International Journal of General Medicine

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Clinical and Laboratory Discriminators for Tuberculosis and Lymphoma in Adults Presenting with Fever of Unknown Origin: A Prospective Cohort Study

Nana Xie[1,2], Fangbing Tian[2], Wencong Zhang[2], Jia Chen[2], Wenyuan Zhang[2], Qiurong Ruan[3], Jianxin Song[2]

[1]Department of Respiratory Medicine, Traditional Chinese and Western Medicine Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; [2]Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; [3]Institute of Pathology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Correspondence: Jianxin Song, Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Email songsingsjx@sina.com, Qiurong Ruan, Institute of Pathology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430040, People's Republic of China, Email ruanqiurong@sina.com

Background: Tuberculosis and lymphoma are the common causes of fever of unknown origin (FUO) and show some similar clinical symptoms. The purpose of this study was to analyze the clinical characteristics of tuberculosis and lymphoma to find effective methods to distinguish them.

Methods: A cohort including 100 tuberculosis and 81 lymphoma patients in FUO was prospectively enrolled. A predictive model of tuberculosis based on clinical parameters was established by using logistic regression equation, and its efficacy was evaluated by Receiving operating curve (ROC).

Results: Both lymphoma and tuberculosis were more common in middle-aged and elderly males (P=0.043), and the total fever duration was relatively long (P=0.086). Muscle pain (P=0.017) and chills (P=0.045) were more common in tuberculosis patients, while hepatosplenomegaly (P<0.001) and lymphadenopathy (P<0.001) were more prevalent in lymphoma patients. The positive rate of T-SPOT.TB in the tuberculosis group was significantly higher than that in the lymphoma group (P<0.001). In the lymphoma group, LDH and SF were all significantly increased (P<0.001), while ALB and PLT were significantly decreased (P<0.001). The AUC of the diagnostic prediction model for tuberculosis established by combining parameters was 0.96 (95% CI, 0.935–0.986), with a sensitivity of 90.9% and a specificity of 87.1%. A validation cohort consisted of 42 patients with FUO from other departments during the same period, the AUC of the validation cohort was 0.948 (95% CI, 0.886–0.999), with a sensitivity of 90% and a specificity of 90.9%.

Conclusion: The integration of clinical parameters facilitates enhanced discriminative capacity between tuberculosis and lymphoma.

Keywords: fever of unknown origin, tuberculosis, lymphoma, differential diagnosis

Introduction

Fever of unknown origin (FUO) is a challenging clinical syndrome characterized by prolonged fever (>3 weeks), multiple recorded temperatures >38.3°C, and undiagnosed after 3 outpatient visits or 3 days of inpatient investigation.[1] The etiological spectrum of FUO is complex and heterogeneous, with infectious diseases, non-infectious inflammatory diseases (NIID), and malignant neoplasms constituting the three predominant categories.[2] Among malignant etiologies, lymphoma has been consistently identified as the most prevalent cause,[3,4] while tuberculosis remains one of the leading infectious causes worldwide.

Tuberculosis, a chronic infectious disease mediated by Mycobacterium tuberculosis, remains a significant global health burden and a leading cause of morbidity and mortality worldwide. As one of the most prevalent causes of FUO,

https://doi.org/10.2147/IJGM.S574415
Received: 5 November 2025
Accepted: 18 April 2026
Published: 28 April 2026

tuberculosis is frequently misdiagnosed or diagnosed with delay, particularly in cases lacking typical respiratory symptoms or characteristic imaging findings.[5,6] Lymphoma, a heterogeneous group of hematological malignancies originating from the lymphatic system, encompasses both Hodgkin's and non-Hodgkin's subtypes. Lymphoma is the highest proportion of malignant neoplastic diseases, accounting for more than 50%.[1,7] Studies have shown that some lymphoma patients presents with nonspecific clinical manifestations and ambiguous imaging findings, often necessitating repeated invasive procedures such as lymph node biopsies for definitive diagnosis.[4]

In recent years, Gene Xpert MTB/RIF and HGTS have significantly enhanced the sensitivity and specificity of tuberculosis diagnosis.[8] Concurrently, ^{18}F-FDG PET/CT and pathological analysis have improved the diagnostic rate of lymphoma.[9,10] However, both may only present with fever in the early stage and lack specific signs, and anti-infective and antiviral treatments are usually ineffective, making differential diagnosis difficult, resulting in missed diagnosis, misdiagnosis, and exacerbating the condition. The purpose of this study was to analyze the clinical characteristics and laboratory data of tuberculosis and lymphoma, build a simple and practical differential diagnosis model, and provide reference for the etiology diagnosis of FUO.

Materials and Methods

Patients and Study Design

A total of 181 patients (tuberculosis=100, lymphoma=81) with classic FUO (age≧18 years) who were admitted to the Department of Infection of Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) between January 2014 and May 2021 were enrolled in this prospective study. The inclusion criteria were as follows:[1,11](1) Multiple documented fever (>38.3°C); (2) Fever lasting for at least 3 weeks; (3) Undiagnosed etiology after comprehensive evaluation, including 3 outpatient visits or 3 days of hospitalization; (4) Definitive diagnosis of tuberculosis[12] or lymphoma[13] confirmed by histopathological examination or pathogenetic evidence. Exclusion criteria: (1) Patients not meeting the criteria for classic FUO; (2) FUO cases with confirmed etiologies other than tuberculosis or lymphoma (Figure 1).

