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ORIGINAL RESEARCH

Nutritional Indices Predict All Cause Mortality in Patients with Multi-/Rifampicin-Drug Resistant Tuberculosis

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Background: Multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) with high mortality remains a public health crisis and health security threat. This study aimed to explore the predictive value of nutritional indices for all-cause mortality (ACM) in MDR/RR-TB patients.

Methods: We retrospectively recruited MDR/RR-TB patients between January 2015 and December 2021, randomly assigning them to training and validation cohorts. Patients were divided into high nutritional risk groups (HNRGs) and low nutritional risk groups (LNRGs) based on the optimal cut-off value obtained from receiver operating characteristic (ROC) analyses of the hemoglobin-albumin-lymphocyte-platelet (HALP) score, prognostic nutritional index (PNI), and controlling nutritional status (CONUT) score. In the training cohort, Kaplan-Meier survival curves and Log rank tests were used to compare overall survival (OS) between the groups. Cox risk proportion regression analyses were used to explore the risk factors of ACM in patients with MDR/RR-TB. The predictive performance of ACM was assessed using area under the curve (AUC), sensitivity and specificity of ROC analyses.

Results: A total of 524 MDR/RR-TB patients, with 255 in the training cohort and 269 in the validation cohort, were included. Survival analyses in the training cohort revealed significantly lower OS in the HNRGs compared to the LNRGs. After adjusting for covariates, multivariate analysis identified low HALP score, low PNI and high CONUT score were independent risk factors for ACM in MDR/RR-TB patients. ROC analyses demonstrated good predictive performance for ACM with AUCs of 0.765, 0.783, 0.807, and 0.811 for HALP score, PNI, CONUT score, and their combination, respectively. Similar results were observed in the validation set.

Conclusion: HALP score, PNI, and CONUT scores could effectively predict ACM in patients with MDR/RR-TB. Hence, routine screening for malnutrition should be given more attention in clinical practice to identify MDR/RR-TB patients at higher risk of mortality and provide them with nutritional support to reduce mortality.

Keywords: multidrug- and rifampicin- resistant tuberculosis, all- cause mortality, nutrition

Introduction

Tuberculosis (TB) is a global health concern, with high morbidity and mortality rates. Compared with drug-sensitive TB, multidrug- and rifampicin-resistant TB (MDR/RR-TB) has longer treatment time, higher treatment cost, poorer treatment outcomes and a higher risk of mortality, which is a serious obstacle to TB control.[1] The Global Tuberculosis Report 2023 by the World Health Organization (WHO) reported that estimated 410,000 new cases of MDR/RR-TB in 2022.[2] A previous study reported that the mortality of MDR/RR-TB patients reached 14.68%.[3] Therefore, decreasing the mortality of MDR/RR-TB patients is gradually becoming a crucial problem in the treatment of anti-TB medicines for TB.

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Malnutrition is strongly associated with the incidence, treatment, and prognosis of TB. Many studies have shown that malnutrition increases the risk of incidence of TB,[4,5] treatment failure[6] and mortality.[7–11] On the contrary, a randomized controlled trial of Reducing the Activation of TB by Improving Nutritional Status (RATIONS) from India indicated that nutritional support can reduce the incidence of TB and reduce mortality.[12,13] In addition, some previous studies and meta-analyses have provided evidence that undernutrition increases the risk of unsuccessful treatment outcomes and mortality in patients with MDR-TB.[14–16] Hence, the assessment and management of nutritional status is greatly significant for the long-term prognosis of TB patients.

At present, many methods, including BMI,[17] nutritional risk screening (NRS) 2002,[18] geriatric nutritional risk index (GNIRI),[4] hemoglobin-albumin-lymphocyte-platelet (HALP) score,[19] prognostic nutritional index (PNI),[4] and controlling nutritional status (CONUT)[4] can assess the nutritional status. However, few studies have explored the correlation between nutritional status and mortality in patients with TB, let alone in MDR/RR-TB patients. Studies of 1075 sample cohorts revealed that the NRS 2002, COUNT score, GNIRI, and PNI were associated with all-cause mortality (ACM) in TB patients.[4] A retrospective study of 93 TB patients suggested that the NRS 2002 and PNI could predict mortality in TB patients.[20] Additionally, previous studies have explored the risk factors related to nutritional status of poor treatment outcomes or mortality in MDR-TB patients, such as anemia,[21] low BMI,[22] and decreased albumin (ALB).[23]

In conclusion, the predictive value of nutritional indices for mortality in MDR/RR-TB patients is unclear. Therefore, the purpose of the present study was to investigate the predictive value of nutritional indices, including the HALP score, PNI and CONUT score, for ACM in patients with MDR/RR-TB.

Materials and Methods

Patients and Study Design

This retrospective cohort study enrolled 728 participants diagnosed with MDR/RR-TB according to drug susceptibility testing (DST) or GeneXpert MTB/RIF at Wuhan Jinyintan Hospital, Tongji Medical College, Huazhong University of Science and Technology (Infectious Disease Hospital) between January 2015 and December 2021. Patients were treated according to the Treatment Guidelines for Drug Resistant TB.[24] The inclusion criteria were: (1) laboratory-confirmed diagnosis of TB with at least rifampicin resistance; (2) more than 18 years old; (3) had documented treatment outcome in the dataset. The exclusion criteria were:(1) death before treatment; (2) non-tuberculous mycobacteria infection; (3) refusal to undergo treatment.

