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ORIGINAL RESEARCH

Role of the Systemic Inflammatory Response Index in Predicting Disease Severity and Prognosis in Idiopathic Pulmonary Arterial Hypertension

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Introduction: Mounting evidence indicates a possible connection between the systemic inflammatory response index (SIRI) and the prognosis of heart failure, but its role in idiopathic pulmonary arterial hypertension (IPAH) is not well understood. This study aimed to investigate the relationship between SIRI and variables such as functional ability, echocardiography results, hemodynamic measurements, and long-term outcomes in patients with IPAH.

Methods: The study included 426 consecutive IPAH patients who underwent right heart catheterization at Fuwai Hospital from January 2013 to December 2020. SIRI was calculated using composite inflammation indicators from routine blood tests. The main outcome measure was clinical deterioration. Spearman correlation coefficients were used to assess associations between SIRI and indicators of IPAH severity. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal SIRI threshold and predictive ability. Kaplan-Meier analysis and Cox proportional hazard models were used to examine the relationship between SIRI and clinical deterioration.

Results: SIRI showed positive associations with indicators such as N-terminal pro-brain natriuretic peptide, right ventricular end-diastolic diameter, pericardial effusion, mean pulmonary arterial pressure, and pulmonary vascular resistance. Conversely, SIRI had inverse relationships with 6-minute walking distance and left ventricular end-diastolic diameter. Kaplan-Meier curves revealed a significantly higher rate of clinical deterioration in individuals with SIRI > 0.741 compared to those with SIRI ≤ 0.741 ($P < 0.001$). Adjusted Cox analysis showed SIRI remained an independent predictor of clinical worsening (hazard ratio 1.366, 95% confidence interval 1.073–1.738, $P = 0.011$). ROC analysis demonstrated SIRI provided additional predictive value beyond the risk assessment score of the European Society of Cardiology/European Respiratory Society.

Discussion: In summary, SIRI could predict the severity and prognosis of IPAH independently. It was associated with various indicators of IPAH severity and was a significant predictor of clinical deterioration. SIRI also offered additional predictive value beyond existing risk assessment scores.

Keywords: prognosis, pulmonary arterial hypertension, risk factor, systemic inflammatory response index

Introduction

Pulmonary arterial hypertension (PAH) is characterized by a gradual escalation in both pulmonary artery pressure and pulmonary vascular remodeling. It signifies the end stage of various cardiopulmonary conditions, leading to right-sided heart failure and death.[1] The outlook for this ailment is bleak, and individuals face significant financial strain. Consequently, clinicians should identify individuals with PAH who may be at elevated risk of mortality. To offer improved clinical guidance, it is advisable to utilize risk stratification and clinical markers that can anticipate the severity and prognosis of the disease.

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The development of PAH is intricate and not well comprehended. PAH development is associated with hemodynamic abnormalities, genetic mutations, epigenetic dysregulation, oxidative stress, immune reactions, inflammation, and fibrosis, as indicated by prior research.[2,3] Multiple research studies have examined the correlation between markers of inflammation and PAH. C-reactive protein (CRP) and the ratio of CRP to albumin are strongly linked to the clinical outcomes of patients with PAH and their responses to targeted pharmacotherapy.[4,5] The clinical outcomes of PAH patients and their responses to targeted drugs are significantly associated with CRP and the CRP to albumin ratio. Additionally, the pro-inflammatory proteins, cytokines interleukin-6 and stromal-derived factor alpha are strongly linked to worsening hemodynamics in PAH. Moreover, they also play a distinct role in negative consequences, including lung transplantation and mortality.[6,7] Additionally, the neutrophil-to-lymphocyte ratio (NLR), which is a hematological measure linked to inflammation, is an independent prognosticator for mortality and clinical decline in PAH.[8]

The systemic inflammatory response index (SIRI), a novel inflammation biomarker, is determined by multiplying the neutrophil count with the monocyte count and dividing it by the lymphocyte count.[9] Previous research has shown that SIRI poses a threat to cardiovascular mortality and is linked to the development and outlook of different cardiovascular and respiratory conditions, including congestive heart failure, chronic obstructive pulmonary disease, and acute coronary syndrome.[10–12] Considering that individuals with PAH have the potential to develop right heart failure, it is reasonable to assume that the SIRI is pertinent to the results encountered by PAH patients. Nevertheless, there is a scarcity of clinical proof regarding the correlation between the SIRI and PAH.

Consequently, we carried out a retrospective cohort investigation to examine the association between the SIRI and the functional condition, echocardiographic factors, hemodynamic factors, and prognosis in individuals diagnosed with PAH.

Methods

Study Design and Population

This retrospective cohort study was conducted in Fuwai hospital, Chinese Academy of Medical Sciences (Beijing, China). Between January 2013 and December 2020, our institute diagnosed idiopathic pulmonary arterial hypertension (IPAH) in 438 consecutive patients who had undergone right heart catheterization (RHC). Inclusion criteria included (1) patients aged 18 years and older; (2) patients with hemodynamic characteristics of PAH by RHC; (3) patients without other causes of PAH according to the guidelines and were eventually diagnosed with IPAH.[13,14] The exclusion criteria included the following: (1) existence of cancer, such as blood cancer and tumors; (2) presence of inflammatory conditions or ongoing infection; and (3) absence of data regarding neutrophil, monocyte, lymphocyte, and platelet counts. Malignancy, inflammatory conditions and ongoing infection were assessed using the International Classification of Diseases (Tenth Revision codes) in the electronic medical record. The study included 426 patients with IPAH after excluding those who met the exclusion criteria.