IGRA Testing

All enrolled patients underwent interferon-gamma release assay (IGRA) testing using one of two commercially available kits depending on institutional availability: the whole blood-based TB-IGRA CLIA Microparticles assay (Autobio Diagnostics Co., Zhengzhou, China; positive cut-off: ≥14.0 pg/mL) or the PBMC-based T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK; positive cut-off: ≥6 spots). Both assays were performed strictly according to manufacturers' instructions. Indeterminate results—defined as failed positive control or excessive background per each manufacturer's criteria—were excluded from the primary complete-case analysis, as detailed in Figure 1. Sensitivity analysis confirmed that exclusion of indeterminate cases did not introduce significant selection bias ($P > 0.05$ for baseline characteristics).

This study was one of the series of cohort studies conducted by our research group. Regarding FUO research, our research group registered at http://www.clinicaltrials.gov (registration number: NCT02035670) on 14 January 2014 and the research protocol was reviewed and approved by the Huazhong University of Science and Technology Clinical Trial Ethics Committee ([2014]EC-No.16) and Clinical Trial Ethics Committee of Tongji Hospital ([2023]TJ-JRB20230425). The study was proceeded in accordance with relevant guidelines and regulations of human researches, and the Declarations of Helsinki. Written informed consent was obtained from all participants and/or their legal guardians. All enrolled patients had follow-up evaluations by telephone within 6 months.

Data Collection

Comprehensive patient data were systematically collected through a standardized protocol, including detailed medical history acquisition utilizing a validated written questionnaire previously developed by our research group,[14] meticulous physical examinations, and thorough review of medical records. Demographic and clinical characteristics, including gender, age, duration of fever, and peak body temperature, were documented. Associated symptoms such as chills, night sweats, myalgia, skin rash, and weight loss were recorded. Clinical signs including hepatosplenomegaly,

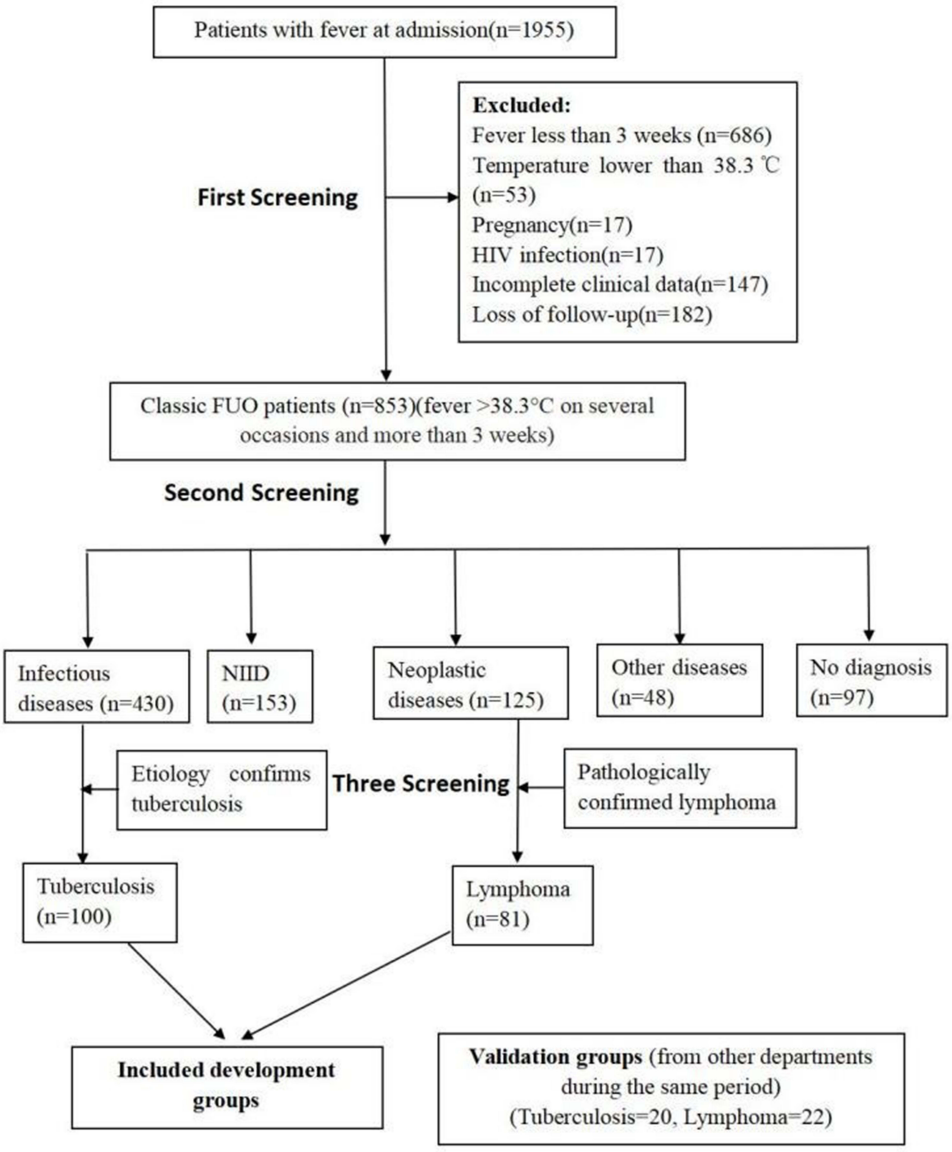

Figure 1 Flow chart of inclusions/exclusion criteria.

