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Association Between Indices of Peripheral Blood Inflammation and Cavitary Pulmonary Tuberculosis

Xiaoshan He, Hongbiao Hou, Yuting Jiang, Xiaohuan Huang

Department of Infectious Diseases, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, People's Republic of China

Correspondence: Xiaoshan He, Department of Infectious Diseases, Meizhou People's Hospital, Meizhou, People's Republic of China, Email hxshan1999@163.com

Objective: To explore inflammation markers of C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), and systemic inflammatory response index (SIRI) in the differential diagnosis of cavitary pulmonary tuberculosis (PTB) from non-cavitary PTB.

Methods: This retrospective study included 1233 patients with PTB, 518 patients were diagnosed with cavitary PTB as case group, while 715 patients which diagnosed with non-cavitary PTB were selected as control group. The clinical data of patients was collected and the levels of inflammation indices were measured. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnosis and analysis of selected indices. Logistic regression analysis was performed to evaluate the factors associated with cavitary PTB.

Results: The CRP, NLR, MLR, PLR, SII, and SIRI in the case group were significantly higher than those in the controls (all $p<0.001$). When cavitary PTB was taken as the endpoint, the optimal diagnostic thresholds of CRP was 35.365 (area under the ROC curve (AUC)=0.601), NLR was 5.740 (AUC=0.595), MLR was 0.525 (AUC=0.577), PLR was 198.255 (AUC=0.602), SII was 1252.045 (AUC=0.628), and SIRI was 2.095 (AUC=0.605), respectively. Logistic regression analysis showed that gender, CRP, PLR, and SIRI were the independent risk factors for cavitary PTB. The sensitivity of the combination of the three indices (CRP+PLR, CRP+SIRI, PLR+SIRI, and CRP+PLR+SIRI) were higher than those of the CRP, PLR, and SIRI.

Conclusion: CRP, PLR, and SIRI levels were associated with an increased likelihood of cavitary PTB. The combined detection of CRP, PLR, and SIRI is promising as a screening marker and may be useful for ruling out PTB with cavitary.

Keywords: cavitary pulmonary tuberculosis, C-reactive protein, platelet-to-lymphocyte ratio, systemic inflammatory response index

Introduction

Tuberculosis (TB) is a highly contagious and chronic disease caused by *Mycobacterium tuberculosis (M. tuberculosis)* infection.[1,2] Although TB is curable and preventable, it poses a threat to human health and leads a major economic burden. About a quarter of the world's population is infected with *M. tuberculosis*, and about one-twentieth to one-tenth of those infected develop TB.[3,4] China ranks third among countries with a high TB burden, accounting for about 7.4% of reported cases globally.[5,6] The lung is the organ most commonly affected by TB infection (known as pulmonary tuberculosis (PTB)), with an estimated lung involvement rate of 79–87%.[7] Cavitary PTB is mainly caused by nodules or masses of tuberculosis and degeneration and necrosis of lesions, resulting in destruction of bronchial wall structure, secretion of liquefied substances through bronchial efflux, and then into the air.[8] The occurrence of cavitation in pulmonary lesions in PTB patients usually indicates that patients may have problems such as poor treatment effect, easy recurrence after treatment, strong transmission, and drug resistance.[8,9] It also poses a public health threat, increasing the risk of person-to-person transmission.[10–12]