Patient information including demographics, smoking and alcohol habits, World Health Organization functional class (WHO-FC), comorbidities and PAH specific medication were collected on the day of admission. On the same day, venous blood samples were collected to obtain the data from blood routine examination, fasting blood lipid, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), liver function test and kidney function test. Automated Hematology analyzer (SYSMEX XN-20) was used to measure hematological parameters. An echocardiogram is completed within 48 hours of admission. RHC and 6-minute walking test were performed when the patients were in stable condition.

The Ethics Committee of Fuwai Hospital granted approval for this study. All patients included in this study provided written informed consent.

Definition of Inflammatory Hematological Markers

The formulas used to calculate the SIRI, NLR, platelet-to-lymphocyte ratio (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 (SvO2), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary artery wedge pressure (PAWP), and pulmonary vascular resistance (PVR). Cardiac output was determined utilizing the Fick method, while the cardiac index (CI) was acquired by dividing the cardiac output by the body surface area. Experienced ultrasonologists in the Department of Echocardiography conducted transthoracic echocardiography in accordance with the latest recommendations.[15]

Risk Stratification Strategy

Patients were classified as low, intermediate, or high risk using the risk stratification strategy established by ESC/ERS in 2015.[16] For each parameter in the prediction model WHO-FC, 6 MWD, NT-proBNP, RAP, CI and SvO2 (Table S1), a range of one to three points were allocated. The risk score for every individual was determined by adding up the total points and dividing it by the number of variables, with the decimal values rounded to the nearest whole number.

Follow-Up and Outcome

The main focus of this study was to assess clinical deterioration, which was defined as the initial instance of any of the subsequent events: all-cause death, lung transplantation, or readmission because of heart failure. Telephonic follow-up was conducted every 3–6 months to monitor clinical outcomes. Two senior clinicians independently assessed all possible events. Upon discordance, consensus was achieved by the supervisors through discussion (QL and ZHL).

Statistical Analysis

Continuous variables are reported as either the average ± deviation or the median [25th–75th percentile]. Counts (percentages) were used to present categorical variables. Appropriate statistical tests, such as independent-sample *t*-test, Mann–Whitney *U*-test, chi-square test, or Fisher's exact test, were used to compare the two groups. Spearman correlation coefficients were utilized to investigate the associations between the SIRI and various other variables. To assess the relationship between the continuous SIRI values and clinical deterioration, a restricted cubic spline curve was used. To predict clinical worsening and compare the diagnostic performance of the SIRI and other inflammatory hematological markers, an analysis was conducted using the receiver operating characteristic (ROC) curve to determine the ideal cutoff value. The Kaplan–Meier method was utilized to derive survival curves, which were then compared using the Log rank test. The univariate COX regression analysis was conducted to identify potential risk factors for clinical deterioration. Factors that had a P-value less than 0.05, indicating significant clinical importance, were included in the multivariate COX regression model. In order to eliminate any factors that could affect the results, age and gender were taken into account and adjusted for in model 1. Model 2 was modified by incorporating model 1 along with additional factors such as WHO-FC, 6 MWD, NT-proBNP, and PH-specific medications. Based on model 2, model 3 underwent additional adjustments for SvO2, mPAP, CI, and PVR. The presence of multicollinearity was tested using the variance inflation factor (VIF) method, where a VIF≥10 indicates multicollinearity. To identify interaction effects, subgroup analyses were conducted. The effectiveness of the SIRI in predicting risk was assessed using DeLong's test in comparison to other established risk assessment tools. The level of statistical significance was determined to be $P < 0.05$ (two-sided). R-studio (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) was utilized for conducting data analysis.

Results

Baseline Characteristics

This study included 426 individuals diagnosed with IPAH, with a median age of 31 years, of which 77.5% were female. The median BMI was 22.6 kg/m^2. The disparities in the variables between patients experiencing clinical deterioration and those without are presented in Table 1. Patients who encountered clinical deterioration exhibited a notably inferior WHO-FC rating and a more limited 6 MWD. In contrast to patients who did not experience clinical deterioration, individuals