lymphadenopathy, and polyserositis were carefully evaluated. Laboratory investigations encompassed a panel of diagnostic tests: Tuberculosis infection T lymphocyte spot test (T-SPOT.TB), complete blood count (White blood cell count [WBC], hemoglobin [Hb], absolute neutrophil count[ANC]; neutrophil percentage [NP], platelet count (PLT), et al), blood cultures, blood chemistry, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), serum ferritin (SF), lactate dehydrogenase (LDH), interleukin-6 (IL-6) and other indicators. Pathological examinations, including bone marrow aspiration biopsy, lymph node aspiration biopsy, etc.; as well as treatment and prognosis.

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies (n) and percentages (%), with between-group comparisons conducted using χ^2-tests or Fisher's exact tests. Continuous variables were assessed for normality; normally distributed data were presented as mean ±standard deviation (SD) and analyzed using *t*-tests, while non-normally distributed data were expressed as median (first quartile [Q1], third quartile [Q3]) and analyzed using non-parametric tests. A two-sided P-value <0.05 was considered statistically significant.

Potential diagnostic indicators were initially identified through univariate analysis, with variables showing P-values <0.2 subsequently included in multivariate logistic regression analysis. The multivariate analysis employed a significance threshold of P<0.05 (two-sided), with results expressed as odds ratios (OR) and 95% confidence intervals (CI). A binary logistic regression equation was utilized to construct the diagnostic prediction model, with its performance evaluated using receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) quantification. AUC values approaching 1.0 indicated superior diagnostic accuracy of the model.

Results

Comparison of Clinical Features Between Tuberculosis and Lymphoma

The study cohort comprised 181 patients, including 117 male (64.64%), the median age was 53 (38, 63) years, and the median total fever duration was 41 (31, 66) days. Among the 100 tuberculosis cases, extrapulmonary manifestations predominated (68 cases), with the most frequent sites being lymph node (27 cases), abdominal cavity (14 cases), and intracranial involvement (14 cases). Of the 81 lymphoma cases, non-Hodgkin's lymphoma constituted the majority, with the top three cases being aggressive B-cell lymphoma (27 cases), extronodal NK/T-cell lymphoma (15 cases), angioimmunoblastic T-cell lymphoma (9 cases), and only 3 cases of classic Hodgkin's lymphoma (3.7%).

The clinical characteristics of tuberculosis and lymphoma were compared (Table 1). It was observed that male patients predominated in both disease groups, with a notably higher male-to-female ratio in lymphoma (2.68:1). The median age of onset was higher in lymphoma patients compared to tuberculosis, and the median total duration of fever was also longer in lymphoma. However, no statistically significant differences were found between the two groups regarding age, maximum body temperature (Tmax°C), or duration of fever (P>0.05). Notably, a significant proportion of tuberculosis patients experienced chills (43%) and myalgia (34%)(P<0.05). Weight loss was reported in over 30% of patients in both groups (P=0.635). The incidence of rash was similar in both diseases (P=0.002). Night sweats were infrequent in both groups (P=0.689). Among the three major physical signs, hepatosplenomegaly was significantly more prevalent in lymphoma compared to tuberculosis (P<0.001). Lymphadenopathy was observed in both diseases but was markedly more frequent in lymphoma (P<0.001). In contrast, polyserositis was uncommon in both tuberculosis and lymphoma (P=0.054).

Comparison of Laboratory Data Between Tuberculosis and Lymphoma

Analysis of laboratory data in Table 2 revealed that 65% of tuberculosis patients exhibited T-SPOT.TB reactivity, compared to only 9.9% of lymphoma patients (P<0.001). WBC, Hb, NP and E% were slightly lower in lymphoma

Table 1 Comparison of Clinical Features Between Tuberculosis and Lymphoma

Features	Lymphoma (n=81)	Tuberculosis (n=100)	*P* value
Gender			0.043
Male	59 (72.8%)	58 (58%)	
Female	22 (27.2%)	42 (42%)	
Age(years)	56 (43.5–62)	49.5 (32–65)	0.203
Tmax (°C)	39.5 (39–40)	39.3 (39–40)	0.171
Duration of fever (days)	44 (32.5–70)	37 (30–65.75)	0.086
Polyserositis	12 (14.8%)	11 (11%)	0.504
Lymphadenopathy	67 (82.7%)	47 (47%)	<0.001
Hepatosplenomegaly	57 (70.4%)	26 (26%)	<0.001
Chill	23 (28.4%)	43 (43%)	0.045
Muscle/joint pain	14 (17.3%)	34 (34%)	0.017
Night sweats	14 (17.3%)	13 (13%)	0.689
Weight loss	28 (34.6%)	31 (31%)	0.635
Skin rash	12 (14.8%)	14 (14%)	0.002

Note: Tmax C, maximum body temperature. Categorical variables are presented as number (%) and continuous variables are presented as mean±SD or median (Q1, Q3).