Data Collection

Baseline data, including demographic characteristics (age and sex), history of treatment, smoking, drinking, co-infection (bacteria, fungi, HIV, hepatitis B virus, and Hepatitis C virus), underlying disease (diabetes mellitus, hypertension, and malignancy), Underlying Pulmonary disease (pulmonary heart disease and COPD), and laboratory parameters [hemoglobin (HGB) (g/L), ALB (g/L), lymphocyte count (10^9/L), platelet count (10^9/L), and total cholesterol (mmol/L), were obtained from the electronic medical record system. In addition, the computing methods for the HALP score, PNI, and CONUT score are shown in Table 1. The primary outcome of interest was mortality. The definition of censoring and overall survival time (OS) reference the previous literature.[3] Data regarding follow-up outcomes were extracted from the national electronic case registry.

Grouping

All patients with MDR/RR-TB were randomly classified into training and validation cohorts to ensure study reproducibility. In addition, patients with MDR/RR-TB were classified into high nutritional risk groups (HNRGs) and low nutritional risk groups (LNRGs) according to the optimal cut-off values of the HALP score, PNI, and CONUT score, calculated using the receiver operating characteristic (ROC) curve.

Table 1 The Computing Method of HALP Score, PNI, and COUNT

Variables	Formula				
HALP score	Hemoglobin (g/L)×serum albumin (g/L)×lymphocyte count (10^9/L)/platelet count (10^9/L)				
PNI	Albumin (g/dL) + 5×lymphocyte count (10^9/L)				
CONUT score	Parameters	Normal	Light	Moderate	Severe
	Serum albumin (g/L)	≥35	30–34.9	25–29.9	<25
	Score	0	2	4	6
	Total lymphocyte (109/L)	≥1.6	1.2–1.599	0.8–1.199	<0.8
	Score	0	1	2	3
	Total cholesterol (mmol/L)	≥10	7.78–10	5.56–7.78	<5.56
	Score	0	1	2	3

Abbreviations: HALP score, hemoglobin-albumin-lymphocyte-platelet score; PNI, prognostic nutritional index; CONUT, controlling nutritional status score.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the SPSS (IL SPSS) version 22 and R software version 4.2.1. The numerical variables of normal distribution or approximate normal distribution are presented as mean ± standard deviation, and differences were compared using the Student's *t*-test. Categorical variables are presented as n (%), and the chi-square test was used for comparisons between the groups. The differences in OS between the groups were compared using Kaplan-Meier survival curves and Log rank tests. Cox risk proportion regression analyses were used to explore the risk factors of ACM in patients with MDR/RR-TB. Statistical significance was set at P<0.05. Receiver operating characteristic (ROC) curves were used to calculate the optimal cutoff values of nutritional indices (HALP score, PNI and CONUT scores) and to evaluate the predictive performance of ACM in patients with MDR/RR-TB. In addition, we also operated the ROC curves for single parameters such as ALB HGB and lymphocyte count to further evaluate the predictive value of the three nutritional indices. DeLong's test was used to compare the area under the curve (AUCs).

Result

Clinical Characteristics and Nutrition Indices

A total of 524 patients with MDR/RR-TB diagnosed and treated at the Wuhan Jinyintan Hospital were randomly classified into training (n=255) and validation (n=269) cohorts. The median follow-up time of the cohort was 2 years (24.30 months; IQR, 13.42–24.47). The age was 42.66±15.06 (rang, 18–82 years). In addition, 79 (15.08%) patients with MDR/RR-TB died during the follow-up period. As shown in Supplementary Table 1, although there were significant differences in bronchiectasis and pulmonary cavitation (P<0.05), the remaining characteristics showed no significant differences between the training and validation cohorts (P>0.05), indicating that the two cohorts were independent of each other and that the data from the two cohorts could be used for mutual validation.

In the training cohort, Tables 2–4 showed that the clinical characteristics of patients with MDR/RR-TB in the HNRGs and LNRGs according to the optimal cut-off values of the HALP, PNI, and CONUT scores. The accuracy of the cutoff values, sensitivity, specificity, and Youden index of nutritional indices in the training cohort are shown in Supplementary Table 2. MDR/RR-TB Patients in the LNRGs, including those with a HALP score>16.85, PNI>38.7, and COUNT score<6.5, had higher OS, lower mortality, and lower prevalence of fungal co-infection, pulmonary heart disease, bronchiectasis, destroyed lung, pulmonary cavitation, and pleural effusion than those in the HNRGs (P<0.05). Additionally, MDR/RR-TB patients with a PNI>38.7 had a lower prevalence of smoking, HIV coinfection, and COPD (P<0.05). MDR/RR-TB patients with a CONUT score≥6.5 had a higher prevalence of HIV co-infection (P<0.05).

Kaplan-Meier Curves for OS in Training Set and Validation Set

In training cohort, survival analyses suggested that patients with MDR/RR-TB in the HNRGs had lower OS than those in the LNRGs (Figure 1A–C), with the HALP score (median OS:20.02 vs 24.37 months, P<0.05), PNI (median OS:19.23 vs

Table 2 Baseline Characteristics of Participants with Low and High Nutritional Risk According to HALP Score in the Training Set