Table 1 Baseline Characteristics of Study Population

Variables	Non-CW (n = 294)	CW (n = 132)	P-value
Age, years	31.0 [26.0–38.0]	32.0 [26.8–38.0]	0.828
Female, n (%)	237 (80.6)	93 (70.5)	0.028*
BMI, kg/m^2	22.5 [20.4–24.9]	22.8 [20.3–25.4]	0.462
WHO-FC, n (%)			<0.001*
I or II	179 (60.9)	55 (41.7)	
III or IV	115 (39.1)	77 (58.3)	
6 MWD, m	430 [372–475]	404 [360–446]	0.001*
Smoking, n (%)	27 (9.2)	19 (14.4)	0.152
Alcohol intake, n (%)	18 (6.1)	11 (8.3)	0.529
Diabetes mellitus, n (%)	8 (2.7)	4 (3.0)	1.000
Hypertension, n (%)	30 (10.2)	14 (10.6)	1.000
PH specific medication, n (%)	244 (83.0)	105 (79.5)	0.472
Laboratory data			
NT-proBNP, pg/mL	778 [253–1647]	1561 [1018–2398]	<0.001*
White blood cell, 10^9/L	6.4 [5.3–7.8]	8.0 [6.6–8.9]	<0.001*
Neutrophil, 10^9/L	3.8 [2.9–4.8]	4.9 [4.0–6.2]	<0.001*
Lymphocyte, 10^9/L	2.1 [1.7–2.7]	2.1 [1.7–2.6]	0.521
Monocyte, 10^9/L	0.4 [0.3–0.4]	0.5 [0.4–0.5]	<0.001*
Hemoglobin, g/L	152 [137–167]	160 [142–173]	0.022*
Platelets, 10^9/L	196 [162–251]	202 [162–245]	0.871
Albumin, g/L	44.0 ± 5.5	42.8 ± 5.2	0.033*
ALT, IU/L	22.5 [15.2–34.0]	25.0 [17.8–41.0]	0.034*
AST, IU/L	26.0 [21.0–34.0]	25.0 [19.8–36.0]	0.940
Triglyceride, mmol/L	1.2 [0.9–1.7]	1.3 [0.9–1.8]	0.323
Cholesterol, mmol/L	4.2 ± 0.9	4.1 ± 1.1	0.202
Serum creatinine, umol/L	72.1 [62.9–81.9]	74.3 [61.4–83.7]	0.332
Blood urea nitrogen, mmol/L	5.0 [4.2–6.2]	5.6 [4.6–6.9]	<0.001*
Inflammatory Hematological Ratios			
SIRI	0.58 [0.41–0.79]	1.06 [0.68–1.51]	<0.001*
SII	357 [239–496]	470 [305–685]	<0.001*
NLR	1.77 [1.33–2.24]	2.36 [1.75–2.93]	<0.001*
PLR	92.9 [72.9–121.0]	96.3 [69.4–122.0]	0.799

(*Continued*)

Table 1 (Continued).

Variables	Non-CW (n = 294)	CW (n = 132)	P-value
Echocardiography			
Pericardial effusion, n (%)	39 (13.3)	35 (26.5)	0.001*
LA, mm	29.0 [27.0–32.0]	29.0 [27.0–32.0]	0.942
LVED, mm	37.0 [32.0–41.0]	35.0 [32.0–38.0]	0.003*
LVEF, mm	65.0 [60.0–68.8]	63.3 [60.0–69.0]	0.155
RVED, mm	32.0 [28.0–37.0]	35.0 [29.0–40.0]	<0.001*
TRV, m/s	4.4 [4.0–4.8]	4.6 [4.1–4.9]	0.014*
sPAP, mmHg	88.3 ± 22.6	93.9 ± 22.0	0.017*
Hemodynamics			
S_VO_2, %	69.4 [64.8–73.1]	67.2 [63.6–72.4]	0.031*
mRAP, mmHg	4.0 [2.0–7.0]	5.0 [2.0–8.3]	0.068
mPAP, mmHg	53.0 [45.0–63.0]	56.5 [49.0–70.0]	0.011*
PAWP, mmHg	7.0 [5.0–9.0]	7.0 [4.0–9.3]	0.906
CI, L/min/m^2	2.8 [2.3–3.4]	2.6 [2.2–3.1]	0.008*
PVR, wood units	11.6 [8.3–15.3]	13.5 [10.2–17.6]	<0.001*

Notes: Data are presented as mean ± standard deviation, median [25th–75th percentile] or number (percentage). *P < 0.05.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CI, Cardiac index; CW, Clinical worsening; LA, 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; PAWP, Pulmonary arterial wedge pressure; PH, Pulmonary hypertension; PLR, platelet-to-lymphocyte ratio; 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.

with worsening clinical condition exhibited significantly elevated levels of NT-proBNP, mPAP, and PVR, while demonstrating significantly reduced values of albumin, SvO2, and CI. Patients with clinical worsening had significantly higher SIRI, SII, and NLR values than those without clinical worsening. During the index hospitalization, targeted therapy for PAH was administered to around 81.9% of the participants. The rest of the individuals declined to undergo this treatment primarily due to the financial strain it would cause, their inability to tolerate it, and concerns regarding potential negative consequences.

Based on the ROC curve analysis, the SIRI exhibited an AUC of 0.761 in predicting clinical deterioration. The optimal threshold was determined to be 0.714, demonstrating a sensitivity of 73.5% and specificity of 70.1%. Patients with SIRI > 0.714 exhibited notably poorer pulmonary hemodynamics compared to those with SIRI ≤ 0.714, evident through higher mPAP and increased PVR (Table S2).

Association Between SIRI and Established Disease Severity Markers of PAH

According to Table 2, SIRI exhibited a strong correlation with the 6 MWD, ln (NT-proBNP), various echocardiographic parameters including left ventricular end diastolic (LVED), right ventricular end diastolic (RVED), pericardial effusion, as well as pulmonary hemodynamic parameters such as mPAP and PVR. Furthermore, the SIRI showed a tendency to correspond with the CI. Nevertheless, there were no associations found between the SIRI and WHO-FC (r = 0.058, P =

Table 2 Spearman Correlation Analysis Between SIRI with Established Markers of PAH Severity

Variables	Correlation Coefficient (r_s)	*P* Value
WHO-FC	0.058	0.229
6MWD	−0.108	0.025*
ln (NT-proBNP)	0.132	0.006*
Echocardiography		
LVEF	−0.046	0.346
LA	0.001	0.980
LVED	−0.100	0.038*
RVED	0.133	0.006*
sPAP	0.069	0.155
Pericardial effusion	0.100	0.040*
Hemodynamics		
S_vO_2	−0.025	0.607
mRAP	0.019	0.691
mPAP	0.191	<0.001*
Cardiac index	−0.086	0.075
PVR	0.187	<0.001*
PAWP	<0.001	0.998

Notes: saturation; WHO-FC, World Health Organization functional class. *P < 0.05.

