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ORIGINAL RESEARCH

Predictive Value of Serum Immune-Inflammatory Markers for Adverse Pregnancy Outcomes in Pregnant Women with Thrombophilia: A Retrospective Cohort Study

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Background: Thrombophilia combined with pregnancy poses significant risks for adverse pregnancy outcomes. Unfortunately, there are no indicators at high risk for predicting adverse pregnancy outcomes. This study investigates the predictive efficiency of serum immune-inflammatory markers on adverse pregnancy outcomes.

Methods: This retrospective cohort study includes 223 pregnant women diagnosed with thrombophilia who delivered at the Fujian Provincial Hospital South Branch from January 2022 to April 2024. Clinical information and pregnancy outcomes were collected. The systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and lactate dehydrogenase (LDH) were calculated using blood samples. The relationship and predictive accuracy between immune-inflammatory markers and adverse pregnancy outcomes were analyzed.

Results: In this study, 50 (22.4%) patients had adverse pregnancy outcomes. Significant differences were observed in neutrophils counts, monocytes counts, LDH, SII, and SIRI levels between the adverse pregnancy outcome groups (APOs) and the control groups ($P<0.05$). The area under the receiver operating characteristic (ROC) curve analysis revealed that SII (AUC=0.762), SIRI (AUC=0.764), and LDH (AUC=0.732) had high predictive values for adverse pregnancy outcomes. Notably, the combined model had the highest AUC of 0.805. Multivariate logistic regression identified SII had the highest odd ratio (OR) (OR=8.512; 95% CI (3.068–23.614)), followed by LDH (OR=4.905; 95% CI (1.167–11.101)), SIRI (OR=3.549; 95% CI(0.847–8.669)), and neutrophils count (OR=1.726; 95% CI (0.563–2.938)) as independent risk factors for adverse outcomes.

Conclusion: Elevated levels of immune-inflammatory markers such as SII, SIRI, and LDH level are strong predictors of adverse pregnancy outcomes in thrombophilia-complicated pregnancies. These markers are significantly associated with maternal-neonatal outcomes. Our findings underscore the importance of monitoring immune-inflammatory markers in pregnant women with thrombophilia to improve maternal and neonatal outcomes.

Keywords: Thrombophilia, Maternal-neonatal Outcomes, Immune, Inflammatory

Introduction

Thrombophilia refers to the state of genetic or acquired defects in anticoagulant protein, coagulation factor, fibrinolytic protein, or acquired risk factors leading to thromboembolism in the human body.[1] Thrombophilia does not necessarily develop thrombotic disease but may affect the uteroplacental circulation, leading to placental microthrombosis. Also, it can pose significant risks during pregnancy, leading to complications such as fetal loss, preeclampsia, and intrauterine growth restriction (IUGR).[2] These complications not only threaten maternal and fetal health but also impose substantial emotional and financial burdens on affected families. The main type of thromboembolism is venous thromboembolism

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(VTE), which is the leading cause of maternal death during pregnancy and postpartum.[3] The prevalence of thrombophilia in pregnant women varies widely, but it is estimated to affect approximately 10–15% of the population.[2] Pregnancy can cause the maternal coagulation system to tilt toward hypercoagulability.[4] Related studies have shown that pregnant women in pregnancy have a 5–10-fold increased risk of VTE compared with non-pregnant women of the same age.[5–7] The risk of thrombosis during pregnancy starts from the first trimester and then gradually increases, reaching its highest before and after delivery.[7,8] Therefore, pregnancy patients with easy thrombolysis belong to high-risk pregnant women who need special care.

