Original Article

Thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-plasmininhibitor complex (PIC), and tissue plasminogen activator-inhibitor complex (t-PAIC) assessment of fibrinolytic activity in postpartum hemorrhage: a retrospective comparative cohort study

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Background: Detecting the changes of coagulation function in the early stage of postpartum hemorrhage (PPH), which is the leading cause of maternal death, is the key to treatment this serious disease, however, there is less effective assessment methods. Thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-plasmininhibitor complex (PIC), and tissue plasminogen activator-inhibitor complex (t-PAIC) are the new direct indicators for coagulation and fibrinolysis, and considered sensitive molecular markers of the fibrinolytic system changing. The aim of this study was to investigate the changes of these 4 new indicators in the early stage of PPH.

Methods: We retrospectively reviewed the new coagulate indicators, TM, TAT, PIC, and t-PAIC, obtained from PPH patients at Guangzhou Women and Children's Medical Center from January 2021 to July 2021. According to the amount of blood loss, the patients were divided into 3 groups: Mild group (blood loss <1,500 mL, n=17), Severe group (blood loss ≥1,500 mL, n=24); another 12 women who did not experience PPH were selected as the Normal group (n=12). The four indicators were measured at the time of PPH happened, or immediately when baby was born in the Normal group, and evaluated for the prediction of PPH.

Results: The t-PAIC level of the Severe group was significantly lower than the other 2 groups (Normal group *vs.* Mild group *vs.* Severe group: 13.9±2.0 *vs.* 9.4±1.8 *vs.* 7.5±0.9, P=0.020), and the PIC level was the highest (Normal group *vs.* Mild group *vs.* Severe group: 1.1±0.2 *vs.* 2.7±0.8 *vs.* 2.9±0.6, P=0.012). There was no significant difference in TM and TAT among the 3 groups. The odds ratio (OR) value of t-PAIC was 0.822, 95% confidence interval (CI): 0.697–0.970, P=0.020. The area under the curve (AUC) of PIC was 0.5, and t-PAIC was 0.775, the cut-off point was 6.295, the specificity was 75%, and the sensitivity was 75%.

Conclusions: With the increasing of blood loss, t-PAIC decreased gradually, and is associated with severe PPH. This indicator may be a new predictor of PPH, and should be used in the early period of PPH for treatment.

Keywords: Postpartum hemorrhage (PPH); thrombomodulin (TM); thrombin-antithrombin complex (TAT); plasmin-α2-plasmininhibitor complex (PIC); tissue plasminogen activator-inhibitor complex (t-PAIC)

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Introduction

Postpartum hemorrhage (PPH) is one of the most serious complications in obstetrics. It is the leading cause of maternal death in both developing and developed countries (1), and leads to severe anemia requiring blood transfusion, and adverse pregnancy outcomes such as like disseminated intravascular coagulopathy (DIC), hysterectomy, multisystem organ failure, and maternal death (2). Despite a dramatic reduction in maternal deaths from PPH, severe PPH (sPPH) incidence has generally shown an increasing trend from 2016 and has consistently remained at a high level over the recent 2 years in China (3).

The activation of the coagulation cascade is one of the elements required to control PPH. Physiologically, at the end of pregnancy, women are in a hyper-coagulable state, with increased levels of procoagulants [fibrinogen (F)V, FVII, FVIII, FIX, FX, FXII, vWF, and FIB] in plasma, especially during the peripartum period (4,5). This hyper-coagulability can help to minimize blood loss during the delivery. Hemostatic impairment is a common cause of PPH. When PPH occurs, the blood loss is accompanied by substantial consumption of clotting substances, which can lead to coagulation dysfunction, even DIC. Coagulation impairment make it more difficult to hemostasis, therefore, detection and treatment at the early stage of PPH is very important. The standard coagulation test cannot assess the body's ability to form a clot; it focuses almost exclusively on plasma factors, which are not suitable to assess clinical coagulopathy, especially in bleeding patients (4). Some researches suggested that the fibrinogen less than 2 g/L was associated with severity of bleeding (6,7), however, due to the detection method, fibrinogen deficiency during hemorrhage is often delayed, at least 60 min (8). Thromboelastography (TEG) is mainly used to assess general coagulation and fibrinolysis status to guide blood transfusion in PPH patients (9), but its effect in the prediction of hemorrhage and blood-transfusion is limited (10).

Thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-plasmininhibitor complex (PIC), and tissue plasminogen activator-inhibitor complex (t-PAIC) are new indicators which directly reflect the fibrinolysis and the activity of the endothelial system. TM is a kind of type I transmembrane glycoprotein expressed on the luminal surface of endothelial cells (11). It can capture thrombin and activates protein C, which along with protein S degrades factors Va and VIIIa (12). TAT is generated following the deactivation of thrombin and it is regarded as a responsive biomarker for thrombin formation and coagulation activation (12,13). PIC is a marker for the activation of fibrinolysis, and reflects the degree of plasmin activation (14). t-PAIC is formed by plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA), bound at a 1:1 concentration. An increase in the t-PAIC complex means an increase in the concentration of t-PA in the blood, which can be considered a molecular marker of the fibrinolytic system or vascular endothelial cell damage (15).

Currently, there is still no accurate, effective, and highly sensitive indicators to evaluate the changes of coagulation function in the early stage of PPH. These new four coagulation indicators reflect changes of the elements related to the hemostasis, so we hypothesized that in the early stage of PPH, these 4 new indicators of clotting function have already changed, and may predict the severity of PPH. In this study, we retrospectively analyzed the changes of these 4 new indicators in patients with PPH and discussed their application in predicting PPH. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5221/rc).

Highlight box

Key findings

- With the increasing of blood loss during PPH period, t-PAIC gradually decreased and PIC increased. T-PAIC is associated with severe PPH.

What is known and what is new?

- Fibrinolytic hyperactivity is one of the early characteristics of PPH.
- The gradual decrease of t-PAIC with the increase of blood loss reflects the change of fibrinolytic system in the early stage of PPH.

What is the implication, and what should change now?

- T-PAIC may be used as a new predictor in early period of severe PPH, we should use this indicator for treatment.

Methods

Patients

As described in *Figure 1*, a total 41 patients who were diagnosed PPH were enrolled in this study. The eligibility criteria were as follows: (I) patients diagnosed PPH according to the diagnostic criterion in the American

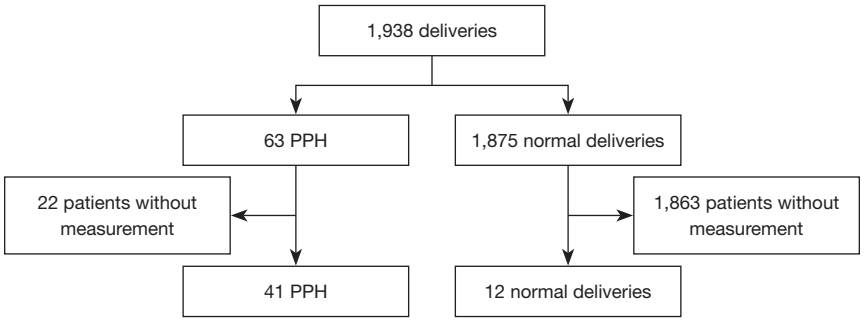

Figure 1 Flow chart of study population. PPH, postpartum hemorrhage.

College of Obstetricians and Gynecologists (ACOG) PPH guideline: vaginal delivery blood loss >500 mL, cesarean delivery >1,000 mL within 24 hours (16); (II) PPH patients who immediately accepted testing of the new coagulator indicators when the PPH just happened. All the cases happened in the first hour of postpartum. According to the blood loss, the patients were divided into 3 groups: Mild group (blood loss 500–1,500 mL, n=17), Severe group (blood loss >1,500 mL, n=24), and Normal group (blood loss <500 mL, n=12). Concurrently, another 12 normal pregnant women without PPH were enrolled in this study according to the same day and the same midwifes or cesarean section operators as the patients, and these 4 indicators were tested immediately when the baby was born. The exclusion criteria were as follows: (I) preterm labor; (II) patients complicated with abnormal coagulation function before delivery; (III) patients who received interventional embolization of uterine artery therapy; (IV) comorbidity of liver disorders, kidney disorders, hematological disorders, malignancy, familial thromboembolism, autoimmune disorders, and serious systemic bacterial or viral infections; and (V) refusal to undergo testing of these indicators. The maternal and fetal demographic characteristics, postpartum complications, maternal age, gestational age, and maternal basic diseases were also included. All participants signed an informed consent form. This research was approved by institutional ethics board of Guangzhou Women and Children's Medical Center (No. 215A01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Sample collection and measurement of coagulation markers