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TB causes an especially high rate of cavitation, and from 29–87% of PTB patients are diagnosed with cavitary disease.[11] A tuberculous cavity is a pathological air-filled void within the lung parenchyma delineated by a distinct border or wall.[13] In patients infected with *M. tuberculosis*, the pathological processes of exudation, hyperplasia, and necrosis occur sequentially in the diseased tissues, followed by the formation of cavities in locally necrotic tissues through liquefaction, absorption, or bronchial drainage.[14,15] Once a tuberculosis cavity appears, it suggests a high bacterial content in the lesion, high infectiousness, and a high risk of spreading along the bronchial tubes. And it can be more harmful to both society and individuals if not diagnosed and treated in a timely manner. Variability in size, morphology, and wall composition exists within tuberculosis cavities, and can be assessed through non-invasive radiological imaging techniques.[16,17] Although imaging examination has become an important diagnostic method for PTB at present, cavitary PTB is prone to multiple manifestations on imaging, which may inevitably lead to misdiagnosis in clinical practice.[18,19] Therefore, it is of clinical significance to study the valuable markers of cavitary PTB. *M. tuberculosis* may causes cavities indirectly by promoting an immune response, thus developing cavitary PTB. There is an immune environment in the focal center of tuberculosis infection, and the interaction between pro-inflammatory and anti-inflammatory is crucial to the progression and prognosis of tuberculosis.[20,21] Various immune cells are involved in maintaining the balance of immune environment.[22–24] Immunological response plays important role in development of cavitary PTB.

The indices of peripheral blood inflammation reflect the immune state of the body. Complete blood count (CBC) parameters such as neutrophils, lymphocytes, monocytes, and platelets, have been suggested as diagnostic and prognostic markers for many diseases.[25–28] The indices derived from the parameter conversion of CBC also have certain clinical value. Systemic immune inflammation index (SII) and system inflammation response index (SIRI) are two markers of systemic immune inflammation, and their links to a number of diseases are being revealed.[29–31] The platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) are the ratios of the levels of two types of cells in peripheral blood respectively, which can reflect an individual's immune status to pathogenic bacterial infection and the severity of the disease.[32] These new immune inflammatory indicators have attracted considerable attention in recent years.[33–35] In addition, the neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) levels have been found to be associated with chronic bacterial pulmonary infections.[36] However, the relationship between these inflammatory markers and cavitary PTB remains unclear. The aim of this study was to investigate the value of these inflammatory indices in differentiating cavitary PTB from non-cavitary PTB.

Materials and Methods

Study Population

It was a retrospective study with a total of 1233 PTB patients treated in Meizhou People's Hospital from May 2016 to December 2020 were selected as the study objects. This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[37] During the study period, 518 patients were diagnosed with cavitary PTB in the case group, whereas the other 715 patients diagnosed with non-cavitary PTB were selected as the control group. PTB patients were diagnosed according to the criteria of "WS 288–2017 Pulmonary Tuberculosis Diagnosis"[7] by microbiological diagnosis. Based on the above findings, cavitary PTB was diagnosed using pulmonary imaging, which suggested accompanying emptiness.

Inclusion criteria were as follows: (1) clinically diagnosed PTB; (2) patients were ≥18 years old; and (3) the patients with complete medical records. The exclusion criteria were: (1) patients were <18 years old; (2) patients with incomplete clinical data; and (3) patients with leukemia, HIV infection, septic shock, organ failure, malignancy, and mental disorder. Clinical data were collected from all of the study subjects, including age, gender, fever, respiratory symptoms, expectoration, and extrapulmonary tuberculosis. All participants were informed on the study procedures and goals and the informed consent was obtained from all the participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital. We have de-identified the details of all subjects to protect the privacy of participants.

Methods for Detecting Hematological Parameters

2mL venous blood was drawn from each subject and collected in an ethylenediamine tetraacetic acid (EDTA) anticoagulant tube. Complete blood count and CRP analysis of blood samples was performed using a Sysmex XE-2100 hematology analyzer (Sysmex Corporation, Japan) and Olympus AU5400 system (Olympus Corporation, Tokyo, Japan), respectively, according to standard operating procedure. Complete blood count includes neutrophils, lymphocytes, monocytes, and platelets. NLR, PLR, and MLR values were obtained by dividing the cell counts in the measured complete blood count by each other: NLR=neutrophil/lymphocyte; PLR=platelet/lymphocyte; MLR=monocyte/lymphocyte. The inflammation indices SII and SIRI were calculated according to the following formulas: SII=platelet×neutrophil/lymphocyte; SIRI=monocyte×neutrophil/lymphocyte.

