

Association Between Pre-delivery Coagulation Indicators and Invasive Placenta Accreta Spectrum

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Abstract

Objectives: To analyze the association between pre-operational coagulation indicators and the severity of placenta accreta spectrum (PAS), as well as blood loss volume during operation.

Methods: Hospitalized patients of the obstetric department in a major hospital from 2018 to 2020 who were clinically and/or pathologically diagnosed with invasive PAS were included. Univariate and multivariate logistic regression and Poisson regression models were used to quantify the association between each of the 6 coagulation indicators and PAS severity (measured by FIGO grade) as well as maternal outcomes.

Results: Ninety-five patients (46 FIGO grade 2 and 49 FIGO grade 3) were included. Higher PT [adjusted OR (aOR): 5.54; 95% CI, 1.80 to 17.07] and FDP (aOR: 1.19; 95% CI, 1.01–1.42) levels were associated with an increased risk of FIGO grade 3 after adjusting for covariates. D-dimer [incidence rate ratio (IRR): 1.19; 95% CI, 1.05 to 1.35] and FDP (IRR: 1.03; 95% CI, 1.01–1.04) levels were significantly associated with higher blood loss volume after adjusting for covariates.

Conclusion: Preoperative coagulation indicators, especially PT, D-dimer and FDP, are associated with disease severity and blood loss volume during operation of invasive PAS. The underlying mechanism for the coagulation profile of PAS patients warrants further analysis.

Synopsis: Preoperative coagulation indicators, especially PT, D-dimer and FDP, are associated with disease severity and blood loss volume during operation among invasive placenta accreta spectrum patients.

Keywords

placenta accreta spectrum, invasive PAS, coagulation indicators, FIGO grades, blood loss volume

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Introduction

Placenta accreta spectrum (PAS) is one of the most severe complications during pregnancy.¹ Abnormal adherence of the placenta to the uterus can be classified as placenta accreta (PA), increta (PI) and percreta (PP) according to invasion depth. The latter 2 types are regarded as invasive PAS.² Over the past four decades, the incidence of PAS has risen dramatically from 1 in 30 000 pregnancies to 1 in 533 pregnancies for women who underwent cesarean delivery.^{3–5} Patients with PAS, especially invasive PAS, present considerably higher risks of catastrophic hemorrhage and organ injury, as well as higher morbidity and mortality for both the mother and fetus,^{3,5} yet the pathogenesis mechanism behind PAS remains unclear.

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Recent studies suggested that coagulation and fibrinolytic functions of PAS patients could be disrupted, which meant that these functions could be related to the incidence and development of PAS. Shamshirsaz et al.⁶ analyzed the coagulation data among PAS patients before massive blood loss during surgery. The coagulopathy profile was found in 30.1% (37/123) of PAS patients, with changes in platelet (PLT) count, international normalized ratio (INR) and fibrinogen (FIB-C), while the study did not find an association between the change in coagulation indicators and the depth or severity of placental invasion in PAS. In addition, it is unclear whether this change occurred before surgery. Jauniaux et al.^{7,8} found that thick fibrinoid deposits are common in abnormally invasive villous tissue, indicating abnormal fibrinolysis function in PAS. This finding suggested that the disrupted coagulation profile of PAS had occurred prior to massive hemorrhage during delivery. Since coagulation indicators can be affected by intraoperative bleeding, exploring the relationship between preoperative coagulation indicators and PAS severity is critical to reveal the potential pathogenesis of PAS and explore the possible changes in the clinical indexes of PAS patients.

In sum, this study aims to explore the association between six routinely tested coagulation indicators before delivery and the severity grades of PAS, as well as blood loss volume during operation for invasive PAS.

Materials and Methods

Study Population

This study was conducted in a tertiary teaching hospital in Beijing, China. The hospital's obstetrics department is one of the referral centers to manage high-risk pregnancies in the region and delivers more than 6000 infants every year. This study was reviewed and approved by the institutional ethics committee of Peking University First Hospital (2019[175]).

