Am J Transl Res 2024;16(11):6564-6572
www.ajtr.org /ISSN:1943-8141/AJTR0159154

Original Article

Risk factors in immune-related recurrent spontaneous abortion and construction of predictive models

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Received July 13, 2024, Accepted October 13, 2024; Epub November 15, 2024; Published November 30, 2024

Abstract: Objectives: To explore the risk factors associated with immune-related recurrent spontaneous abortion (IRSA) and to develop a predictive model to identify high-risk individuals, aiming to provide theoretical guidance for RSA prevention. Methods: This retrospective study included 120 patients with RSA who were treated at Jiangxi University of Traditional Chinese Medicine Hospital between January 2022 and January 2024. Patients were divided into two groups based on the nature of their miscarriages: the IRSA group (observation group, n=58) and the non-IRSA group (control group, n=62). Univariate and multivariate analyses were conducted to identify independent risk factors for IRSA. Using these factors, a nomogram prediction model was constructed and validated with R software (version 4.1.2). Results: Independent prognostic factors for immune-related RSA included average platelet aggregation rate (95% CI 1.005-4.387; P=0.027), hemoglobin (95% CI 0.856-6.205; P=0.014), antiphospholipid antibodies (95% CI 0.954-5.465; P=0.024), triglycerides (TG) (95% CI 1.009-8.369; P=0.016), and free triiodothyronine (FT3) (95% CI 1.236-7.069; P=0.026). Using these factors, a nomogram was developed for predicting immune-related RSA incidence. The model achieved an AUC of 0.7975882 (95% CI 0.635-0.947), indicating good predictive accuracy, and decision curve analysis demonstrated positive net benefits. Conclusion: FT3, TG, antiphospholipid antibodies, hemoglobin, and average platelet aggregation rate are independent risk factors for IRSA onset.

Keywords: Immune, recurrent spontaneous abortion, risk factors, predictive models

Introduction

Recurrent spontaneous abortion (RSA) refers to the consecutive loss of two or more fetuses before 28 weeks of pregnancy, including consecutive biochemical pregnancies. Its incidence rate ranges from 1-5% [1, 2]. The etiology of RSA is multifactorial and includes immunological factors (autoimmunity, alloimmunity), anatomical abnormalities (e.g., intrauterine adhesions, uterine fibroids), endocrine abnormalities (e.g., insulin resistance, polycystic ovary syndrome, thyroid dysfunction), and chromosomal abnormalities in either the embryo or the parents (e.g., chromosomal translocations, aneuploidies) [3-6]. Recent research indicates that approximately 50-60% of RSA cases are related to immune dysfunction, leading to the classification of such cases as immune-related recurrent spontaneous abortion (IRSA) [7, 8].

The etiology of IRSA remains largely unknown, imposing considerable psychological stress on affected individuals and presenting a significant clinical challenge. Factors contributing to IRSA are complex and may include genetic predispositions, reproductive anatomy, endocrine imbalances, infections, immune dysregulation, thrombotic disorders, and other influences (e.g., environmental exposures, lifestyle factors, physical and psychological stress, and medication use) [9-11]. Dinda et al. suggest that genetic polymorphisms might predispose certain individuals to immune abnormalities associated with RSA, potentially affecting immune responses and increasing susceptibility [12]. Consequently, patients with IRSA are highly susceptible to psychological issues, with about 40% experiencing depression or anxiety to varying degrees [13].

Identifying patients at risk for IRSA based on personal and medical history prior to concep-

https://doi.org/10.62347/RPMF6124

tion could enable proactive diagnostic and therapeutic interventions, reducing the incidence of IRSA. However, to our knowledge, no prediction model currently exists to assess IRSA risk.

Given the complexity of IRSA and recent advancements in related research, establishing a comprehensive, standardized etiological screening process for IRSA patients is essential. This approach involves identifying IRSA-related risk factors, predicting its occurrence, and implementing early interventions to prevent further miscarriages and improve pregnancy outcomes. This study aims to identify IRSA risk factors and develop a predictive model to support more effective clinical management of IRSA.