Abbreviations: LA, 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; PAH, Pulmonary arterial hypertension; 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.

0.229), left atrial size (r = 0.001, P = 0.980), or left ventricular ejection fraction (r = −0.046, P=0.346). Furthermore, SIRI rose with an abbreviated ESC/ERS risk score (low-risk vs intermediate-high, mean ± standard deviation, 0.74 ± 0.51 versus 0.91 ± 0.62, P = 0.004) (Figure 1).

Prognostic Value of SIRI

Over the course of the average follow-up duration of 3.09 years, a total of 132 (31.0%) individuals encountered clinical deterioration. To be more precise, out of the total participants, 42 individuals (31.8%) lost their lives, one participant underwent a lung transplant, and 89 individuals (67.4%) had to be readmitted to the hospital as a result of heart failure. Next, we established the SIRI as an ongoing factor, taking the median as the benchmark, and employed restricted cubic spline regression to apply the unaltered COX proportional hazards model. Figure 2 displayed unaltered spline plots indicating a non-linear correlation between the SIRI and the hazard ratio (HR)

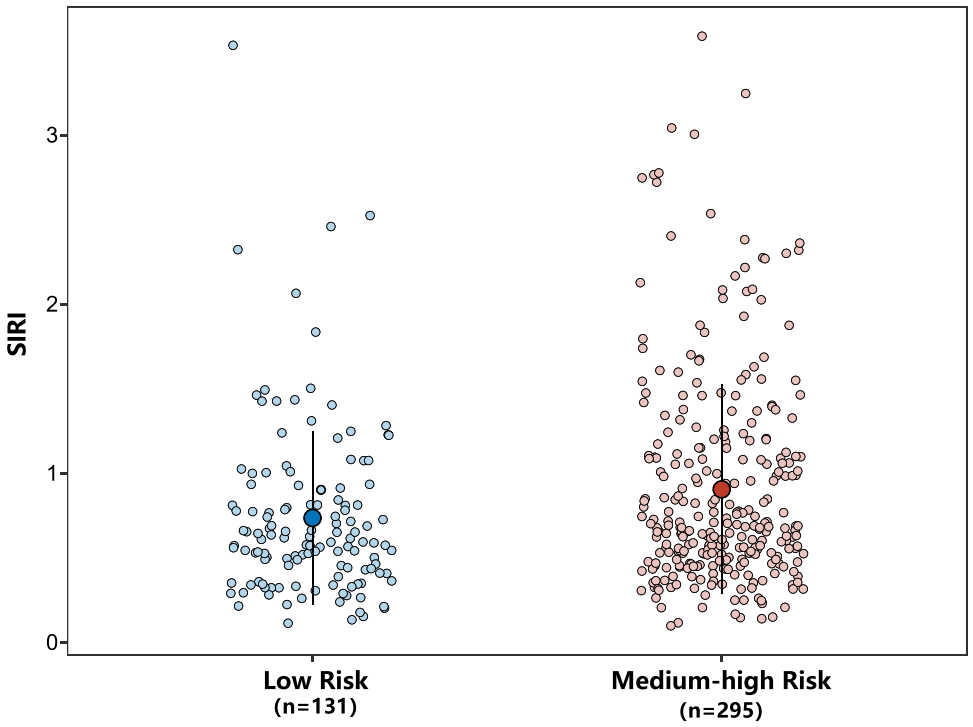

Figure 1 The association between SIRI and the abbreviated European Society of Cardiology /European Respiratory Society Risk Score. SIRI, Systemic inflammatory response index.

