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ORIGINAL RESEARCH

Association of Systemic Inflammatory Response Index with Disease Severity and Adverse Outcome in Chronic Thromboembolic Pulmonary Hypertension

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Background: Composite inflammatory markers, such as the systemic inflammatory response index (SIRI), are associated with the severity and progression of several cardiovascular diseases. However, the relationship between SIRI and chronic thromboembolic pulmonary hypertension (CTEPH) remains unclear. We hypothesized that elevated SIRI levels would correlate with disease severity and independently predict adverse clinical outcomes in patients with CTEPH. This study aimed to clarify the predictive value of SIRI in patients with CTEPH.

Methods: This retrospective cohort study included 383 patients with CTEPH treated at Fuwai Hospital between June 2013 and June 2021. Receiver operating characteristic (ROC) curve analysis was used to compare the diagnostic performance of SIRI to other inflammatory indices and identify the optimal cutoff value. Kaplan-Meier analysis and Cox proportional hazard models were used to examine the relationship between SIRI and clinical worsening.

Results: During a mean follow-up period of 30.6 months, 79 participants experienced clinical worsening. The SIRI was significantly correlated with established markers of CTEPH severity, including the 6-minute walk distance, N-terminal pro-brain natriuretic peptide, and hemodynamic parameters. Kaplan–Meier curve revealed that individuals with a SIRI $\geq$ 0.80 exhibited significantly poorer survival rates and a shorter time to clinical worsening compared to those with a SIRI < 0.80 (P < 0.01). Adjusted Cox proportional hazards analysis revealed that SIRI remained an independent predictor of clinical worsening (hazard ratio (HR) 2.033; 95% confidence interval (CI) 1.227–3.370). ROC analysis revealed that SIRI exhibited the highest area under the curve value of 0.730 (95% CI 0.659–0.810). Incorporating SIRI into The COMPERA 2.0, the risk score improved its predictive value for adverse outcomes in patients with CTEPH.

Conclusion: SIRI is a valuable prognostic marker for CTEPH, correlating with established markers of disease severity and independently predicting clinical worsening. SIRI provides additional prognostic predictive value when used in conjunction with the risk score of COMPERA 2.0.

Keywords: chronic thromboembolic pulmonary hypertension, prognosis, risk factors, inflammation

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolism that causes pulmonary hypertension, which can lead to right heart failure and mortality.[1] For patients with CTEPH and mean pulmonary artery pressure (mPAP) greater than 50 mmHg, the 5-year survival rate is only 10%.[2] Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH and can lead to a cure for some patients. Approximately 30% of patients still

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have persistent or residual pulmonary hypertension after pulmonary endarterectomy, and 37% are unable to undergo surgery due to contraindications, such as difficulty in reaching the lesion site.[3–5] Balloon pulmonary angioplasty (BPA), which has emerged in recent years, also improves hemodynamics, exercise tolerance, and prognosis in patients with inoperable CTEPH.[6] However, approximately 22% of patients experience residual pulmonary hypertension after pulmonary artery balloon dilatation.[7] The mechanisms of residual pulmonary hypertension (PH) are multifactorial, potentially involving preexisting small-vessel pathology, mismatched thrombus burden and hemodynamic improvement, variations in surgical techniques, and institutional experience.[5] Interesting reports suggest that a combination approach of PEA and BPA, rather than a single strategy, could lead to significant clinical improvements in the prognosis of CTEPH.[8] Furthermore, currently available targeted drugs have limited therapeutic effects in treating patients with CTEPH.[9] Therefore, risk stratification and clinical markers should be used to predict disease severity and prognosis.

The pathophysiology of CTEPH involves unresolved pulmonary thromboembolism progressing to fibrotic vascular lesions, characterized by incompletely resolved thrombi, collagen deposition, inflammatory cytokine-driven fibroblast migration, and infiltration of immune cells, forming persistent obstructive fibrotic material in pulmonary arteries.[10] Several studies have shown that genetic factors, inflammation, and abnormalities in the coagulation and fibrinolytic systems are involved in the progression of CTEPH, highlighting the complexity of its pathogenesis.[10–12] Recent studies have shown increasing interest in the role of inflammation in disease progression. A chronic inflammatory state has been observed in patients with CTEPH. Fibrous plaques have been found to be enriched with infiltration of inflammatory cells such as T lymphocytes and macrophages in specimens from patients with CTEPH.[13] Elevated serum levels of tumor necrosis factor-alpha, interleukin (IL)-6, IL-8, and macrophage inflammatory protein-1alpha (MIP-1α) have also been found to be elevated in patients with CTEPH.[14] Recent studies have highlighted the significant role of the NLRP3 inflammasome in PH, suggesting it as a potential therapeutic target for CTEPH.[8]

In addition to single inflammation indicators, such as C-reactive protein (CRP), increasing attention has been paid to composite inflammation indicators, such as the systemic inflammatory response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), which are calculated by combining individual inflammation indicators. Among these, the SIRI is a more comprehensive composite inflammation indicator that reflects body inflammation based on monocyte, neutrophil, and lymphocyte counts. The SIRI has been found to be associated with the prognosis of cardiovascular diseases such as hypertension, stroke, and heart failure.[15–17] A recent study also indicated that SIRI can independently predict the severity and prognosis of patients with idiopathic pulmonary arterial hypertension (IPAH).[18] Given that patients with CTEPH also undergo pulmonary vascular remodeling and develop right heart failure in the advanced stages of the disease, we hypothesized that SIRI could also play an important role in disease assessment and prognosis prediction in patients with CTEPH.

Studies on CTEPH and its association with composite inflammatory markers are limited. To bridge this gap, we conducted a retrospective cohort study to investigate the association between the SIRI and functional indices, echocardiographic and hemodynamic parameters, and disease prognosis in patients with CTEPH.

Methods

Study Design and Population

This retrospective cohort study included 397 patients with CTEPH treated at Fuwai Hospital between June 2013 and June 2021. The inclusion criteria were (1) patients aged 18 years and older; (2) patients with hemodynamic characteristics of CTEPH on right heart catheterization (RHC).[19–21] Exclusion criteria included: (1) the presence of cancer, such as blood cancer or tumors; (2) the presence of inflammatory conditions or ongoing infection; and (3) the absence of data on neutrophil, monocyte, lymphocyte, and platelet counts. Malignancy, inflammatory conditions, and ongoing infection were assessed using the International Classification of Diseases (Tenth Revision codes) in electronic medical records. This study included 383 patients with CTEPH after excluding those who met the exclusion criteria (Supplementary Figure S1).