Methods

Study design and patient selection

The medical records of 120 patients with recurrent spontaneous abortion treated at Jiangxi University of Traditional Chinese Medicine Hospital between January 2022 and January 2024 were retrospectively reviewed. Patients were categorized into two groups based on the etiology of miscarriage: the IRSA group (observation group, n=58) and the non-IRSA group (control group, n=62). The protocol was approved by the Ethics Committee of Jiangxi University of Traditional Chinese Medicine Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with two or more instances of abortion, biochemical pregnancy, or embryo implantation failure. (2) Patients with a normal chromosomal karyotype. (3) Patients aged ≥18 years without significant hearing or vision impairment, or dementia. (4) Patients with a normal uterine cavity, as confirmed by ultrasound or hysteroscopy.

Exclusion criteria: (1) Patients diagnosed with polycystic ovary syndrome or uterine fibroids. (2) Patients with genital tract infections, including positive findings in cervical/vaginal secretions and viral infection screenings (e.g., TORCH). (3) Patients with prior immunotherapy. (4) Patients with infectious, endocrine, genetic diseases, or hypercoagulable conditions.

Diagnostic criteria

(1) Abortion: Defined as the termination of pregnancy before 28 weeks of gestation, with fetal weight less than 1000 grams [14]. (2) Biochemical Pregnancy: A condition where human chorionic gonadotropin (β-hCG) levels in blood or urine exceed normal values, but no gestational sac is visible on ultrasound [15]. (3) IRSA: Characterized by a history of two or more consecutive miscarriages without a live birth or stillbirth, with no chromosomal or anatomical abnormalities detected in routine etiological screening, and without concurrent infectious or endocrine diseases [16].

Outcome measures

Detailed patient information was retrieved from the hospital information system (HIS), including clinical characteristics, medical history, and both clinical and biochemical indicators. Then the primary outcomes covered the concordance index (c-index), a calibration curve, DCA, and area under the receiver operating characteristic (ROC) curve (AUC). The secondary outcomes included the clinical data and laboratory indicators. Clinical characteristics encompassed age, body mass index (BMI), smoking and alcohol history, previous gestational weeks of miscarriage, antiphospholipid antibody, and abortion frequency. Laboratory indicators included routine blood tests, thyroid function, coagulation-related indicators (DIC, thromboelastogram), 25-hydroxyvitamin D, erythrocyte sedimentation rate, glucose metabolism, blood lipids, renal function, and antiphospholipid syndrome (APS) markers (quantitative assays of anticardiolipin, anti-β2 glycoprotein 1 antibody, and lupus anticoagulant).

Sample size estimation

Sample size was calculated using power analysis, following the formula: corrected sample size = sample size/(1 - [% attrition/100]) [17]. A final sample size of approximately 100 was determined.

Statistical analysis

Data analysis and statistical plotting were performed using IBM SPSS 25.0 (IBM, New York, USA) and R software (Version 4.2.0, https://www.r-project.org/). For normally distributed

Table 1. Comparison of general characteristics between the two groups

	Control group (n=62)	Observation group (n=58)	χ^2/t	P
Age	32.95±4.65	32.64±5.21	0.543	0.587
≥35	16 (25.81%)	19 (32.76%)		
30-35	20 (32.26%)	21 (36.21%)		
≤30	26 (41.93%)	18 (31.03%)		
Abortion frequency			9.087	0.006
≥3	14 (22.58%)	28 (48.28%)		
<3	48 (77.42%)	30 (50.72%)		
Antiphospholipid antibody			4.784	0.027
Single Yang	14 (22.58%)	22 (37.93%)		
Shuangyang	16 (25.81%)	14 (24.14%)		
San Yang	2 (3.23%)	0 (0.00%)		
Antinuclear antibody	42 (67.74%)	37 (63.79%)	0.897	0.357
25(OH)VD_3	28.65±9.64	23.41±8.64	-3.078	0.001
Maximum platelet aggregation rate	56.78±17.48	6.08±1.57	1.987	0.047
Average platelet aggregation rate	52.47±18.27	68.57±20.85	6.459	0.012
BMI	20.11±1.27	20.89±2.27	0.398	0.078
Smoking	14 (22.58%)	13 (22.41%)	0.108	0.754
Drinking	13 (20.97%)	13 (22.41%)	1.497	0.475
Previous gestational weeks of miscarriage	13.43±3.45	16.38±2.89	1.574	0.207

Note: BMI: body mass index, 25(OH)VD_3: 25-hydroxyvitamin D_3.

data, values were expressed as mean ± standard deviation (mean ± SD) and analyzed using the two-sample t-test. Non-normally distributed data were presented as median and quartiles, with the Mann-Whitney U test used for comparisons. Categorical data were expressed as frequency and compared using the chi-square or Fisher's exact test.