The blood samples [2.0 mL, Becton, Dickinson, and Co. (BD) Vacutainer with sodium citrate anticoagulant, Shanghai, China] were collected at the point of the PPH having just occurred, before blood transfusion or tranexamic acid was used. In the normal group, the blood samples were collected within 1 hour after delivery. Within the 30 minutes of sample collection, blood sample was centrifugated at 3,000 g for 10 minutes. Then, TM, TAT, PIC, and t-PAIC levels were tested immediately via qualitative chemiluminescence enzyme immunoassay performed on an automatic chemiluminescence analyzer (Wondfo FC-302; Wondfo Biotech, Guangzhou, China) in line with product's instructions (Wondfo TM Assay Kit, China; Wondfo t-PAIC Assay Kit, China; Wondfo TAT Assay Kit, China; Wondfo PIC Assay Kit, China). All results were processed by the Wondfo FC-302 automated chemiluminescence immune detection system. Before detection, the coagulation analyzer was calibrated in line with the manufacturer's instructions. Quality control was conducted every day to make sure the precision of analyzer.

Statistical analysis

All data analysis was performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). One-way analysis of variance (ANOVA) and Welch test was utilized for calculating the differences among 3 groups. Logistic regression analysis and receiver operating curve (ROC) analysis were carried out to measure the best serum index for PPH. A P value <0.05 was considered to indicate significance.

Results

General characteristics

Totals of 41 PPH cases and 12 normal cases were included

Table 1 Demographic characteristics of the patients

Characteristics	PPH group	Normal group
Maternal age, y (mean ± SD)	33.2±4.6	30.2±5.6
Parity, n (%)		
Nulliparous	7 (7/41, 17.1)	6 (6/12, 50.0)
Multiparous	34 (34/41, 82.9)	6 (6/12, 50.0)
Fetus, n (%)		
1	38 (38/41, 92.7)	12 (12/12, 100)
2	3 (3/41, 7.3)	0
BMI, kg/m^2 (mean ± SD)	26.6±5.5	24.3±2.2
Delivery week, w (mean ± SD)	37.8±2.8	38.1±3.1
Delivery method		
Vaginal delivery, n (%)	11 (11/41, 26.8)	7 (7/12, 58.3)
Cesarean section, n (%)	30 (30/41, 73.2)	5 (5/12, 41.7)
Bleeding volume (mean ± SD)	2,128±1,346	403±103
Blood transfusion, n (%)	30 (30/41, 73.2)	0
DIC, n (%)	3 (3/41, 7.3)	0
Previa placenta, n (%)	13 (13/41, 31.7)	0
Accreta placenta, n (%)	9 (9/41,30.0)	0
Hypertension disorders, n (%)	4 (4/41, 9.8)	0
Neonatal weight, g (mean ± SD)	3,120±912	3,036±817

PPH, postpartum hemorrhage; BMI, body mass index; DIC, disseminated intravascular coagulopathy.

in the study. As described in *Table 1*, the average age of PPH group cases was 33.2±4.6 years, and the gestational age at delivery was 37.8±2.8 weeks; 73.2% (30/41) of cases underwent cesarean deliveries. The average blood loss of the PPH group was 2,128±1,346 mL; sPPH (>1,500 mL) was recorded in 58.5% of cases (24/41), and DIC occurred in 3 cases. The average blood loss of the Normal group was 403±103 mL.

The different general clinical characteristics among 3 groups

We divided the PPH patients into 2 groups, according to the bleeding volumes: Severe group (>1,500 mL, n=24), and Mild group (<1,500 mL, n=17). After comparison with the Normal group (n=12), no statistically significant differences among the 3 groups were observed in terms of maternal age, gestational age, body mass index (BMI), and neonatal weight (*Table 2*).

The differences of TM, TAT, PIC, and t-PAIC among 3 groups

At the time of hemorrhage, we evaluated TM, TAT, PIC, and t-PAIC among the 3 groups. Significant differences in t-PAIC were observed among the 3 groups, as follows: 9.4±1.8 *vs.* 7.5±0.9 *vs.* 13.9±2.0 in the Mild, Severe, and Normal groups, respectively (P=0.020); and PIC value were 2.7±0.8 *vs.* 2.9±0.6 *vs.* 1.1±0.2 (P=0.012); the other indicators: TM and TAT were not significantly different among the 3 groups (*Table 3*).

The relationship between severe PPH and these 4 new indicators

We conducted logistic regression analysis to evaluate the relationship between PPH and these 4 new indicators. As shown in *Table 4*, the odds ratio (OR) value of t-PAIC was 0.822, 95% confidence interval (CI) 0.697 to 0.970, P=0.020 (*Table 4*).