Patient information, including demographics, smoking and alcohol habits, World Health Organization functional class (WHO-FC), comorbidities, history of BPA or PEA, and PH-specific medications, were collected on the day of admission.

On the same day, venous blood samples were obtained for routine blood examinations, N-terminal pro-brain natriuretic peptide (NT-proBNP), liver function tests, and kidney function tests. An automated Hematology analyzer (SYSMEX XN-20) was used to measure hematological parameters. Echocardiography was completed within 48 hours of admission. RHC and a 6-minute walking test were performed once the patients were in stable condition.

This study was approved by the Ethics Committee of Fuwai Hospital (Approval number: 2024-2301), and written informed consent was obtained from all patients.

Definition of Inflammatory Hematological Markers

The formulas used to calculate SIRI, NLR, PLR, and systemic immune inflammation index (SII) were as follows: SIRI = (neutrophil count × monocyte count)/lymphocyte count. NLR = neutrophil count/lymphocyte count. PLR = platelet count/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count.

RHC and Echocardiographic Examination

During RHC, the hemodynamic profile at baseline was assessed at end-expiration, which included measurements of mixed venous oxygen saturation (SvO_2), right atrial pressure, mPAP, and pulmonary artery wedge pressure (PAWP). Cardiac index was calculated by dividing the cardiac output by the body surface area. Pulmonary vascular resistance (PVR) was calculated using the standard formula. Experienced ultrasonologists in the Department of Echocardiography conducted comprehensive transthoracic echocardiography, systematically assessing pericardial effusion presence, left atrial diameter (LAD), left ventricular end-diastolic diameter (LVED), left ventricular ejection fraction (LVEF), right ventricular end-diastolic diameter (RVED), tricuspid regurgitation velocity (TRV), and systolic pulmonary artery pressure (sPAP). To minimize interobserver variability, standard operating procedures and uniform measurement protocols based on the latest guidelines were strictly followed.[22]

Risk Stratification Strategy

Patients were classified as low-, intermediate-low-, intermediate-high-, or high-risk using the 4-strata The COMprehensive PAH Risk Assessment (COMPERA) 2.0 risk score (Supplementary Table S1).[23–25] For each parameter in the prediction model (WHO-FC, NT-proBNP levels, and 6-minute walk distance (6 MWD)), a score ranging from 1–4 points was assigned. The individual risk score was determined by summing the total points and dividing by the number of variables, with decimal values rounded to the nearest integer.

Follow-Up and Outcome

The main objective of this study was to assess clinical worsening, defined as the initial instance of any of the following events: all-cause mortality, lung transplantation, or readmission due to heart failure. Telephonic follow-ups were conducted every 3–6 months to monitor clinical outcomes. All potential events were independently assessed by two senior clinicians, with any discrepancies resolved through discussion and consensus among the supervisors (QL and ZHL).

Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median [25th–75th percentile], while categorical variables are presented as counts (percentages). Continuous variables were tested for normality using the Shapiro–Wilk test. Data are presented as mean ± standard deviation (normally distributed) or median [interquartile range] (non-normally distributed). Statistical tests were chosen based on normality outcomes. Appropriate statistical tests, including the independent-sample *t*-test, Mann–Whitney *U*-test, chi-square test, and Fisher's exact test, were used to compare the two groups. Spearman correlation coefficients were used to examine the associations between SIRI and other variables. The relationship between continuous SIRI values and clinical worsening was evaluated using a restricted cubic spline curve. To predict clinical worsening and compare the diagnostic performance of SIRI with that of other inflammatory hematological markers, receiver operating characteristic (ROC) curve analysis was conducted to identify the optimal cutoff value. Survival curves were generated using the Kaplan–Meier method and compared with the Log rank test. Univariate Cox regression analysis was performed to identify potential risk factors for clinical worsening. Variables with

a P-value <0.05 were included in the multivariate Cox regression model. Model 1 was adjusted for age, and sex as confounding factors. Model 2 further incorporated WHO-FC, 6MWD, and ln(NT-proBNP). Model 3 was built on model 2 by adding adjustments for PH-specific medications, and BPA or PEA status. Multicollinearity was assessed using the variance inflation factor (VIF), with a threshold of VIF ≥10 indicating the presence of multicollinearity. Subgroup analyses were conducted to explore the interaction effects. DeLong's test were used to compare whether incorporating SIRI into the COMPERA 2.0 risk score can improve the predictive performance of the score. Statistical significance was defined as $P < 0.05$ (two-sided). All data analyses were performed using R Studio (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

This study included 383 participants diagnosed with CTEPH, with a median age of 57 years, of whom 49.35% were female. The median body mass index was 23.67 kg/m^2. The disparities at baseline in variables between patients with and without clinical worsening are presented in Table 1. Patients who experienced clinical worsening demonstrated a significantly worse WHO-FC rating and a more limited 6MWD than those without clinical worsening. Additionally, these patients exhibited markedly higher NT-proBNP, mPAP, mean right atrial pressure (mRAP), and PVR, along with