Despite advances in medical care, thrombophilia was the leading cause of maternal and fetal morbidity and mortality, with an estimated maternal mortality rate of 1–2% in affected pregnancies.[9] Current diagnostic and therapeutic strategies, including anticoagulation therapy, have limitations, particularly in predicting and preventing adverse pregnancy outcomes. As for all pregnant women combined with thrombophilia, there is no conclusive evidence to support anticoagulation. Therefore, identifying the high-risk groups with adverse pregnancy outcomes and providing special care is conducive to reducing adverse pregnancy outcomes. Recent studies have highlighted the role of immune-inflammatory markers in various obstetric complications. Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI) are novel biomarkers that have shown promise in predicting outcomes in conditions such as cancer and cardiovascular diseases.[10] SII and SIRI, derived from blood, reflect the balance between pro-inflammatory and anti-inflammatory responses the local immune status and systemic inflammation throughout the human body.[11–13] During pregnancy, immune-inflammatory responses are crucial in maternal and fetal health.[14] Importantly, lactate dehydrogenase (LDH), as a marker of systemic inflammation, can modulate the immune microenvironment by increasing the production of lactate and promoting immunosuppression.[15,16] However, those immune inflammatory biomarkers have not been extensively studied in pregnant women with thrombophilia.

Given the severe implications of thrombophilia during pregnancy, it is crucial to identify reliable biomarkers that can predict adverse pregnancy outcomes early, thereby enabling timely interventions and improving maternal and fetal prognosis. This study focuses on the potential of early pregnancy peripheral blood immune-inflammatory markers, specifically the SII, SIRI, and LDH, to predict adverse pregnancy outcomes in women with thrombophilia.

Material and Methods

The Participant's Samples

This study is a retrospective cohort study. We collected and analyzed the clinical data of pregnant women with thrombolysis who delivered in the obstetric department of Shengli Clinical Medical College of Fujian Medical University, Fuzhou University Affiliated Provincial Hospital from January 2022 to April 2024. We finally included 223 pregnant women in this study following the inclusion and exclusion criteria. Basic clinical information and pregnancy outcomes of participants were collected. In additional, there are two researchers entered and cross-checked all clinical records and employed standardized data collection protocols at the same time to ensure the accuracy and completeness of clinical data collection.

All the study participants must meet the following inclusion criteria: (1) Pregnant women diagnosed with thrombophilia according to guidelines;[17] (2) mother age > 20years; (3) gsingleton pregnancy; (4) regular pregnancy check-up with complete data and delivery in the hospital. Exclusion criteria were as follows: (1) hypertension, diabetes, severe heart, brain, liver, kidney complications, and cancer history before pregnancy; (2) acute and chronic blood diseases before or during pregnancy; (3) active SLE, active nephritis or prednisone> 20mg; (4) multiple pregnancies; (5) incomplete clinical data.

Diagnostic Criteria for Thrombophilia

The diagnostic criteria for thrombophilia refer to the Chinese Guidelines for Diagnosis and Treatment of thrombophilia 2021 edition)[17] including hereditary thrombophilia and acquired thrombophilia. Hereditary thrombophilia mainly includes protein S deficiency, protein C deficiency, antithrombin III deficiency, and hyperhomocysteinemia. Acquired thrombophilia primarily refers to autoimmune diseases, including antiphospholipid syndrome, systemic lupus

erythematosus, ankylosing spondylitis, rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome, and undifferentiated connective tissue disease.

Definition

Adverse pregnancy outcomes: adverse pregnancy outcomes if study subjects meet one or more of the following conditions: (1) fetal death after 12 weeks of gestation except for anatomical or chromosomal abnormalities; (2) newborns with severe complications such as asphyxia; (3) premature delivery or termination below 36 weeks due to gestational hypertension, preeclampsia or placental insufficiency; (4) small gestational age (SGA) newborns, defined as birth weight below the 5th percentile and no anatomical or chromosomal abnormalities.[18]

Peripheral Blood Cell Counts

For all participants, venous blood was collected using anticoagulant tubes at the early gestation stages (8–14 weeks) and stored in a 4°C before analysis. White blood cell (WBC) counts, neutrophils counts, lymphocytes counts, monocytes counts, and platelets counts in peripheral blood were performed using flow cytometry (XE-3000, SYSMES, Kobe, Japan). Based on the blood cell count, the two markers were calculated with the following formula: SII=Platelets count X Neutrophils count/Lymphocytes count, SIRI=Monocytes count X Neutrophils count/lymphocytes count.[19,20] LDH was detected with a chemiluminescent microparticle with Architect i2000SR (IMX; Abbott Diagnostics, Chicago, IL, USA).