Patients diagnosed with invasive PAS pathologically and/or clinically between 2018 and 2020 were included. The diagnosis criteria were as follows: (1) pathological criteria²: abnormal implantation of chorionic villi upon superficial or deep myometrium without a decidual layer based on microscopic diagnosis; (2) clinical diagnostic criteria: clinical grading was applied according to 2019 International Federation of Gynecology and Obstetrics (FIGO) guidelines⁹: Significant amounts of hypervascularity in the uterine serosa without placenta invasion through the uterine serosa were classified as FIGO grade 2. In FIGO grade 3, placental tissue invades through the surface of the uterus and/or to parametrial regions or adjacent organs.

Additional inclusion criteria: (1) live birth; (2) gestational weeks ≥ 28 weeks. Patients with outlier/missing data in critical variables or have co-morbidity diagnoses/drug use related to the coagulation process (eg, coagulopathy) were excluded.

Data Collection

All data were extracted from the inpatient medical records, which included (1) demographic characteristics [age and body mass

index (BMI) before delivery]; (2) history of gestation and uterine surgery [gravidity, parity, abortion, cesarean section, myomectomy and endometrial injury]; (3) characteristics specific to the current gestation [gestational weeks, in vitro fertilization (IVF), placenta previa, male fetal sex and comorbidities (diabetes, hypertensive disorders of pregnancy, hyperlipidemia, hyperthyroidism and hypothyroidism)]; and [4] perioperative events [hysterectomy, blood loss volume during operation, blood transfusion, adjacent organ injury, confirmed with pathology, length of operation, length of stay, application of abdominal aortic balloon occlusion and core surgical team]. For ultrasonic assessment, the images were graded by 2 physicians from the imaging department independently according to the ultrasonic grading system developed by Cali et al.¹⁰ It is a four-grade (0, 1, 2 and 3) system that was designed for patients with placenta previa-complicated PAS. The grading criteria were as follows: PAS 0: placenta previa; PAS 1: the presence of at least two placental lacunae, loss of the clear zone or bladder wall interruption; PAS 2: PAS 1 plus uterovesical hypervascularity; and PAS 3: signs of increased vascularity in the inferior part of the lower uterine segment extending into the parametrial region.

The coagulation test results were selected from the preoperative test closest to the timepoint of abdominal aortic balloon implantation or cesarean section operation and within 2 weeks before delivery. Tests of coagulation indicators were performed on an automatic coagulation analyzer (ACL TOP700). The coagulation indicators included the number of PLT, PT (prothrombin time), prothrombin time ratio (PTR), prothrombin activity (PA), INR, activated partial thromboplastin time (APTT), activated partial thromboplastin time ratio (APTTR), fibrinogen (FIB-C), fibrin degradation products (FDP) and thrombin time (TT).

Statistical Analysis

Categorical data were presented as counts and percentages using chi-square tests or Fisher exact tests for group comparison. For continuous variables, independent sample *t* tests were used to compare the means between the groups when the data conformed to the normal distribution. Nonnormally distributed data were presented as medians and interquartile ranges ($[M(P_{25}\sim P_{75})]$) and were compared using rank-sum tests.

As APTTR, PTR, INR and PA are calculated from APTT and PT, respectively, these four indicators are not included in the analysis. Univariable and multivariable logistic regression models were used to investigate the association between each coagulation indicator and the clinical classification of PAS (FIGO grade 2 or FIGO grade 3) before and after adjusting for covariates (ultrasonic score, gestational week, history of cesarean section and placenta previa in current pregnancy). The association between coagulation indicators and the amount of blood loss during operation was analyzed using Poisson regression with robust standard errors, with and without adjustment for possible confounding factors (ultrasonic score, maternal age, gestational week, whether accompanied by comorbidities and whether hysterectomy was performed).¹¹ Because the ultrasonic score was only applied for invasive patients

with placenta previa, regression analyses involving the ultrasonic score excluded patients without placenta previa. A two-sided P value <0.05 was considered significant for all analyses. The statistical analyses were conducted using Stata software (version 15.0; StataCorp, Texas, USA).