Characteristics	LNRGs (HALP score>16.85) (n=149)	HNRGs (HALP score≤16.85) (n=106)	P-value
Overall survival	20.91±7.12	17.47±8.87	0.000
Mortality	8 (5.37%)	28 (26.42%)	0.000
Age	42.99±15.44	44.28±15.57	0.514
Gender			
Male	104 (69.8%)	74 (69.81%)	
Female	45 (30.20%)	32 (30.19%)	0.998
Retreatment	111 (74.50%)	79 (74.53%)	0.995
Extrapulmonary Tuberculosis	13 (8.72%)	14 (13.21%)	0.252
Smoking	52 (34.9%)	46 (43.40%)	0.169
Drinking	20 (13.42%)	19 (17.92%)	0.325
Co-infection			
Bacterium	8 (5.88%)	7 (6.60%)	0.680
Fungus	19 (12.75%)	28 (26.42%)	0.006
HIV	1 (0.67%)	4 (3.77%)	0.078
Hepatitis B virus	19 (12.75%)	14 (13.21%)	0.915
Hepatitis C virus	2 (1.34%)	1 (0.94%)	0.771
Underlying disease			
Diabetes mellitus	24 (16.11%)	16 (15.09%)	0.826
Hypertension	8 (5.37%)	7 (6.60%)	0.680
Malignancy	3 (2.01%)	3 (2.83%)	0.672
Underlying Pulmonary disease			
Pulmonary heart disease	7 (4.70%)	14 (13.21%)	0.015
Bronchiectasis	54 (36.24%)	55 (51.89%)	0.013
COPD	12 (8.05%)	10 (9.43%)	0.699
Pulmonary Imaging			
Destroyed lung	6 (4.03%)	14 (13.21%)	0.007
Pulmonary cavitation	93 (62.42%)	81 (76.42%)	0.018
Pleural effusion	22 (14.77%)	40 (37.74%)	0.000
Nutritional indices			
HALP score	32.81±13.45	9.89±4.14	0.000
PNI	45.58±5.2	36.65±5.5	0.000
CONUT score	4.42±1.44	7.52±2.12	0.000

Abbreviations: HNRGs, high nutritional risk groups; LNRGs, low nutritional risk groups; HIV, human immunodeficiency virus; HALP score, hemoglobin-albumin-lymphocyte-platelet score; COPD, chronic obstructive pulmonary disease; PNI, prognostic nutritional index; CONUT score, controlling nutritional status score.

Table 3 Baseline Characteristics of Participants with Low and High Nutritional Risk According to PNI in the Training Set

Characteristics	LNRGs (PNI>38.7) (n=175)	HNRGs (PNI≤38.7) (n=80)	P-value
Overall survival	21.05±6.76	16.05±9.53	0.000
Mortality	10 (5.71%)	26 (32.5%)	0.000
Age	41.71±15.28	47.5±15.25	0.005
Gender			
Male	118 (67.43%)	60 (75.00%)	
Female	57 (32.57%)	20 (25.00%)	0.222

(*Continued*)

Table 3 (Continued).

Characteristics	LNRGs (PNI>38.7) (n=175)	HNRGs (PNI≤38.7) (n=80)	P-value
Retreatment	132 (75.43%)	58 (72.5%)	0.619
Extrapulmonary Tuberculosis	15 (8.57%)	12 (15.00%)	0.122
Smoking	60 (34.29%)	38 (47.50%)	0.044
Drinking	25 (14.29%)	14 (17.5%)	0.508
Co-infection			
Bacterium	7 (4.00%)	8 (10.00%)	0.059
Fungus	23 (13.14%)	24 (30.00%)	0.001
HIV	1 (0.57%)	4 (5.00%)	0.018
Hepatitis B virus	19 (10.86%)	14 (17.50%)	0.143
Hepatitis C virus	1 (0.57%)	2 (2.50%)	0.185
Underlying disease			
Diabetes mellitus	24 (13.71%)	16 (20.00%)	0.200
Hypertension	9 (5.14%)	6 (7.50%)	0.458
Malignancy	4 (2.29%)	2 (2.50%)	0.917
Underlying Pulmonary disease			
Pulmonary heart disease	7 (4.00%)	14 (17.50%)	0.000
Bronchiectasis	65 (37.14%)	44 (55.00%)	0.007
COPD	11 (6.29%)	11 (13.75%)	0.049
Pulmonary Imaging			
Destroyed lung	9 (5.14%)	11 (13.75%)	0.018
Pulmonary cavitation	110 (62.86%)	64 (80.00%)	0.006
Pleural effusion	28 (16.00%)	34 (42.50%)	0.000
Nutritional indices			
HALP score	28.88±14.56	11.04±9.27	0.000
PNI	45.56±4.39	33.8±3.87	0.000
CONUT score	4.44±1.16	8.48±1.76	0.000

Abbreviations: HNRGs, high nutritional risk groups; LNRGs, low nutritional risk groups; HIV, human immunodeficiency virus; HALP score, hemoglobin-albumin-lymphocyte-platelet score; COPD, chronic obstructive pulmonary disease; PNI, prognostic nutritional index; CONUT score, controlling nutritional status score.

Table 4 Baseline Characteristics of Participants with Low and High Nutritional Risk According to CONUT Score in the Training Set

Characteristics	HNRGs (CONUT score≥6.5) (n=75)	LNRGs (CONUT score<6.5) (n=180)	P-value
Overall survival	15.82±9.47	21.01±6.87	0.000
Mortality	26 (34.67%)	10 (5.56%)	0.000
Age	46.35±16.04	42.36±15.12	0.068
Gender			
Male	57 (76.00%)	121 (67.22%)	0.000
Female	18 (24.00%)	59 (32.78%)	0.164
Retreatment	56 (74.67%)	134 (74.44%)	0.970
Extrapulmonary Tuberculosis	12 (16.00%)	15 (8.33%)	0.070
Smoking	35 (46.67%)	63 (35.00%)	0.081
Drinking	14 (18.67%)	25 (13.89%)	0.334

(*Continued*)

Table 4 (Continued).