Statistics

In this study, the SPSS 26.0 version (IBM, Armonk, NY, USA) was used for the statistics and analysis, And the drawing was performed with the GraphPad Prism 9 software package. Measurement data are expressed as standard deviation (x ±s); the group differences of continuous variables meeting the normal distribution are tested by *t*-test; the differences of continuous variables not conforming to the normal distribution by Mann–Whitney *U*-test. Count data are expressed as rate, and chi-square tests are used to compare between groups. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the effectiveness of peripheral blood biomarkers (SII, SIRI, and LDH) in predicting adverse pregnancy outcomes in the first trimester. In addition, Spearman's rank correlation coefficient was also used to determine the relationship between peripheral blood biomarkers (SII, SIRI, and LDH) and maternal-neonatal outcomes. Multivariate logistic regression analysis was used to assess risk factors for adverse pregnancy outcomes in pregnant women with thrombophilia. Firstly, the univariate regression analysis was conducted on the variables one by one, and the p-value of less than 0.1 was included in the final regression analyse. The difference at P-values <0.05 was considered statistically significant in all statistical tests.

Results

The Primary Clinical Characteristic of Maternal-Neonatal Outcomes

Finally, 223 pregnant women combined with thrombophilia were enrolled in this study. The primary clinical information of all pregnant women is shown in Table 1. The mean age of the study population was 31.93±4.00 years, and the mean BMI was 21.81±3.15 cm^2/kg. Among them, the median gravidy was 2 (1–7), and the median parity was 0 (0–3). Moreover, 15 (6.70%) patients had a history of recurrent abortion, and 62 (27.80%) had gestational diabetes (GDM). And 44 (19.7%) patients were diagnosed with gestational hypertension. During pregnancy, 161 (72.20%) women used aspirin, and 147 (65.90%) received heparin. In addition, the median gestational week was 35^{+4} (10^{+4}-41) weeks. And more than half of women 143 (64.1%) had cesarean section. Regarding neonatal outcomes, 11 (4.90%) neonatal deaths occurred. Most newborns are delivered after 28 weeks. So, their prognosis is excellent. The average birth weight of the newborns was 2942.86±715.32g. 15(6.70%) infants were diagnosed as small-for gestational-age (SGA), 10 (4.70%) had neonatal asphyxia, and 67 (31.60) were admitted to the NICU.

Table 1 Clinical Characteristics of the Study Population

Characteristics		Number of cases (%)
Mother	Maternal age (years)	31.93±4.00
	BMI (cm2/kg)	21.81±3.15
	Gravidy	2 (1–7)
	Parity	0(0–3)
	Recurrent Abortion	15 (6.70%)
	GA at delivery (weeks)	35^{+4} (10^{+4}- 41)
	Cesarean delivery	143(64.1%)
	GDM	62 (27.80%)
	Gestational hypertension	44 (19.7%)
	Aspirin Use	161 (72.20%)
	Heparin Use	147 (65.90%)
	WBC($\times10^9$/L)	8.63±2.21
	Neutrophils($\times10^9$/L)	6.06±1.91
	Lymphocyte ($\times10^9$/L)	2.00±0.57
	Monocyte ($\times10^9$/L)	0.45±0.15
	Plates ($\times10^9$/L)	248.69±71.65
	LDH (U/L)	152.97±32.96
	SII($\times10^9$/L)	822.67±428.93
	SIRI($\times10^9$/L)	1.44±0.88
Newborn	GA at delivery (week)	
	<28wk	7 (3.10%)
	≥28 to <37 wk	40 (17.9%)
	≥37wk	176 (78.9%)
	Birth weight (g)	2942.86±715.32
	Macrosomia	5 (2.20%)
	SGA	15 (6.70%)
	Apgar score (1 min)	9.57±1.24
	Apgar score (5 min)	9.83±0.79
	Apgar score (10 min)	9.91±0.40
	Mortality	11 (4.90%)
	Neonatal asphyxia	10 (4.70%)
	NICU admission	67 (31.60%)

Notes: Continuous variables are presented as mean ± SD (range) and categorical variables as n (%). Recurrent abortion was defined as at least three spontaneous abortions.

