Original Article

Role of variation in platelet indices in pregnancy-related pathological complications and the prediction of postpartum hemorrhage: a case-control study

Yuanling Zuo[1], Jiayi Wang[1], Xueyou Zhang[1], Chunji Gu[2], Jianming Zhang[2,3]

[1]Department of Blood Transfusion, The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Department of Clinical Laboratory, Suzhou Municipal Hospital, Suzhou, China; [3]Department of Clinical Laboratory, Suzhou Hospital Affiliated to Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, China

Contributions: (I) Conception and design: Y Zuo; (II) Administrative support: J Zhang; (III) Provision of study materials or patients: J Wang; (IV) Collection and assembly of data: X Zhang; (V) Data analysis and interpretation: C Gu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jianming Zhang. Department of Clinical Laboratory, Suzhou Hospital Affiliated to Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, China. Email: ghost.loveme@163.com.

Background: Pregnancy-related pathological complications (PPCs) increase the risk of postpartum hemorrhage (PPH), Platelet activation and destruction are expected outcomes of PPCs. This study sought to compare the platelet indices of non-pregnant (NP) child-bearing aged women, healthy pregnant (HP) women, and women with PPCs, and investigate the use of these indices in PPH prediction.

Methods: This retrospective clinical study included 260 NP child-bearing aged women and 119 pregnant women. Of the 119 pregnant patients, 69 had HPs and 50 suffered from PPCs. Further, 50 patients delivered with PPH. We compared the platelet counts (PCs), mean platelet volumes (MPVs), platelet distribution widths (PDWs), plateletcrits (Pcts), MPV ratios (PC/MPV and Pct/MPV), alpha angles (angles), and maximum amplitudes (MAs) of the patients using Sysmex XN10 hematology analyzer and TEG 5000 Hemostasis analyzer system, respectively.

Results: With the exception of PDW, there were significant differences in the platelet parameters of the NP, HP, and PPC patients ($P<0.05$). The intergroup comparison results showed that the NP patients differed significantly from the HP and PPC patients in terms of age, MA, PC, Pct, and Pct/MPV ($P<0.0125$). Further, the HP and PPC patients differed significantly in terms of Pct, MPV, PC/MPV, and Pct/MPV ($P<0.0125$). Additionally, the univariate analysis showed that in the PPC patients, low MPV values were strongly related to PPH [odds ratio (OR) =0.012, P=0.003; OR =0.331, P=0.047].

Conclusions: Women with PPCs had significantly lower PC, Pct, PC/MPV and Pct/MPV values, but significantly higher MA and MPV values. PPHs were strongly related to PPC and low MPV values. A timely accurate diagnosis and evaluating MPV values may be useful in the prediction of PPH.

Keywords: Pregnancy; pathological complication; postpartum hemorrhage (PPH); platelet indices

Submitted Sep 30, 2022. Accepted for publication Dec 12, 2022.
doi: 10.21037/apm-22-1196
View this article at: https://dx.doi.org/10.21037/apm-22-1196

Introduction

During pregnancy, coagulation, anticoagulation, and the fibrinolytic system change significantly due to the increased circulation of clotting factors, decreased natural anticoagulants, and fibrinolytic activities, which results in a state of hypercoagulability that is necessary to maintain placental function and ensure the rapid and effective control of bleeding at the time of placental separation (1,2).

This state is further exaggerated in patients suffering from pregnancy-related pathological complications (PPCs), such as preeclampsia (PE), gestational hypertension (GH), and gestational diabetes mellitus (GDM) (3-5). The World Health Organization defines postpartum hemorrhage (PPH) as >500 mL of blood loss, and PPH is the leading cause of maternal mortality worldwide in pregnancies (6,7). In China, the number of women suffering from PPH has increased as the 2-child policy has implemented over the 7 years. In addition, reports have suggested that PPCs increase the risk of PPH (8-11). The pathophysiology mechanism of PPH is not fully understood; however, the close monitoring of platelet activation and function during pregnancy, especially in patients with complications, is of great importance.

Platelet parameters, such as platelet counts (PCs), platelet distribution widths (PDWs), mean platelet volume (MPVs), and plateletcrits (Pcts), have been widely used in cardiovascular, inflammatory and autoimmune diseases patients to predict platelet function, destruction, and production (12-15). Platelet activation and destruction are expected outcomes of PPCs (1,16,17). MPV, Pct, and PDW variations can be detected by new-born platelet production in the bone marrow and releases fresh and large platelets into the circulation were stimulated (16,18). However, to some extent, these parameters fail to provide comprehensive information about the kinetics of platelet function. Thromboelastography (TEG), especially alpha angles (Angles) and maximum amplitudes (MAs), offer an approach for assessing the dynamic interaction of platelet and plasma clotting factors (19).