Results

Demographic and Clinical Characteristics of the Included Patients

Ninety-five women were included (Figure 1), among whom 51.6% (49/95) were classified as FIGO grade 3, and 31.6% (30/95) had pathological confirmation. Compared with FIGO grade 2 patients, FIGO grade 3 patients had a significantly higher proportion of patients with a previous cesarean section history, shorter gestational weeks at delivery and higher ultrasound scores. A total of 93.9% (46/49) of the FIGO grade 3 patients had placenta previa compared to 78.3% among FIGO grade 2 patients. The peri-operational events and clinical outcomes of the two groups were significantly different (Table 1).

The Association Between Coagulation Indicators and FIGO Grades

Regarding the differences in preoperative coagulation indicators levels between the two FIGO grade groups, the median of PT

(s) was longer in the FIGO grade 3 group than in the FIGO grade 2 group [medians and interquartile ranges ([M[P₂₅~P₇₅]]) 10.9 (10.6–11.4) versus 10.6 (10.3–10.9), $P<0.001$], while D-dimer (mg/L) [M(P₂₅~P₇₅) 0.70 (0.58–1.08) versus 0.44 (0.33–0.67), $P=0.001$] and FDP (mg/L) [M(P₂₅~P₇₅) 4.90 (3.70–9.40) versus 3.15 (2.35–5.40), $P=0.002$] were significantly higher in FIGO grade 3 than in FIGO grade 2 patients (Table 2).

The univariable logistic regression analysis showed that PT [odds ratio (OR) 4.30; 95% confidence interval (95% CI) 1.74 to 10.64] and FDP (OR, 1.17; 95% CI, 1.02–1.34) were significantly associated with a higher risk of FIGO grade 3. In the multivariable analysis adjusted only for ultrasonic staging system score (Model B), PT (adjusted OR [aOR] 5.03; 95% CI, 1.69–14.99) and FDP (aOR, 1.19; 95% CI, 1.01–1.41) were significant predictors of FIGO grade 3. With further adjustment for gestational age at delivery, a history of cesarean section and maternal age (Model C), PT (aOR, 5.54; 95% CI, 1.80–17.07) and FDP (aOR, 1.19; 95% CI, 1.01–1.42) were still independently associated with a higher risk of FIGO grade 3 (Table 3).

The Association Between Coagulation Indicators and Blood Loss Volume During Operation

Table 4 shows the association between the coagulation indicators and blood loss volume during cesarean section. The univariable Poisson regression model showed that PT, FIB-C,