Abbreviations: BMI, body mass index; GA, gestational age; GDM, gestational diabetes;WBC, white blood cell; LDH, lactate dehydrogenase; SII,systemic immune inflammation index; SIRI,systemic inflammation response index; SGA, small-for gestational-age; NICU, neonatal intensive care unit.

The Association Between the Serum Immune-Inflammatory Biomarkers and Adverse Pregnancy Outcomes with Thrombophilia

In this study, 50 (22.4%) patients had adverse pregnancy outcomes. The results showed that maternal age, BMI, gravidy, parity, GDM, and the use of heparin and aspirin during pregnancy were not associated with adverse pregnancy outcomes. However, some serum immune-inflammatory biomarkers, such as neutrophils counts, monocytes counts, LDH levels, SII, and SIRI levels, were significantly different in adverse pregnancy outcomes and control groups ($P <= 0.05$) (Table 2).

Predictive Value of Serum Immune-Inflammatory Biomarkers for Adverse Pregnancy Outcome with Thrombophilia

To further explore the effect of immune-inflammatory biomarkers in peripheral blood on adverse pregnancy outcomes, we performed ROC analyses of SII, SIRI, and LDH levels to predict adverse pregnancy outcomes in women with

Table 2 The Association Between Adverse Pregnancy Outcome

Variable	No APOs (N=173) n (%)	APOs (N=50) n (%)	P-value
Maternal age (years)	31.95±4.09	31.86±3.74	0.884
BMI(cm^2/kg)	21.68±2.99	22.25±3.63	0.258
Gravidy	2 (1–7)	2(1–7)	0.634
Parity	0 (0–3)	1(0–3)	0.471
Recurrent Abortion	12 (6.90%)	3 (6.00%)	0.816
GDM	49 (28.32%)	13(26.00%)	0.746
Aspirin Use	127 (73.40%)	34 (68.00%)	0.452
Heparin Use	115(66.50%)	32 (64.00%)	0.745
WBC($\times10^9$/L)	8.56±2.14	8.89±2.45	0.356
Neutrophils($\times10^9$/L)	5.36±1.83	6.37±2.13	0.038
Lymphocyte ($\times10^9$/L)	2.02±0.57	1.90±0.56	0.200
Monocyte ($\times10^9$/L)	0.44±0.13	0.56±0.18	0.024
Plates ($\times10^9$/L)	247.43±52.34	253.04±67.71	0.742
LDH (U/L)	146.66±22.95	174.78±49.48	<0.001
SII($\times10^9$/L)	730.24±232.40	1142.50±713.72	<0.001
SIRI($\times10^9$/L)	1.24±0.49	2.14±0.71	<0.001

Notes: Categorical data were analysed using chi-squared tests, and continuous data with t-tests.

Abbreviations: APO, adverse pregnancy outcome; BMI, body mass index; GDM, gestational diabetes;WBC, white blood cell; LDH, lactate dehydrogenase; SII,systemic immune inflammation index; SIRI,systemic inflammation response index.

thrombophilia. We found that the AUC of SII, SIRI, and LDH levels for predicting adverse pregnancy outcomes were 0.762, 0.764, and 0.732, respectively. Moreover, the optimal cut-off for the SII, SIRI, and LDH levels were 886.62, 1.45, and 159, respectively. Furthermore, the combined model with SII, SIRI, and LDH levels had the highest AUC (0.805) (Figure 1). In addition, multivariate logistic regression analysis showed that neutrophils counts, SII, SIRI, and LDH levels were independent risk factors for adverse pregnancy outcomes. As shown in Table 3, the SII level had the highest odd ratio (OR) (OR=8.512; 95% CI (3.068–23.614)), followed by LDH level (OR = 4.905; 95% CI (1.167–11.101)), SIRI level (OR=3.549;95% CI(0.847–8.669)) and Neutrophils counts (OR=1.726; 95% (0.563–2.938)).