Data Processing and Statistical Analysis

SPSS 26.0 and GraphPad Prism 8.0 were used for statistical analysis of the experimental data. Data with non-normal distributions were described as medians and quartiles and were evaluated using the Mann–Whitney *U*-test. Categorical variables were represented numerically and as percentages, and compared using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of CRP, NLR, MLR, PLR, SII, and SIRI to distinguish cavitary PTB. Logistic regression analysis was used to analyze factors related to cavitary PTB. $p<0.05$ were considered statistically significant.

The following indices were used to evaluate the clinical diagnostic efficacy of CRP, PLR, SIRI, and their combination on cavitary PTB:

Sensitivity=number of true positive cases/(number of true positive cases + number of false negative cases);

Specificity=number of true negative cases/(number of true negative cases + number of false positive cases);

Positive predictive value=number of true positive cases/(number of true positive cases + number of false positive cases);

Negative predictive value=number of true negative cases/(number of true negative cases + number of false negative).

Results

The Clinical Features and Peripheral Blood Inflammatory Markers of PTB Patients with and without Cavitary

A total of 1233 PTB cases were included in this study. Among them, there were 715 cases (589 men and 126 women) in the control group, of which 278 patients were aged <60 years and 437 were aged ≥60 years; and 518 cases (455 men and 63 women) in the study group, of which 232 patients were aged <60 years and 286 were aged ≥60 years. The proportion of patients aged <60 years in the study group was significantly higher than that in the control group ($p=0.040$). The CRP, NLR, MLR, PLR, SII, and SIRI levels in study group were significantly higher than those in the control group (all $p<0.001$). Clinical characteristics including fever, shortness of breath/difficulty breathing, expectoration, and extrapulmonary tuberculosis were not significantly different between the two groups (all $p>0.05$) (Table 1).

The Optimal Cutoff Values of Peripheral Blood Inflammatory Markers by ROC Curve Analysis

When cavitary PTB was considered as the endpoint of CRP, NLR, MLR, PLR, SII, and SIRI, the critical value of CRP was 35.365 (sensitivity 56.4%, specificity 60.6%, area under the ROC curve (AUC): 0.601), the NLR cutoff value was 5.740 (sensitivity 54.1%, specificity 60.3%, AUC: 0.595), the MLR cutoff value was 0.525 (sensitivity 61.2%, specificity 50.8%, AUC: 0.577), the PLR cutoff value was 198.255 (sensitivity 66.6%, specificity 50.2%, AUC: 0.602), the SII cutoff value was 1252.045 (sensitivity 67.4%, specificity 50.9%, AUC: 0.628), and the SIRI cutoff value was 2.095 (sensitivity 80.9%, specificity 35.7%, AUC: 0.605) (Figure 1).

Table 1 Comparison of Clinical Features and Peripheral Blood Inflammatory Markers Between Cavitary Pulmonary Tuberculosis Group and Non-Cavitary Pulmonary Tuberculosis Group