Table 2 Comparison of Laboratory Data Between Tuberculosis and Lymphoma

Variable	Normal Range	Unit	Lymphoma (n=81)	Tuberculosis (n=100)	*P* value
T-SPOT.TB	Negative		8 (9.9%)	65 (65%)	<0.001
ALB	35-52	g/L	31 (26–34.7)	35.35 (30.43–37.95)	<0.001
ALP	40-130	U/L	103 (66.5–268)	82 (55–131.75)	0.013
WBC	3.5–9.5	*10^9/L	5.48 (3.37–7.52)	5.95 (4.33–8.54)	0.069
ANC	1.8–6.3	*10^9/L	3.36 (1.98–5.55)	4.35 (2.91–6.71)	0.017
NP	40-75	%	69.9 (56.75–81.8)	73.05 (65.1–82.33)	0.051
E%	0.4-8	%	0.2 (0–1.25)	0.4 (0–1.18)	0.352
M%	3-10	%	10.1 (45.2–14.45)	8.2 (5.25–10.7)	0.012
L%	20-50	%	17.9 (11–28.4)	17.5 (10.45–25.7)	0.501
Hb	130-175	g/L	102 (86–122.5)	105 (90.25–118.5)	0.62
PLT	125-350	*10^9/L	137 (87.5–229)	235 (170–316.25)	<0.001
ESR	0-20	mm/H	28 (9–77)	55 (21.5–87.75)	0.035
LDH	125-225	U/L	390 (277–589)	205.5 (163.25–248.75)	<0.001
SF	15-150	ug/L	1069.6 (551.2–2289.8)	490 (314.9–876.8)	<0.001
PCT	<0.05	ng/mL	0.22 (0.16–0.57)	0.13 (0.07–0.33)	<0.001
CRP	<10	mg/L	76.1 (25.6–139.4)	61.8 (27.8–99.1)	0.059
IL-6	<7	pg/L	39.08 (17.29–9.94)	34.24 (13.91–56.3)	0.164

Note: Categorical variables are presented as number (%) and continuous variables are presented as mean±SD or median (Q1, Q3).
Abbreviations: T-SPOT.TB, tuberculosis infection T lymphocyte spot test; ALB, albumin; ALP, alkaline phosphatase; WBC, white blood count; ANC, absolute neutrophil count; NP, neutrophil percent; E%, eosinophil percentage; M%, monocyte percentage; L%, lymphocyte percentage; Hb, hemoglobin; PLT, platelet; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; SF, serum ferritin; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6.

than in tuberculosis, but these differences were not statistically significant (P≥0.05). ANC was marginally lower in lymphoma (P=0.017), while ALB and PLT were significantly lower in lymphoma compared to tuberculosis (P<0.001). ESR was higher in tuberculosis (P=0.035), whereas SF and LDH were significantly lower in tuberculosis than in lymphoma (P<0.001). PCT was slightly elevated in lymphoma (P<0.001). CRP and IL-6 levels were moderately higher in lymphoma, though the differences did not reach statistical significance (P=0.059 and P=0.164, respectively).

Establishment of the Prediction Model for Differentiating Tuberculosis

Using logistic regression analysis, variables with P<0.2 in univariate analysis and confounding factors (age and sex) were included in the multivariate analysis. Statistically significant factors (P<0.05) from the multivariate analysis were incorporated into a binary logistic regression equation, the tuberculosis prediction model was as follows: logit(P) =4.966*T-SPOT.TB (reactive=1)-0.056*age-1.764*lymphadenopathy (present=1)-1.376*hepatosplenomegaly (present=1)+0.064*NP+0.023*ESR-0.009*LDH+0.0003*SF-0.016*CRP+1.888. The model demonstrated an AUC of 0.96 (95% CI, 0.935–0.986), with a sensitivity of 90.9% and a specificity of 87.1% at a cutoff value of 0.78. Meanwhile, the positive predictive value(PPV) of this model is 90.1%, and the negative predictive value(NPV) is 88.8%. Furthermore, the diagnostic performance of the combined parameters was superior to that of any individual variable (AUC of the combined model > AUC of any single variable) (see Table 3 and Figure 2a).

An independent external validation cohort comprising 42 FUO patients from other departments (including 20 tuberculosis cases and 22 lymphoma cases) was established. Among the 20 tuberculosis patients, 2 had pulmonary tuberculosis, 3 had tuberculous pleuritis, and the remainder had extra-pulmonary tuberculosis (including intestinal tuberculosis, lymph node tuberculosis, and tuberculous meningitis). All 22 lymphoma cases were non-Hodgkin lymphoma, consistent with the trends observed in the FUO cohort. The clinical characteristics of this validation cohort showed no statistically significant differences compared to the prediction cohort (P>0.05). ROC curve analysis further confirmed the model's accuracy, revealing an AUC of 0.948 (95% CI, 0.886–0.999) in the validation cohort. At a cutoff value of 0.809, the model demonstrated a sensitivity of 90% and a specificity of 90.9% (Figure 2b). Meanwhile, the PPV