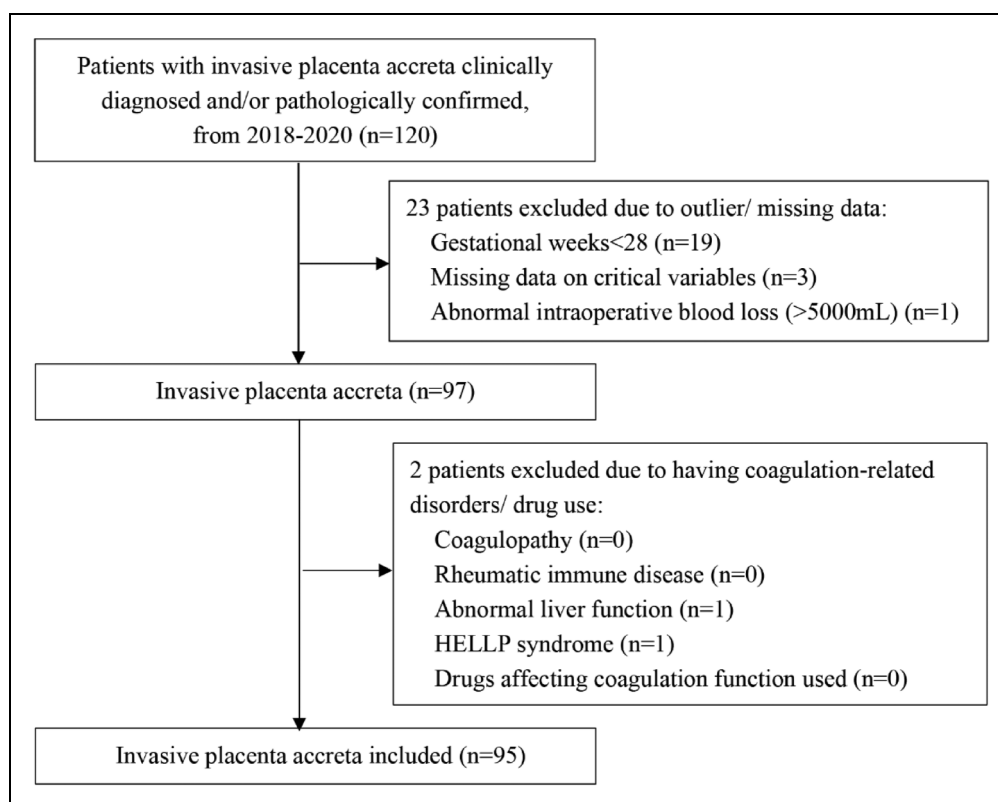


Figure 1. Flow chart of inclusion /exclusion process.

Table 1. Demographic and clinical characteristics by FIGO grades.

Variables	FIGO grade 2 (n = 46)	FIGO grade 3 (n = 49)	P value
General data			
Age (mean ± SD)	35.0 ± 4.4	34.1 ± 3.9	0.294
BMI before delivery (kg/m ²) (mean ± SD)	27.4 ± 3.0	27.5 ± 3.8	0.861
Previous history (before the pregnancy with PAS)			
Gravidity ≥3, n (%)	29 (63.0)	30 (61.2)	0.855
Parity ≥2, n (%)	10 (21.7)	14 (28.6)	0.444
Abortion, n (%)	39 (84.8)	38 (77.6)	0.369
Cesarean section, n (%)	37 (80.4)	46 (93.9)	0.049
Myomectomy, n (%)	4 (8.7)	2 (4.1)	0.426
Endometrial injury, n (%)	10 (21.7)	5 (10.2)	0.123
Current pregnancy			
Gestational weeks at delivery, (mean ± SD)	35.0 (34.0–36.0)	34.0 (33.0–35.0)	0.003
Ultrasound grading system scores ≥2 ^a , n (%)	20 (55.6)	36 (78.3)	0.028
Comorbidity, n (%)	16 (34.8)	17 (34.7)	0.993
Fetal sex as male, n (%)	22 (47.8)	26 (53.1)	0.610
IVF, n (%)	2 (4.3)	0 (0.0)	0.232
Placenta previa, n (%)	36 (78.3)	46 (93.9)	0.027
Peri-operational events			
Interventional therapy, n (%)	7 (15.2)	31 (63.3)	<0.001
Core surgical team, n (%)	27 (58.7)	42 (85.7)	0.003
Hysterectomy, n (%)	0 (0.0)	9 (18.4)	0.003
Blood loss count (ml), [M(P25~P75)]	1000.0 (700.0–1400.0)	1800.0 (1200.0–2800.0)	<0.001
Blood transfusion, n (%)	29 (63.0)	45 (91.8)	0.001
Adjacent organs injury, n (%)	0 (0.0)	7 (14.3)	0.013
Pathology confirmed, n (%)	9 (19.6)	21 (42.9)	0.015
Operation time (min), [M(P25~P75)]	89.5 (80.0–112.0)	138.0 (113.0–169.0)	<0.001
Length of stay (day), [M(P25~P75)]	8.5 (7.0–13.0)	12.0 (9.0–21.0)	<0.001

Abbreviations: BMI, Body Mass Index; IVF, in-vitro fertilization; PAS, placenta accreta spectrum; FIGO, International Federation of Gynecology and Obstetrics; mean ± SD: mean ± standard deviation; M(P25~P75): median (25% percentile~75% percentile)

^an = 82 (36 FIGO grade 2 and 46 FIGO grade 3) as international Ultrasound Scoring System only applies to PAS patients with placenta previa.

Table 2. Coagulation indicator levels by FIGO grades.