Table 1 Baseline Characteristics of Study Population

Variables	Non-CW (n = 304)	CW (n = 79)	P-Value
Demographics			
Age, years	56.00 [48.00–64.00]	59.00 [52.00–66.50]	0.056
Female, n (%)	151 (49.67)	38 (48.10)	0.903
Han ethnicity, n (%)	296 (97.37)	78 (98.73)	0.692
BMI, kg/m^2	24.02 [21.93–26.12]	22.53 [20.15–24.81]	0.003
Current smoking, n (%)	90 (29.61)	21 (26.58)	0.698
Alcohol intake, n (%)	68 (22.37)	18 (22.78)	0.937
Clinical evaluation and comorbidities			
WHO-FC, n (%)			<0.001
I or II	173 (56.91)	23 (29.11)	
III or IV	131 (43.09)	56 (70.89)	
6 MWD, m	383.25 ± 94.39	316.78 ± 91.47	<0.001
History of PTE, n (%)	198 (65.13)	51 (64.56)	0.924
Diabetes mellitus, n (%)	66 (21.71)	35 (44.30)	<0.001
Arterial hypertension, n (%)	86 (28.29)	22 (27.85)	0.938
OSA, n (%)	98 (32.24)	15 (18.99)	0.031
Laboratory data			
NT-proBNP, pg/mL	697.10 [155.02–1847.50]	1933.00 [1103.10–3420.50]	<0.001
White blood cell, 10^9/L	6.06 [5.22–7.16]	6.08 [5.30–7.46]	0.742
Neutrophil, 10^9/L	3.70 [3.04–4.50]	4.04 [3.34–4.90]	0.022
Lymphocyte, 10^9/L	1.79 [1.49–2.34]	1.56 [1.27–1.85]	<0.001
Monocyte, 10^9/L	0.33 [0.27–0.41]	0.40 [0.32–0.47]	<0.001
Hemoglobin, g/L	155.00 [139.75–167.00]	156.00 [141.00–173.50]	0.225
Platelets, 10^9/L	221.50 [184.75–274.00]	192.00 [168.50–237.50]	0.007
Albumin, g/L	42.41 ± 4.64	41.00 ± 5.13	0.029
ALT, IU/L	23.00 [16.00–34.25]	21.00 [15.00–30.50]	0.233
Serum creatinine, umol/L	83.41 [70.96–93.68]	86.28 [72.52–98.05]	0.076

(*Continued*)

Table 1 (Continued).

Variables	Non-CW (n = 304)	CW (n = 79)	P-Value
Inflammatory Hematological Ratios			
SIRI	0.67 [0.47–0.89]	0.94 [0.67–1.48]	<0.001
SII	445.91 [313.62–603.45]	543.97 [368.05–794.88]	0.005
NLR	2.00 [1.51–2.57]	2.66 [1.96–3.47]	<0.001
PLR	121.22 [93.14;157.76]	130.19 [100.25–174.60]	0.111
Echocardiography			
Pericardial effusion, n (%)	50 (16.45)	24 (30.38)	0.008
LAD, mm	33.00 [30.00–37.00]	33.00 [30.00–36.00]	0.572
LVED, mm	41.00 [37.00–46.00]	38.00 [34.50–41.50]	<0.001
LVEF, %	65.00 [60.00–68.00]	64.00 [60.00–68.00]	0.930
RVED, mm	31.00 [27.75–36.25]	36.00 [32.00–42.00]	<0.001
TRV, m/s	4.30 [3.73–4.74]	4.40 [4.10–4.93]	0.008
sPAP, mmHg	81.28 ± 26.36	91.14 ± 21.92	0.001
Hemodynamics			
S_VO_2, %	68.53 [63.54–73.20]	65.95 [61.62–69.70]	<0.001
mRAP, mmHg	6.00 [4.00–8.00]	9.00 [4.00–12.00]	0.001
mPAP, mmHg	45.73 ± 13.23	54.41 ± 14.52	<0.001
PAWP, mmHg	10.00 [7.00–12.00]	10.00 [8.00–12.00]	0.167
Cardiac index, L/min/m^2	2.82 [2.31–3.31]	2.49 [2.13–2.95]	0.009
PVR, wood units	8.89 [5.67–12.05]	12.19 [8.60–15.15]	<0.001
Treatment			
Anticoagulant, n (%)	294 (96.71)	76 (96.20)	0.736
PH-specific therapy, n (%)	224 (73.68)	61 (77.22)	0.620
PH combination therapy, n (%)	35 (11.51)	18 (22.78)	0.016
BPA or PEA, n (%)	233 (76.64)	45 (56.96)	0.001

Notes: Data are presented as mean ± standard deviation, median [25th–75th percentile] or number (percentage).
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BPA, balloon pulmonary angioplasty; LAD, left atrium dimension; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NLR, neutrophil-to-lymphocyte ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; OSA, obstructive sleep apnea; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PLR, platelet-to-lymphocyte ratio; PTE, pulmonary thromboembolism; PVR, pulmonary vascular resistance; RVED, right ventricular end-diastolic diameter; 6 MWD, 6-min walk distance; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; sPAP, systolic pulmonary arterial pressure; S_VO_2, mixed venous oxygen saturation; TRV, tricuspid regurgitation velocity; WHO-FC, World Health Organization functional class.

significantly lower cardiac index and SvO_2 levels. Patients with clinical worsening also had significantly elevated SIRI, SII, and NLR values compared to those without clinical worsening. During the index hospitalization, approximately 74.4% of the participants received targeted therapy for PH. The remaining patients declined treatment, primarily due to financial constraints, treatment intolerance, or concerns about potential clinical worsening.

Based on the ROC curve analysis, SIRI exhibited an area under the curve (AUC) of 0.730 for predicting clinical worsening. The optimal threshold was determined to be 0.80, with a sensitivity of 69.6% and specificity of 66.4%. Patients with SIRI > 0.80 exhibited notably poorer pulmonary hemodynamics compared to those with SIRI ≤ 0.80, as evidenced through higher mPAP, increased PVR, and lower cardiac index (Table 2).

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Table 2 Baseline Variables in Groups with High or Low Levels of SIRI