Table 3 Potential Diagnostic Indicators for the Diagnosis of Tuberculosis and Results of Multivariate Regression Analysis

Variable	OR	S.E.	95% CI of OR	*P* value	AUC
Gender (male)	0.777	0.718	0.19–3.174	0.725	/
Age (years)	0.945	0.02	0.908–0.984	0.006	0.522
T-SPOT.TB	14.347	1.087	1.705–20.745	<0.001	0.597
Lymphadenopathy	0.171	0.63	0.05–0.589	0.005	0.389
Hepatosplenomegaly	0.253	0.609	0.077–0.833	0.024	0.413
Chill	2.117	0.679	0.56–8.005	0.269	/
Muscle/joint pain	2.059	0.729	0.493–8.6	0.322	/
Skin rash	0.388	1.71	0.014–11.078	0.58	/
ALB	1.018	0.069	0.889–1.167	0.792	/
ALP	1.001	0.002	0.997–1.004	0.756	/
NP	1.066	0.023	1.018–1.116	0.007	0.476
M%	0.925	0.077	0.796–1.075	0.309	/
PLT	1.002	0.003	0.996–1.009	0.463	/
ESR	1.023	0.009	1.005–1.041	0.012	0.441
LDH	0.991	0.002	0.986–0.996	<0.001	0.358
SF	1.0003	0.0001	1.0001–1.0004	0.001	0.348
CRP	0.984	0.006	0.973–0.996	0.007	0.444

Note: "/" indicates that the indicators of the multi-factor analysis do not have statistical significance (P > 0.2), and the AUC results were not calculated.

Abbreviations: OR, odds ratio; S.E., Standard Error; CI, confidence interval; AUC, Area under the curve; T-SPOT.TB, tuberculosis infection T lymphocyte spot test; ALB, albumin; ALP, alkaline phosphatase; NP, neutrophil percent; M%, monocyte percentage; PLT, platelet; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; SF, serum ferritin; CRP, C-reactive protein.

of the verification queue is 90%, and the NPV is 90.9%. Furthermore, the calibration curves of the training and validation queues are shown in Figure 3, and the confusion matrix is presented in Table 4. The above results indicate that the established model has reliable predictive performance.

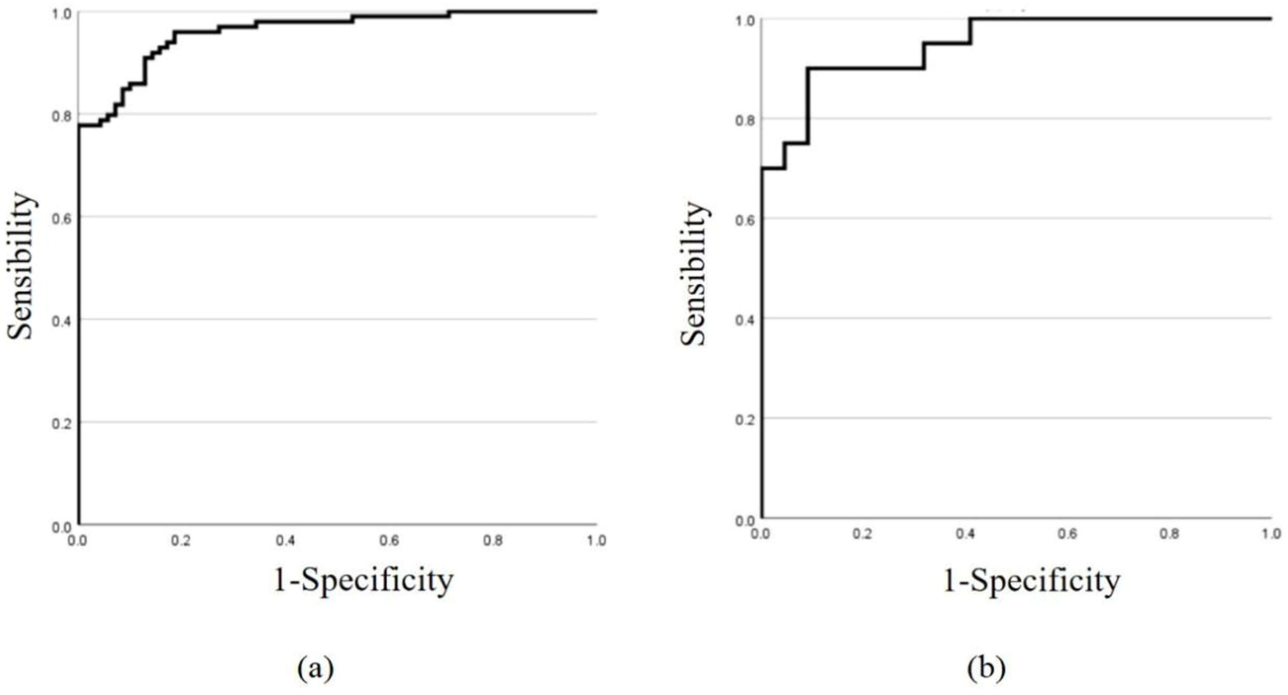

Figure 2 (**a**) ROC curve of development cohort; (**b**) ROC curve of the validation cohort.