Variables	Total (n=1233)	Non-cavitary pulmonary tuberculosis group (n=715)	Cavitary pulmonary tuberculosis group (n=518)	*p* values
Gender				
Male, n (%)	1044 (84.7%)	589 (82.4%)	455 (87.8%)	0.010
Female, n (%)	189 (15.3%)	126 (17.6%)	63 (12.2%)	
Age (Years)				
<60, n (%)	510 (41.4%)	278 (38.9%)	232 (44.8%)	0.040
≥60, n (%)	723 (58.6%)	437 (61.1%)	286 (55.2%)	
Fever				
No, n (%)	1050 (85.2%)	608 (85.0%)	442 (85.3%)	0.935
Yes, n (%)	183 (14.8%)	107 (15.0%)	76 (14.7%)	
Shortness of breath/Difficulty breathing				
No, n (%)	942 (76.4%)	549 (76.8%)	393 (75.9%)	0.734
Yes, n (%)	291 (23.6%)	166 (23.2%)	125 (24.1%)	
Expectoration				
No, n (%)	542 (44.0%)	326 (45.6%)	216 (41.7%)	0.182
Yes, n (%)	691 (56.0%)	389 (54.4%)	302 (58.3%)	
Extrapulmonary tuberculosis				
No, n (%)	1129 (91.6%)	653 (91.3%)	476 (91.9%)	0.756
Yes, n (%)	104 (8.4%)	62 (8.7%)	42 (8.1%)	
Peripheral blood inflammatory markers				
CRP, median (P25, P75)	31.58 (8.31, 75.78)	22.76 (6.28, 67.80)	45.88 (14.68, 85.15)	<0.001
NLR, median (P25, P75)	5.33 (3.33, 8.47)	4.86 (3.05, 7.67)	6.11 (3.77, 10.17)	<0.001
MLR, median (P25, P75)	0.57 (0.38, 0.84)	0.50 (0.33, 0.80)	0.63 (0.43, 0.89)	<0.001
PLR, median (P25, P75)	223.50 (148.50, 350.42)	197.78 (136.15, 315.00)	250.63 (171.88, 388.65)	<0.001
SII, median (P25, P75)	1461.10 (823.80, 2551.60)	1236.00 (701.33, 2187.33)	1782.53 (1038.47, 3228.84)	<0.001
SIRI, median (P25, P75)	3.41 (1.85, 6.75)	3.07 (1.60, 5.81)	4.22 (2.36, 7.96)	<0.001

Abbreviations: CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; p25, 25th percentile; p75, 75th percentile.

Logistic Regression Analysis of Related Factors for PTB Patients with Cavitary

In univariable analysis, male (odds ratio (OR): 1.545, 95% confidence interval (CI): 1.115–2.141, p=0.009), age <60 years old (OR: 1.275, 95% CI: 1.014–1.604, p=0.038), and CRP≥35.365 (OR: 1.984, 95% CI: 1.577–2.496, p<0.001), NLR≥5.740 (OR: 1.785, 95% CI: 1.420–2.244, p<0.001), MLR≥0.525 (OR: 1.626, 95% CI: 1.293–2.046, p<0.001), PLR≥198.255 (OR: 2.011, 95% CI: 1.591–2.542, p<0.001), SII≥1252.045 (OR: 2.142, 95% CI: 1.693–2.709, p<0.001), and SIRI≥2.095 (OR: 2.346, 95% CI: 1.796–3.065, p<0.001) were associated with an increased risk of cavitary PTB. In the multivariable logistic regression model, age <60 years old (OR: 1.312, 95% CI: 1.028–1.674, p=0.029), CRP ≥35.365 (OR: 1.573, 95% CI: 1.203–2.056, p=0.001), PLR ≥198.255 (OR: 1.464, 95% CI: 1.062–2.018, p=0.020), and SIRI ≥2.095 (OR: 1.785, 95% CI: 1.248–2.553, p=0.002) were significantly associated with an increased risk of cavitary PTB. The association between age, CRP, PLR, and SIRI remained significant in cavitary PTB after adjustment for potential covariates (Table 2).

The Diagnostic Efficacy of CRP, PLR, SIRI, and Their Combination on Cavitary Pulmonary Tuberculosis

As shown in Table 3, the order of sensitivity from low to high is: CRP, PLR, CRP + PLR, SIRI, CRP + SIRI, PLR + SIRI, CRP + PLR + SIRI, and the combination of three indices has the highest sensitivity of 89.4%. The order of specificity from low to high is: CRP + PLR + SIRI, PLR + SIRI, CRP + SIRI, SIRI, CRP+PLR, PLR, and CRP, CRP had

