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Coagulation parameters predictive of repeated implantation failure in Chinese women

A retrospective study

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Abstract

Repeated implantation failure (RIF) greatly influences pregnancy rate after assisted reproductive technologies (ART) with elusive causes. Our study aimed to explore coagulation parameters in association with RIF and establish a model to predict the risk of RIF in Chinese women.

Coagulation parameters, including prothrombin time (PT), thrombin time (TT), activated partial prothrombin time (APTT), D-dimer (DD), fibrin degradation products (FDP), fibrinogen (FG), and platelet aggregation induced by arachidonic acid (AA) and adenosine diphosphate (ADP) were measured in RIF patients and controls. A logistic regression model was built by using the purposeful selection to select important factors for the prediction of RIF.

Between 92 RIF patients and 47 controls, we found a statistically significant difference in all of the coagulation parameters except APTT, FDP and platelet aggregation induced by ADP. The purposeful selection method selected PT (odds ratio [OR] = 0.28, 95% CI: 0.12-0.66, $P = .003$), APPT (odds ratio [OR] = 0.76, 95% CI: 0.63-0.91, $P = .004$), TT (odds ratio [OR] = 0.75, 95% CI: 0.53-1.08, $P = .124$), and platelet aggregation induced by AA (odds ratio [OR] = 1.27, 95% CI: 1.11-1.44, $P = .0003$) as important predictors of RIF risk. ROC curve analysis indicated that the area under ROC curve (AUC) of the model was 0.85 with an optimal cut-off point of the predicted probability being $P = .65$, leading to a sensitivity of 0.83 and a specificity 0.75.

We found that coagulation parameters including PT, APTT, TT and platelet aggregation induced by AA are predictive of RIF in Chinese women. Our results highlight the potential of anti-coagulation therapies to lower the risk of RIF.

Abbreviations: AA = arachidonic acid, ADP = adenosine diphosphate, AMH = anti-muller hormone, APO = adverse pregnancy outcomes, APTT = activated partial prothrombin time, ART = assisted reproductive technologies, CI = confidence interval, DD = D-dimer, FDP = fibrin degradation products, FG = fibrinogen, FSH = follicle stimulating hormone, IVF-ET = in vitro fertilization and embryo transfer, OR = odds ratio, PT = prothrombin time, PTS = prethrombotic state, RIF = repeated implantation failure, ROC = receiver operating characteristic, RSA = recurrent spontaneous abortion, SD = standard deviation, TT = thrombin time, TXA2 = thromboxane A2.

Keywords: thrombophilia, repeated implantation failure, coagulation, prediction

1. Introduction

Approximately 10 to 15% women of childbearing age in the world suffer from infertility.[1] In recent years, with the rapid development of assisted reproductive technologies (ART), many infertility patients had successful pregnancy through the use of in vitro fertilization and embryo transfer (IVF-ET). ART have become a part of the routine care, with a prevalence ranging from 0.1% to 3.9% of all live born children in Europe and an average

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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of 2% in some regions of the USA,[2,3] and the number keeps growing.[4] The advancement of ART and their derived technologies led to an increased implantation rate as high as 30% to 40% and a clinical pregnancy rate as high as 50% to 60%.[5] Unfortunately, some couples fail to successfully gestate despite repeated transplants of good quality embryos.[6] Such patients are diagnosed as having recurrent implantation failure (RIF), and they are often under tremendous psychological, economic and social pressure. It remains to be a great challenge to improve the success rate of transplanted embryos in reproductive medicine.

The mechanisms underlying RIF are multifocal, including chromosomal abnormalities, anatomy, endocrine, infection and immunity. However, in about 10% of patients with RIF, the underlying mechanisms remain to be unexplained and may be closely related to prethrombotic state (PTS).[7] Although there is still no consensus regarding the causes of such RIFs, recent studies seem to indicate a close relationship between RIF and the state of hypercoagulability in such patients.[8,9] PTS can lead to embryo implantation failure, and is considered as a risk factor for a variety of adverse pregnancy outcomes (APO).[10,11] When the body is in PTS, the patient's endometrial blood flow may change, and the blood vessels are prone to form tiny thrombi. This can result in receptive disorder and difficulty of embryo implantation or poor placental circulation after implantation, leading to increased plant failure rate and embryo loss rate.[12] Currently, there are no clear guidelines and diagnostic criteria for PTS in patients with RIF. This article aims to analyze blood coagulation factors in association with RIF to establish a model for the prediction of the risk of RIF in Chinese women.

