 mL/ min
AST	0.15 (0.10 to 0.20)	53 U/L	0.12 (0.04 to 0.21)	13 U/L
ALT	0.10 (0.06 to 0.15)	11 U/L	0.07 (0.05 to 0.08)	61 U/L
Gamma GT	0.13 (0.09 to 0.17)	93 U/L	0.09 (0.08 to 0.11)	15 U/L
Albumin	0.12 (0.05 to 0.20)	2.5 g/dL	0.13 (0.04 to 0.22)	5.7 g/dL
PCR	0.09 (0.02 to 0.16)	1.7 mg/L	0.10 (0.02 to 0.18)	127 mg/L

Table 4
Sensibility and specificity for clinically relevant categories of hematological variables.

Parameters	Sensitivity (95 % confidence interval)	Specificity (95 % confidence interval)
Anemia (hemoglobin < 13 g/dL in males and <12 g/dL in females	0.71 (0.67 to 0.75)	0.51 (0.49 to 0.53)
WBC > 11 x 10^3/uL	0.29 (0.26 to 0.33)	0.81 (0.80 to 0.82)
Platelet count > 500 x 10^3/uL	0.20 (0.15 to 0.24)	0.80 (0.79 to 0.82)
Glycemia > 125 mg/dL	0.09 (0.04 to 0.14)	0.93 (0.93 to 0.94)
eGFR < 50 mL/min	0.07 (0.03 to 0.11)	0.90 (0.88 to 0.92)
AST > 36 U/L (women) or >4 U/L (men)	0.27 (0.24 to 0.29)	0.78 (0.76 to 0.81)
ALT > 36 U/L (women) or >43 U/L (men)	0.21 (0.17 to 0.26)	0.82 (0.80 to 0.84)
Gamma GT > 32 U/L (women) or >150 U/L (men)	0.15 (0.12 to 0.17)	0.86 (0.85 to 0.87)
Albumin < 2.5 g/dL	0.10 (0.08 to 0.12)	0.92 (0.89 to 0.95)
CRP > 5 mg/L	0.74 (0.68 to 0.79)	0.27 (0.26 to 0.28)