Table 2 The basic clinical characteristics among 3 groups

Characteristics	Mild group (n=17), mean ± SD	Severe group (n=24), mean ± SD	Normal group (n=12), mean ± SD	P value
Maternal age, y	33.5±5.6	33.1±3.9	29.8±5.7	0.119
BMI, kg/m^2	27.0±2.9	26.3±6.6	24.2±2.2	0.331
Delivery week, w	38.4±2.0	37.4±3.2	38.2±3.3	0.525
Neonatal weight, g	3,096±601	3,142±1,017	3,010±847	0.919

BMI, body mass index.

Table 3 The differences of TM, TAT, PIC, and t-PAIC among 3 groups

Variables	Mild group (n=17), mean ± SD	Severe group (n=24), mean ± SD	Normal group (n=12), mean ± SD	P value
TM	7.7±0.5	7.5±0.3	7.4±0.8	0.887
TAT	13.5±2.7	18.4±4.9	12.4±4.1	0.676
PIC	2.7±0.8	2.9±0.6	1.1±0.2	0.012
t-PAIC	9.4±1.8	7.5±0.9	13.9±2.0	0.020

TM, thrombomodulin; TAT, thrombin-antithrombin complex; PIC, α2-plasmin inhibitor-plasmin complex; t-PAIC, tissue plasminogen activator-inhibitor complex.

Table 4 Univariate logistic regression analyses for these four indicators associated with PPH

Variables	OR (95% CI)	P value
TM	1.172 (0.778–1.767)	0.448
TAT	0.983 (0.907–1.065)	0.680
PIC	2.077 (0.829–5.205)	0.119
t-PAIC	0.822 (0.697–0.970)	0.020

PPH, postpartum hemorrhage; TM, thrombomodulin; TAT, thrombin-antithrombin complex; PIC, α2-plasmin inhibitor-plasmin complex; t-PAIC, tissue plasminogen activator-inhibitor complex; OR, odds ratio; CI, confidence interval.

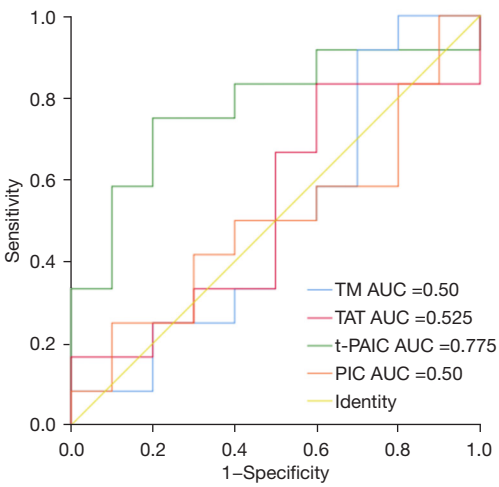

Figure 2 Receiver operating characteristic analysis for disseminated intravascular coagulation. TM, thrombomodulin; AUC, area under the curve; TAT, thrombin-antithrombin complex; t-PAIC, tissue plasminogen activator-inhibitor complex; PIC, α2-plasmin inhibitor-plasmin complex.

Finally, we analyzed the cut-off-point of these 4 indicators to predict sPPH (bleeding volume >1,500 mL). As described by the ROC curve in *Figure 2*, t-PAIC was the most effective predictor of sPPH, with an area under the curve (AUC) was 0.775, P=0.024. The Youden's index was 0.50, the cut-off point was 6.295, the specificity was 75%, and the sensitivity was 75%.

Discussion

In this study, we evaluated the association between PPH and the 4 new coagulation indicators: TM, TAT, PIC, and t-PAIC. The results of this study suggested that as the volume of blood loss increased, the level of PIC increased but that of t-PAIC decreased. There was the association between the decreased level of t-PAIC and sPPH. It appeared that TM and TAT were not related with the occurrence of PPH. t-PAIC may be one of the new

indicators to reveal early hyperfibrinolysis.

Normal pregnancy is associated with changes in hemostasis, including an increase of clotting factors and decrease of fibrinolytic activity and anticoagulants. Fibrinogen, FVII, FVIII, FIX, FX, and FXII levels are raised in the pregnancy and attain the highest levels at full term. At the same time, the circulating levels of free protein S and protein C are decreased in this process (17,18). Moreover, the circulating thrombin-activatable fibrinolysis inhibitor (TAFI) level is also raised in the third trimester of pregnancy (17). In pregnancy, the systemic level of t-PA is increased, but its activity reduced due to the enhancement of fibrinolysis inhibitors (19). Following the increasing level of plasminogen, the a2-antiplasmin level is reduced (20); at the same time, the circulating levels of PAI-1 and PAI-2 are increased (21). All of these changes contribute to a prothrombotic state; the clotting system takes to prothrombotic direction to prevent PPH.