Coagulation indicator [M(P ₂₅ ~P ₇₅)]	FIGO grade 2 (n = 46)	FIGO grade 3 (n = 49)	P value
PT (s)	10.6 (10.3–10.9)	10.9 (10.6–11.4)	<0.001
APTT (s)	26.5 (25.5–27.1)	26.0 (24.9–28.0)	0.777
FIB-C (mg/L)	4.10 (3.54–4.42)	3.77 (3.45–4.05)	0.055
D-dimer (mg/L)	0.44 (0.33–0.67)	0.70 (0.58–1.08)	0.001
FDP (mg/L) ^a	3.15 (2.35–5.40)	4.90 (3.70–9.40)	0.002
TT (s)	13.1 (12.5–14.3)	13.2 (12.7–14.0)	0.546
PLT (×10 ⁹ /L)	195 (157–225)	184 (156–227)	0.944

Abbreviations: PAS, placenta accreta spectrum; FIGO, International Federation of Gynecology and Obstetrics; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB-C, fibrinogen; FDP, fibrin degradation products; TT, thrombin time.

^aThe sample size for D-dimer and FDP was 79 as the coagulation test results before the operation did not have these two items for 16/95 (16.84%) patients.

D-dimer and FDP were associated with blood loss volume. After adjusting for covariates in model B and model C, D-dimer and FDP were significantly associated with an increase in blood loss volume during the operation. After adjusting for all the covariates in model C, the incidence rate ratio (IRR) of D-dimer was 1.19 (95% CI, 1.05–1.35), which means that a per unit increase in D-dimer may lead to an average 19% increase in blood loss. In addition, a per unit increase in FDP may lead to an average 3% increase in blood loss (IRR, 1.03; 95% CI, 1.01–1.04).

The marginal effect of the coagulation indicators and its effect on the blood loss volume were shown in Figure 2. Among the six coagulation indicators investigated, the FDP and D-dimer levels were significantly associated with the increasing trend of blood loss volume during operation after adjusting for covariates. PT and APTT levels also showed an association with the upward trend of blood loss volume, but the association was not significant. Moreover, the increase in FIB-C was inversely associated with the increase in blood loss volume (Figure 2).

Table 3. The association between coagulation indicators and FIGO grades.

Coagulation indicator [M(P ₂₅ ~P ₇₅)]	Univariate			Multivariable					
	Model A			Model B			Model C		
	<i>n</i>	Crude OR (95%CI)	<i>P</i> value	<i>n</i>	Adjusted OR (95% CI)	<i>P</i> value	<i>n</i>	Adjusted OR (95% CI)	<i>P</i> value
PT (s)	95	4.30 (1.74–10.64)	0.002	82	5.03 (1.69–14.99)	0.004	82	5.54 (1.80–17.07)	0.003
APTT (s)	95	1.05 (0.89–1.25)	0.541	82	1.04 (0.86–1.25)	0.695	82	1.05 (0.87–1.26)	0.627
FIB-C (mg/L)	95	0.55 (0.29–1.05)	0.069	82	0.77 (0.38–1.55)	0.464	82	0.79 (0.39–1.62)	0.528
D-dimer (mg/L)	79	2.15 (0.96–4.82)	0.062	72	2.64 (0.90–7.71)	0.077	72	2.67 (0.88–8.11)	0.083
FDP (mg/L)	79	1.17 (1.02–1.34)	0.023	72	1.19 (1.01–1.41)	0.036	72	1.19 (1.01–1.42)	0.041
TT (s)	95	1.12 (0.82–1.55)	0.477	82	1.05 (0.74–1.48)	0.789	82	1.05 (0.74–1.47)	0.798
PLT (×10 ⁹ /L)	95	1.00 (0.99–1.01)	0.946	82	1.00 (0.99–1.02)	0.383	82	1.00 (0.99–1.02)	0.436

Model A: adjusted for no covariate; Model B: adjusted for ultrasonic score (*n* = 82 as international Ultrasound Scoring System only applies to PAS with placenta previa.); Model C: Gestational age at delivery, the history of cesarean section and maternal age were adjusted for in addition to the covariates in Model B.

Table 4. The association between coagulation indicators and blood loss volume during operation.