The Relationships Between the Serum Immune-Inflammatory Biomarkers and Maternal-Neonatal Outcomes with Thrombophilia

Table 4 shows that immune-inflammatory markers in maternal peripheral blood, such as neutrophils count, monocytes count, SII, SIRI, and LDH levels were significantly associated with maternal outcomes. The higher occurrence of gestational hypertension indicated by higher monocytes count, higher SII level, and SIRI level (r=0.201, P=0.003; r=0.157, P=0.019; r=0.252, P <0.001; r=0.282, P <0.001; r=−0.351, P<0.001). The associations between serum immune-inflammatory markers and neonatal outcomes are shown in Table 4. Elevated SII, SIRI, and LDH levels were associated with lower neonatal weight (r=−0.157, P=0.019; r=−0.181, P=0.007; r=−0.213, P=0.001). Moreover, increased LDH levels significantly related to lower Apgar (1 min), Apgar (5 min), and Apgar (10 min) (r=−0.146, P=0.033; r=−0.195, P=0.004; r=−0.180, P=0.008). Finally, we found that higher neutrophils count, SII, SIRI, and LDH levels were related to higher neonatal mortality (r=−0.132, P=0.049; r=−0.249, P <0.001; r=−0.180, P=0.007; r= −0.143, P=0.033).

Discussion

Thrombophilia poses significant risks during pregnancy, potentially leading to adverse maternal and neonatal outcomes.[2] The heightened risk of thromboembolic events in pregnant women with thrombophilia necessitates vigilant monitoring and management to mitigate complications such as preeclampsia, fetal growth restriction, and preterm birth.[2,3] Therefore, pregnancy patients with easy thrombolysis belong to high-risk pregnant women who need special care. Understanding