Characteristics	HNRGs (CONUT score≥6.5) (n=75)	LNRGs (CONUT score<6.5) (n=180)	P-value
Co-infection			
Bacterium	8 (10.67%)	7 (3.89%)	0.036
Fungus	24 (32.00%)	23 (12.78%)	0.000
HIV	4 (5.33%)	1 (0.56%)	0.012
Hepatitis B virus	13 (17.33%)	20 (11.11%)	0.177
Hepatitis C virus	1 (1.33%)	2 (1.11%)	0.881
Underlying disease			
Diabetes mellitus	13 (17.33%)	27 (15.00%)	0.641
Hypertension	4 (5.33%)	11 (6.11%)	0.810
Malignancy	2 (2.67%)	4 (2.22%)	0.831
Underlying Pulmonary disease			
Pulmonary heart disease	14 (18.67%)	7 (3.89%)	0.000
Bronchiectasis	42 (56.00%)	67 (37.22%)	0.006
COPD	10 (13.33%)	12 (6.67%)	0.084
Pulmonary Imaging			
Destroyed lung	12 (16.00%)	8 (4.44%)	0.002
Pulmonary cavitation	58 (77.33%)	116 (64.44%)	0.044
Pleural effusion	33 (44.00%)	29 (16.11%)	0.000
Nutritional indices			
HALP score	10.06±6.06	28.79±14.92	0.000
PNI	33.62±3.97	45.3±4.57	0.000
CONUT score	8.72±1.59	4.45±1.12	0.000

Abbreviations: HNRGs, high nutritional risk groups; LNRGs, low nutritional risk groups; HIV, human immunodeficiency virus; HALP score, hemoglobin-albumin-lymphocyte-platelet score; COPD, chronic obstructive pulmonary disease; PNI, prognostic nutritional index; CONUT score, controlling nutritional status score.

24.37 months, P<0.05), and CONUT score (median OS:18.33 vs 24.35 months, P<0.05). Similarly, in the validation cohort, the OS of MDR/RR-TB patients in HNRGs were lower than that in LNRGs (Figure 1D–F), with HALP score (median OS:22.83 vs 24.37 months, P<0.05); PNI (median OS:19.20 vs 24.37 months, P<0.05), and CONUT score (median OS:22.60 vs 24.33 months, P<0.05).

Cox Regression Analyses for All-Cause Mortality in the Training Set and Validation Set

The HALP score, PNI, CONUT, age, sex, drinking, bacterial co-infection, fungal co-infection, malignancy, pulmonary heart disease, bronchiectasis, COPD, destroyed lung, and pleural effusion were significantly associated with ACM in unadjusted and multivariable-adjusted Cox regression analyses (Table 5 and Supplementary Table 3). The adjusted multivariate Cox risk proportion regression revealed that a low HALP score (adjusted HR: 3.405, 95% CI: 1.411–8.215, P=0.006), low PNI (adjusted HR: 3.970, 95% CI: 1.662–9.485, P=0.002), and high CONUT score (adjusted HR: 4.734, 95% CI: 1.946–11.516, P=0.001) were independent risk factors for ACM in patients with MDR/RR-TB, which was also consistent with the results in the validation cohort (Table 5).

Diagnostic Efficiency of Three Nutritional Indices for Mortality in the Training Set and Validation Set

ROC analyses revealed that the area under the curve of the HALP score was 0.765(95% CI:0.681–0.850; cut-off value: 16.85; sensitivity: 0.643; specificity: 0.797), PNI was 0.783(95% CI:0.693–0.873; cut-off value: 38.7; sensitivity: 0.755; specificity: 0.719) and CONUT score was 0.807(95% CI:0.733–0.880; cut-off value: 6.5; sensitivity: 0.684; specificity: 0.748) in the training cohort (Figure 2A). Similarly, the validation cohort showed equally good predictive performance,

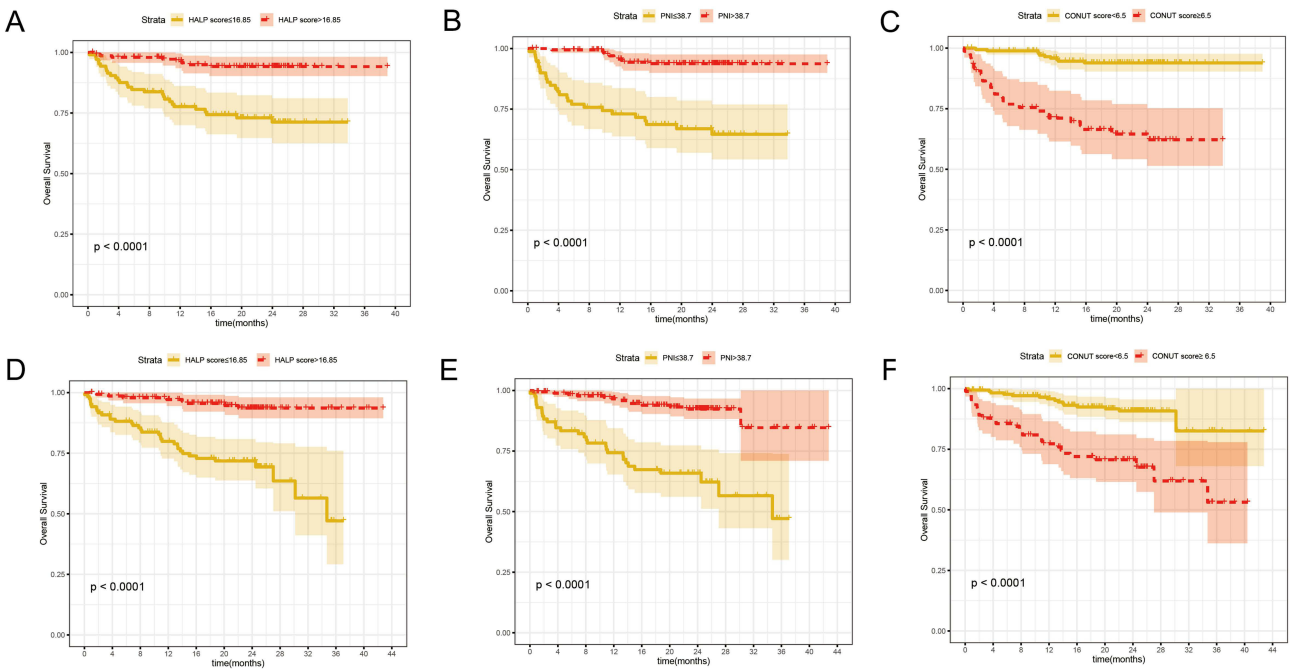

Figure 1 Overall survival of patients with MDR/RR-TB according to nutritional indices in the training cohort and the validation cohort.
Note: (**A**) HALP score, (**B**) PNI, and (**C**) CONUT score in the training cohort; (**D**) HALP score, (**E**) PNI, and (**F**) CONUT score in the validation cohort.
Abbreviations: HALP score, hemoglobin albumin-lymphocyte-platelet score; PNI, prognostic nutritional index; CONUT score, controlling nutritional status score.