Variables	SIRI<0.80 (n =224)	SIRI ≥ 0.8 (n = 159)	P-Value
Demographics			
Age, years	55.00 [48.00–64.00]	58.00 [50.00–65.00]	0.056
Female, n (%)	120 (53.57)	69 (43.40)	0.063
Han ethnicity, n (%)	219 (97.77)	155 (97.48)	0.857
BMI, kg/m^2	23.45 [21.48–26.03]	24.02 [21.48–26.15]	0.388
Current smoking, n (%)	56 (25.00)	55 (34.59)	0.054
Alcohol intake, n (%)	43 (19.20)	43 (27.04)	0.091
Clinical evaluation and comorbidities			
WHO-FC, n (%)			0.024
I or II	126 (56.25)	70 (44.03)	
III or IV	98 (43.75)	89 (55.97)	
6 MWD, m	383.96 ± 100.81	349.23 ± 88.97	<0.001
History of PTE, n (%)	152 (67.86)	97 (61.01)	0.202
Diabetes mellitus, n (%)	49 (21.88)	52 (32.70)	0.024
Arterial hypertension, n (%)	57 (25.45)	51 (32.08)	0.192
OSA, n (%)	68 (30.36)	45 (28.30)	0.748
Laboratory data			
NT-proBNP, pg/mL	669.50 [150.07–1936.75]	1333.00 [378.20–2361.00]	0.001
White blood cell, $10^9/L$	5.70 [4.95–6.48]	6.70 [5.94–7.88]	<0.001
Neutrophil, $10^9/L$	3.36 [2.74–3.84]	4.57 [3.97–5.44]	<0.001
Lymphocyte, $10^9/L$	1.90 [1.52–2.48]	1.62 [1.27–1.88]	<0.001
Monocyte, $10^9/L$	0.31 [0.26–0.37]	0.41 [0.33–0.50]	<0.001
Hemoglobin, g/L	153.00 [139.00–167.00]	157.00 [141.00–170.50]	0.191
Platelets, $10^9/L$	213.50 [177.75–261.00]	219.00 [185.00–280.50]	0.108
Albumin, g/L	42.44 ± 4.72	41.66 ± 4.82	0.118
ALT, IU/L	22.00 [15.00–34.25]	22.00 [16.00–33.50]	0.839
Serum creatinine, umol/L	82.81 [70.98–93.25]	85.59 [72.22–97.79]	0.126
Echocardiography			
Pericardial effusion, n (%)	42 (18.75)	32 (20.13)	0.838
LAD, mm	33.00 [30.00–36.00]	33.00 [30.00–37.00]	0.722
LVED, mm	41.00 [36.00–46.00]	40.00 [37.00–44.00]	0.738
LVEF, %	65.00 [60.00–68.12]	64.00 [60.00–68.00]	0.850
RVED, mm	31.00 [28.00–37.00]	33.00 [29.00–39.00]	0.049
TRV, m/s	4.30 [3.80–4.80]	4.24 [3.80–4.80]	0.900
sPAP, mmHg	82.67 ± 26.05	84.23 ± 25.48	0.557
Hemodynamics			
S_VO_2, %	67.97 [62.85–73.23]	67.70 [63.58–71.45]	0.426
mRAP, mmHg	6.00 [4.00–8.00]	7.00 [4.00–10.00]	0.023
mPAP, mmHg	46.20 ± 13.38	49.37 ± 14.52	0.030
PAWP, mmHg	9.00 [7.00–12.00]	10.00 [8.00–12.00]	0.025
Cardiac index, $L/min/m^2$	2.88 [2.29–3.43]	2.69 [2.21–3.09]	0.013
PVR, wood units	9.27 [5.90–12.27]	10.34 [6.70–14.02]	0.029

(*Continued*)

Table 2 (Continued).

Variables	SIRI<0.80 (n =224)	SIRI ≥ 0.8 (n = 159)	P-Value
Treatment			
Anticoagulant, n (%)	215 (95.98)	155 (97.48)	0.608
PH-specific therapy, n (%)	165 (73.66)	120 (75.47)	0.778
PH combination therapy, n (%)	29 (12.95)	24 (15.09)	0.653
BPA or PEA, n (%)	176 (78.57)	102 (64.15)	0.003

Notes: Data are presented as mean ± standard deviation, median [25th–75th percentile] or number (percentage).
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BPA, balloon pulmonary angioplasty; LAD, left atrium dimension; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; OSA, obstructive sleep apnea; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PTE, pulmonary thromboembolism; PVR, pulmonary vascular resistance; RVED, right ventricular end-diastolic diameter; 6 MWD, 6-min walk distance; SIRI, systemic inflammatory response index; sPAP, systolic pulmonary arterial pressure; S_vO_2, mixed venous oxygen saturation; TRV, tricuspid regurgitation velocity; WHO-FC, World Health Organization functional class.

Association Between SIRI and Established Disease Severity Markers of CTEPH

As shown in Table 3, SIRI exhibited a correlation with the 6MWD, ln(NT-proBNP), and pulmonary hemodynamic parameters such as PAWP, mRAP, and cardiac index. Nevertheless, no associations were observed between the SIRI and

Table 3 Spearman Correlation Analysis Between SIRI with Established Markers of CTEPH Severity

Variables	Correlation Coefficient (r_s)	*P* Value
WHO-FC	0.069	0.179
6MWD	−0.119	0.020
ln (NT-proBNP)	0.153	0.003
Echocardiography		
LVEF	0.025	0.632
LAD	0.036	0.486
LVED	0.011	0.832
RVED	0.087	0.089
TRV	0.026	0.608
sPAP	0.043	0.405
Pericardial effusion	0.010	0.844
Hemodynamics		
S_vO_2	−0.050	0.326
mPAP	0.093	0.069
PAWP	0.142	0.005
PVR	0.079	0.121
Cardiac index	−0.139	0.006
mRAP	0.136	0.007

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; LAD, left atrium dimension; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RVED, right ventricular end-diastolic diameter; 6MWD, 6-min walk distance; SIRI, systemic inflammatory response index; sPAP, systolic pulmonary arterial pressure; S_vO_2, mixed venous oxygen saturation; TRV, tricuspid regurgitation velocity; WHO-FC, World Health Organization functional class.

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WHO-FC (r = 0.069, P = 0.179), left atrium dimension (r = 0.036, P = 0.486), left ventricular ejection fraction (r = 0.025, P = 0.642), left ventricular end-diastolic diameter (r = 0.011, P = 0.832), right ventricular end-diastolic diameter (r = 0.087, P = 0.089), mPAP (r = 0.093, P = 0.069), PVR (r = 0.079, P = 0.121), or SvO_2 (r = -0.050, P = 0.326). Furthermore, SIRI rose with an COMPERA 2.0 risk score (low-risk vs intermediate-high, median [25th–75th percentile], 0.681 [0.497-0.920] vs 0.790 [0.548-1.079], P = 0.039 (Figure 1).