Binding of TM with thrombin can reduce the activity of thrombin and enhance the activity of protein C (12). TAT depends on ATIII, and indicates the activation of the coagulation system (22). PIC reflects the balance of the fibrinolysis and anti-fibrinolysis system and the rise of PIC level can indicate the activation of plasmin (23). Therefore, the new 4 indicators also change during pregnancy. Wu *et al.* analyzed the changes of TAT, TM, t-PAIC, and PIC during pregnancy among healthy Chinese women. They discovered that TAT, TM, and t-PAIC levels were raised gradually from trimester 1 to trimester 3, while the PIC level remained stable during pregnancy (24). We used these 4 items to evaluate the effect of PPH on coagulation function and found that PIC and t-PAIC changed in both PPH groups. These results suggest that the fibrinolytic system changes at the early stage of PPH. In some previous studies, detailed below, these 4 items were used to forecast the possibility of early thrombosis of the patients. Mei *et al.* found that TAT, PIC, t-PAIC, and TM could serve as effectively diagnostic and prognostic biomarkers of DIC in some human diseases, and the combination of these 4 biomarkers showed better efficacy (25). Jin *et al.* suggested that in corona virus disease 2019 (COVID-19) patients, these 4 indicators were associated with the disease severity, and t-PAIC was an independent risk factor for death of patients (26).

Due to t-PAIC can reflect the balance of fibrinolysis by t-PA and de-fibrinolysis by PAI-1, it can be applied for assessing fibrinolytic dysfunction (27). Thus, t-PAIC was considered as the key marker of fibrinolytic system, suggesting thrombus progression. In venous thromboembolism (VTE) (28) and acute myocardial infarction (29), t-PAIC is a risk index of thrombosis. In addition, t-PAIC is of important value in the diagnosis of DIC (25). In our study, t-PAIC decreased with the severity of the bleeding, and was associated with the severity of PPH; it can be used to predict the occurrence of PPH. As the PPH occurs in the state of fibrinolytic hyperactivity, t-PAIC decreased with the increase of bleeding with the consumption of coagulation factors. These results confirmed that during PPH, fibrinolytic hyperactivity is one of the earliest manifestations and is related to the degree of hemorrhage. A study reported that following management of other risk factors, every 1 g/L decrease of fibrinogen can lead to a 26-fold increase of sPPH (6).

As a key component of coagulation, fibrinogen is the main factor affecting the final stage of clot formation, and participate in the initiation of intrinsic and extrinsic coagulation pathways. Currently, the pathogenesis of the decrease of fibrinogen in PPH remains unclear, only know that it may be related to the blood loss, which will deplete coagulation factors, and reduce the levels of factors involving in coagulation activation (20). The routine laboratory parameters for testing PPH and coagulation changes, include hemoglobin, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fbg), which cover the coagulation and fibrinolysis systems. However, detection the levels of these parameters usually need greater than or equal to 2 hours, that cannot detect the early stage of PPH and thrombosis, and insensitive to pre-thrombotic state and pre-DIC. The new indicators PIC and t-PAIC have more advantages in these areas.

There were some limitations in this study. It was a retrospective study; we excluded the PPH patients who had been treated with uterine artery interventional embolization; and the population of the study was relatively small, so the PPH cutoff point of t-PAIC was only 0.775. Under normal conditions, t-PAIC level reaches its peak at 8 a.m. in the morning and reduced in the evening. The level of t-PAIC in our research was detected under emergency condition, which may have had a little affect the value of t-PAIC. In this study, we have not yet conducted clinical validation of this cut-off value, in future, we will execute a prospective cohort study to explore the applications of these 4 parameters.

Conclusions

In conclusion, fibrinolytic hyperactivity is one of the early

characteristics of PPH. T-PAIC and fibrinogen levels decreased progressively with the increasing blood loss, and t-PAIC should be used to predict the severity of PPH when PPH occurs at the early stage.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5221/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5221/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5221/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients who participated in this study signed an informed consent form, and this study was approved by institutional ethics board of Guangzhou Women and Children's Medical Center (No. 215A01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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