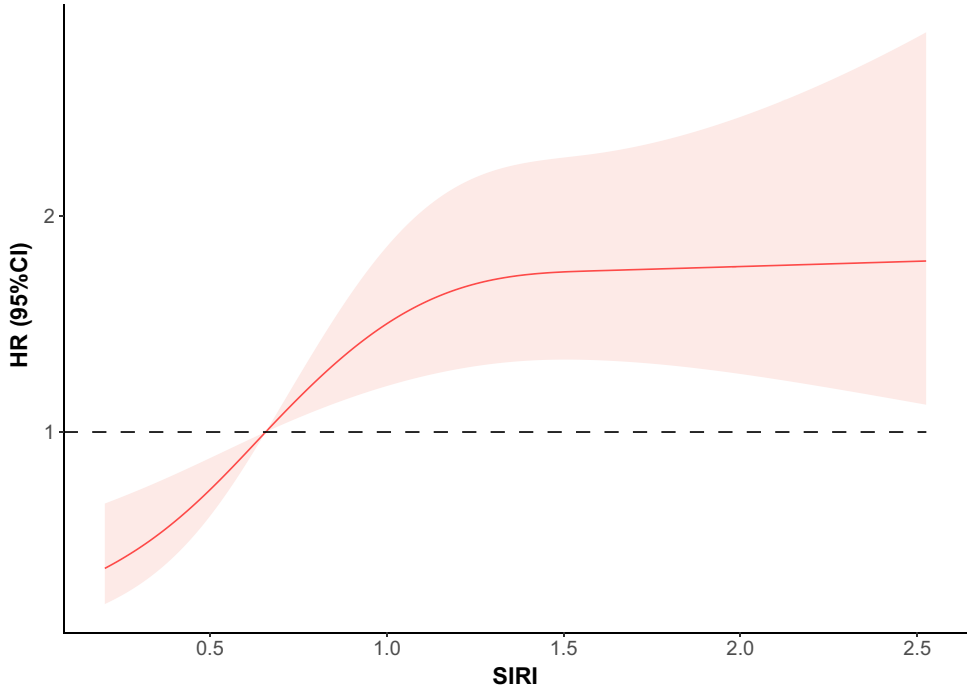

Figure 2 Hazard ratios of clinical worsening as a function of baseline SIRI. SIRI as a continuous variable fitted an unadjusted COX regression model using restricted cubic spline regression. SIRI, Systemic inflammatory response index; CI, confidence interval; HR, hazard ratio.

concerning clinical deterioration. Based on the Kaplan–Meier curve, individuals with SIRI>0.741 exhibited notably inferior survival rates and experienced a shorter duration until clinical deterioration compared to those with SIRI≤0.741 (log-rank $P < 0.001$, Figure 3).

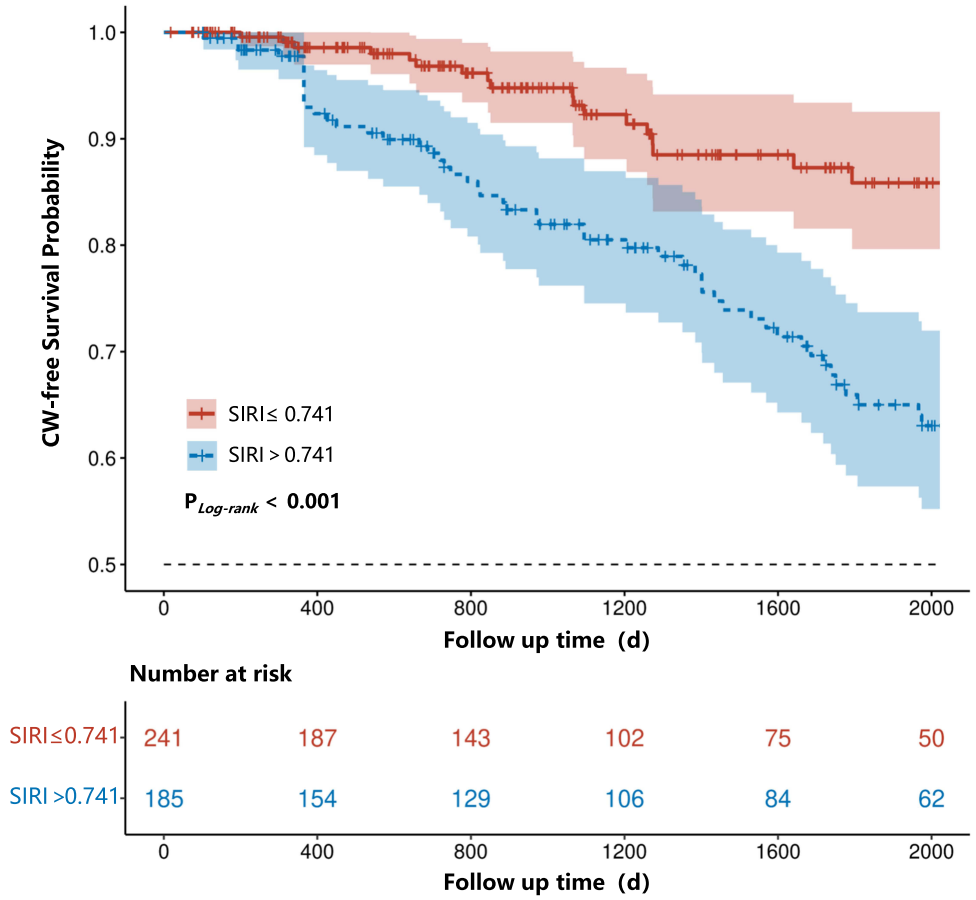

Figure 3 Kaplan-Meier curves for patients with IPAH classified by baseline levels of SIRI. SIRI, Systemic inflammatory response index; IPAH, Idiopathic pulmonary arterial hypertension.

In order to expand our assessment of the prognostic significance of the SIRI in predicting clinical deterioration, we created three COX regression models (Table 3). In the first model, the likelihood of experiencing clinical deterioration was roughly twice as high in the high SIRI category, taking demographic variables into account (HR 2.262, 95% confidence interval [CI] 1.520–3.366, compared to the low SIRI category). In model 2, after accounting for covariates in model 1 along with WHO-FC,

Table 3 Predictive Value of SIRI for Clinical Worsening

	SIRI, Continuous		SIRI>0.714*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted	1.476 (1.185–1.838)	<0.001	2.262 (1.529–3.346)	<0.001
Model 1	1.487 (1.188–1.862)	<0.001	2.262 (1.520–3.366)	<0.001
Model 2	1.332 (1.050–1.691)	0.018	1.973 (1.315–2.961)	0.001
Model 3	1.366 (1.073–1.738)	0.011	2.061 (1.367–3.107)	<0.001

Notes: Model 1: Adjusted for age and gender. Model 2: Adjusted for variables from Model 1 plus WHO-FC, 6MWD, ln (NT-proBNP) and PH specific medication. Model 3: Adjusted for variables from Model 2 plus S_VO_2, mPAP, CI and PVR. *Reference group in patients with SIRI≤0.714.