Prognostic Value of SIRI

Over an average follow-up duration of 30.6 months, 79 (20.6%) patients experienced clinical worsening. Subsequently, we treated the SIRI as a continuous variable, using the median value as the reference point, and applied restricted cubic spline regression within the unadjusted Cox proportional hazards model. As shown in Figure 2, the unadjusted spline

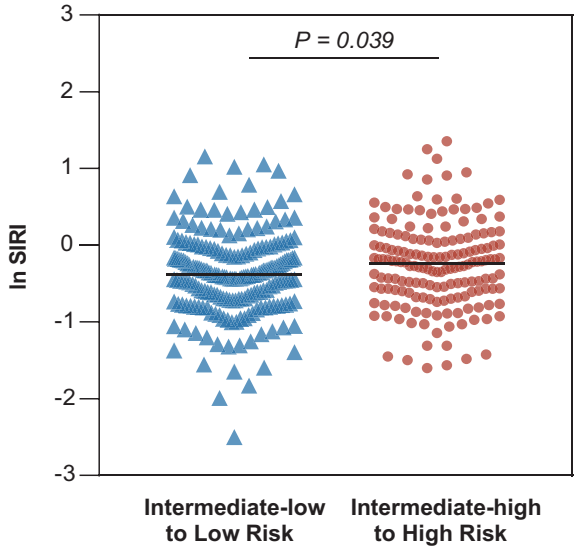

Figure 1 The association between SIRI and the 4-strata COMPERA 2.0 risk score. The solid black line is the median.
Abbreviation: SIRI, Systemic inflammatory response index.

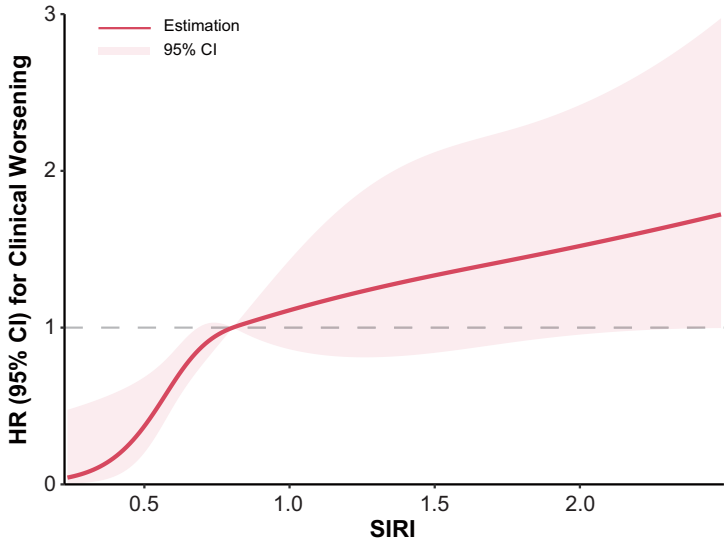

Figure 2 Restricted cubic spline curves for clinical worsening according to the SIRI. SIRI as a continuous variable fitted an unadjusted Cox regression model using restricted cubic spline regression.
Abbreviations: SIRI, Systemic inflammatory response index; CI, confidence interval; HR, hazard ratio.

plots revealed a monotonically increasing relationship between SIRI and the hazard ratio (HR) for clinical worsening. According to the Kaplan–Meier curve, individuals with a SIRI ≥ 0.80 exhibited significantly poorer survival rates and a shorter time to clinical worsening compared to those with a SIRI < 0.80 (log-rank P < 0.01, Figure 3).

To further evaluate the prognostic value of SIRI in predicting clinical worsening, we developed three Cox regression models (Table 4). In Model 1, which accounted for demographic variables, patients in the high SIRI category had approximately three times the likelihood of clinical worsening compared to those in the low SIRI category (HR 2.655, 95% confidence interval (CI) 1.628–4.329, P<0.001). In Model 2, which adjusted for variables in Model 1 along with WHO-FC, 6MWD, and ln(NT-proBNP), the association between high SIRI and clinical worsening remained statistically significant (HR 2.089, 95% CI 1.271–3.432, P=0.004). Similarly, in Model 3, which included additional adjustments for PH-specific medication, and BPA or PEA, the findings remain consistent (HR 2.033, 95% CI 1.227–3.370, P=0.006). When analyzed as a continuous variable, SIRI was independently associated with clinical worsening across all three models in patients with CTEPH, regardless of the adjustment model used. No collinearity issues were detected in the multivariate Cox analysis, and no significant interaction effect was observed in the subgroup analysis (Figure 4).

Comparison with Other Inflammatory Hematological Ratios

ROC curve analysis was used to compare the ability of different inflammatory hematological ratios to predict clinical worsening (Figure 5). Among the four markers associated with inflammation, SIRI exhibited the highest AUC value of 0.730 (95% CI 0.659–0.810). Using Delong's test for comparing AUCs, SIRI exhibited a significantly superior performance compared to NLR (ΔAUC 0.043, P = 0.044), PLR (ΔAUC 0.172, P < 0.01), and SII (ΔAUC 0.127, P < 0.01). The sensitivity, specificity, Youden index, positive predictive value, and negative predictive value for SIRI, SII, PLR, and NLR are shown in Supplementary Table S2. To further elucidate the predictive value of SIRI for clinical worsening, we compared it with the COMPERA 2.0 risk assessment. Incorporating SIRI as a continuous variable into the COMPERA 2.0 model, the predictive value of the risk score significantly improved (DeLong's test, P <0.001;