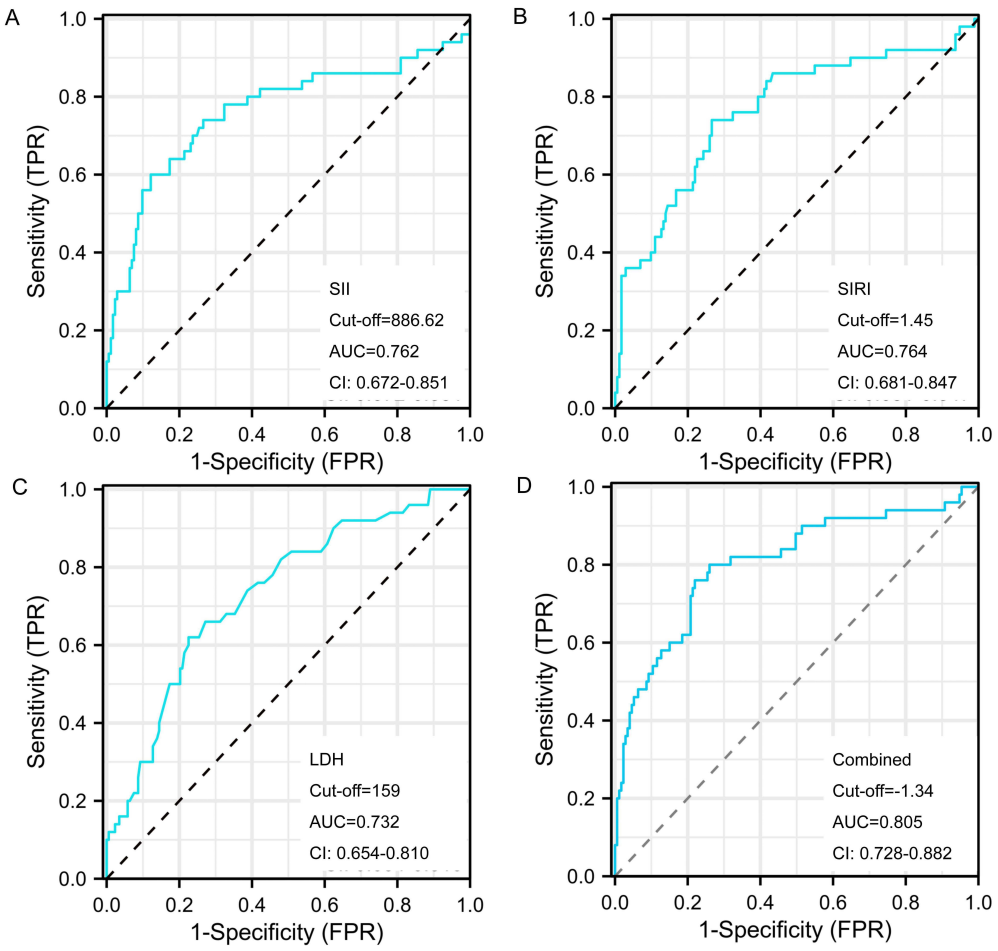

Figure 1 Cut-off, the optimal novel systemic inflammation markers level is used to predict the outcome of cervical cerclage according to the ROC curve. (**A**) SII level; (**B**) SIRI level; (**C**) LDH level; (**D**) combined model.

Abbreviations: SII, systemic immune inflammation index; SIRI, systemic inflammation response index; LDH, lactate dehydrogenase; AUC, the area under the ROC curve; CI, confidence interval.

the potential high-risk pregnant women is crucial for developing effective preventive and therapeutic strategies. However, there are no indicators for predicting adverse pregnancy outcomes.

This retrospective cohort study analyzed clinical data from 223 pregnant women diagnosed with thrombophilia. The baseline of the study population found that the proportion of gestational hypertension and gestational diabetes was 19.7% and 27.8%, which was actually consistent with the proportion reported in other articles.[21] By examining peripheral blood immune-inflammatory markers such as SII, SIRI, and LDH levels, we aimed to elucidate their predictive value for

Table 3 Independent Risk Factors for Predicting the Adverse Pregnancy Outcome

Factors	OR	95% CI	p-value
Neutrophils($\times10^9$/L)	1.726	0.563–2.938	0.014
Monocyte ($\times10^9$/L)	1.560	0.155–4.616	0.427
SII ($\times10^9$/L) (≥886.62)	8.512	3.068–23.614	<0.001
SIRI ($\times10^9$/L) (≥1.45)	3.549	0.847–8.669	<0.001
LDH (U/L) (≥159)	4.905	1.167–11.101	<0.001

Abbreviations: OR, odd ratio; CI,confidence interval;LDH, lactate dehydrogenase; SII,systemic immune inflammation index; SIRI,systemic inflammation response index;

Table 4 Relationships Between the Inflammatory Markers and Maternal-Neonatal Outcomes

Variable		Neutrophils	Monocyte	SII	SIRI	LDH
GDM	r-value	0.053	0.047	0.056	0.078	0.038
	p-value	0.427	0.488	0.402	0.246	0.574
Gestational hypertension	r-value	0.201	0.157	0.252	0.282	0.099
	p-value	0.003	0.019	<0.001	<0.001	0.141
Recurrent Abortion	r-value	−0.019	0.079	−0.024	−0.020	0.071
	p-value	0.777	0.241	0.719	0.761	0.293
Cesarean delivery	r-value	−0.086	−0.110	0.023	−0.035	0.052
	p-value	0.203	0.101	0.730	0.603	0.437
Birth weight (g)	r-value	−0.012	0.122	−0.157	−0.181	−0.213
	p-value	0.864	0.071	0.019	0.007	0.001
Apgar score (1 min)	r-value	0.029	−0.010	−0.067	−0.129	−0.146
	p-value	0.677	0.888	0.333	0.060	0.033
Apgar score (5 min)	r-value	0.040	0.066	−0.111	−0.120	−0.195
	p-value	0.561	0.335	0.104	0.079	0.004
Apgar score (10 min)	r-value	0.089	0.043	−0.053	−0.059	−0.180
	p-value	0.194	0.528	0.442	0.391	0.008
Mortality	r-value	−0.132	0.005	−0.249	−0.180	−0.143
	p-value	0.049	0.943	<0.001	0.007	0.033
NICU admission	r-value	0.027	−0.014	0.109	0.203	0.133
	p-value	0.698	0.834	0.113	0.003	0.053