Variables with statistically significant differences were included in a binary multivariate logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for independent predictors of immune-related RSA. Statistical significance was set at P<0.05.

A nomogram for predicting immune-related RSA was constructed using R software. The model's discriminatory ability was assessed using the ROC curve and AUC. Calibration was evaluated with a calibration plot, and clinical applicability was determined through a Decision Curve Analysis (DCA) plot.

Results

Comparison of general characteristics between the two groups

No significant differences were observed between the two groups in general clinical data such as age, antinuclear antibody presence, smoking, drinking, and previous gestational weeks of miscarriage (all P>0.05). However, significant differences were found in abortion frequency, antiphospholipid antibodies, 25(OH)VD_3, maximum platelet aggregation rate, and average platelet aggregation rate (all P<0.05) (**Table 1**).

Comparison of endocrine-related index levels between the two groups

Significant differences were identified between the groups in levels of 2h insulin, FT3, TSH, and TG (all P<0.05). However, there were no significant differences in T3, T4, FT4, thyroglobulin, thyroid globulin antibody, peroxidase antibody, fasting blood glucose, fasting insulin, C-peptide at fasting, 2h blood glucose, 2h C-peptide, CHO, HDL, and LDL levels between the two groups (all P>0.05) (**Table 2**).

Comparison of routine blood parameters between the two groups

The two groups showed no significant differences in routine blood parameters, including white blood cell (WBC), neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio, basophil ratio, neutrophil count, lymphocyte

Table 2. Comparison of endocrine-related index levels between the two groups

	Control group (n=62)	Observation group (n=58)	t	p
T3	1.78±0.25	1.87±0.21	1.009	0.165
T4	112.23±24.01	112.54±17.04	0.278	0.112
FT3	5.65±1.65	10.18±0.57	5.498	0.024
FT4	19.87±12.65	16.54±2.87	0.487	0.123
TSH	12.68±8.54	15.98±8.51	6.125	0.012
Thyroglobulin	15.65±6.24	12.34±9.54	1.665	0.154
Thyroid globulin antibody	50.24±7.45	49.58±7.41	1.024	0.124
Peroxidase antibody	56.24±7.68	56.41±7.12	0.098	0.147
Fasting blood glucose	4.98±0.64	4.82±0.41	0.287	0.087
Fasting insulin	11.65±6.34	10.87±3.54	0.065	0.090
Empty dispersed C-peptide	1.69±0.54	1.28±0.54	0.125	0.128
2h blood glucose	5.64±1.12	5.89±1.32	0.089	0.336
2h insulin	46.57±32.45	42.74±28.65	0.274	0.047
2h C-peptide	4.56±1.98	4.69±1.81	0.015	0.189
CHO	3.98±1.89	3.97±0.79	0.256	0.178
TG	1.28±1.01	6.87±0.37	3.897	0.048
HDL	1.56±0.54	1.98±0.24	0.087	0.124
LDL	2.29±0.72	2.18±0.87	0.474	0.074

Note: T3: triiodothyronine, T4: thyroxine, FT3: Free Triiodothyronine, FT4: Free Thyroxine, FSH: Thyroid Stimulating Hormone, CHO: cholesterol, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

Table 3. Comparison of routine blood parameters between the two groups

	Observation group (n=58)	Control group (n=62)	t	p
WBC	6.87±4.65	6.48±1.78	0.398	0.178
Neutrophil ratio	0.78±0.31	1.03±0.56	0.278	0.165
Lymphocyte ratio	0.36±0.16	0.36±0.18	0.871	0.187
Monocyte ratio	0.16±0.07	0.21±0.14	0.487	0.154
Eosinophil ratio	0.49±0.28	0.59±0.27	0.874	0.289
Basophil ratio	0.59±0.47	0.64±0.52	1.264	0.254
Neutrophil count	3.98±1.65	3.64±1.56	1.007	0.165
Lymphocyte count	1.89±0.56	1.59±0.54	0.458	0.154
Number of monocytes	0.36±0.14	0.64±0.24	1.364	0.178
Number of eosinophils	0.13±0.05	0.45±0.04	0.174	0.297
Number of basophils	0.46±0.16	0.65±0.11	0.184	0.123
RBC	4.69±0.37	4.49±0.78	0.174	0.378
Hemoglobin	96.87±12.87	139.25±20.87	-7.156	0.034

Note: WBC: White Blood Cell, RBC: Red Blood Cell.

count, monocyte count, eosinophil count, basophil count, and red blood cell (RBC) count (all P>0.05). However, there was a significant difference in hemoglobin levels between the two groups (P<0.05) (**Table 3**).