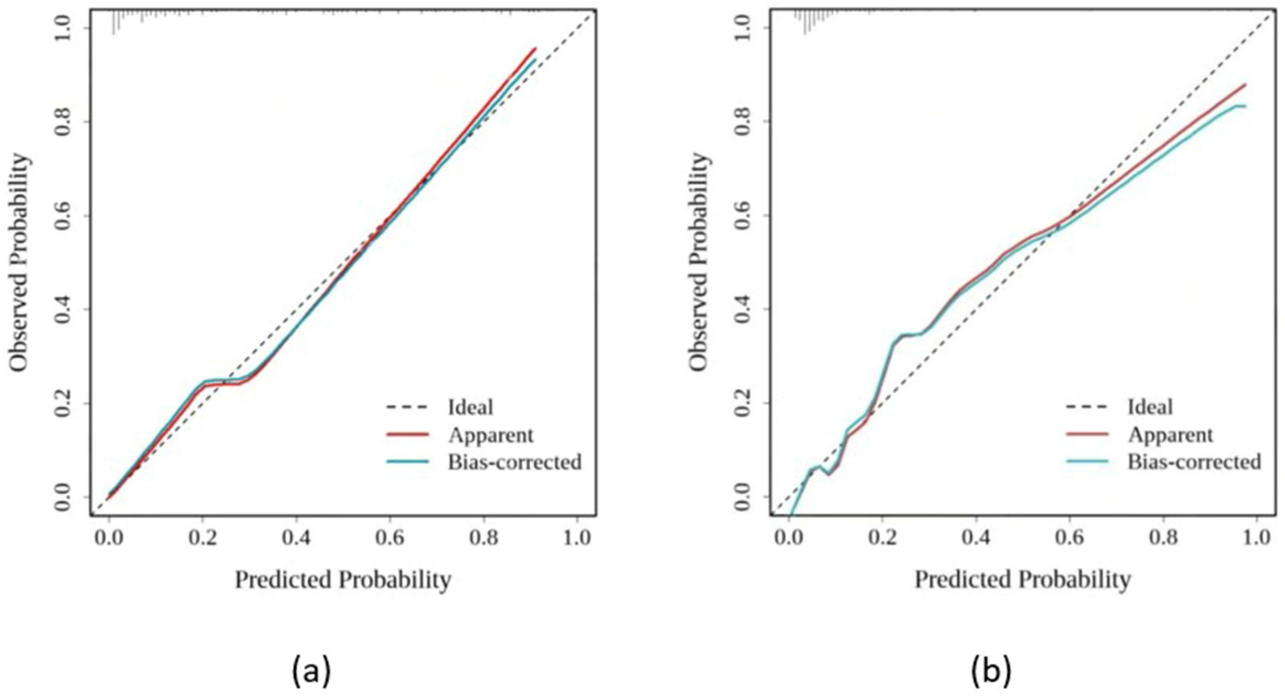

Figure 3 (**a**) Correction curve of development cohort; (**b**) Correction curve of the validation cohort.

Discussion

Tuberculosis remains one of the most common causes of FUO and is a prevalent infectious etiology of FUO in China.[3,4] Epidemiological surveillance, both domestically and internationally, indicates a rising incidence of extra-pulmonary tuberculosis, which predominantly accounts for tuberculosis cases in FUO.[15] In this study, extra-pulmonary tuberculosis significantly outnumbered pulmonary tuberculosis (68% vs. 32%). Lymphoma, the most frequent neoplastic cause of FUO, continues to hold a critical position among malignant etiologies, despite a declining trend in the proportion of neoplastic diseases in FUO over the past decade in China (12% vs. 7.9%).[3,4] Notably, 81 lymphoma cases in this study included only 3 cases of classical Hodgkin lymphoma, with the majority being non-Hodgkin lymphoma, aligning with trends observed in previous studies.[7,9,16]

In this study, both tuberculosis and lymphoma exhibited a higher prevalence in male patients, with prolonged fever duration and overlapping clinical manifestations such as hepatosplenomegaly, lymphadenopathy and rash, underscoring the importance of differential diagnosis between these two conditions. However, in clinical practice, relying solely on a single clinical or laboratory feature is insufficient for accurate diagnosis. This study systematically analyzed and compared the clinical characteristics and laboratory indicators of tuberculosis and lymphoma, developed a predictive model for tuberculosis diagnosis, and validated its efficacy. The findings highlight the superior diagnostic performance of a multi-parameter approach in differentiating tuberculosis from lymphoma.