Abbreviations: CI, Cardiac index; HR, Hazard ratio; ln, logarithmically transformed; NT-proBNP, N-terminal pro-brain natriuretic peptide; mPAP, Mean pulmonary arterial pressure; 6MWD, 6-min walk distance; PH, Pulmonary hypertension; PVR, Pulmonary vascular resistance; SIRI, Systemic inflammatory response index; S_VO_2, Mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

6 MWD, ln (NT-proBNP), and PH-specific medication, the association with clinical deterioration remained statistically significant in the high SIRI category (HR, 1.973; 95% CI 1.315–2.961). Comparable findings were noted following complete covariate adjustment in model 3 (HR 2.061, 95% CI 1.367–3.107). The analysis of SIRI as a continuous variable revealed independent associations between SIRI and its 3 models with clinical deterioration in IPAH patients, irrespective of the adjustment model employed. There were no issues of collinearity identified in the multivariate Cox analysis. The correlation between SIRI and clinical deterioration remained consistent among various subcategories, especially in individuals classified as WHO-FC I or II, and those with PVR≤12 wood units (Figure 4).

Comparison with Other Inflammatory Hematological Ratios

The ROC analysis was used to compare the ability of predicting clinical worsening among different inflammatory hematological ratios (Figure 5). Out of the 4 markers associated with inflammation, SIRI exhibited the highest AUC value of 0.761 (95% CI 0.713–0.807). By using Delong's test for comparing AUCs, it was found that the AUC of SIS exhibited a significantly superior performance in comparison to PLR (ΔAUC 0.253, $P < 0.001$), SII (ΔAUC 0.125, $P < 0.001$), and NLR (ΔAUC 0.073, $P < 0.001$). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for SIRI, SII, PLR, and NLR were described in Table S3. In order to enhance understanding of the predictive significance of the SIRI for clinical deterioration, we compared it to the condensed ESC/ERS risk assessment. The AUCs declined in the following sequence: SIRI + abbreviated ESC/ERS risk score (0.787) > abbreviated ESC/ERS risk score (0.643). When the abbreviated ESC/ERS risk score was combined with SIRI, it resulted in an increased predictive value (DeLong's test, $P <0.001$; Figure S1).

Discussion

In this retrospective study, we discovered that the SIRI was linked to poorer functional condition and heightened hemodynamic condition in individuals with PAH. High SIRI levels are autonomous indicators of unfavorable prognosis in PAH individuals.

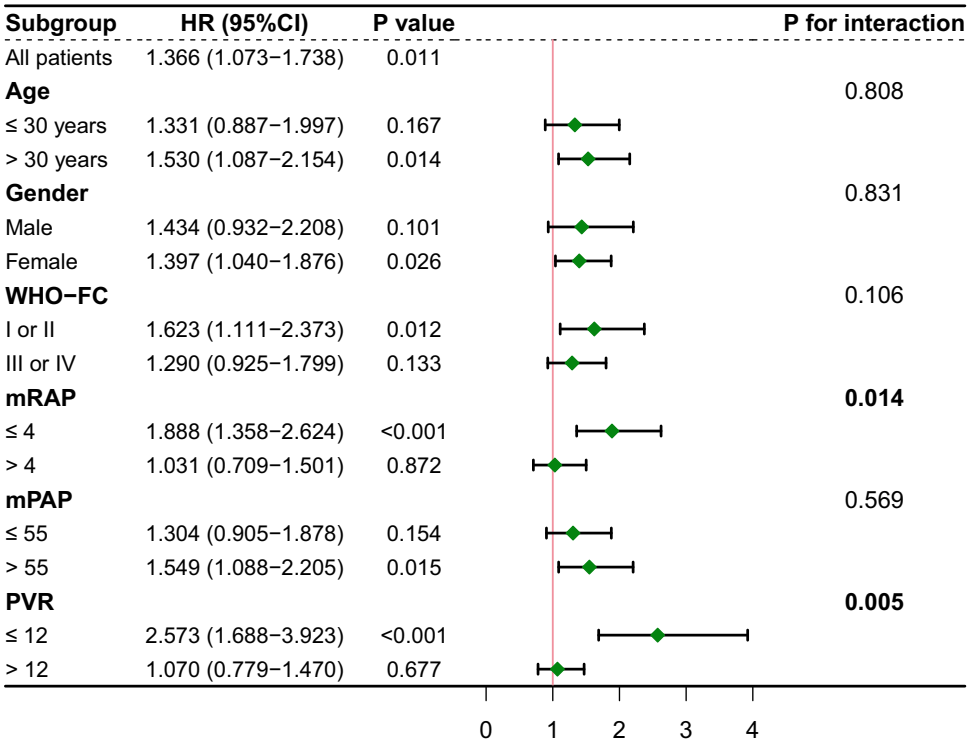

Figure 4 Forest plot of hazard ratios by patient subgroups. HR, hazard ratio; WHO-FC, World Health Organization functional classes; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure. P-values less than 0.05 are highlighted in bold.