Univariate and multivariate analysis

Variables such as abortion frequency, 25(OH) VD_3, maximum platelet aggregation rate, average platelet aggregation rate, 2h insulin, hemoglobin, antiphospholipid antibody, TG, FT3, and TSH were included in the univariate analysis. The univariate analysis showed significant associations for average platelet aggregation rate (95% CI 0.656-1.595; P=0.040), hemoglobin (95% CI 0.504-0.987; P=0.037), antiphospholipid antibody (95% CI 1.039-1.513; P=0.018), TG (95% CI 1.306-3.132; P=0.002), and FT3 (95% CI 1.574-8.235; P=0.003) (**Table**

Table 4. Univariate analysis of influencing factors of IRSA

Index	β	SE	OR (95% CI)	Wald	P
Abortion frequency	-0.049	0.143	0.952 (0.719-1.261)	0.116	0.733
25(OH)VD_3	-0.078	0.099	0.925 (0.761-1.123)	0.623	0.430
Maximum platelet aggregation rate	-1.069	0.743	0.343 (0.080-1.473)	2.070	0.150
Average platelet aggregation rate	0.069	0.743	0.343 (0.656-1.595)	7.070	0.040
2h insulin	0.004	0.002	1.004 (0.999-1.009)	2.534	0.111
Hemoglobin	0.001	0.007	0.714 (0.504, 0.987)	7.798	0.037
Antiphospholipid antibody	0.226	0.096	1.254 (1.039-1.513)	5.580	0.018
TG	0.704	0.223	2.023 (1.306-3.132)	9.970	0.002
FT3	0.609	0.333	3.589 (1.574, 8.235)	10.378	0.003
TSH	0.007	0.009	1.007 (0.990-1.025)	0.628	0.428

Note: 25(OH)VD_3: 25-hydroxyvitamin D_3, TG: triglyceride, FT3: Free Triiodothyronine, TSH: Thyroid Stimulating Hormone, IRSA: immune-related recurrent spontaneous abortion.

Table 5. Multivariate analysis of influencing factors of IRSA

	β	SE	p	OR (95% CI)
Average platelet aggregation rate	4.569	1	0.027	1.333 (1.005-4.387)
Hemoglobin	-3.387	1	0.014	1.287 (0.856-6.205)
Antiphospholipid antibody	-3.987	1	0.024	3.498 (0.954-5.465)
TG	4.897	1	0.016	4.398 (1.009-8.369)
FT3	5.687	1	0.026	2.398 (1.236-7.069)

Note: β: regression coefficient, SE: standard error, OR: odds ratio, TG: triglyceride, FT3: Free Triiodothyronine, IRSA: immune-related recurrent spontaneous abortion.

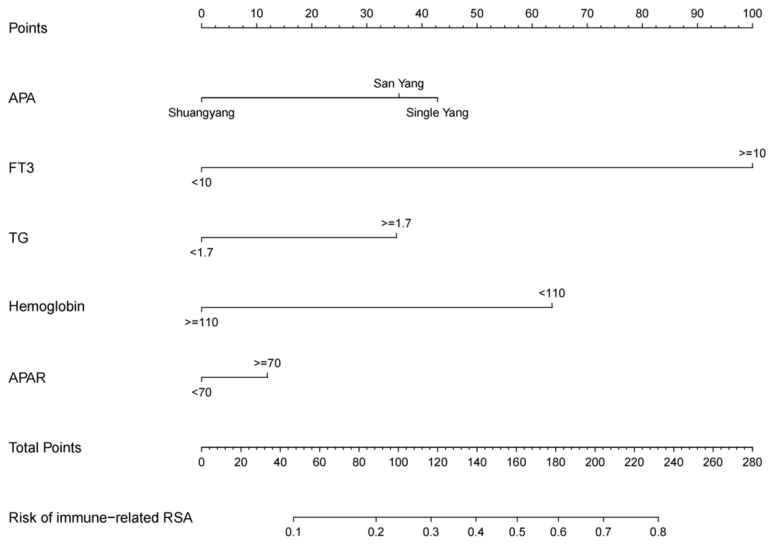

Figure 1. Nomogram for predicting IRSA. IRSA: immune-related recurrent spontaneous abortion, TG: triglyceride, FT3: Free Triiodothyronine, APA: Antiphospholipid antibody, APAR: Average platelet aggregation rate.