Table 4 Confusion Matrix of the Research Cohort and the Validation Cohort

Cohort	TP	FN	FP	TN	PPV	NPV
Training	91	9	10	71	90.1%	88.8%
Validation	18	2	2	20	90.0%	90.9%

Abbreviations: TP, True Positive; FN, False Negative; FP, False Positive; TN, True Negative; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

https://doi.org/10.2147/IJGM.S574415

This study identified a male predominance in both tuberculosis (58%) and lymphoma (72.8%), with lymphoma showing a more pronounced male preponderance, consistent with prior reports.[3,16] Wang WX et al showed that male patients combined with other clinical parameters were more likely to be diagnosed with infection or malignancy.[17] Although the median age difference between the two groups was not statistically significant (P=0.203), lymphoma patients were older, suggesting a potential role of aging in lymphomagenesis. ChenJ et al showed that elderly (>53 years) patients with concomitant lymphadenopathy in FUO were more likely to be diagnosed with lymphoma.[7] Clinically, tuberculosis patients more frequently presented with myalgia (34%) and chills (43%), likely attributable to infection-induced cytokine storms, such as tumor necrosis factor-α release.[18] In contrast, lymphoma patients exhibited higher rates of hepatosplenomegaly (70.4%) and lymphadenopathy (82.7%), reflecting tumor cell infiltration and immune dysregulation.[19] These manifestations align with previous studies,[3] offering preliminary diagnostic clues. While lymphoma-associated rashes were polymorphic, tuberculosis-related rashes predominantly presented as erythema nodosum or tuberculids, symmetrically distributed on extensor surfaces, likely due to immune complex deposition or tuberculin hypersensitivity.[20] Notably, although rash incidence was similar (14%) and univariate analysis showed statistical significance (P=0.006), multivariate analysis revealed no significant difference (P=0.58), indicating that rash is not a specific marker for differentiating tuberculosis from lymphoma in FUO.

Laboratory findings demonstrated significant differences in T-SPOT.TB reactivity between tuberculosis and lymphoma groups (65% vs. 9.9%, P<0.001), validating its clinical utility as a specific immune response marker for tuberculosis, though its negative predictive value remains limited, consistent with prior meta-analyses.[21,22] Notably, 35% of tuberculosis patients showed T-SPOT.TB non-reactivity, underscoring the need to recognize that negative results do not entirely exclude infection.

IGRAs are cell-mediated immunity assays that detect T-cell responses to MTB-specific antigens. Unlike tuberculin skin tests, IGRAs show no cross-reactivity with BCG vaccination or most non-tuberculous mycobacteria. They offer advantages including easy specimen collection, high sensitivity, and rapid results, facilitating widespread clinical use.[23] However, a Beijing-based study demonstrated that while IGRAs alone have high sensitivity for diagnosing active tuberculosis in febrile patients, their specificity is limited.[24] This limitation stems from the inability of positive IGRA results to distinguish active disease from latent infection or old healed tuberculosis, along with potential false negatives in elderly and immunocompromised populations.[25,26] Recent efforts have integrated IGRAs with long non-coding RNAs, imaging features, and clinical manifestations to develop predictive models for early pulmonary tuberculosis detection.[27] Although numerous studies have investigated predictors for fever of unknown origin (FUO) etiology,[9,10,17] no predictive model specifically addresses tuberculosis diagnosis in FUO. The present study fills this gap by combining IGRAs with clinical parameters to differentiate between tuberculosis and lymphoma in FUO patients.

Lymphoma patients exhibited significantly lower ALB and PLT levels (P<0.001), reflecting tumor-related consumption, while elevated LDH and SF levels (P<0.001) were associated with accelerated glycolysis, tissue damage, and tumor-associated inflammation.[28,29] However, the mechanisms underlying the elevation of SF and LDH are different: SF elevation is driven by hyperactive pro-inflammatory cytokine release and iron dysregulation in malignant lymphoproliferation, while increased LDH stems from enhanced glycolytic metabolism and high turnover of neoplastic lymphocytes. Previous studies have shown that a decrease in three lines in FUO or low PLT combined with other clinical parameters may tend to diagnose malignant tumors, especially lymphoma, while patients with high LDH (>370U/L) were more likely to have neoplastic disease, and patients with low LDH (≤340U/L) were more likely to have infectious disease.[7,17,30]

In contrast, tuberculosis patients showed only mild elevations in LDH and SF, consistent with localized necrosis and inflammation, but lacking the sustained proliferative features of malignancy.[3,16] ESR was significantly higher in tuberculosis (55 mm/H vs. 28 mm/H, P=0.035), reflecting its chronic infectious nature, while CRP, PCT, and IL-6 were mildly elevated in both groups, indicating systemic inflammation with limited specificity. Studies have shown that CRP may be elevated in acute infections, active tuberculosis, active rheumatic diseases, malignant tumors and other diseases.[31]

Despite significant advancements in medical technology, the proportion of undiagnosed cases of FUO in China has shown an increasing trend over the past decade, rising from 8.2% to 12.2%.[4] In recent years, numerous studies have

developed various diagnostic prediction models by integrating clinical parameters, significantly enhancing the accuracy of FUO etiology identification. For instance, Dakappa et al achieved a diagnostic accuracy of 91.3% using an artificial neural network to classify infectious and non-infectious causes.[32] Zhao MZ et al established a scoring system with an AUC of 0.83, while Jiang H et al developed an algorithm with an accuracy ranging from 81.68% to 96.17%.[33] Wang WX et al proposed a predictive model with an AUC of 0.84, and Zhou X et al introduced a method for diagnosing adult-onset Still's disease (AOSD) with an accuracy of 92.4%.[17,34] Furthermore, Chen J et al and Ying S et al constructed models for infectious diseases and AOSD, respectively, while Wan L et al and Chen J et al demonstrated outstanding performance in distinguishing AOSD from lymphoma and diagnosing lymphoma with lymphadenopathy, with AUC values of 0.855 and 0.93, respectively.[7,16,30,35] Additionally, Tian FB et al developed a predictive model for hemophagocytic syndrome with an AUC of 0.889.[36] These models exhibit high sensitivity and specificity, providing robust tools for clinicians to elucidate the underlying causes of FUO.