2. Materials and methods

2.1. Study participants

This study included consecutive female patients with RIF treated from October 2018 to December 2019 at the Department of Reproductive Genetics of The First People's Hospital of Yunnan Province. The data for the control group was taken from female patients who had no history of implantation failure but underwent IVF/ICSI-ET due to male factors at the Department of Gynecology at this hospital. All patients were asked for a detailed medical history, and underwent a karyotype analysis, a systemic and gynecological examination and endocrine examination.

Patients were diagnosed as having RIF if they were younger than 40 years old and were not pregnant after ≥3 transplants (including fresh and frozen embryo transfer cycles) or ≥4 high-quality embryos transfer. We adopted the following inclusion criteria in determining study eligibility:

1) patients had normal ovarian function, basal sinus follicles ≥5, basal follicle stimulating hormone (FSH) < 10 U/L and anti-muller hormone (AMH) > 1.1 ng/mL;
2) patient did not undergo anticoagulant therapy, such as oral aspirin and low molecular weight heparin injection;
3) patients had normal results in ultrasound or laparoscopic examination;
4) karyotype analysis indicated that both couples were normal; and
5) patients had no reproductive tract infection and genital malformation.

Patients were excluded from the study if:

1) there were chromosomal abnormalities in either men or women;
2) they had abnormalities in ultrasound or laparoscopic examination, including abnormal uterine cavity, endometrial polyps and intrauterine adhesions; or
3) they had oviduct effusion or other medical diseases, such as hypertension, diabetes and thyroid abnormalities.

This study was approved by Research Ethics Committee of The First People's Hospital of Yunnan Province (No. 20180716). Informed consent was obtained from all participants.

2.2. Laboratory analysis

Fasting blood was obtained from all participants upon their first clinical visit or on the following day. Data from the coagulation assays, glucose tolerance test, and insulin release test were then collected from all the study subjects. The coagulation assays included prothrombin time (PT), activated partial prothrombin time (APTT), thrombin time (TT), fibrinogen (FG), D-Dimer (DD), and fibrin degradation products (FDP). Platelet aggregation was performed on these subjects with induction by arachidonic acid (AA) and adenosine diphosphate (ADP). Coagulation data prior to the implementation of any treatment were obtained via the fully automated hemostasis testing system ACL TOP 700 (Instrumentation Laboratory, Bedford, MA, USA) using the following batches: N0972444 (PT), N0278340 (APTT), N0872044 (TT), N0378488 (FIB), B28206 (DD), and B30626 (FDP). The platelet aggregation rate was measured by optical turbidimetry using Agg RAM platelet aggregation instrument and the corresponding test reagents (Helena Laboratories, Beaumont, TX, USA). The detection inducers were arachidonic acid and adenosine diphosphate.

2.3. Statistical analysis

Continuous data were presented as mean ± SD and compared using a Wilcoxon rank-sum test. We employed purposeful selection to select important predictors to be used in the logistic regression model. Purposeful selection follows a slightly different logic from the conventional variable selection methods for logistic regressions, such as forward selection, backward selection and stepwise selection. It can select not only significant variables but also important confounders, and exhibited superior performance than existing methods in simulation studies.[13] In performing purposeful selection, the presence of RIF acted as the response variable, and we included age and the coagulation assays as candidate variables for variable selection. We used all the recommended settings for the inclusion and retention of variables, confounding criteria, and inclusion of noncandidate variables.

We then plotted a receiver operating characteristic (ROC) curve to evaluate the sensitivity and specificity of the built model, and the optimal cut point of the predicted probabilities was determined using the Yuden index, which measures the vertical distance from the uninformative diagonal to the cut point.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., NC). $P < .05$ was considered to be statistically significant.

Table 1

Basic characteristics of the study participants.

