Original Article The predictive value of thromboelastography, routine blood indices, ultrasound parameters, and placental thickness in determining fetal outcome

Liang Guo¹, Juan Qi², Na Li³, Lina Ma⁴, Xin Zhang⁵

1Department of Gynaecology and Obstetrics, Xianyang Maternal and Child Health Care Hospital, Xianyang 712046, Shaanxi, China; 2Department of Medical Imaging, Shaanxi Rehabilitation Hospital, Xi'an 710065, Shaanxi, China; 3Department of Laboratory, Xianyang Women and Children Hospital, Xianyang 712046, Shaanxi, China; 4Department of Gynaecology and Obstetrics, Northwest Women's and Children's Hospital, Xi'an 710003, Shaanxi, China; 5Department of Ultrasound, Xianyang Maternal and Child Health Care Hospital, Xianyang 712046, Shaanxi, China

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Abstract: Objective: To evaluate the predictive value of thromboelastography, routine blood indices, ultrasound measurements, and placental thickness for fetal outcome. Methods: A retrospective analysis of 218 expectant mothers at our hospital from April 2020 to June 2022 was conducted. Mothers were classified into favorable (n=164) and adverse (n=54) fetal outcome groups. We compared thromboelastography, blood counts, and ultrasound parameters, including placental thickness, between the two groups. Predictive models using lasso regression were developed for individual assessment type and their combinations. Model efficacies were evaluated by ROC curves and Delong's test. Results: Thromboelastography indicated significantly higher values of R (P=0.004), Angle (P<0.001), and MA (P=0.002) while notably lower K (P<0.001) in the adverse outcome group compared to the favorable outcome group. Peripheral blood analysis showed elevated levels of WBC (P<0.001), CRP (P=0.001), and PLR (P<0.001) in the adverse outcome group. Ultrasound assessments revealed significant increases in S/D (P<0.001), PI (P=0.016), RI (P<0.001), and placental thickness (P<0.001) in the adverse outcome group. The areas under the curve (AUCs) for the thromboelastography (4 features), peripheral blood indices (3 features), ultrasound parameters (4 features), and combined index model (11 features) were 0.774, 0.779, 0.961, and 0.978, respectively. Delong's test indicated that the combined model's AUC did not significantly differ from that of the ultrasound parameters (P>0.05) but was superior to the models based on thromboelastography, peripheral blood indices, and placental thickness alone (P<0.001). Conclusion: This study underscores the unparalleled predictive value of ultrasound metrics in identifying the risk of adverse pregnancy outcomes, highlighting their critical role in prenatal risk assessment and monitoring frameworks.

Keywords: Thromboelastography, routine blood indices, ultrasonography, placental thickness, fetal outcome

Introduction

Adverse fetal outcomes, such as neonatal distress, the need for neonatal intensive care unit (NICU) admission, and neonatal mortality, pose significant medical and public health challenges [1]. These adverse conditions not only jeopardize the survival and healthy development of the newborn, but also have a profound emotional and socioeconomic impact on the mother and her family [2]. Ensuring a healthy pregnancy, primarily through the prevention and

management of conditions that may lead to these adverse outcomes, is a critical goal within maternal and child health. The impacts of such outcomes go beyond immediate physical health concerns, affecting mental health, family stability, and broader socioeconomic implications [3]. Several predictive models have been developed to identify risk factors associated with adverse pregnancy outcomes. For example, models based on maternal characteristics, medical history, and traditional biomarkers such as PT, APTT, D-dimer, and fibrinogen have

been widely used [4, 5]. However, these models often have limitations. They may not fully capture the dynamic changes in coagulation status during pregnancy, potentially leading to less accurate predictions. In addition, some models rely heavily on invasive testing or complex procedures that are not always feasible in routine clinical practice [6]. Therefore, the development of a predictive model to identify various risk factors associated with adverse pregnancy outcomes is essential.

Thromboelastography is a comprehensive laboratory test for evaluating blood coagulation. It provides detailed insight into the coagulation process, including initiation, formation, stabilization, and dissolution of clots [7]. During pregnancy, thromboelastography can be instrumental in identifying potential coagulation abnormalities and plays a critical role in predicting and managing complications such as preeclampsia and placental abruption [8]. Previous research has demonstrated the potential of thromboelastography-related markers to predict adverse maternal pregnancy outcome [9].