Coagulation indicator [M(P ₂₅ ~P ₇₅)]	Univariate			Multivariable					
	Model A			Model B			Model C		
	<i>n</i>	IRR (95% CI)	<i>P</i> value	<i>n</i>	IRR (95% CI)	<i>P</i> value	<i>n</i>	IRR (95% CI)	<i>P</i> value
PT (s)	95	1.33 (1.11–1.59)	0.002	82	1.05 (0.87–1.28)	0.585	82	1.09 (0.89–1.33)	0.399
APTT (s)	95	1.03 (1.01–1.08)	0.082	82	1.02 (0.99–1.05)	0.213	82	1.02 (0.99–1.05)	0.148
FIB-C (mg/L)	95	0.78 (0.67–0.92)	0.002	82	0.93 (0.80–1.07)	0.302	82	0.90 (0.78–1.05)	0.170
D-dimer (mg/L)	79	1.23 (1.13–1.34)	<0.001	72	1.13 (1.01–1.27)	0.038	72	1.19 (1.05–1.35)	0.006
FDP (mg/L)	79	1.03 (1.02–1.04)	<0.001	72	1.02 (1.00–1.03)	0.043	72	1.03 (1.01–1.04)	0.003
TT (s)	95	1.01 (0.93–1.11)	0.750	82	0.99 (0.92–1.07)	0.823	82	1.00 (0.92–1.08)	0.934
PLT (×10 ⁹ /L)	95	1.00 (1.00–1.00)	0.111	82	1.00 (1.00–1.00)	0.446	82	1.00 (1.00–1.00)	0.373

Abbreviations: IRR: incidence-rate ratio.

Model A: adjusted for no covariate; Model B: adjusted for ultrasonic score [*n* = 82 (36 FIGO grade 2 and 46 FIGO grade 3) due to international Ultrasound Scoring System only applies to PAS with placenta previa.], maternal age, gestational week, comorbidities and hysterectomy; Model C: interventional therapy and surgical teams were adjusted for in addition to the covariates in Model B.

Discussion

This study found that the preoperative coagulation profile, especially PT and FDP, was significantly associated with a higher risk of FIGO grade 3 PAS after adjusting for canonical risk factors. In addition, D-dimer and FDP were significantly associated with blood loss volume during the operation.

As PT reflects exogenous coagulation function, an increase in PT implies a hypocoagulability status in FIGO grade 3 compared with FIGO grade 2.¹² FDP and D-dimer are degradation products created by fibrinolytic enzymes acting on crosslinked fibrin,¹³ and the increase in FDP and D-dimer levels might imply fibrinolytic hyperactivity in FIGO grade 3. The association identified by this study indicated hypocoagulability and hyperfibrinolysis status along with PAS deterioration. Shaiker et al.¹⁴ found that the plasminogen activator inhibitor 1 (PAI-1) level was lower in PAS cases than in gestational-age-matched controls. As the major inhibitor of the fibrinolytic system, the reduction in PAI-1 may also represent a state of

hyperfibrinolysis. Jauniaux et al.^{7,8} found fibrinolytic hyperactivity in PAS placenta pathology, showing thick basal plate fibrinoid deposits in areas of abnormally adherent and invasive villous tissues. They raised the hypothesis that fibrinoid deposits may be attributed to abnormal maternal vascular remodeling in PAS involving the dilation of radial and arcuate arteries, in which the increase in the blood flow velocity and volume in the intervillous space resulting in chronic shear forces may lead to fibrin deposition,⁷ followed by consumption of fibrin and changes in fibrinolytic function. However, the specific mechanism by which abnormal fibrinolytic function is involved in the occurrence and development of PAS is still unknown.

During pregnancy, due to physiological adaptation, the hemostatic system presents as a relatively hypercoagulable state with decreased anticoagulation function.^{15,16} To exclude the influence of pregnancy on coagulation indicators, the results from other study focused on differences between pregnancies or not in the same area (North China) were compared,¹⁷ which presented PT were lower [9.7 (8.6–12.4)] than nonpregnancy [11.0 (9.7–