	RIF (n = 97)	Control (n = 50)	P
Age	31.32 ± 3.05	30.38 ± 3.18	.087
Prothrombin time (s)	10.37 ± 0.67	11.11 ± 0.82	**<.0001**
Activated partial prothrombin time (s)	31.52 ± 2.67	32.47 ± 2.96	.092
Thrombin time (s)	14.93 ± 1.42	16.42 ± 1.91	**<.0001**
Fibrinogen (g/L)	2.65 ± 0.40	2.47 ± 0.40	.018
D-Dimer (mg/L)	0.22 ± 0.11	0.15 ± 0.07	**.0001**
Fibrin degradation products (μg/mL)	0.92 ± 0.47	0.83 ± 0.38	.385
platelet aggregation induced by arachidonic acid (%)	89.02 ± 3.84	85.75 ± 4.45	**<.0001**
platelet aggregation induced by adenosine diphosphate (%)	84.90 ± 6.89	83.26 ± 7.24	.181

Data were presented as mean ± SD, and compared using Wilcoxon rank-sum test.
RIF = repeated implantation failure, SD = standard deviation.
P values <.05 indicate statistical significance and are shown in bold.

3. Results

3.1. Basic characteristics of the study participants

A total of 92 patients with RIF and 47 healthy controls were included in the analyses. The basic characteristics of the study participants are presented in Table 1. Briefly, patients with RIF had shorter PT (10.37 ± 0.67 vs 11.11 ± 0.82, $P < .0001$) and TT (14.93 ± 1.42 vs 16.42 ± 1.91, $P < .0001$), increased platelet aggregation induced by AA (89.02 ± 3.84 vs 85.75 ± 4.45, $P < .0001$), and elevated FG (2.65 ± 0.40 vs 2.47 ± 0.40, $P = .018$) and DD (0.22 ± 0.11 vs 0.15 ± 0.07, $P = .0001$). There was no statistically significant difference in APTT (31.52 ± 2.67 vs 32.47 ± 2.96, $P = .092$), FDP (0.92 ± 0.47 vs 0.83 ± 0.38, $P = .385$) and platelet aggregation induced by ADP (84.90 ± 6.89 vs 83.26 ± 7.24, $P = .181$).

3.2. Association with RIF

Univariate logistic regression showed that age ($P = .096$) and platelet aggregation induced by ADP ($P = 0.196$) were not significantly associated with RIF. In contrast, platelet aggregation induced by AA and coagulation parameters except APTT and FDP were significantly associated with RIF (Table 2). Moreover, the purposeful selection method selected PT (odds ratio [OR] = 0.28, 95% CI: 0.12-0.66, $P = .003$), APPT (odds ratio [OR] = 0.76, 95% CI: 0.63-0.91, $P = .004$), TT (odds ratio [OR] = 0.75, 95% CI: 0.53-1.08, $P = .124$), and platelet aggregation induced by AA (odds ratio [OR] = 1.27, 95% CI: 1.11-1.44, $P = .0003$) as important predictors of RIF risk (Table 3).

Table 2

Association with RIF by univariate logistic regression analysis.

	OR (95% CI)	P
Age	1.10 (0.98-1.24)	.096
Prothrombin time (s)	0.24 (0.13-0.44)	**<.0001**
Activated partial prothrombin time (s)	0.88 (0.77-1.00)	.062
Thrombin time (s)	0.59 (0.46-0.74)	**<.0001**
Fibrinogen (g/L)	3.43 (1.28-9.16)	**.014**
D-Dimer (mg/L)	>999.99 (63.18->999.99)	**.0004**
Fibrin degradation products (μg/mL)	1.58 (0.69-3.59)	.278
Platelet aggregation induced by arachidonic acid (%)	1.22 (1.10-1.34)	**<.0001**
Platelet aggregation induced by adenosine diphosphate (%)	1.03 (0.98-1.09)	.196

P values <0.05 indicate statistical significance and are shown in bold.
CI, confidence interval; OR, odds ratio; RIF, repeated implantation failure.