4). These factors were then incorporated into the multivariate analysis, which confirmed that average platelet aggregation rate (95% CI 1.005-4.387; P=0.027), hemoglobin (95% CI 0.856-6.205; P=0.014), antiphospholipid antibody (95% CI 0.954-5.465; P=0.024), TG (95% CI 1.009-8.369; P=0.016), and FT3 (95% CI 1.236-7.069; P=0.026) are independent prognostic factors for immune-related RSA (**Table 5**).

Development and validation of the nomogram

Using results from the multivariate logistic regression analysis, a nomogram was developed incorporating the independent risk factors FT3, TG, antiphospholipid antibody, hemoglobin, and average platelet aggregation rate (**Figure 1**). The calibration curve (**Figure 2**) in the training set demonstrated close alignment with the ideal curve, indicating that the model's predictions for immune-related RSA risk are consistent with actual risk, con-

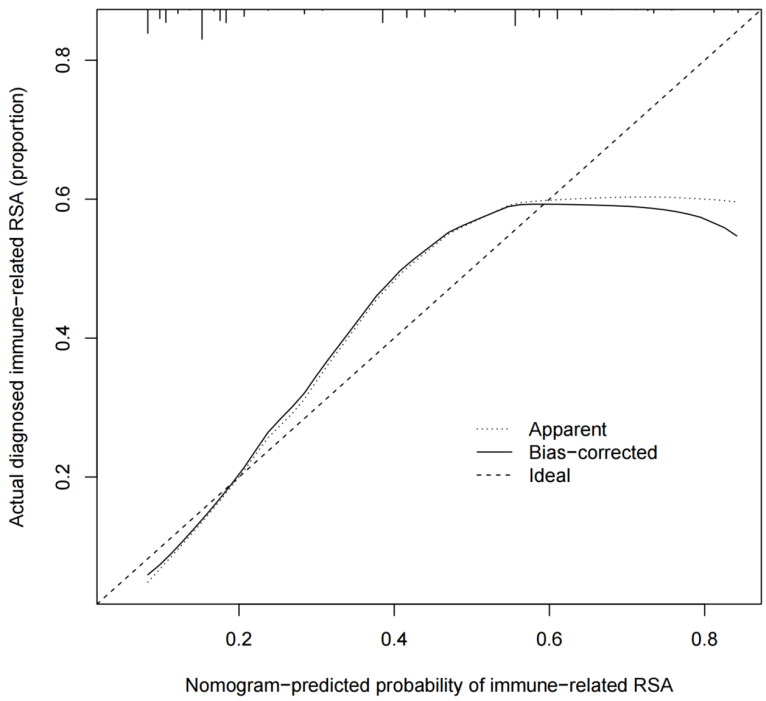

Figure 2. Calibration curve of the nomogram. RSA: Related recurrent spontaneous abortion.