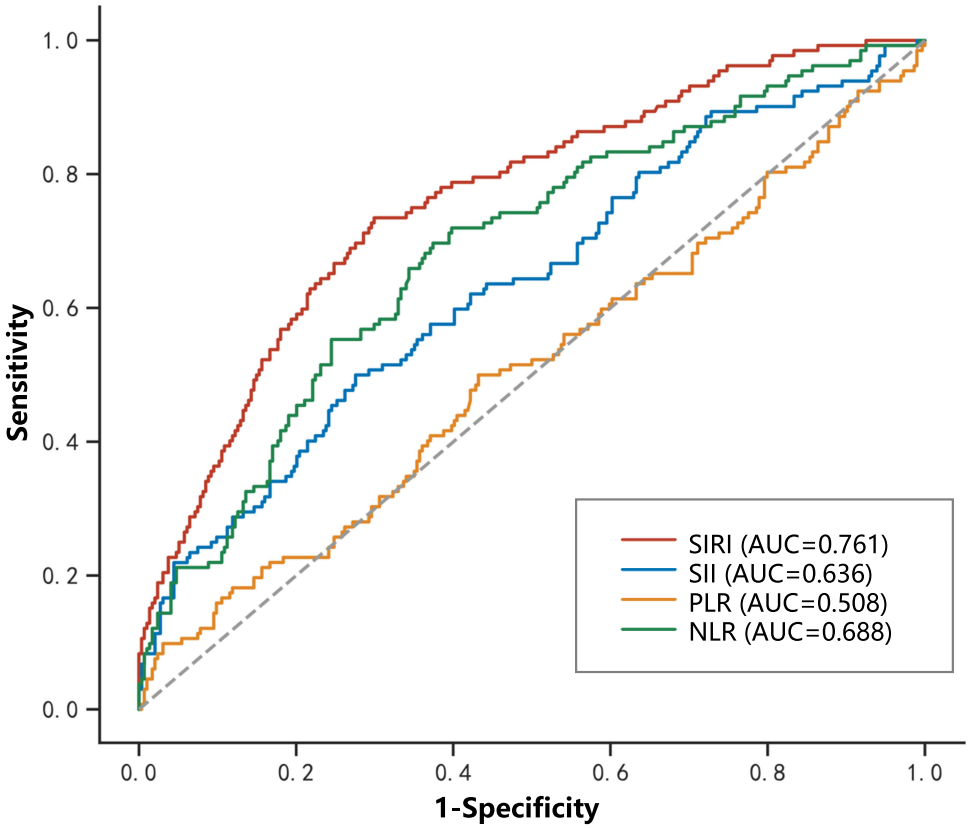

Figure 5 Receiver operating characteristic curves of SIRS, SII, NLR and PLR for clinical worsening. NLR, Neutrophil-to-lymphocyte ratio; SIRI, Systemic inflammation response index; SII, Systemic immune-inflammation index; PLR, Platelet-to-lymphocyte ratio.

As far as we know, there has been no prior investigation into the relationship between the SIRI and PAH. Consistent with the results in heart failure, we found that the SIRI showed a favorable correlation with NT-proBNP, RVED, pericardial effusion, mPAP, and PVR, while indicating an unfavorable correlation with 6 MWD and LVED. Furthermore, our study demonstrated that the SIRI functioned as a standalone indicator of mortality from PAH or readmission caused by heart failure, even after considering other influencing factors. As a result, the SIRI holds the capacity to transform into a crucial measure for assessing the severity of diseases and the outcomes of clinical cases in individuals with PAH.

The exact physiological processes that explain the connection between the SIRI and PAH are still not known. While the precise development of PAH is complex and varied, contemporary studies indicate that inflammation plays a significant role in contributing to PAH. The activation of inflammatory reactions may result in harm and impairment in endothelial cells, resulting in the infiltration of inflammatory cells and constriction of the vascular wall, ultimately leading to vascular remodeling.[17] Inflammation can additionally trigger platelet activation and disturb the coagulation process, inappropriately activating pulmonary vascular smooth muscle cells (PASMCs), leading to the creation of blood clots and thickening of the vascular wall.[18] Additionally, inflammation has the ability to trigger immune responses and apoptosis, which can further undermine the integrity and functionality of blood vessels.[19] Different inflammatory cells, such as neutrophils, monocytes, and lymphocytes, have been seen near the reconstructed pulmonary vascular system in lung biopsies of people with PAH.[20] Previous research has shown a connection between the degree of vascular inflammation and pulmonary hemodynamics, vascular restructuring, and the overall health outcomes in patients with PAH.[21] Hence, it is essential to assess the inflammatory condition while evaluating the prognosis of individuals with PAH. Neutrophils, lymphocytes, and monocytes have been found to have an impact on the prognosis of individuals with acute or chronic heart failure, as indicated by prior studies.[22–24] Right heart failure is a common occurrence in PAH patients. By combining NLR and MLR, the SIRI overcomes the constraints of traditional markers and inflammatory cells when it comes to predicting prognosis. In a prior investigation, it was demonstrated that SIRI outperformed NLR in forecasting significant adverse cardiac incidents after percutaneous coronary intervention in

patients with acute coronary syndrome.[10] SIRI, which is determined by the quantities of neutrophils, monocytes, and lymphocytes in the peripheral blood, has the potential to function as a strong and dependable prognostic marker in patients with PAH.