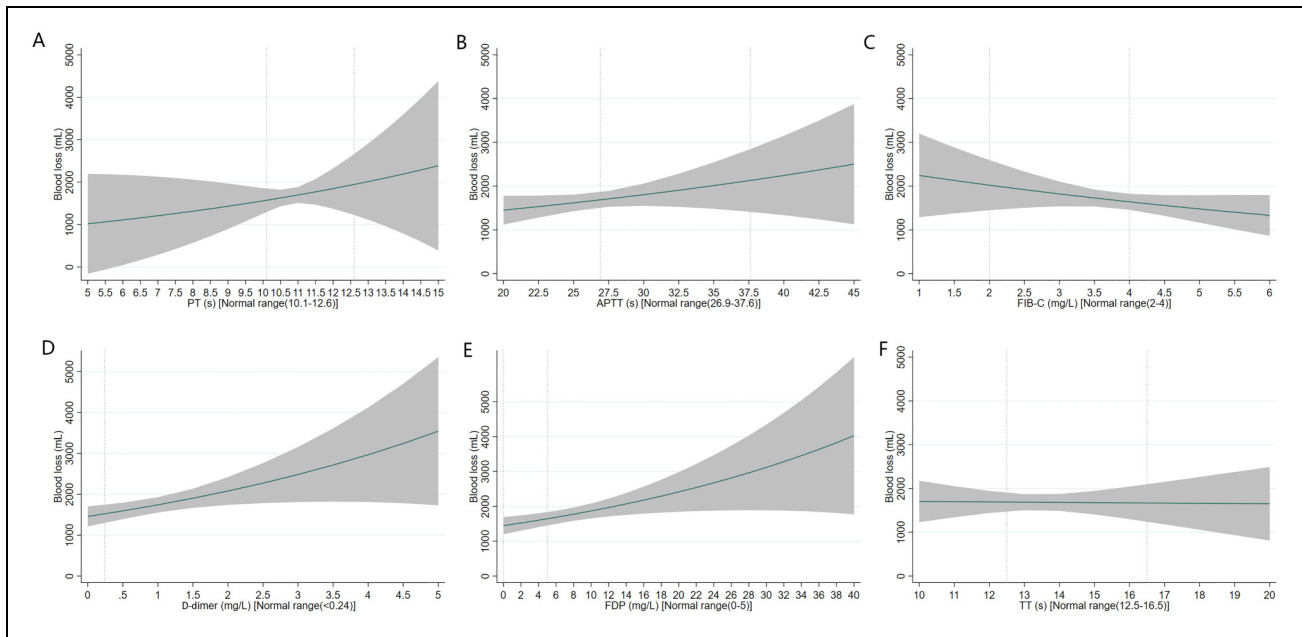


Figure 2. The marginal effect diagrams of Poisson regression (Model C).

The correlation of coagulation indicators and blood loss volume during operation in the model that adjusted for ultrasonic score, maternal age, gestational week, comorbidity, hysterectomy interventional therapy and surgical teams. The dotted lines in each panel describe the normal reference range for coagulation indicators of the hospital. After incorporating the normal reference range for each coagulation indicator of the hospital as dotted lines in each panel of Figure 2, it was showed that the 95% CI (the shadowed area) of the coagulation indicators normal ranges were narrower than in the rest of the indicator continuum. This implied that the prediction models were more precise within the normal ranges of the indicators and the confidence intervals would considerably wider as the indicator values became more abnormal

12.6)]. We found that this decreasing pattern was alleviated in PAS [FIGO2, 10.6 (10.3–10.9); FIGO3, 10.9 (10.6–11.4)], suggesting a relative hypocoagulation function in PAS. Moreover, D-dimer was higher in pregnant women [0.50 (0.14–2.82)] than in age-matched nonpregnant women [0.08 (0.02–0.23)]. In PAS, there was a similar tendency in FIGO grade 2 [0.44 (0.33–0.67)] and even an increase in FIGO grade 3 [0.70 (0.58–1.08)], which confirms the abnormal fibrinolytic hyperactivity in PAS.

The features of hypocoagulability and hyperfibrinolysis disturbance found in PAS may be related to the pathogenesis of excessive trophoblast invasion.¹⁸ As the major regulator of the hypoxic signaling pathway in cellular proliferation, angiogenesis and metastasis, hypoxia inducible factor-1 α (HIF-1 α) has been shown to participate in the response to hypoxia and regulate the balance of oxygen in trophoblasts.^{19,20} The significantly increased HIF-1 α in trophoblasts of PAS²¹ could trigger endothelial expression of tissue factor (TF),²² which is a high-affinity receptor and cofactor for factor (F)VII/VIIa. Given that the TF-FVIIa complex is the primary initiator of the clotting cascade, an increase in TF can induce the subsequent consumption of coagulation factors and activation of fibrinolytic function.²³ The findings suggested that with the excessive invasion of trophoblasts, coagulation indicators depletion and the activation of fibrinolytic function may lead to hypocoagulability and hyperfibrinolysis in PAS.