with AUCs of 0.764(95% CI:0.689–0.839; cut-off value: 16.85; sensitivity: 0.624; specificity: 0.814), 0.782(95% CI:0.712–0.852; cut-off value: 38.7; sensitivity: 0.757; specificity: 0.698), and 0.742(95% CI:0.662–0.823; cut-off value: 5.5; sensitivity: 0.610; specificity: 0.767), respectively (Figure 2B). In addition, AUC of HGB was 0.688(95% CI:0.592–0.784; cut-off value: 118.5; sensitivity: 0.548; specificity: 0.452), ALB was 0.748 (95% CI:0.644–0.852; cut-off value: 33.2; sensitivity: 0.776; specificity: 0.75) and lymphocyte count was 0.701(95% CI:0.609–0.794; cut-off value: 1.105; sensitivity: 0.594; specificity: 0.806) in the training cohort (Figure 2A) and in the validation cohort (Figure 2B) was 0.705(95% CI:0.623–0.787; cut-off value: 115.5; sensitivity: 0.624; specificity: 0.721), 0.723 (95% CI: 0.645–0.801;

Table 5 Unadjusted and Multivariate Cox Risk Proportion Regression Analyses for All-Cause Mortality

	Training set				Validation set			
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
HALP score								
Low nutritional risk (>16.85)	Ref		Ref		Ref		Ref	
High nutritional risk (≤16.85)	5.520 (2.514–12.123)	0.000	3.405 (1.411–8.215)[a]	0.006	6.245 (2.896–13.468)	0.000	7.763 (3.071–19.620)[a]	0
PNI								
Low nutritional risk (>38.7)	Ref		Ref		Ref		Ref	
High nutritional risk (≤38.7)	7.110 (3.423–14.771)	0.000	3.970 (1.662–9.485)[a]	0.002	5.792 (3.015–11.125)	0.000	5.285 (2.530–11.040)[a]	0.000
CONUT score								
Low nutritional risk (<6.5)	Ref		Ref		Ref		Ref	
High nutritional risk (≥6.5)	7.830 (3.770–16.264)	0.000	4.734 (1.946–11.516)[a]	0.001	4.008 (2.136–7.518)	0.000	3.684 (1.829–7.5419)[a]	0.000

Note: [a]Multivariable Cox regression was adjusted for potential risk factors, including age, gender, retreatment, extrapulmonary tuberculosis, smoking, drinking, co-infection, bacterium, fungus, HIV, hepatitis B virus, hepatitis C virus, underlying disease (diabetes mellitus, hypertension, and malignancy), underlying pulmonary disease (pulmonary heart disease, bronchiectasis, and COPD), destroyed lung, pulmonary cavitation, and pleural effusion.
Abbreviations: HIV, human immunodeficiency virus; HALP score, hemoglobin-albumin-lymphocyte-platelet score; COPD, chronic obstructive pulmonary disease; PNI, prognostic nutritional index; CONUT score, controlling nutritional status score.

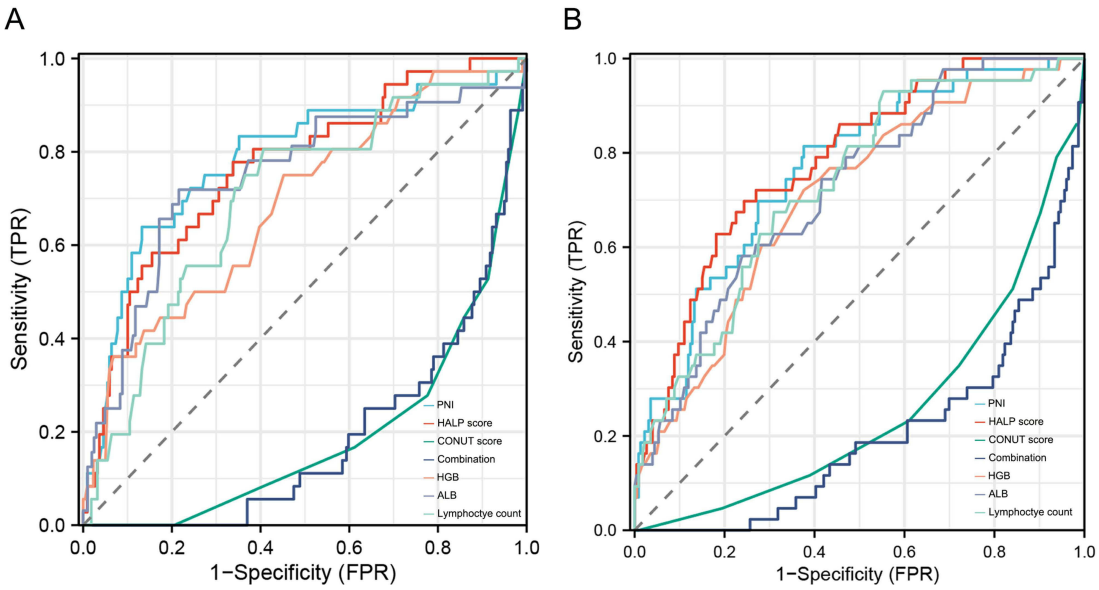

Figure 2 ROC curves for nutritional indices (HALP score, PNI, CONUT score and their combination) and simple parameters (HGB, ALB and lymphocyte count) in the training cohort and the validation cohort.