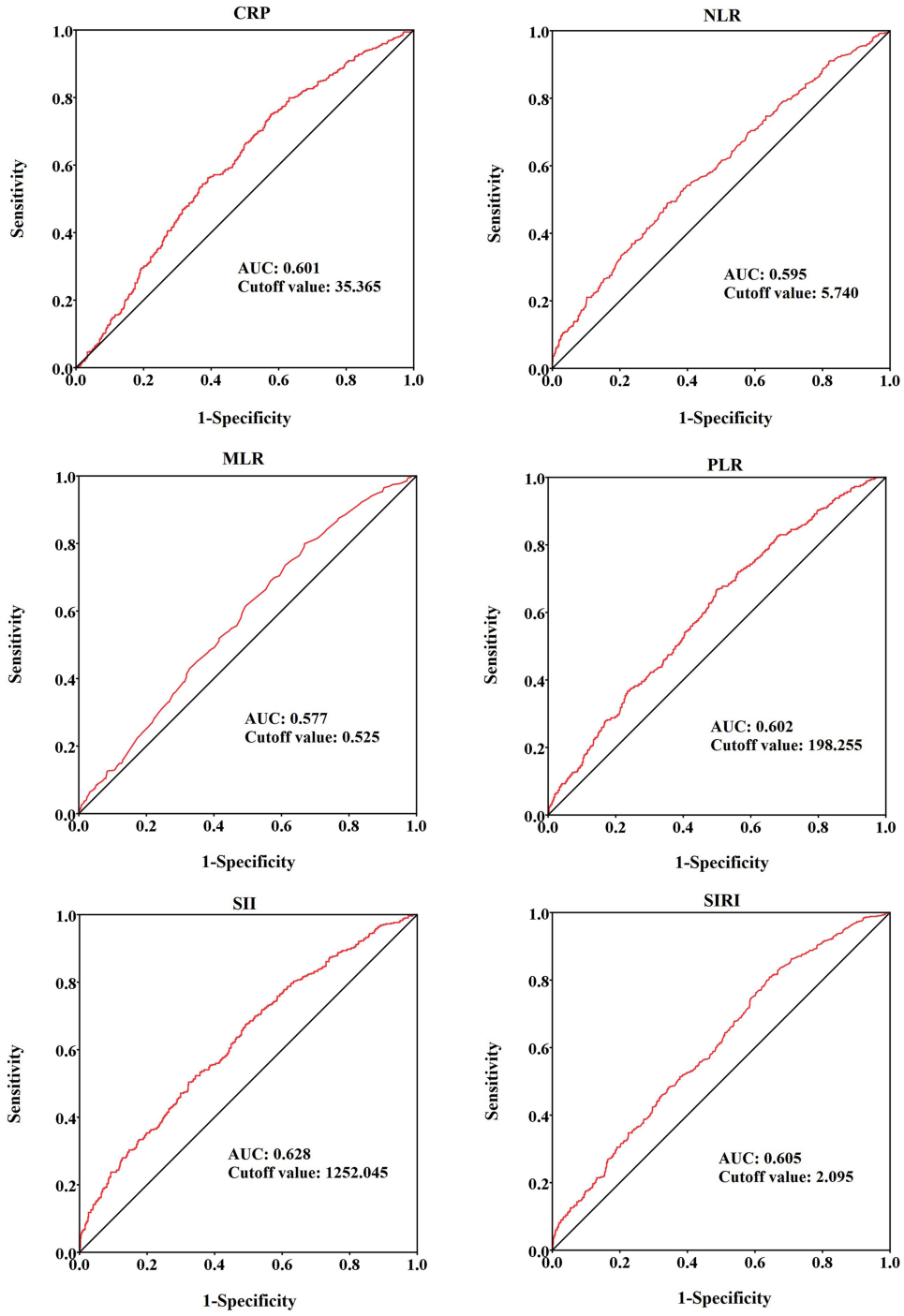

Figure 1 The ROC curve of CRP, NLR, MLR, PLR, SII, and SIRI for the predicting cavitary PTB.
Abbreviations: CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; PTB, pulmonary tuberculosis.

the highest specificity value (60.6%). CRP had the highest positive predictive value (50.9%), and CRP + SIRI had the highest negative predictive value (75.0%).