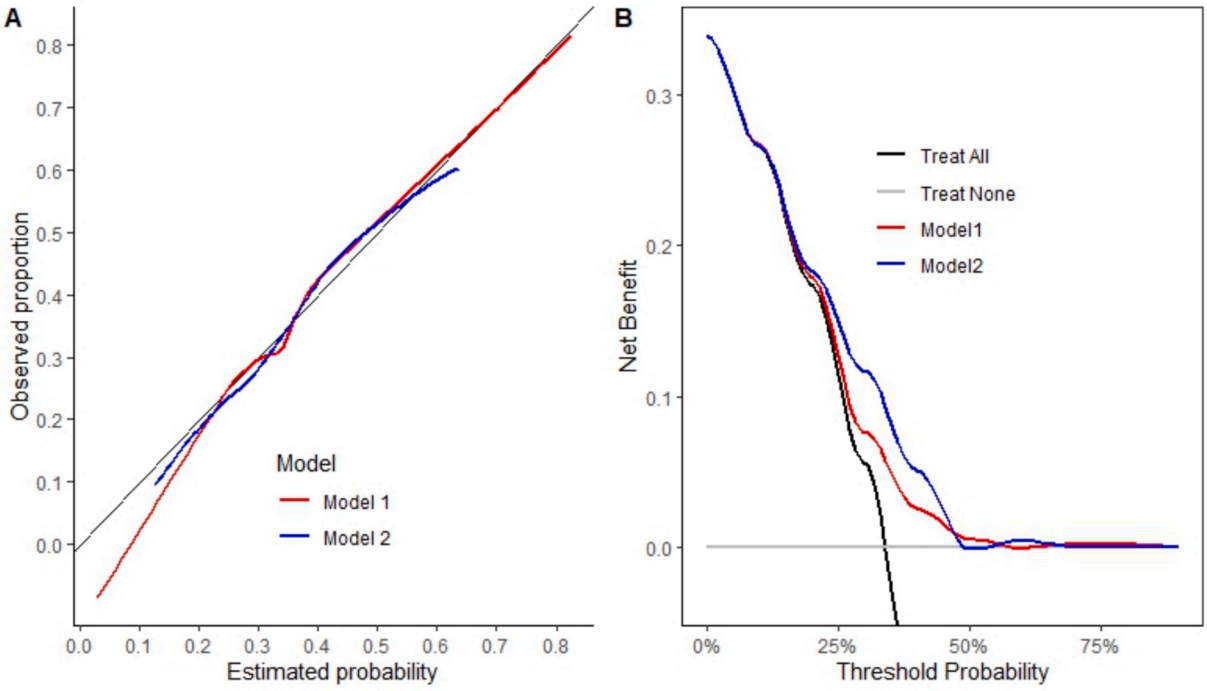

Fig. 2. Calibration curves (A) and decision curves (B) for the risk prediction models. Higher net benefit suggests higher clinical utility. Model 1: model including the hematological variables as continuous variables. Model 2: model including the hematological variables as clinically relevant categories.

utility only in the 30–60 % threshold range. This underscores the need for further research to identify additional biomarkers or incorporate non-hematological parameters, such as imaging or molecular markers, to enhance predictive models.

Our study has several limitations. First, the definition of TB severity relied on a non-standardized score that included the TIMIKA score, time of sputum conversion, and the need for oxygen supplementation. While these criteria are clinically relevant, they may not fully capture the complexity of TB severity. Second, the retrospective design limited data quality and consistency, as missing values required imputation, which could introduce bias. Third, pre-existing biochemical alterations due to other conditions could not be excluded, as baseline blood parameters prior to admission were unavailable.

In conclusion, hematological markers, while rapid, cost-effective, and easy to perform, may not offer sufficient discriminative ability for TB severity. Future research should focus on integrating molecular biomarkers, advanced imaging modalities, and comprehensive clinical data to develop robust predictive models for TB severity. Such models could facilitate early identification of high-risk patients and improve resource allocation in TB-endemic settings.

CRediT authorship contribution statement

Francesco Di Gennaro: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Data curation, Conceptualization. **Giacomo Guido:** Writing – original draft, Project administration, Funding acquisition. **Sergio Cotugno:** Conceptualization. **Francesco Cavallin:** Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Data curation, Conceptualization. **Mariantonietta Pisaturo:** Supervision, Conceptualization. **Lorenzo Onorato:** Validation, Supervision. **Federica Zimmerhofer:** Data curation. **Luca Pipitò:** Data curation. **Giuseppina De Iaco:** Supervision, Conceptualization. **Giuseppe Bruno:** Data curation. **Massimo Fasano:** Data curation. **Agostina Pontarelli:** Data curation. **Annarita Botta:** Data curation. **Tiziana Iacovazzi:** Data curation. **Rossana Lattanzio:** Data curation. **Virginia Di Bari:** Data curation. **Gianfranco Panico:** Data curation. **Raffaella Libertone:** Data curation. **Caterina Monari:** Data curation. **Alessia Musto:** Data curation. **Mariangela Niglio:** Data curation. **Federica De Gregorio:** Data curation. **Gaetano Brindicci:** Data curation. **Carmen Rita Santoro:** Data curation. **Luigi Ronga:** Data curation. **Roberta Papagni:** Supervision. **Elda De Vita:** Writing – original draft, Data curation. **Francesco Rosario Paolo Ieva:** Data curation. **Loredana Alessio:** Methodology, Visualization, Data curation. **Gina Gualano:** Data curation, Conceptualization. **Salvatore Minniti:** Writing – review & editing, Supervision. **Giovanni Battista Buccoliero:** Supervision. **Sergio Lo Caputo:** Supervision. **Sergio Carbonara:** Conceptualization. **Antonio Cascio:** Supervision. **Roberto Parrella:** Supervision. **Fabrizio Palmieri:** Supervision. **Nicola Coppola:** Supervision. **Annalisa Saracino:** Supervision.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2025.100517.

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