3.3. Model discrimination and calibration

The corresponding area under the ROC curve (AUC) is 0.85 (Fig. 1), indicating that the built regression model has a good discrimination ability. The optimal cut point of the predicted probabilities as determined by the Youden index was $P = .65$, which led to a sensitivity of 0.83 and a specificity of 0.75. As shown in the calibration plot of the prediction model (Fig. 2), the calibration curve is close to the diagonal reference line, indicating that the predicted and empirical probabilities are similar and that the built prediction model fits the data well.

4. Discussion

In this paper, we examined the association of coagulation assays with RIF risk and assessed their predictive values. We identified PT, APTT, TT and platelet aggregation induced by AA as important predictors of RIF. The prediction model has good discrimination and calibration. Our analyses revealed the important relationship between coagulation assays and RIF risk, and highlighted the potential of employing proper anticoagulant therapies to improve implantation rate.

The hemostatic system plays a vital role in embryogenesis, proliferation and placenta development. The target organ of the physiological interaction between the reproductive and the hemostatic system is the placenta. Uteroplacental circulation, resembling venous circulation at low pressure and velocity, is prone to thrombotic complications.[14] A balance of coagulation, fibrinolysis and vascular remodeling is essential for a successful

Table 3

Multivariate logistic regression for association with RIF.

	OR (95% CI)	P
Prothrombin time (s)	0.28 (0.12-0.66)	**.003**
Activated partial prothrombin time (s)	0.76 (0.63-0.91)	**.004**
Thrombin time (s)	0.75 (0.53-1.08)	**.124**
Platelet aggregation induced by arachidonicacid (%)	1.27 (1.11-1.44)	**.0003**

We included variables selected by purposeful selection. INR and PTA were excluded from the candidate list because these two variables were computed and including them might induce multicollinearity. CI = confidence interval, OR = odds ratio, RIF = repeated implantation failure.
P values <.05 indicate statistical significance and are shown in bold.

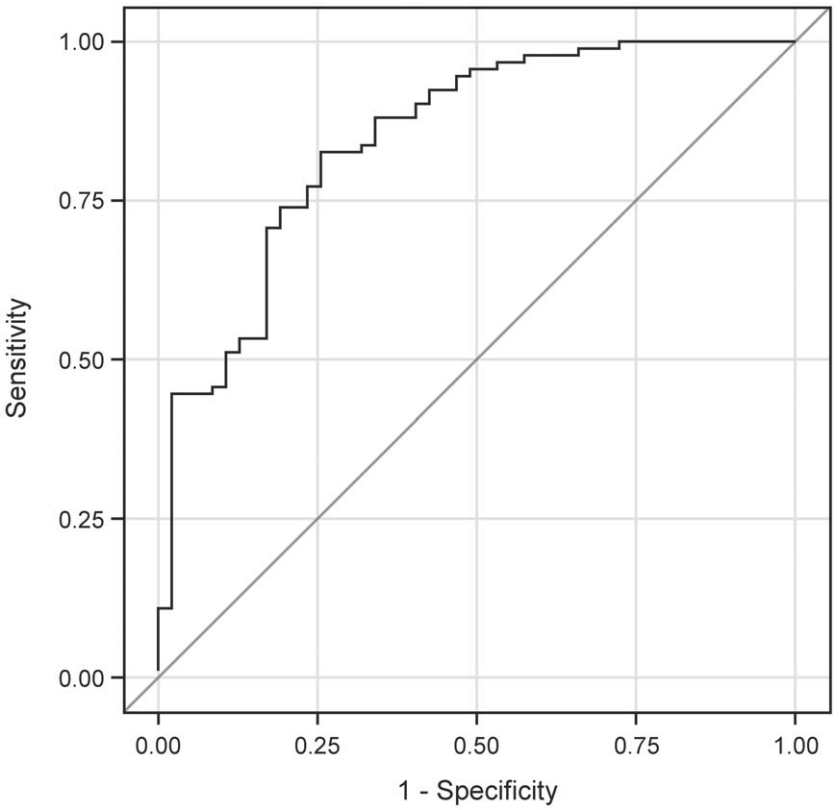

Figure 1. ROC curve of the prediction model for RIF. AUC is 0.85 for the prediction model. ROC = receiver operating characteristic, AUC = under the ROC curve, RIF = repeated implantation failure.