Routine blood indices, including white blood cell count, platelet count, and C-reactive protein (CRP), provide insight into the inflammatory state, coagulation status, and overall health of expectant mothers. These factors are critical in influencing pregnancy outcomes [10, 11]. Ultrasound, a non-invasive technique, plays a critical role in assessing placental function and fetal well-being by measuring placental thickness, which provides direct insight into the nutritional status of the fetus [9]. The health of the placenta, which serves as the primary interface between the mother and fetus, is fundamental to fetal growth and development [12]. Abnormalities in placental thickness may signal underlying placental dysfunction, such as dysplasia or abruption, potentially leading to adverse outcomes such as fetal growth restriction or preterm birth. Tao et al. [13] highlighted a positive correlation between plateletlymphocyte ratio (PLR) and adverse pregnancy outcomes in gestational diabetes mellitus, suggesting its importance as a predictor of such outcomes. In addition, Zheng et al. [14] demonstrated the utility of prenatal assessment of cervical length and placental thickness in women with placenta previa for evaluation of pregnancy and perinatal outcomes, further

emphasizing the importance of these measurements in maternal-fetal medicine.

Although the relationships between thromboelastographic indices, routine blood indices, and ultrasound-measured placental thickness with adverse pregnancy outcomes have been examined individually, their collective examination in a unified model remains rare. This study aims to integrate these indicators into a comprehensive predictive model to enhance risk assessment and improve perinatal care.

Materials and methods

Patient sourcing

The medical records of women who gave birth in our hospital from April 2020 to June 2022 were selected for this retrospective analysis. The study was conducted with the approval of Xianyang Maternal and Child Health Care Hospital Medical Ethics Committee. A total of 218 samples were collected according to the following defined inclusion and exclusion criteria.

Inclusion exclusion criteria

Inclusion criteria: (1) Age range of 18-35 years; (2) Engagement in regular labor and delivery processes; (3) Singleton pregnancy status; (4) Complete maternal clinical data.

Exclusion criteria: (1) Presence of pre-pregnancy chronic conditions such as diabetes mellitus; (2) Existence of severe organ pathologies affecting the heart, brain, or kidneys; (3) Presence of chronic diseases like tumors or autoimmune dysfunction.

Basic and maternal data

Basic information included maternal age, number of pregnancies, number of deliveries, prepregnancy body mass index (BMI), past medical history and family medical history. Maternal data included weight change during pregnancy, blood pressure monitoring, blood glucose control (especially for pregnant women with diabetes), urinalysis results, routine blood tests, liver and kidney function indicators, and thromboelastography. Pregnancy complications encompassed gestational diabetes mellitus, hypertensive disorders of pregnancy, pre-eclampsia, and placental abnormalities, etc.

Sample information collection

Patient data were meticulously collected from outpatient records, hospital admissions, and case systems. Baseline information included age, number of parity, gestational age, prepregnancy body mass index (BMI), pre-pregnancy fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPBG), pre-pregnancy systolic blood pressure (SBP), and pre-pregnancy diastolic blood pressure (DBP). Thromboelastography assessments included several parameters: the R value, which indicates clotting factor functionality; the K value, which reflects clotting rate; the angle, an indicator of fibrinogen function; and the MA, which evaluates platelet function. Routine blood indices included white blood cells (WBC), platelets (PLT), neutrophils (NEU), lymphocytes (LYM), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prothrombin time (PCT). Ultrasound assessments and placental thickness measurements were also performed, including systolic/diastolic velocity ratio (S/D), resistance index (RI), pulsatility index (PI), and placental thickness.

Note: Thromboelastograms, peripheral blood indices, ultrasound parameters and placental thickness measurements were performed at 28 weeks' gestation. Thromboelastography and ultrasound are not routinely performed on all pregnant women at our hospital. These tests are specifically recommended for patients who have been identified as being at risk for thrombotic complications. The decision to perform these tests is based on a comprehensive assessment of each patient's history, clinical presentation, and specific risk factors associated with thrombosis. Patients volunteered for thromboelastography or ultrasound examination at the time of testing.

Thrombosis risk diagnosis

Thrombotic risk diagnosis involves a comprehensive assessment of clinical indicators and risk factors. These factors may include but not limited to a personal or family history of thrombotic events, the presence of certain genetic mutations, and clinical signs of susceptibility to thrombosis. A multidisciplinary team of obstetricians, haematologists and other relevant specialists work together to determine the suitability of thromboelastography and ultrasound for each patient [15].

Indicator test methods

Thromboelastography Assay: Whole blood was anticoagulated using 2 mL of sodium citrate. Subsequently, 1 mL of this anticoagulated blood was transferred to a reagent vial, gently inverted five times, and allowed to stand for four minutes. To commence the analysis, 20 μL of calcium chloride activator was added to the reaction cup, followed by adding 340 μL of activated whole blood. This process was conducted using a Ward IHTEG12 automated TEG analyzer.