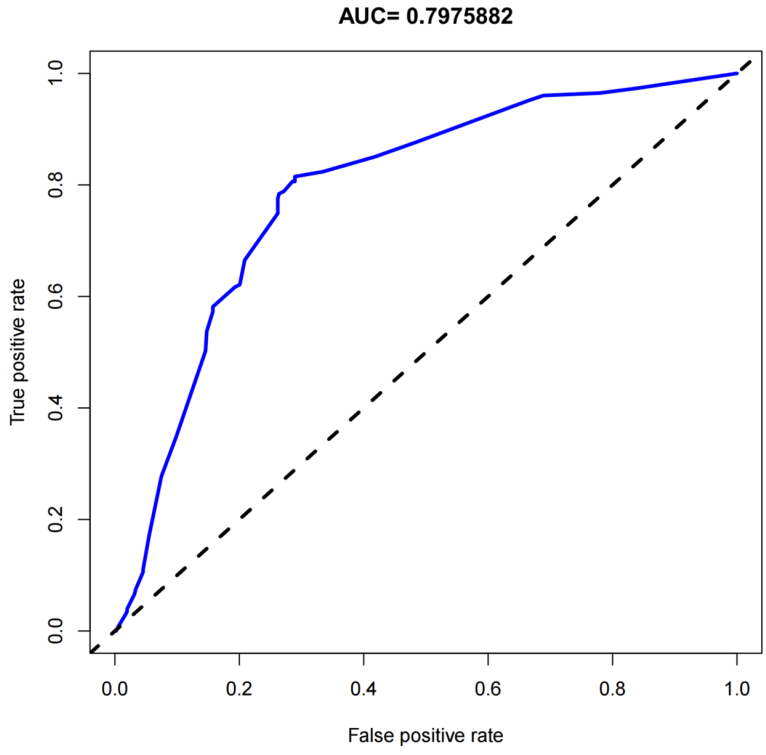

Figure 3. ROC curve area. The value of the area under ROC curve (AUC) was 0.7975882 (95% confidence interval of 0.635-0.947). ROC: Receiver Operating Characteristic.

firming high model accuracy. Additionally, the area under the ROC curve (AUC) was 0.798, suggesting good predictive performance for immune-related RSA (**Figure 3**).

Clinical utility evaluation and validation

DCA indicated that the nomogram provides a high level of clinical utility for predicting immune-related RSA risk (**Figure 4**). DCA findings suggest that, within a predicted probability range of 20%-60% for immune-related RSA, application of the nomogram model is beneficial in clinical settings.

Discussion

This study retrospectively analyzed 120 patients with RSA, focusing on general clinical data and various clinical indicators to identify independent risk factors for IRSA. The findings revealed that FT3, TG, antiphospholipid antibody, hemoglobin, and average platelet aggregation rate are independent risk factors for IRSA onset. Using these five identified risk factors, a predictive model for IRSA risk was successfully developed, evaluated, and validated.

FT3 emerged as an independent risk factor for immune-related RSA. Studies indicate that thyroid hormones play a crucial role in regulating physiological processes, including reproduction. Specifically, imbalances in thyroid function, particularly alterations in FT3 levels, can significantly affect the immune system and pregnancy outcomes [17-19]. Thyroid hor-

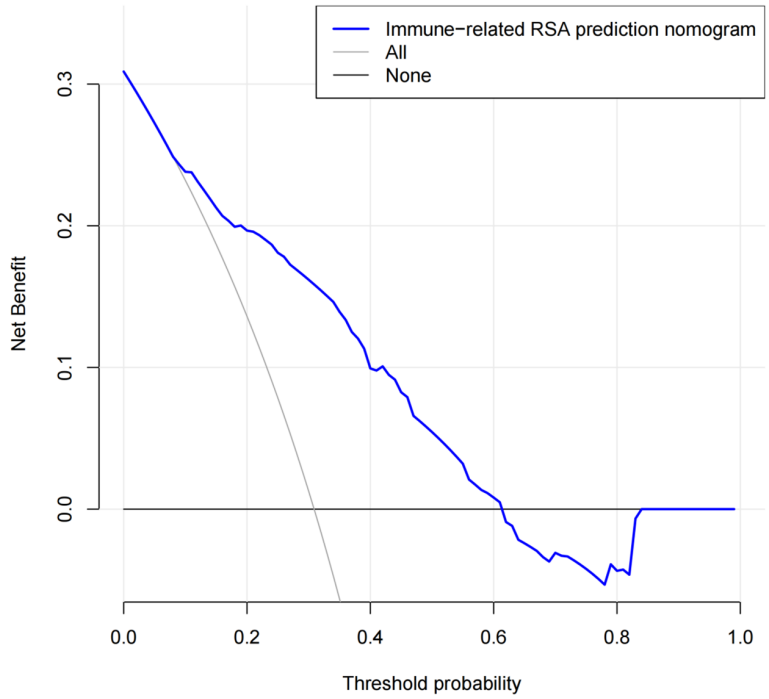

Figure 4. Decision curve analysis of the nomogram model. RSA: Related recurrent spontaneous abortion.

mone receptors are widely expressed in immune cells, and changes in FT3 levels can directly impact immune cell function and behavior. Abnormal FT3 levels may lead immune cells to produce excessive pro-inflammatory cytokines or alter immune regulation, thereby exacerbating immune-mediated pregnancy damage. Elevated FT3 levels can disrupt immune system function, leading to imbalances in immune regulation that affect homeostasis. This imbalance may result in excessive immune cell activation and dysregulated cytokine production [20]. Moreover, abnormal thyroid hormone levels, such as elevated FT3, can adversely affect the endometrium, which is critical for embryo implantation and maintenance, leading to inadequate endometrial receptivity and impairing proper embryo development [21]. Thus, monitoring and maintaining appropriate thyroid function, including FT3 levels, may be crucial in managing at-risk pregnancies and improving outcomes.