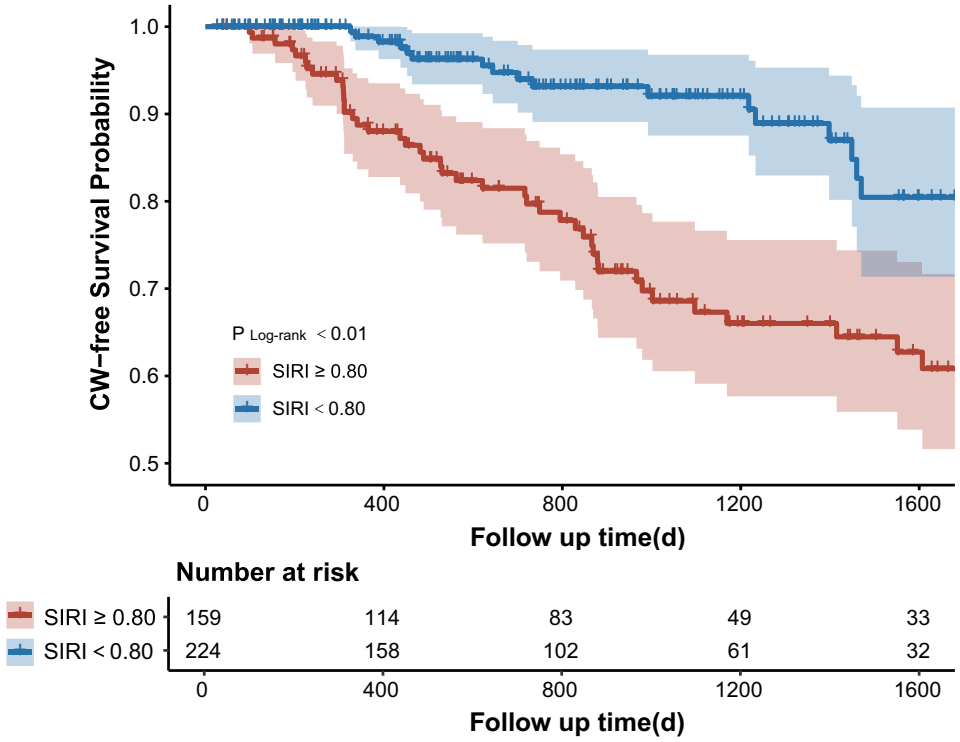

Figure 3 Kaplan-Meier curves for patients with CTEPH classified by baseline levels of SIRI.
Abbreviations: SIRI, Systemic inflammatory response index; CTEPH, chronic thromboembolic pulmonary hypertension.

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Table 4 Predictive Value of SIRI for Clinical Worsening in Patients with CTEPH

	SIRI (Continuous)		SIRI≥0.80*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted	1.714 (1.332, 2.207)	<0.001	2.647 (1.634, 4.287)	<0.001
Model 1	1.676 (1.284, 2.188)	<0.001	2.655 (1.628, 4.329)	<0.001
Model 2	1.454 (1.110, 1.905)	0.007	2.089 (1.271, 3.432)	0.004
Model 3	1.488 (1.106, 2.001)	0.009	2.033 (1.227, 3.370)	0.006

Notes: Model 1: Adjusted for age, and sex. Model 2: Adjusted for variables from Model 1 plus WHO-FC, 6MWD, and ln (NT-proBNP). Model 3: Adjusted for variables from Model 2 plus PH-specific medication, BPA or PEA. * Reference group in patients with SIRI<0.80.

Abbreviations: BPA, balloon pulmonary angioplasty; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; HR, hazard ratio; ln, logarithmically transformed; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-min walk distance; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SIRI, systemic inflammatory response index; WHO-FC, World Health Organization functional class.

Supplementary Figure S2).The AUC values followed the descending order: SIRI + abbreviated COMPERA 2.0 risk score (0.770) outperformed the abbreviated COMPERA 2.0 risk score alone (0.699).

Discussion

In this retrospective study, we found an association between the SIRI and both disease severity and prognosis in patients with CTEPH. To the best of our knowledge, no previous studies have investigated the relationship between SIRI and CTEPH. We found that SIRI was associated with known indicators of disease severity in patients with CTEPH. Even after adjusting for other confounders, the SIRI remained an independent predictor of clinical worsening in patients with CTEPH. In addition, ROC analysis revealed that SIRI could improve the predictive power of the COMPERA 2.0 risk stratification tool for adverse outcomes in patients with CTEPH.

The pathology of CTEPH is characterized by organized thromboembolic material and vascular remodeling, triggered or enhanced by a combination of defective angiogenesis, impaired fibrinolysis, and endothelial dysfunction.[1] However, the mechanisms underlying unabated thrombofibrosis and vascular remodeling remain unknown. The concept of "inflammatory thrombosis" has been proposed, suggesting that inflammation triggers the abnormal multiplication of fresh thrombi on the endothelial surface and the transformation of fresh thrombi into fibrotic tissue.[26] This idea is supported by previous studies. Patients with CTEPH have a markedly proinflammatory state, and a large infiltration of macrophages, lymphocytes, and neutrophils has been observed in specimens from patients who underwent PEA.[27] Serum levels of IL-6, IL-8, IP-10, interferon gamma-induced mono-factor, and MIP-1α levels are significantly elevated in patients with CTEPH compared to control participants.[10] Smolders et al[28] found increased production of inflammatory cytokines IL-8, MCP-1, IL-1β, C-C Motif Chemokine Ligand 5, Intercellular Adhesion Molecule 1, and Vascular Cell Adhesion Molecule 1 in endothelial cells of CTEPH. CRP contributed to persistent obstruction of proximal pulmonary arteries in CTEPH by promoting vascular remodeling, endothelial dysfunction, and in situ thrombosis.[29] Inflammation is also strongly associated with CTEPH prognosis. Preoperative CRP levels >10 mg/L were associated with severe hemodynamics and poor early prognosis after endarterectomy in patients with CTEPH.[30] Additionally, CRP level at diagnosis was an independent and significant predictor of CTEPH outcomes, and CRP levels decreased after PEA.[31] In a study by Zabini et al,[10] IP-10 levels in patients with CTEPH negatively correlated with cardiac output, 6MWD, and carbon monoxide diffusion, whereas IL-6 levels positively correlated with PVR, right atrial pressure, and NT-proBNP. Additionally, high-sensitivity CRP was associated with pulmonary hemodynamics and long-term mortality, as shown in a prospective study by Hadinnapola et al.[32] For patients with inoperable CTEPH, multiple BPAs treatments resulted in significant reductions in circulating cytokine levels. Notably, reductions in IL-6 levels revealed a positive correlation with overall hemodynamic improvement after a series of BPA treatments.[33] Thus, inflammation may be involved in the development of chronic thrombosis in patients with CTEPH, potentially influencing both disease severity and prognosis.