Peripheral Blood Marker Analysis: A complete blood count (CBC) was performed with 5 mL of whole blood using a Sysmex XN-2000 analyzer. Levels of CRP and PCT were determined using an enzyme-linked immunosorbent assay (ELISA).

Placental and Umbilical Artery Ultrasonography: Measurements of placental thickness and umbilical artery blood flow were carried out at 28 weeks of gestation using a GE ViE9 ultrasound machine equipped with a 2-10 MHz probe. Placental thickness was measured three times at the probe's thickest vertical point. Three consecutive cardiac cycles were selected for the umbilical artery (UA) blood flow analysis. The S/D ratio, resistance index (RI), and pulsatility index (PI) were calculated. These procedures were performed by an experienced attending ultrasound physician, ensuring precision and reliability.

Definition of Adverse Fetal Outcome: Adverse outcomes were defined as conditions such as fetal distress and admission to the neonatal intensive care unit. The poor outcome group were defined based on whether the fetus had fetal distress. The rest of the patients were placed into the good outcome group [16]. Participants were stratified into a favorable outcome group (n=164) and an unfavorable outcome group (n=54) based on prespecified outcome definitions.

Observation indicators

Main observational indices: Lasso regression was used to develop predictive models using

Fetal outcome prediction model

Figure 1. Study flowchart.

thromboelastography, peripheral blood indices, and ultrasound parameters. In addition, a comprehensive model was formulated by integrating variables from all three models above to assess and compare their differences.

Secondary observational indices: The differences in baseline data, thromboelastography parameters, peripheral blood index parameters, and ultrasound parameters were compared between the two groups of patients $(Figure 1)$.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. Counted data were expressed

as percentages, and rates were compared between groups using x^2 tests. Measured data was expressed as mean \pm standard deviation (x±s), and a t-test was used. The diagnostic value of the model was analyzed using the ROC curve. The area under the curve (AUC) of the diagnostic ability of each method was calculated and statistically analyzed using the Delong test. The best cut-off value was obtained by ROC analysis, and the corresponding sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated. Lasso regression was performed using the "glmnet" package in R software $(4.3.2)$ with family = "Gaussian", alpha =1, and unfolds =10. *P*-value <0.05 was considered significant.

Table 1. Baseline information

Note: BMI, Body Mass Index; FPG, Fasting Plasma Glucose; 2hPBG, 2-hour Postprandial Blood Glucose; SPB, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Note: R-value (coagulation factor function parameter), K-value (coagulation rate), Angle (fibrinogen function parameter), MA (platelet function parameter).

Results

Comparison of baseline information between two groups

Comparison of the baseline data between the two groups revealed that there were no significant differences between the good outcome group and the poor outcome group in terms of parity (P=0.320), number of pregnancies (P=0.917), pre-pregnancy BMI (P=0.226), prepregnancy FPG (P=0.095), pre-pregnancy 2hPBG (P=0.328), pre-pregnancy SBP (P= 0.400), or pre-pregnancy DBP (P=0.754). However, there was a significant difference in the age of the patients between the two groups $(P=0.036)$ (Table 1).

Comparison of thromboelastography indicators between the two groups

Subsequently, we compared the thromboelastography indexes between the two groups. It was found that maternal R (P=0.004), angle (P<0.001), and MA (P=0.002) were significantly higher in the poor outcome group than those in the good outcome group (Table 2), while maternal K (P<0.001) was significantly lower in the poor outcome group than in the good outcome group (Table 2).

Comparison of routine blood indices between the two groups

Subsequently, we compared the peripheral blood indices between the two groups. It was found that maternal WBC (P<0.001), CRP (P=0.001), and PLR (P<0.001) levels in the poor outcome group were significantly higher than those in the good outcome group (Table 3). There were no significant differences in PLT (P=0.129), NEU (P=0.251), LYM (P=0.128), NLR (P=0.981) or PLR (P=0.063) between the two groups (Table 3).

Comparison of ultrasound parameters between the two groups

We then compared the ultrasound parameters between the two groups. Maternal S/D (P<0.001), PI (P=0.016), RI (P<0.001), and placental thickness (P<0.001) were significantly

Testing value	Poor outcome group (n=54)	Good outcome group (n=164)	t	P
WBC $(*10^9)$	11.05 [10.22, 11.76]	10.07 [9.67, 10.80]	4.732	< 0.001
PLT $(\times 10^9)$	216.81 ± 26.94	223.40±28.78	-1.532	0.129
NEU (\times 10 ⁹)	$10.82 + 2.06$	$10.43 + 2.44$	1.153	0.251
LYM $(x 10^9)$	2.49 ± 0.36	2.40 ± 0.38	1.535	0.128
CRP (mg/L)	7.86±3.21	6.23 ± 2.61	3.389	0.001
NLR	4.44 [3.65, 5.17]	4.46 [3.64, 5.19]	0.025	0.981
PLR	88.03 [76.90, 101.41]	94.39 [81.19, 104.38]	-1.858	0.063
PCT (ng/ml)	0.57 ± 0.12	$0.50 + 0.10$	3.504	< 0.001