placentation. The process of angiogenesis makes it possible for fibrin to avoid excessive accumulation in placental vessels and intervillous spaces. On the other hand, one of the infertility mechanisms involves the deposit of thrombosis and fibrin in placental vessels, leading to placental insufficiency.[15,16]

Abnormality of the hemostatic system can lead to thrombosis or hemorrhage. The hypercoagulable state before the formation of thrombosis, known as PTS, is a pathological process caused by various factors, including the dysfunction/disorder of coagulation, anticoagulation, and fibrinolysis system. During the formation and development of thrombus, endothelial cells are damaged which can activate the internal and external coagulation pathways, thereby causing hypercoagulability and generating a large amount of thrombin to form thrombus.[17] Platelets play an important role in the process of physiological hemostasis and pathological thrombosis. After vascular injury, and active substances released from endothelial cells, chemotactic platelets adhere to the damaged site, and activate platelets in combination with corresponding surface receptors. Activated platelets release stored substances, such as ADP, serotonin, platelet activating factor and AA-induced thromboxane A2 (TXA2), to initiate and promote platelet aggregation. Platelet aggregation rate is an indicator of platelet aggregation function. High platelet aggregation rate results in coagulation reactions and thrombi development.[18]

It was found that RIF patients had decreased plasma fibrinolytic activity.[16] In our study, we found a significantly decreased level of PT, APTT and TT, and a significantly elevated level of FG, DD, FDP and platelet aggregation induced by AA and ADP in patients with RIF. In our prediction model for RIF, the risk of RIF increased with a decreased level of PT, APTT and TT, and an elevated platelet aggregation induced by AA. PT corresponds with extrinsic pathways of coagulation cascade, and APTT reflects the endogenous coagulation pathway. A decrease in PT and APTT values was associated with hypercoagulable state which is a sensitive and commonly used screening index of the coagulation system.[19,20] TT reflects *in vivo* anticoagulant, and shortened TT indicates hypofibrinolysis. With the onset of coagulation, fibrin monomers are generated by FG into FDP, which reflects overall fibrinolytic activity.[20] On the other hand, agonists in blood such as ADP and AA activate platelet function and promote platelet aggregation, which reflects a prethrombotic state and thrombotic diseases.[18]

In some cases, recurrent spontaneous abortion (RSA) and RIF may represent different manifestations of the same pathogenic spectrum. Thrombosis is one of the main causes of RSA,[21] and researches aiming at elucidating the thrombotic causes of RSA and RIF were encouraged.[22] In recent years, increasing evidences support that RIF is related to PTS[9] which may influence the balance of coagulation-fibrinolysis system to a certain extent, leading to enhanced coagulation function.

Previous studies found that thrombophilia could affect successful implantation of embryos.[12] Our previous research showed that the resistance of uterine artery blood flow in the middle luteal phase of patients with thrombosis was significantly higher than that in the control group,[23] and the blood flow velocity of the uterus was in a high resistance state because of hypercoagulability, which resulted in insufficient perfusion of the