Notes: Analysis was performed using Spearman's rank correlation analysis.
Abbreviations: GDM, gestational diabetes; LDH, lactate dehydrogenase; SII,systemic immune inflammation index; SIRI,systemic inflammation response index;

adverse pregnancy outcomes. Our findings indicated significant differences in these markers between women with and without adverse pregnancy outcomes, suggesting their potential utility in risk stratification and management. The results showed that the AUC of SII, SIRI, and LDH levels for predicting adverse pregnancy outcomes were relatively high. These findings are consistent with previous studies that have demonstrated the utility of SII in predicting adverse outcomes in different clinical settings.[22] Similarly, elevated SIRI levels, which incorporate monocytes counts, reflect heightened systemic inflammation and have been associated with poor maternal and fetal outcomes.[23]

Moreover the combined model with SII, SIRI, and LDH levels had the highest AUC (0.805). This suggests that a multifactorial approach incorporating these markers could enhance predictive accuracy. In addition, multivariate logistic regression analysis showed that neutrophils counts, SII, SIRI, and LDH levels were independent risk factors for adverse pregnancy outcomes. And the SII level had the highest OR. It is reported that elevated LDH levels have been related to adverse pregnancy outcomes, including preeclampsia and intrauterine growth restriction,[24] which corroborates our results. The clinical implications of this study are substantial and multifaceted. The identification of SII, SIRI, and LDH levels as reliable predictors of adverse pregnancy outcomes could revolutionize prenatal care for women with thrombophilia. By incorporating these biomarkers into routine screening protocols, healthcare providers can identify high-risk pregnancies earlier, allowing for timely interventions that could mitigate potential complications. This proactive approach aligns with the growing emphasis on personalized medicine, where treatment strategies are tailored to individual risk profiles. Moreover, our study underscores the importance of monitoring inflammatory markers in pregnant women, which could contribute to developing new therapeutic targets and strategies to modulate immune responses to improve pregnancy outcomes. These results can influence clinical guidelines and policy-making, advocating for the integration of immunological assessments in prenatal care protocols for women with thrombophilia. Therefore, it is possible to predict pregnancy outcomes through relevant indicators in the peripheral blood in the early pregnancy, find out high-risk groups early, and achieve early intervention to reduce adverse pregnancy outcomes.

Despite our study's strengths and innovative aspects, several limitations must be acknowledged. Firstly, this is a retrospective study, which inherently carries risks of selection bias and limits the ability to establish causality. Therefore, a prospective study and a randomized controlled trial are necessary for the future. Secondly, our study was conducted at a single center, the results may be influenced by unit-specific practices and affect the generalizability of the findings to broader populations. Furthermore, multicenter studies with larger sample sizes need to be practice. Such studies would provide more robust evidence and enhance the external validity of our findings, ultimately contributing to a more comprehensive understanding of the role of immune-inflammatory markers in pregnancy outcomes. Additionally, Inflammatory markers such as SII and SIRI can be affected by various conditions unrelated to thrombosis, including chronic disease and metabolic status, and thus comparison with controls with similar levels of inflammatory markers may provide further clarity in future studies through case-control studies.

In conclusion, our study highlights the significant association between elevated immune-inflammatory markers, such as SII, SIRI, and LDH, and adverse pregnancy outcomes in women with thrombophilia. These markers demonstrated robust predictive value for adverse consequences. The combination of SII, SIRI, and LDH provided the highest predictive accuracy, suggesting that these markers could be valuable tools for the early identification of at-risk pregnancies. Our findings underscore the importance of monitoring immune-inflammatory markers in pregnant women with thrombophilia to improve maternal and neonatal outcomes, which helps to find out high-risk groups early, and achieve early intervention and provide a personalized surveillance and treatment.

Patient Consent for Publication

The Hospital Ethics Committee of Fujian Provincial Hospital, approved the study (K2024-05-011) and complied with the Declaration of Helsinki. And all individuals participating in this study signed written informed consent.

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

All authors declare that they have no competing interests.

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