Table 3. Comparison of routine blood indices between two outcome groups

Note: WBC, White Blood Cells; PLT, Platelets; NEU, Neutrophils; LYM, Lymphocytes; CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; PCT, Prothrombin Time.

Note: S/D, systolic/diastolic velocity ratio; RI, resistance index; PI, pulsatility index.

higher in the poor outcome group than those of the good outcome group (Table 4).

Construction of predictive models

To elucidate the predictive capabilities of each index for adverse outcomes, we constructed 4 models: one with thromboelastography, one with peripheral blood indices, one with ultrasound parameters, and a combined model incorporating indices for all three categories (Figure 2). The effectiveness of the 4 models in predicting adverse outcome was compared by ROC curves. The AUCs of the thromboelastography (4 features), peripheral blood index (3 features), ultrasound parameters (4 features), and combined index models (11 features) were 0.774, 0.779, 0.961, and 0.978, respectively (Figure 3; Table 5). Subsequent comparisons showed that there were no statistical differences between the AUCs of the combined model and ultrasound parameter model, or between the AUCs of the thromboelastography model and peripheral blood index models (all P>0.05). However, the AUCs of combined model and ultrasound parameter model were significantly higher than those of the thromboelastography and peripheral blood index models (P<0.05) (Table 6).

Discussion

This study has shown that a comprehensive model integrating thromboelastographic indices, peripheral blood indices, and ultrasound measurements of placental thickness markedly enhances the predictive capability for adverse pregnancy outcome compared to models based on individual indicators. The combined model achieved an AUC value of 0.978, significantly outperforming those based solely on thromboelastography or peripheral blood indices while demonstrating equivalence to the ultrasound parameters model. This underscores the critical role of a multifaceted analytical approach in enhancing the precision of predictive assessments.

Initially, the study assessed the thromboelastography model's efficiency in foretelling adverse pregnancy outcome, utilizing four pivotal thromboelastographic indices: the R-value, the K-value, the Angle, and the MA-value. This model, aimed at evaluating the coagulation profile of expectant mothers, exhibited an AUC of 0.774, showcasing its predictive potential. Thromboelastography, a test that elaborates the coagulation cascade in whole blood, is increasingly recognized for its utility in predicting pregnancy complications.

Fetal outcome prediction model

Figure 2. Lasso regression for the construction of models using Thromboelastography, peripheral blood indices, ultrasound parameters, or their joints. A. Joint model. B. Thromboelastography indicator model. C. Peripheral blood index model. D. Ultrasound parameter model.

Figure 3. ROC curves of the 4 models. A. Thromboelastography model. B. Peripheral blood index model. C. Ultrasound parameter model. D. Joint model.

Table 5. ROC curve parameters

Table 6. Comparison of ROC curves

Prior research has highlighted thromboelastography's role in managing coagulation disorders and postpartum hemorrhage, facilitating swift diagnosis and treatment [17, 18]. Furthermore, studies by Li et al. [19] have pinpointed thromboelastography as a significant predictor of clinical pregnancy and miscarriage outcome. Our findings resonate with these earlier works, advocating thromboelastography's informative value in predicting adverse pregnancy outcome. This efficacy stems from its comprehensive evaluation of the coagulation system, offering dynamic insights into the initiation, formation, stabilization, and dissolution of clots [20]. Such assessments detect nuanced coagulation shifts, fostering early complication diagnosis and guiding clinical interventions byrealtime monitoring. Thus, thromboelastography holds considerable promise in pregnancy management, enhancing maternal health and safety.

As an essential tool for assessing immune status, inflammation levels, and coagulation, routine blood indices play a significant role in predicting adverse pregnancy outcomes [21]. Due to the wide availability and the non-invasive nature of obtaining these indices, routine blood indices provide clinicians with a convenient, real-time way to monitor the risk of complications during pregnancy. For example, Zhang et al. [22] identified a strong and consistent association between maternal leukocyte counts and increased risk of adverse pregnancy outcome in a study involving 24,143 cases. Additionally, Yakiştiran et al. [23] found a moderate negative association between maternal PLR levels and adverse neonatal outcome, suggesting that PLR, an indicator easily calculated in clinical settings, may predict adverse neonatal outcome. Furthermore, Che et al. [24] found that higher lymphocyte/monocyte ratios in the second trimester were associated with lower gestational age at delivery and that complete blood counts in the second trimester could be used to predict poor obstetric outcome. These findings enhance our understanding of the underlying biological mechanisms of pregnancy complications and provide a solid scientific basis for developing management and prevention strategies for adverse pregnancy outcome. By regularly monitoring these simple and cost-effective blood parameters, physicians can provide a more personalized risk assessment for pregnant women and implement timely and appropriate interventions to reduce the incidence of adverse pregnancy outcome.