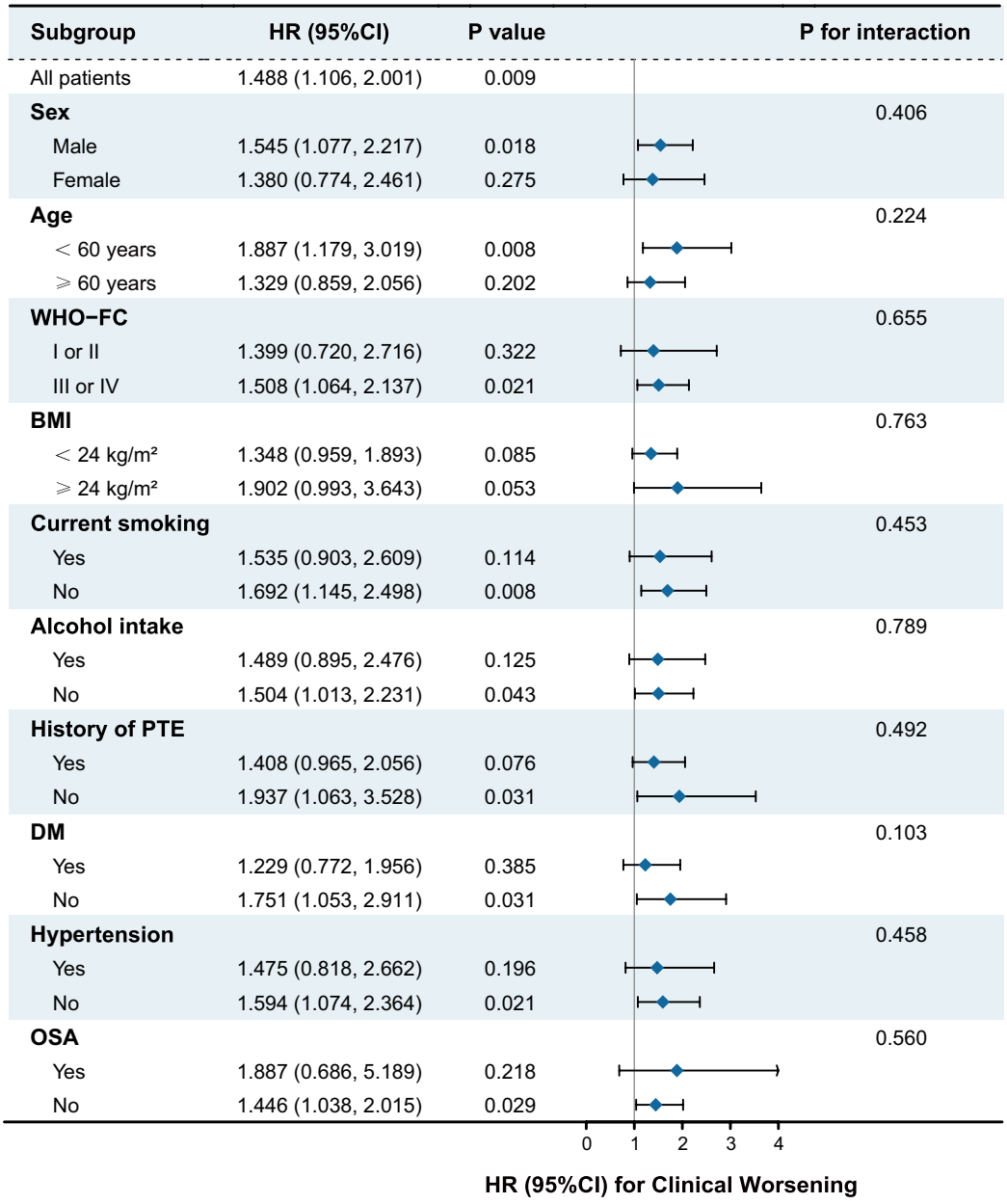

Figure 4 Subgroup and interaction analyses of the association between SIRI and primary endpoint events.
Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; OSA, obstructive sleep apnea; PTE, pulmonary thromboembolism; WHO-FC, World Health Organization functional classes.

Our study demonstrates that the SIRI is an independent predictor of clinical worsening in CTEPH, even after adjusting parameters such as treatment modalities. These findings align with prior evidence linking inflammation to CTEPH progression. For instance, elevated cytokines (eg, IL-6, CRP) and immune cell infiltration in thrombi support the biological plausibility of SIRI—a composite marker of neutrophils, monocytes, and lymphocytes—as a reflection of systemic inflammation driving thrombofibrosis. However, unlike previous studies focusing on isolated biomarkers, our work underscores the superiority of composite indices in capturing the multifactorial inflammatory-thrombotic interplay unique to CTEPH.

Complex inflammatory indicators, such as NLR, PLR, LMR, and SIRI, can provide detailed information about inflammation and immune activity during cardiovascular events. For example, SIRI values at 12 hours after percutaneous coronary intervention were found to predict poor long-term prognosis in patients with acute ST-segment elevation

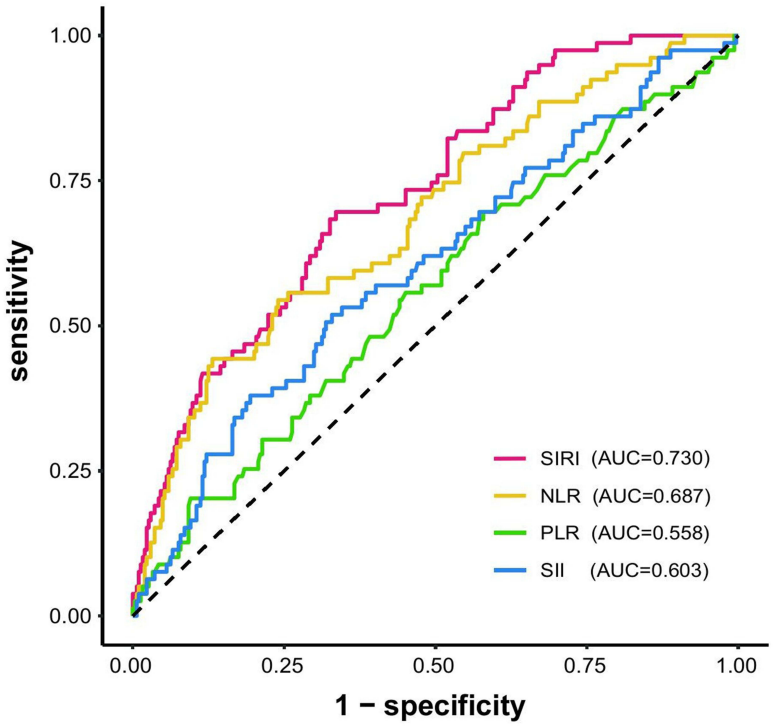

Figure 5 Receiver operating characteristic curves of SIRS, SII, NLR and PLR to predict clinical worsening.
Abbreviations: AUC, area under the curve; NLR, Neutrophil-to-lymphocyte ratio; SIRI, Systemic inflammation response index; SII, Systemic immune-inflammation index; PLR, Platelet-to-lymphocyte ratio.