Discussion

Cavitary lesions are more frequent in patients with PTB,[38] and deserve further attention. The assessment of cavitary PTB mainly relies on the determination of imaging manifestations, but requires extensive clinical experience and detection

Table 2 Logistic Regression Analysis of Related Factors of Cavitary Pulmonary Tuberculosis

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Gender (Male/Female)	1.545 (1.115–2.141)	0.009	1.395 (0.989–1.967)	0.058
Age (<60/≥60, years old)	1.275 (1.014–1.604)	0.038	1.312 (1.028–1.674)	0.029
Fever (Yes/No)	0.977 (0.711–1.344)	0.886	0.649 (0.460–0.917)	0.140
Shortness of breath/Difficulty breathing (Yes/No)	1.052 (0.806–1.372)	0.709	0.923 (0.687–1.241)	0.598
Expectoration (Yes/No)	1.172 (0.932–1.472)	0.174	1.207 (0.934–1.559)	0.150
Extrapulmonary tuberculosis (Yes/No)	0.929 (0.617–1.399)	0.725	0.808 (0.524–1.246)	0.335
CRP (≥35.365/<35.365)	1.984 (1.577–2.496)	<0.001	1.573 (1.203–2.056)	0.001
NLR (≥5.740/<5.740)	1.785 (1.420–2.244)	<0.001	1.050 (0.766–1.440)	0.763
MLR (≥0.525/<0.525)	1.626 (1.293–2.046)	<0.001	0.761 (0.550–1.052)	0.098
PLR (≥198.255/<198.255)	2.011 (1.591–2.542)	<0.001	1.464 (1.062–2.018)	0.020
SII (≥1252.045/<1252.045)	2.142 (1.693–2.709)	<0.001	1.267 (0.872–1.840)	0.214
SIRI (≥2.095/<2.095)	2.346 (1.796–3.065)	<0.001	1.785 (1.248–2.553)	0.002

Abbreviations: OR, odds ratio; CI, confidence interval. CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

Table 3 The Diagnostic Efficacy of CRP, PLR, SIRI, and Their Combination on Cavitary Pulmonary Tuberculosis

Peripheral blood inflammatory markers	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CRP	56.4% (292/518)	60.6% (433/715)	50.9% (292/574)	65.7% (433/659)
PLR	66.6% (345/518)	50.2% (359/715)	49.2% (345/701)	67.5% (359/532)
SIRI	80.9% (419/518)	35.7% (255/715)	47.7% (419/879)	72.0% (255/354)
CRP + PLR	77.0% (399/518)	38.0% (272/715)	47.4% (399/842)	69.6% (272/391)
CRP + SIRI	86.3% (447/518)	29.8% (213/715)	47.1% (447/949)	75.0% (213/284)
PLR + SIRI	87.3% (452/518)	25.5% (182/715)	45.9% (452/985)	73.4% (182/248)
CRP + PLR + SIRI	89.4% (463/518)	22.5% (161/715)	45.5% (463/1017)	74.5% (161/216)

Abbreviations: CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio; SIRI, systemic inflammatory response index.

equipment with good resolution.[39] It is of great clinical significance to study the markers of PTB with cavitary and distinguish it from PTB without cavitary. Blood markers provide a potential assessment for distinguishing patients with non-cavitary PTB. This study showed that sex and age are the main factors affecting cavitation. The men had a higher cavitation rate than women, and those aged <60 years old had a higher cavitation rate than patients aged ≥60 years old, which is consistent with previous finding.[40] It may be due to the strong immunity of young and middle-aged people, the clinical symptoms after suffering from *M. tuberculosis* are not obvious, and young and middle-aged patients do not pay enough attention to tuberculosis, resulting in the development of cavity PTB without timely treatment. In addition, the differentiation of clinical manifestations of fever, shortness of breath/difficulty breathing, expectoration, and extrapulmonary tuberculosis was not remarkable in PTB with or without cavitation, indicating the difficulty in determining progression to cavitary tuberculosis from clinical symptoms.[41]

Inflammation plays an important role in the pathogenesis of PTB.[42,43] CRP, NLR, MLR, PLR, SII, and SIRI are novel inflammatory markers currently available.[44] In this study, logistic regression analysis indicated that CRP, PLR, and SIRI were associated with cavitary PTB. This result suggests that elevated CRP, PLR, and SIRI levels are associated with an increased likelihood of cavitary PTB. PLR is elevated in chronic obstructive pulmonary disease (COPD),[45] and asthma,[46] and is strongly associated with common respiratory diseases; however, there are few studies on the relationship between PLR and TB. CRP can be a valuable marker for PTB.[47] Some studies have found that the CRP is a potential indicator to assist in the diagnosis of active TB.[48–50] A study has found that SIRI has auxiliary diagnostic value for bacteria-negative TB.[51] However, the relationship between CRP, SIRI levels and cavitary PTB has not yet been reported.