Neutrophils, the main white blood cells in the circulatory system, play a crucial role in controlling both innate and adaptive immune responses. They demonstrate quick responsiveness during inflammation and are mobilized to regions of sterile inflammation and infection in response to external cues.[25] Monocytes have a crucial function in invading solid tissues and transforming into macrophages, which aids in immune protection and the mending of tissues. Furthermore, recent studies have suggested that inflammatory monocytes have a vital function in promoting the activation and effectiveness of cytotoxic T cells, which are essential for metastasis.[26] On the other hand, the immune system is regulated by lymphocytes through the secretion of antibodies and cytokines, as well as their involvement in cell-killing activities.[27]

Previous studies have shown that the NLR is associated with the WHO-FC and outlook in PAH patients.[8] In PAH, neutrophil elastase (NE), released by neutrophils, is closely associated with abnormal vascular remodeling.[28] The proliferation and migration of PASMCs are stimulated by NE, which leads to the development of PAH by modifying cytokines through proteolytic processes. Elevated in the plasma of PAH patients, myeloperoxidase (MPO), an important enzyme discharged by neutrophils, is linked to an unfavorable prognosis.[29] The Rho kinase pathway can be activated by MPO in rats with PAH, leading to the disruption of pulmonary vascular function and an increase in pressure in the right ventricle.

Zhang et al performed a sequencing analysis on peripheral neutrophils from patients with IPAH and healthy controls, unveiling the distinct increase in gene expression of matrix metallopeptidase 9 (MMP-9).[30] Patients with IPAH who had a greater percentage of neutrophils positive for MMP-9 had an increased mortality risk, taking age and gender into consideration. After neutrophils undergo programmed cell death, they form networks called neutrophil extracellular traps (NETs), which consist of chromatin and cytoplasmic enzymes. The activation of platelets and endothelial cells by NETs could potentially play a crucial role in the progression of PAH. The interaction between primed neutrophils and platelets through endothelial signaling and/or cell-cell interactions can potentially trigger the formation of NETs, thereby creating a feedback loop that is positive in nature.[31]

The recruitment and polarization of monocytes/macrophages are crucial aspects of PAH.[32] Macrophages tend to polarize into 2 phenotypes: M1 (classic) and M2 (alternative). The examination of lung biopsies from rat models with PAH has shown an elevated presence of markers indicating the presence of both M1 and M2 macrophages.[33] Macrophages have a vital function in promoting the advancement of PAH through the release of different chemokines and growth factors, such as C-X3-C motif chemokine receptor 1 and platelet-derived growth factor.[34] Chi et al have demonstrated the upregulation of cyclin D1 and proliferating cell nuclear antigen has been shown in M1 macrophages of patients with PAH, indicating the overexpression of MMP-10.[35] As a result, this process encourages the movement and growth of PASMCs, actively contributing to the remodeling of pulmonary blood vessels and the development of PAH. In comparison to the control group, patients with PAH showed an increase in the expression of C-C chemokine receptor (CCR) type 2 (CCR2) and CCR5 in both PASMCs and macrophages that surrounded the blood vessels.[36] Throughout the progression of PAH, macrophages interact with PASMCs via CCR2 and CCR5 to initiate and exacerbate their migration and proliferation. In patients with PAH, the signaling of endothelial cells in the pulmonary vasculature attracts lymphocytes to sustain an environment of inflammation and provoke an autoimmune reaction.[37] Huertas et al f discovered that a deviation in the leptin pathway results in the malfunction of regulatory T cells, subsequently contributing to the development of IPAH.[38] Hence, it is logical to infer that the SIRI has the ability to forecast the prognosis of PAH.

As an emerging biomarker, the SIRI offers several benefits for clinical use. At first, the necessary factors for determining the SIRI can be acquired through regular blood tests, making it a cost-efficient and convenient method. Furthermore, our inquiry confirmed that the SIRI has the ability to independently anticipate the seriousness and future course of individuals with PAH, demonstrating improved predictive capacity when combined with ESC risk-prediction models. As a result, the SIRI has the potential to become a valuable instrument for assessing the future dangers faced by individuals with PAH. Additional research is necessary to explore its potential in assessing treatment effectiveness and serving as a target for therapy.

Limitations

There were several constraints in our research. First, this was a single-center, retrospective study. Second, the study population only included patients with IPAH and did not include patients with other PH types. Our intention is to perform

an extensive retrospective analysis to examine the correlation between SIRI and the functional condition, as well as the echocardiographic and hemodynamic factors, across all 5 patient categories diagnosed with PH. Third, the neutrophil, monocyte, and lymphocyte counts may change over time. This study included only the initial SIRI, without monitoring its dynamic changes. Further confirmation of our conclusions through large prospective studies is required.

Conclusion

In patients with IPAH, we noticed a correlation between the SIRI and the functional condition, as well as the echocardiographic and hemodynamic factors. The findings showed that the SIRI has the ability to autonomously anticipate clinical decline in individuals suffering from IPAH and offers additional benefits when used alongside the concise ESC/ERS risk score. Consequently, the SIRI serves as a reliable and convenient predictor of prognosis. Further validation of our findings in prospective studies is required.

Research Involving Human Participants and/or Animals

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.

Consent to Participate and Publish

All authors agreed to participate and publish.

Data Sharing Statement

All processed data generated or used during the study are included in the submitted article or Supplementary Material.

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Disclosure

The authors declared that they have no conflicts of interest.

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