Note: (**A**) Training cohort: The AUC (95% CI) of the HALP score, PNI, CONUT score and their combination, HGB, ALB and lymphocyte count were 0.765 (95% CI: 0.681–0.850; cut-off value: 16.85; sensitivity: 0.643; specificity: 0.797), 0.783 (95% CI: 0.693–0.873; cut-off value: 38.7; sensitivity: 0.755; specificity: 0.719), 0.807 (95% CI:0.733–0.880; cut-off value: 6.5; sensitivity: 0.684; specificity: 0.748), 0.811 (95% CI:0.743–0.879; cut-off value: 0.143; sensitivity: 0.758; specificity: 0.722), 0.688 (95% CI:0.592–0.784; cut-off value: 118.5; sensitivity: 0.548; specificity: 0.452), 0.748 (95% CI:0.644–0.852; cut-off value: 33.2; sensitivity: 0.776; specificity: 0.75) and 0.701 (95% CI:0.609–0.794; cut-off value: 1.105; sensitivity: 0.594; specificity: 0.806) respectively. (**B**) Validation cohort: AUC (95% CI) of the HALP score, PNI, CONUT score and their combination, HGB, ALB and lymphocyte count were 0.764 (95% CI:0.689–0.839; cut-off value: 16.85; sensitivity: 0.624; specificity: 0.814), 0.782 (95% CI:0.712–0.852; cut-off value: 38.7; sensitivity: 0.757; specificity: 0.698), 0.742 (95% CI:0.662–0.823; cut-off value: 5.5; sensitivity: 0.610; specificity: 0.767), 0.796 (95% CI:0.725–0.867; cut-off value: 0.211; sensitivity: 0.796; specificity: 0.698), 0.705 (95% CI:0.623–0.787; cut-off value: 115.5; sensitivity: 0.624; specificity: 0.721), 0.723 (95% CI: 0.645–0.801; cut-off value: 32.6; sensitivity: 0.761; specificity: 0.581) and 0.731 (95% CI:0.652–0.809; cut-off value: 1.295; sensitivity: 0.553; specificity: 0.930), respectively.

Abbreviations: HALP score, hemoglobin-albumin-lymphocyte-platelet score; PNI, prognostic nutritional index; CONUT score, controlling nutritional status score; HGB, hemoglobin; ALB, albumin.

cut-off value: 32.6; sensitivity: 0.761; specificity: 0.581) and 0.731 (95% CI:0.652–0.809; cut-off value: 1.295; sensitivity: 0.553; specificity: 0.930), respectively. HALP score, PNI and CONUT score have better predictive performance than simple indicators including HGB, ALB and lymphocyte count for ACM in patients with MDR/RR-TB. Furthermore, the combination of the three nutrition indices showed a better AUC of 0.811(95% CI:0.743–0.879; cut-off value: 0.143; sensitivity: 0.758; specificity: 0.722) and 0.796 (95% CI:0.725–0.867; cut-off value: 0.211; sensitivity: 0.796; specificity: 0.698) than any single index in the two cohorts (Figure 2). DeLong ‘s test showed that there were statistically significant differences in AUC between combination index and HGB, combination index and lymphocyte count in the training set, while there were statistically significant differences in AUC between combination index and ALB, combination index and lymphocyte count in the validation set (Supplementary Table 4).

Discussion

MDR/RR-TB is still a serious issue in global TB control. Studies have shown that malnutrition is associated with MDR mortality,[14,15] and nutritional support can improve the prognosis of TB patients with malnutrition.[5,12,13] Hence, it is important to identify and intervene in malnourished MDR/RR-TB patients with a high risk of death.

Some studies, including our previous studies, have found that some laboratory indicators can predict complications and prognosis in patients with TB,[25,26] however, there were limited studies on nutritional indicators in TB patients. Recently, several nutritional indices, including HALP score, PNI, and CONUT score, have been proven to be used for assessing malnutrition and predicting the prognosis of some diseases,[4,27–31] which are relatively simple, convenient, effective, and practical. However, the effectiveness of these nutritional indices on prognosis prediction in MDR/RR-TB patients is unclear. To the best of our knowledge, this study is the first to explore the relationship between HALP score,

PNI, and CONUT score and ACM in MDR/RR-TB patients and to further evaluate their predictive value for ACM in MDR/RR-TB patients.

The present study revealed that patients in the LNRGs had higher OS than those in the HNRGs. In addition, low HALP score, low PNI, and high CONUT score were independent risk factors for ACM in MDR/RR-TB patients in the adjusted multivariate Cox risk proportion regression analyses. Furthermore, compared with simple parameters such as HGB, ALB and lymphocyte count, the HALP score, PNI, and CONUT have more powerful predictive capabilities for predicting mortality in MDR/RR-TB patients, especially when combined. The possible reason for the inconsistency of AUCs comparison between the combination index and ALB, the combination index and lymphocyte count in the training and validation set is the insufficient sample size.

The HALP, PNI, and CONUT scores were calculated using HGB, ALB, lymphocyte count, platelet count, and total cholesterol (TC). HGB plays an important role in gas exchange in human organs and tissues, and is a diagnostic indicator of anemia. Previous evidence revealed a high prevalence of anemia among TB patients, and TB patients with anemia had an increased risk of death.[32] ALB is a common component of the HALP score, PNI, and CONUT score, and has been proven to reflect nutritional status and systemic inflammation.[33] Franch AG suggested that lower ALB levels had a higher risk of mortality in populations with diseases or healthy populations.[34] As for lymphocyte count and platelet count, lymphocytes reflected the immune regulatory response,[35] and its count was proven to be the predictor of mortality in various diseases.[36] In addition, numerous observational studies report thrombocytosis in patients with TB, and platelet count correlated with disease severity.[37] TC was also an index, reflected nutritional status and systemic inflammation. Previous literature revealed that a cholesterol-rich diet accelerated the sterilization rate of sputum cultures in pulmonary TB patients,[38] and higher TC levels could reduce the risk of TB incidence and mortality.[39] Therefore, HALP score, PNI and CONUT scores could represent nutritional status and reflect the mortality of MDR/RR-TB patients and had good predictive value for mortality, especially when combined.