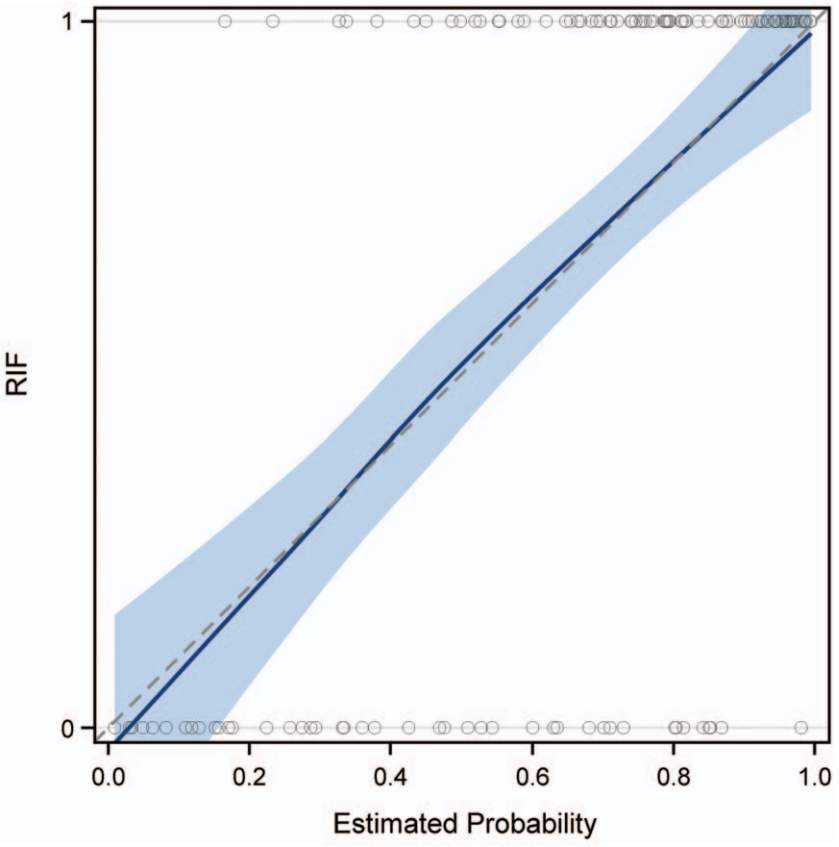

Figure 2. Calibration plot of the prediction model. The dotted diagonal line represents the line of perfect calibration. The solid blue line represents the predicted probability versus the empirical probability. The blue shaded area represents the corresponding 95% confidence band. The calibration curve is close to the diagonal reference line, indicating that the predicted and empirical probabilities are similar and that the built prediction model fits the data well.

uterus, leading to defective endometrial receptivity.[24] Appropriate endometrial receptivity is a key factor in fertilized egg implantation and embryo development. Abnormalities of endometrial receptivity can affect embryo implantation and early embryo development.[25] In patients with RIF who have undergone chromosome replacement and have been identified as having normal quality embryos by PGS, successful implantation and pregnancy are still not optimistic.[24]

A previous study found that patients with RIF had higher levels of D-dimer during IVF-ET than those with successful IVF-ET, suggesting that the occurrence of RIF may be related to prethrombotic state.[26] Another study found that although the D-dimer concentration seemed to be higher in patients with implantation failure after IVF-ET than in patients with successful implantation, but the difference was not statistically significant.[27] Although our finding does not suggest an association of D-dimer concentration with the risk of implantation failure in patients with RIF, the existence of abnormally high values of D-dimer concentration in RIF patients warrants further exploration.

Previous studies indicated that anticoagulation therapy could be effective in improving perinatal outcomes including pregnancy rates in patients with RIF.[27,28] Low molecular weight heparin (LMWH) exerts its anticoagulant effect through the inactivation of factor Xa and the facilitation of the effect of antithrombin.[29] LMWH has exhibited some efficacy in the treatment of RIF across the world. The Consensus of Experts on the Prevention and Treatment of Spontaneous Abortion in China also stated that LMWH can be used to treat RIF.[30] The efficacy of anticoagulants for RIF further suggests a prethrombotic state of RIF and the necessity of the diagnosis of prethrombotic state. Our study supported the feasibility of utilizing coagulation parameters for an accurate prediction of prethrombotic state of RIF.

Our study has limitations. The sample size is relatively limited. Although the purposeful selection is good at selecting important predictors, our model may have missed some important cofounders, and therefore, we could not rule out the possibility of residual confounding. We only included coagulation parameters for prediction, and further studies are needed to examine whether coagulation parameters have additive predictive values beyond the traditional risk parameters for RIF. Unhealthy life styles and psychological stress can also affect the risk of RIF. Unfortunately, such data were not collected at the moment. Future studies with larger sample sizes controlling for such parameters would be helpful to further elucidate the effect of coagulation parameters on RIF risk.

5. Conclusions

In summary, we found that several coagulation parameters are predictive of RIF. Our results highlight the potential of anticoagulation therapies to lower the risk of RIF. Future studies are needed to validate our findings and to explore the efficacy of anticoagulation therapies in the treatment of RIF.

Author contributions

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