Ultrasound parameters play an essential role in the management of pregnancy, especially in assessing fetal health and predicting adverse pregnancy outcome [25, 26]. In the present study, we analyzed the maternal S/D ratio, PI, RI, and placental thickness and observed that these indices were significantly higher in the poor outcome group than those in the good outcome group, suggesting their high sensitivity and specificity in predicting adverse pregnan-

cy outcomes. Elevated S/D ratio, PI, and RI reflect increased resistance to blood flow in the placental and fetal circulation, which indicates placental insufficiency and compromises the supply of nutrients and oxygen to the fetus [27]. Similarly, increased placental thickness may be associated with placenta-related complications such as placental abruption and placenta previa, which increase the risk of preterm labor and fetal growth restriction. Early studies have shown that examination of umbilical cord artery RI and PI by ultrasound is strongly associated with pregnancy outcomes in patients with severe preeclampsia [28]. In addition, Yin et al. [29] found that the AUCs of umbilical artery S/D, PI, and RI in predicting fetal distress were 0.81, 0.76, and 0.74, respectively. Earlier studies by Miwa et al. [30] have indicated that ultrasonographic measurements are the most straightforward test for placental thickness assessment, where placental over-thickness predicts adverse pregnancy outcomes.

At the end of the study, we assessed the value of combining thromboelastographic indices, peripheral blood indices, and ultrasound parameters for predicting adverse pregnancy outcomes. By developing a joint model incorporating these three types of indicators, the results showed that the model's predictive performance (AUC value of 0.978) was significantly better than that of the single-indicator models. Further, Delong's test analysis showed that despite the high predictive performance of the joint model, there was no significant difference compared to the model using ultrasound parameters alone. This suggests that the accuracy of ultrasound parameters alone is comparable to that of the combined multiparameter model in predicting adverse pregnancy outcome and emphasizes the importance of ultrasound parameters in pregnancy management, especially in assessing placental and fetal health status and predicting outcome. Furthermore, this finding suggests that in resource-limited settings, ultrasonography can be used as a cost-effective and straightforward method to efficiently assess risk during pregnancy without the added burden of additional tests. Therefore, ultrasonography should be more widely used in pregnancy management as a core component of pregnancy risk assessment and monitoring.

While this study provides valuable insights into predicting adverse pregnancy outcoms, it has several limitations related to sample size, study design, and data availability. First, the relatively small sample size and the fact that data were obtained from a single medical center may limit the generalizability and representativeness of the results. Second, as a retrospective study, there is potential for data collection bias and omission of information, which may impact the accuracy and reliability of the findings. Additionally, the retrospective design limits inferences of causality and does not allow for an adequate demonstration of a direct causal link between changes in indicators and adverse pregnancy outcomes. Moreover, our study did not include routine coagulation function indicators such as PT, APTT, D-dimer, and fibrinogen because they are not part of the hospital's routine examination at 28 weeks of pregnancy. Economic considerations led some patients to opt for thromboelastography instead of routine coagulation function tests, resulting in missing coagulation data. This limitation prevented us from comparing thromboelastography parameters with traditional coagulation function indicators, which could have provided additional insights. These limitations suggest that future studies should use larger sample sizes, multicenter collaborations, and prospective study designs, as well as include a comprehensive set of coagulation function indicators to enhance the generalizability and reliability of findings.

In summary, this study reveals the unique value of ultrasound parameters in predicting adverse pregnancy outcome, emphasizing their importance as the core of risk assessment and monitoring strategies during pregnancy. This finding supports the recommendation to prioritize the use of ultrasound technology for pregnancy management in resource-limited healthcare settings to improve maternal and infant health outcome.

Disclosure of conflict of interest

None.

Address correspondence to: Xin Zhang, Department of Ultrasound, Xianyang Maternal and Child Health Care Hospital, Qindu District, Xianyang 712046, Shaanxi, China. E-mail: [zhangxinarti](https://doi.org/10.62347/ROVE7306)[cle@126.com](https://doi.org/10.62347/ROVE7306)

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