Furthermore, previous studies have shown that nutritional support had a commendable impact on improvement of lymphocyte count, hemoglobin, and albumin levels in patients with TB,[40,41] and robust nutritional intervention would be highly cost-effective in reducing TB mortality.[5] Therefore, nutrition monitoring should be strengthened and nutritional interventions should be used early to minimize the mortality of MDR/RR-TB patients.

Nevertheless, this study had some limitations. Firstly, the present study was a retrospective single center study. Secondly, this study did not include a control group of non-drug resistant TB and could not compare the difference in nutritional indices between MDR/RR-TB and drug-sensitive TB patients. Therefore, Future prospective, multicenter, large-sample studies are needed to confirm and improve our conclusions.

Conclusion

In conclusion, the HALP, PNI, and CONUT scores were objective and simple nutritional indices and powerful predictors of ACM in MDR/RR-TB patients. Routine screening for the three nutritional indices, especially their combination, should be strengthened in clinical practice to identify high-risk MDR/RR-TB patients with mortality, and could help decrease the mortality of MDR/RR-TB patients using early nutritional interventions.

Data Sharing Statement

The datasets used in this study are obtainable from the corresponding author on request.

Ethics Statement

The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. The Ethics Committee of Wuhan Jinyintan Hospital (KY-2022-06.01) reviewed and approved this study and informed consent was obtained from all patients.

Author Contributions

All authors made a significant contribution to the work reported, whether 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.

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Disclosure

All authors have no competing interests to report in this work.

References

1. Gandhi NR, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet*. 2010; 3759728:1830–1843. doi:10.1016/S0140-6736(10)60410-2
2. World Health Organization. Global tuberculosis report 2023 World Health Organization; 2023. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023. Accessed November 23, 2023.
3. Yu Q, Luo H, Hu S, Sun D, Nie Q, Yan J, The survival analysis of rifampicin/multidrug-resistant tuberculosis patients based on the levels of inflammatory biomarkers: a retrospective cohort study. *Front Cell Infect Microbiol*. 2023;13:1118424.doi: 10.3389/fcimb.2023.1118424
4. Ma JJ, Guo YJ, Li Z, Chen Y, He H, Li WM, Prevalence and prognostic significance of malnutrition risk in patients with pulmonary tuberculosis: a hospital-based cohort study. *Front Public Health*. 2022;10:1039661.doi: 10.3389/fpubh.2022.1039661
5. Sinha P, Lakshminarayanan SL, Cintron C, et al. Nutritional supplementation would be cost-effective for reducing tuberculosis incidence and mortality in India: the ration optimization to impede tuberculosis (ROTI-TB) model. *Clin Infect Dis*. 2022; 754:577–585. doi:10.1093/cid/ciab1033
6. Choi R, Jeong BH, Koh WJ, Lee SY. Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations. *Ann Lab Med*. 2017; 372:97–107. doi: 10.3343/alm.2017.37.2.97
7. Bhargava A, Chatterjee M, Jain Y, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS One*. 2013; 810:e77979. doi:10.1371/journal.pone.0077979
8. Wondmieneh A, Gedefaw G, Getie A, Demis A, Prevalence of undernutrition among adult tuberculosis patients in Ethiopia: a systematic review and meta-analysis. *J Clin Tuberc Other Mycobact Dis*. 2021;22:100211.doi: 10.1016/j.jctube.2020.100211
9. Zachariah R, Spielmann MP, Harries AD, Salaniponi FML. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death. *Trans R Soc Trop Med Hyg*. 2002; 963:291–294. doi: 10.1016/s0035-9203(02)90103-3
10. Dodor E. Evaluation of nutritional status of new tuberculosis patients at the effia-nkwanta regional hospital. *Ghana Med J*. 2008; 421:22–28
11. Bhargava A, Benedetti A, Oxlade O, Pai M, Menzies D. Undernutrition and the incidence of tuberculosis in India: national and subnational estimates of the population-attributable fraction related to undernutrition. *Natl Med J India*. 2014; 273:128–133
12. Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. *Lancet*. 2023; 40210402:627–640. doi:10.1016/S0140-6736(23)01231-X
13. Bhargava A, Bhargava M, Meher A, et al. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India. *Lancet Glob Health*. 2023; 119:e1402–e1411. doi:10.1016/S2214-109X(23)00324-8
14. Wagnew F, Alene KA, Kelly M, Gray D, The effect of undernutrition on sputum culture conversion and treatment outcomes among people with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Inter J Infect Dis*. 2023;127:93–105.doi: 10.1016/j.ijid.2022.11.043
15. Podewils LJ, Holtz T, Riekstina V, et al. Impact of malnutrition on clinical presentation, clinical course, and mortality in MDR-TB patients. *Epidemiol Infect*. 2011; 1391:113–120. doi:10.1017/S0950268810000907
16. Muluneh MA, Zeru AB, Derseh BT, Molla Kebede A, Survival status and predictors of mortality among multidrug-resistant tuberculosis patients in saint peter's specialized hospital, Addis Ababa, Ethiopia. *Can J Infect Dis Med Microbiol*. 2021;2021:6696199.doi: 10.1155/2021/6696199
17. World Health Organization. Guideline: nutritional care and support for patients with tuberculosis. World Health Organization; 2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK189867/. Accessed December 19, 2023.
18. Li Y, Yang F, Zhou H, Shu L, Wang R, Zhao C. Clinical application of NRS-2002 in nutritional risk screening of tuberculosis inpatients. *Ann Palliat Med*. 2021; 105:5322–5328. doi: 10.21037/apm-21-610
19. Chen XL, Xue L, Wang W, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. *Oncotarget*. 2015; 638:41370–41382. doi:10.18632/oncotarget.5629
20. Liu QX, Tang DY, Xiang X, He JQ, Associations between nutritional and immune status and clinicopathologic factors in patients with tuberculosis: a comprehensive analysis. *Front Cell Infect Microbiol*. 2022;12:1013751.doi: 10.3389/fcimb.2022.1013751
21. K B, Singla R, Singla N, et al. Factors affecting the treatment outcome of injection based shorter MDR-TB regimen at a referral centre in India. *Monaldi Arch Chest Dis*. 2022;933. doi: 10.4081/monaldi.2022.2396
22. Wakjira MK, Sandy PT, Mavhandu-Mudzusi AH. Treatment outcomes of patients with MDR-TB and its determinants at referral hospitals in Ethiopia. *PLoS One*. 2022; 172:e0262318. doi: 10.1371/journal.pone.0262318
23. Tang S, Tan S, Yao L, et al. Risk factors for poor treatment outcomes in patients with mdr-tb and xdr-tb in china: retrospective multi-center investigation. *PLoS One*. 2013; 812:e82943. doi:10.1371/journal.pone.0082943
24. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization; 2019.
25. Yan J, Luo H, Nie Q, Hu S, Yu Q, Wang X, A scoring system based on laboratory parameters and clinical features to predict unfavorable treatment outcomes in multidrug- and rifampicin-resistant tuberculosis patients. *IDR*. 2023;16:225–237.doi: 10.2147/IDR.S397304
26. Yu Q, Weng W, Luo H, Yan J, Zhao X, The novel predictive biomarkers for type 2 diabetes mellitus in active pulmonary tuberculosis patients. *Infect Drug Resist*. 2022;15:4529–4539.doi: 10.2147/IDR.S377465