According to the recommendation of overt disseminated intravascular coagulation (DIC) based on the International

Society of Thrombosis and Hemostasis (ISTH) Scoring System, the ISTH overt-DIC diagnostic criteria should depend on fibrin-related markers (FRMs), such as D-dimer. They suggested that the cutoff value of D-dimer of DIC was more than 3.0 $\mu\text{g}/\text{mL}$.²⁴ The lower D-dimer [FIGO3, 0.70 (0.58–1.08)] in our cohort may be due to the data collected before delivery when coagulation and fibrinolysis disorders had not yet been initiated. In addition to DIC, overt coagulopathy, one of the most serious complications of PAS, has been reported in up to 30% of PAS cases.²⁵ It is useful to detect adverse complications early. Our research has reported that the coagulation data may be associated with PAS. Further studies are warranted to determine whether coagulation indicators can further improve early monitoring of PAS.

This study has the following strengths: 1) We included a relatively robust, contemporary cohort of PAS patients with pathologically and/or clinically confirmed PAS diagnoses according to FIGO guidelines.^{2,26} Patients with coagulopathy or other conditions that may alter the levels of coagulation indicators were excluded. 2) Since this was a single-center study, the patients were likely to receive relatively homogeneous inpatient care and surgical procedures, reducing the likelihood of confounders; 3) Multiple regression model was applied to adjust for known influencing factors of PAS severity; and 4) the association between coagulation test profiles and both PAS severity and blood loss volume during surgery was investigated.

There are a few limitations that should be acknowledged. First, as a single-center study, the analysis was limited by the

small sample size and lack of an external cohort to validate the results. Although we have already adjusted for several pregnancy and perioperative factors in the multivariate analysis to explore the association between coagulation factors and PAS severity, variables such as IVF, multiple gestation, and other maternal pathophysiological factors could be further adjusted. The robustness of the association between coagulation factors and blood loss still needs to be examined by sensitivity and stratification analyses by FIGO grades and the presence/absence of pregnancy complications, preferably with a larger sample size. Second, since this was a retrospective analysis, we only included the coagulation test results immediately before the surgery and were thus unable to examine the long-term variation pattern of the indicators during the progression of PAS in the whole gestation period. Future studies may adopt a prospective cohort design to further clarify the changes in coagulation and fibrinolysis profiles during gestational weeks and their association with the dynamic progression of PAS so that possible interventions or time points to intervene can be explored.

In conclusion, this study found that preoperative coagulation indicators, especially PT, D-dimer and FDP, may be associated with disease severity and blood loss volume during operation for invasive PAS. Since coagulation tests are economic, accessible and objective and are already a part of routine antenatal care, the results of this study can be applicable to general obstetric settings.

Future studies may verify the associations found in this study with a larger sample size or adopt a prospective cohort design to further clarify the changes in coagulation and fibrinolysis profiles during the gestational weeks of invasive PAS patients. In that way, it will be intriguing to further explore the diagnostic value of coagulation indicators as supplementary variables to ultrasound assessment in predelivery patient examinations. More importantly, elucidating the changes in the coagulation and fibrinolysis process in PAS is critical to reveal the pathogenesis of disease.

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Author Contribution

ZG and XH designed the research, collected and analyzed the data, prepared tables and figures, and drafted the paper; JM and HY designed the research and revised the article; WZ participated in data collection; HY and HZ provided clinical supervision and revised the manuscript. All authors have read and approved the final manuscript.

Ethics Approval and Informed Consent

This study was reviewed and approved by the institutional ethics committee of Peking University First Hospital on 11 September 2019 (No. 2019[175]). As this is a retrospective observational study, the ethics committee exempted the informed consent process for this study.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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