myocardial infarction.[34] In addition, a large longitudinal study by Lai et al[35] found that elevated SIRI upon admission was an independent risk factor for all-cause and cardiovascular mortality in patients with heart failure and preserved ejection fraction. Additionally, recent studies have also found that SIRI is associated with IPAH and serves as a significant predictor of clinical worsening.[18] In patients with CTEPH undergoing PEA, the NLR upon admission predicted mortality, with a significant correlation between preoperative pulmonary vascular resistance and neutrophil/lymphocyte ratio.[36] Considering the good performance of SIRI in predicting other cardiovascular diseases, and the fact that SIRI is a composite inflammatory index that combines monocyte, lymphocyte, and neutrophil ratios, we hypothesized that SIRI may play an important role in the assessment of disease severity and prognosis in patients with CTEPH.

Normally, a thrombus in an acute pulmonary embolism regresses within 6 months; however, patients with CTEPH develop pathological changes such as slowed regression of the thrombus, fibrosis, and vascular remodeling, which ultimately lead to the development of pulmonary hypertension. The mechanisms underlying thrombus fibrosis and vascular remodeling in CTEPH remain unknown. Quarck et al[27] used immunohistochemistry to analyze predominant vascular lesions in patients with CTEPH and found four types of lesions: neointimal, thrombotic, atherosclerotic, and recanalized. The accumulation of inflammatory cells, including T lymphocytes, macrophages, and neutrophils, was found in all types of lesions. Pathological specimens obtained from Patients with CTEPH undergoing PEA by Kimura et al[37] revealed that MCP-1 was immunoreactive in endothelial cells, smooth muscle cells, and macrophages within the neointima of the pulmonary arteries, suggesting that monocytes/macrophages were involved in the secretion of MCP-1 and were upregulated during pulmonary arterial remodeling. Moreover, plasma MCP-1 levels in patients with CTEPH were significantly correlated with pulmonary vascular resistance. Yang et al[38] found that monocytes are the source of blood-borne tissue factor (TF) in patients with CTEPH and play a key role in thrombosis. TF accumulation leads to vascular endothelial cell damage and activation of the exogenous coagulation pathway, resulting in thrombus formation and deposition in the vessel wall. Vessel narrowing and production of large amounts of inflammatory mediators and cytokines can further induce TF expression and activate the coagulation system, resulting in an inflammation-coagulation-thrombosis cycle.[39] Neutrophils are recruited early to sites of acute inflammation. Neutrophil extracellular traps (NETs) have recently emerged as novel contributors to venous and arterial thrombosis.[40] NETs are shown to be elevated in plasma from patients with CTEPH and in

post-PEA samples. NETs are involved in pro-inflammatory and pro-thrombotic responses within the intimal lumen of the pulmonary vasculature via the reactive oxygen species-induced TLR4 signaling pathway.[41] Fibrosis is a hallmark of non-resolving chronic thrombus, however, the mechanisms leading to fibrotic vascular obstruction remain unknown. Another study revealed the ability of NETs to promote the differentiation of monocytes into activated fibroblasts with the same cellular phenotype as fibroblasts in CTEPH vascular occlusion.[42] This finding suggests that NETs are involved in the progression of chronic thrombosis in CTEPH by promoting thrombofibrosis and inflammation. Transmural distribution of T lymphocytes can be observed in post-PEA specimens from patients with CTEPH, whereas B lymphocytes are located predominantly deep within the lesion, close to the internal elastic lamina and natural media.[27] Lymphocytes provide an inflammatory environment that promotes the phenotypic regulation of myofibroblasts and pulmonary vascular remodeling by smooth muscle cells.[43] Heterogeneous T lymphocyte populations that promote chronic inflammation and autoimmunity have been identified in chronic thrombi. STAT3 expression was upregulated in CD4 + Treg cell clusters, the latter being able to drive Tregs to secrete IL-17 under inflammatory conditions and further promote an inflammatory environment.[44] Additionally, a splenectomy can influence vascular remodeling after CTEPH thrombosis, considering that the spleen is important for B-cell maturation, pathogenic B-cells may play a role in CTEPH pathogenesis.[45,46] Hence SIRI, which combines the three inflammatory cell counts, can predict the prognosis of CTEPH.

The SIRI, a novel biomarker, has numerous advantages for clinical use. As a composite inflammation indicator, SIRI combines monocyte, lymphocyte, and neutrophil counts to provide a more comprehensive picture of the body's inflammatory state. The indicators needed to calculate SIRI can be obtained through routine blood tests, which are economical and convenient. Additionally, this test can be repeated over time to observe changes. Our study found that SIRI was able to independently predict the severity and poor prognosis of patients with CTEPH, with its predictive ability improved when used in combination with COMPERA 2.0. Therefore, SIRI may be an important method for assessing the risk of patients with CTEPH. Future studies should explore its potential application in evaluating treatment efficacy and the role of inflammation as a therapeutic target.

Our study had a few limitations. Our cohort included CTEPH patients with diverse clinical profiles. While we adjusted for treatment-related confounders in multivariate models, unmeasured factors could further influence the conclusion. Second, routine blood tests were performed only at the first admission, and SIRI values were not monitored dynamically throughout the disease. Additionally, the lack of inflammatory mediator data limits mechanistic insights into SIRI's prognostic role in CTEPH. Finally, this was a single-center, retrospective study from China, limiting the extrapolation of our findings to other ethnic or geographic groups with distinct genetic, environmental, or healthcare access profiles. Future prospective, multi-ethnic, multicenter studies are needed to validate SIRI's prognostic utility across diverse populations.

Conclusion

SIRI correlates with known markers of disease severity in patients with CTEPH and independently predicts worsening clinical outcomes in patients with CTEPH. Furthermore, SIRI provides additional prognostic predictive value when used with the COMPERA 2.0 risk score.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study followed the institutional guidelines of the Declaration of Helsinki Ethical Principles for all procedures involving human participants and was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (Approval number: 2024-2301). Written informed consent was obtained from all patients.

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 report no conflicts of interest in this work.

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