27. Sze S, Pellicori P, Kazmi S, et al. Prevalence and prognostic significance of malnutrition using 3 scoring systems among outpatients with heart failure: a comparison with body mass index. *JACC Heart Fail*. 2018; 66:476–486. doi:10.1016/j.jchf.2018.02.018
28. Raposeiras Roubín S, Abu Assi E, Cespón Fernandez M, et al. Prevalence and prognostic significance of malnutrition in patients with acute coronary syndrome. J Am Coll Cardiol. 2020; 767:828–840. doi:10.1016/j.jacc.2020.06.058
29. Xu X, Zhu H, Cai L, et al. Malnutrition is associated with an increased risk of death in hospitalized patients with active pulmonary tuberculosis: a propensity score matched retrospective cohort study. *Infect Drug Resist*. 2022;15: 6155–6164.doi: 10.2147/IDR.S382587
30. Yi H, Chen C, Zhou S, et al. Comparison of three nutritional assessment methods associated with the prognostic impact of laryngeal cancer. *Support Care Cancer*. 2023; 3112:737. doi:10.1007/s00520-023-08148-w
31. Sun R, Zhou Z, Li X, et al. Prognostic significance of preoperative nutritional status for postoperative acute kidney injury in older patients undergoing major abdominal surgery: a retrospective cohort study. *Int J Surg*. 2023. doi: 10.1097/JS9.0000000000000861
32. Isanaka S, Mugusi F, Urassa W, et al. Iron deficiency and anemia predict mortality in patients with tuberculosis. *J Nutr*. 2012; 1422:350–357. doi:10.3945/jn.111.144287
33. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enteral Nutr*. 2019; 432:181–193. doi: 10.1002/jpen.1451
34. Franch-Arcas G. The meaning of hypoalbuminaemia in clinical practice. *Clin Nutr*. 2001; 203:265–269. doi: 10.1054/clnu.2001.0438
35. Cardoso CRL, Leite NC, Salles GF. Importance of hematological parameters for micro- and macrovascular outcomes in patients with type 2 diabetes: the rio de janeiro type 2 diabetes cohort study. *Cardiovasc Diabetol*. 2021; 201:133. doi: 10.1186/s12933-021-01324-4
36. Hong J, Huang QQ, Liu WY, et al. Three nutritional indices are effective predictors of mortality in patients with type 2 diabetes and foot ulcers. *Front Nutr*. 2022;9: 851274.doi: 10.3389/fnut.2022.851274
37. Kirwan DE, Chong DLW, Friedland JS, Platelet activation and the immune response to tuberculosis. *Front Immunol*. 2021;12:631696.doi: 10.3389/fimmu.2021.631696
38. Pérez-Guzmán C, Vargas MH, Quiñonez F, Bazavilvazo N, Aguilar A. A cholesterol-rich diet accelerates bacteriologic sterilization in pulmonary tuberculosis. *Chest*. 2005; 1272:643–651. doi: 10.1378/chest.127.2.643
39. Chidambaram V, Zhou L, Ruelas Castillo J, et al. Higher serum cholesterol levels are associated with reduced systemic inflammation and mortality during tuberculosis treatment independent of body mass index. *Front Cardiovasc Med*. 2021;8: 696517.doi: 10.3389/fcvm.2021.696517
40. Sharan Kumar VG, Pajanivel R, Boratne AV, Vimal Raj R. Impact of dietary counselling on the nutritional status and quality of life among pulmonary tuberculosis patients - A randomized control trial. *Indian J Tuberc*. 2022; 692:201–206. doi: 10.1016/j.ijtb.2021.07.015
41. Benzekri NA, Sambou JF, Tamba IT, et al. Nutrition support for HIV-TB co-infected adults in Senegal, West Africa: a randomized pilot implementation study. *PLoS One*. 2019; 147:e0219118. doi:10.1371/journal.pone.0219118