Regarding the research on FUO, the research team prospectively included 853 classic FUO patients who were hospitalized in the Department of Infectious Diseases of Tongji Hospital, Huazhong University of Science and Technology from January 2014 to May 2021. We conducted a detailed analysis of the etiological composition (infectious diseases, NIID, neoplastic diseases, other diseases, and undiagnosed diseases) and compared the demographic, clinical characteristics, and laboratory data of patients with different etiologies to explore the diagnostic value of related parameters in FUO etiology. The study showed that infectious diseases were the most common cause of FUO, followed by non-infectious inflammatory diseases. Clinical features and common inflammatory indicators were of great value in clarifying the etiology of FUO. And the relevant data have been published.[37] This study, however, aims to differentiate the most common infectious disease (tuberculosis) and the most common non-infectious disease (lymphoma) in FUO. This not only further subdivides and clarifies the detailed etiology of FUO but also reduces the misdiagnosis and missed diagnosis rates of these two diseases, which is of great significance for further improving the precise diagnosis rate of FUO.

Compared with the Zhou team's retrospective study,[3] this prospective study incorporated additional clinical parameters (eg., myalgia, weight loss, night sweats, SF), enhancing diagnostic accuracy. Multivariate analysis identified T-SPOT.TB reactivity, elevated NP, ESR, and SF as risk factors for tuberculosis, while lymphadenopathy, hepatosplenomegaly, advanced age, and elevated LDH were associated with lymphoma. The diagnostic model for tuberculosis demonstrated high accuracy (AUC 0.96, 95% CI, 0.93–0.986; sensitivity 90.9%, specificity 87.1%), with consistent performance in the validation cohort (AUC 0.948, 95% CI, 0.88–0.999; sensitivity 90%, specificity 90.9%). And, the PPV of research cohort is 90.1%, and NPV is 88.8%; the PPV of the verification queue is 90%, and the NPV is 90.9%. Meanwhile, the calibration curves of the two groups of queues have a good fit degree. These results highlight the superior diagnostic efficacy of combined parameters over individual markers, providing a robust tool for clinical practice.

Despite its strengths, there were some limitations. Specifically, the single-center design and relatively small validation cohort introduce potential selection bias and compromise the external validity of our findings, particularly for generalizability to low tuberculosis (TB)-burden nations. To enhance the model's utility in such regions, future adaptations should prioritize recalibrating predictor weights to reflect regional variations in clinical parameter distributions and conducting external validation across geographically diverse cohorts. Additionally, larger multicenter studies are warranted to validate and optimize the model—especially for atypical cases (eg., co-infections or non-tuberculous mycobacterial infections)—and mitigate biases stemming from limited recruitment and sample size constraints. Further exploration of novel biomarkers and AI-driven multi-parameter diagnostic frameworks may also strengthen diagnostic precision in complex clinical scenarios, thereby improving the model's generalizability across varied TB-endemic settings.

Furthermore, a pragmatic clinical pathway for implementing this model in routine practice involves three key steps: (1) screening FUO patients with suspected TB/lymphoma, (2) collecting T-SPOT results and core clinical parameters (eg., inflammatory markers, radiological findings), and (3) calculating the model-derived probability to guide differential diagnosis and subsequent clinical decision-making (eg., further diagnostic workup or treatment initiation).

Conclusions

The substantial clinical and laboratory overlap between TB and lymphoma presents a formidable diagnostic dilemma, especially among patients with FUO. In this single-center prospective cohort study, we demonstrate that integrating clinical features with routine laboratory parameters into a multi-parameter diagnostic model achieves high discriminatory accuracy in distinguishing TB from lymphoma—outperforming individual indicators in both sensitivity and specificity. These findings not only establish a pragmatic clinical framework to address this diagnostic challenge but also provide a foundational dataset to inform subsequent mechanistic investigations into the overlapping pathophysiology of these two conditions. Despite the model's robust performance, its broader clinical translation requires multi-center external validation with expanded sample sizes to confirm generalizability and evaluate real-world clinical impact. Moreover, the incorporation of emerging biomarkers holds significant promise for further refining this diagnostic algorithm, thereby enhancing the precision of clinical decision-making in differentiating TB from lymphoma in complex FUO presentations.

Abbreviations

FUO, Fever of unknown origin; NIID, non-infectious inflammatory diseases; WBC, white blood cell; ANC, absolute neutrophil count; NP, neutrophil percentage; Hb, hemoglobin; PLT, platelets; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; SF, serum ferritin; LDH, lactate dehydrogenase; IL-6, interleukin-6; ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose Positron Emission Computed Tomography Computerized tomography; ROC, receiving operating curve; IGRA, interferon-gamma release assay; AUC, area under the curve.

Data Sharing Statement

Data are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Disclosure

The authors declare no conflicts of interest in this work.

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