Additionally, TG was identified as an independent risk factor for immune-related RSA. Elevated triglycerides can contribute to endothelial dysfunction and inflammation, potentially causing abnormal placental blood vessel function. This affects the supply of nutrients and oxygen to the fetus, raising the risk of miscarriage [22]. Dyslipidemia, particularly elevated triglycerides, can disrupt immune balance by promoting immune cell activation and pro-inflammatory cytokine release, which negatively impacts the pregnancy environment and fetal development, contributing to RSA [23]. Lipid accumulation and related metabolic disturbances may also influence reproductive hormone function and signaling pathways, further impacting pregnancy stability and progression [24].

The results of this study indicate that antiphospholipid antibodies are independent risk factors for IRSA. Antiphospholipid antibodies can interact with cell membranes and proteins, activating platelets and the coagulation cascade, ultimately resulting in a hypercoagulable state [25]. This hypercoagulability can lead to placental thrombosis, infarction, and reduced blood supply to the fetus, which may result in miscarriage. Additionally, antiphospholipid antibodies can directly target trophoblast cells, impairing their functions in implantation, invasion, and development [26]. This interference can compromise placental integrity and functionality, affecting nutrient and gas exchange between mother and fetus. Furthermore, antiphospholipid antibodies can induce an inflammatory response, damaging placental tissues and endothelial cells, thereby compromising pregnancy viability [27]. The presence of these antibodies disrupts multiple aspects of placental function and immune regulation, significantly increasing the risk of IRSA.

This study also suggests that hemoglobin levels are independent risk factors for immune-related RSA. Low hemoglobin levels may result in insufficient oxygen supply to tissues, including the reproductive system [28], potentially disrupting the physiological functions of the uterus and placenta. This can interfere with embryo implantation and development, thereby increasing RSA risk. Moreover, low hemoglobin levels may signal underlying health issues or nutritional deficiencies that adversely impact the immune system [29]. Such deficien-

cies may contribute to immune imbalance, disrupting the tolerance required for successful pregnancy and promoting RSA. Additionally, anemia from low hemoglobin can alter metabolism and microenvironmental conditions, potentially destabilizing pregnancy and increasing susceptibility to immune-related complications [30].

The study also found that average platelet aggregation rate is an independent risk factor for IRSA. Platelets play a pivotal role in immune response. An elevated platelet aggregation rate may signal abnormal platelet activation, which can interact with immune cells and mediators, potentially leading to immune dysregulation in the reproductive system [31]. Abnormal platelet aggregation may impair microcirculation in reproductive organs, reducing nutrient and oxygen delivery, which could damage the endometrium and other tissues, hindering embryo implantation and development [32].

This study does have a few limitations. Firstly, due to the small sample size, single-center design, and retrospective nature of the analysis, there may be inherent biases. Although we made efforts to ensure sample representativeness, the findings may differ in broader populations. Secondly, some relevant factors may not have been fully considered in the analysis. Despite conducting a comprehensive literature review and data analysis, potential factors may have been overlooked. Lastly, while the prediction model underwent internal validation, it lacks external validation, which may affect its accuracy and applicability across different clinical settings and patient groups. Nevertheless, a series of measures were implemented to minimize these limitations. We adhered strictly to scientific protocols in study design and data analysis, carefully interpreting and discussing the results. These limitations are also clearly noted to advise readers to exercise caution when referencing and applying the findings. Future research will aim to expand the sample size, conduct further in-depth studies, and refine the model to improve reliability and applicability.

In conclusion, this study developed a nomogram prediction model based on risk factors for IRSA, demonstrating good predictive performance, high accuracy, and clinical applicability. The model is simple, easy to implement in clinical practice, safe and non-invasive, and widely accepted by both doctors and patients, aiding in the early identification of high-risk populations for IRSA. This model not only enhances the detection rate of IRSA but also reduces complications associated with excessive invasive examinations, providing a cost-effective means for IRSA screening in clinical practice with substantial medical and social significance.

Disclosure of conflict of interest

None.

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