In this study, the inflammation indices of CRP, NLR, MLR, PLR, SII, and SIRI were all significantly elevated in PTB patients with cavitary compared with PTB patients those without cavitary. However, the regression analysis showed that NLR, MLR, and SII were not associated with cavitary PTB. The NLR can be used as a potential marker to distinguish TB from sarcoidosis.[52] NLR has been studied in patients with TB, and scholars at home and abroad have found that NLR is related to the severity of TB, and can be used as a reference indicator for the clinical management of active TB.[53] The NLR can be used to distinguish childhood tuberculosis from other lower respiratory tract infections.[54] The MLR can be used as a diagnostic index of TB.[55] Suryana et al found that high MLR level before treatment was significantly associated with an increased risk of delayed sputum conversion at the end of PTB intensive treatment.[56] Liu et al found that a higher SII was significantly correlated with depression or anxiety symptoms in TB patients,[57] which is one of the few studies on the relationship between SII and TB.

In addition, we investigated the diagnostic efficacy of CRP, PLR, SIRI, and their combination on cavitary PTB, and found that both CRP and PLR had low sensitivity and specificity, whereas SIRI had high sensitivity but low specificity. After combining each index, it showed a great improvement in sensitivity, but a lower specificity than the individual indicators. It suggests that the combination of these markers is promising as a screening marker and may be useful for ruling out PTB with cavitary. However, the combination of markers is not ideal for ruling in PTB with cavitary due to poor specificity, so other tests are needed to confirm whether the individual has the disease. Thus, CRP, PLR, and SIRI could guide cavitary PTB to some extent, but are not very specific. Additionally, some studies have shown that higher levels of tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) in bronchoalveolar lavage fluid from patients with tuberculosis are associated with cavitary diseases.[12,58,59] Unfortunately, this study did not examine the relationship between these inflammatory markers and cavitary PTB.

In conclusion, the combined detection of PTB in men, age >60 years, and CRP (threshold =35.365), PLR (threshold=198.255), and SIRI (threshold=2.095) is helpful for the differential diagnosis of cavitary PTB. This could overcome the limitations of using imaging test assays in areas with a high PTB burden, providing a more convenient and rapid reference for first-line clinicians. Our data suggest that the combination of CRP, PLR, and SIRI has a differential diagnostic significance in cavitary PTB.

This study has some limitations. First, the relationship between haematological indicators of inflammation and cavitary PTB severity and the development of cavity in PTB was not investigated retrospectively. Second, this study was performed in one hospital among patients with cavitary PTB and non-cavitary PTB disease, and the results may be biased because of the incomplete representation of the included subjects. Third, this study only examined the differences in CRP, PLR, MLR, SII, and SIRI levels between cavitary PTB and non-cavitary PTB disease, and did not study the value of other inflammatory indicators in the differential diagnosis of PTB.[60] Future studies should consider these shortcomings for a more complete analysis.

Conclusion

In the present study, among patients with PTB, the age, gender and peripheral blood inflammatory markers (CRP, PLR, and SIRI) were associated with an increased risk of cavitation. In particular, the combination of CRP, PLR, and SIRI showed higher sensitivity for cavitary diagnosis. It suggests that the combination of these markers is promising as a screening marker and may be useful for ruling out PTB with cavitary. It provides additional reference data for clinical treatment of PTB.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals, and provided informed consent and were assured of data confidentiality. The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital. All participants signed informed consent in accordance with the Declaration of Helsinki.

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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.

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Disclosure

The authors declare that they have no competing interests.

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