The platelet parameters of pregnant women need to be monitored and treatment strategies for pregnant women with abnormal parameters need to be formulated. Platelet activation and functions have been assessed based on complete blood counts (CBCs). However, in this study, we also measured platelet parameters related to TEG and explored the relative changes in PPCs, and investigated the correlation between platelet indices and PPH. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1196/rc).

Highlight box

Key findings

- Women with PPCs had significantly lower PC, Pct, PC/MPV and Pct/MPV values, but significantly higher MA and MPV values. PPHs were strongly related to PPC and low MPV values.

What is known and what is new?

- PPCs increase the risk of PPH, Platelet activation and destruction are expected outcomes of PPCs. A diagnosis of PPC and low MPV values were strongly related to PPH.
- Women with PPCs had significantly lower PC, Pct, PC/MPV and Pct/MPV values, but significantly higher MA and MPV values.

What is the implication, and what should change now?

- In prenatal follow-up, a timely accurate diagnosis and evaluating MPV values may be useful in the prediction of PPH.

Methods

Subjects

From January 2019 to December 2021, 386 child-bearing-aged women who underwent TEG and CBCs were enrolled in this retrospective study at The First Affiliated Hospital of Soochow University. Among the patients, 200 were non-pregnant (NP) women who underwent health examinations, 59 were healthy pregnant (HP) women, and 67 were pregnant women suffering from complications, including PE, GH, and/or GDM. Women who received anticoagulant or antiplatelet therapy, or who had been diagnosed with coagulation defects or autoimmune disorders before blood collection were excluded from the study. The eligibility and exclusion criteria for the study are shown in *Figure 1*.

The diagnostic criteria of HP are: HP, the pregnancy process is stable, excluding the following conditions: (I) some systemic diseases, such as severe heart disease, liver disease, kidney disease and autoimmune disease; (II) complicated with some medical diseases: such as pregnancy with hypersplenism, pregnancy with hematopoiesis malignancy, patients receiving radiotherapy or chemotherapy during pregnancy; (III) pregnancy with coagulation system disease or receiving anticoagulation treatment. The diagnostic criteria of PPC are: mainly including patients with diabetes in pregnancy, preeclampsia (PE) patients, and pregnancy with hypertension. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by medical committee board of The First Affiliated Hospital of Soochow University (No. 2022-430). All the patients enrolled in this study gave informed consent for the research.

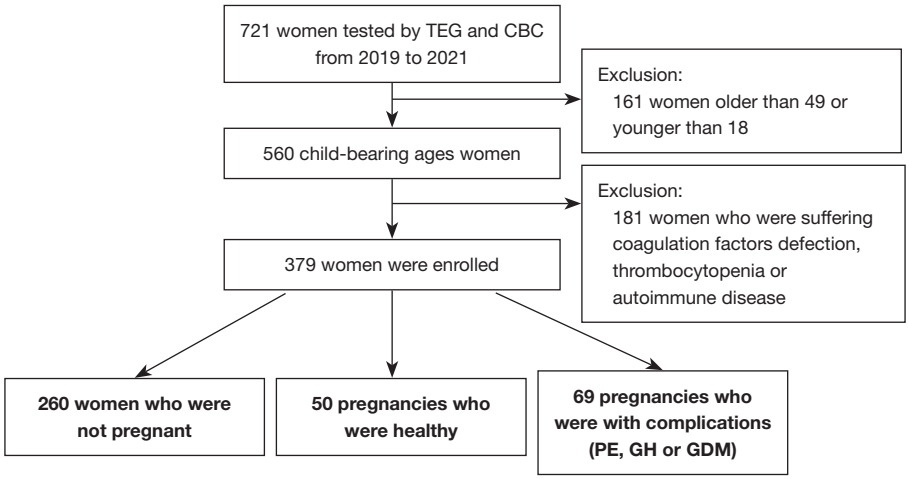

Figure 1 The inclusion and exclusion criteria for the study. TEG, thromboelastography; CBC, complete blood count; PE, preeclampsia; GH, gestational hypertension; GDM, gestational diabetes mellitus.

Study methods

Venous blood samples were collected and tested in accordance with the manufacturer's instructions. For the CBCs, which were tested by a Sysmex XN10 hematology analyzer in EDTA anticoagulation tubes, multiple indices were generated, including white blood cell, red blood cell, and PCs. In relation to the platelet parameters, PC, Pct, PDW, and MPV were evaluated in this study.

For the TEG test, a citrated whole blood sample (1 mL) was pipetted into a kaolin tube (Haemonetics Corporation, Braintree, USA), and the citrated whole blood sample was made to flow down the wall. The blood was capped and mixed with kaolin. The kaolin-activated blood (340 μL) was pipetted into a plain cup in which 20 μL of 0.2 mol/L $CaCl_2$ was pre-pipetted and analyzed using the TEG 5000 Hemostasis Analyzer System (Haemoscope Corporation, Niles, USA). The TEG trace generates a large number of quantitative parameters, among which Angle and MA are widely used to evaluate platelet functions.

Statistical analysis

All statistical analysis were performed using SPSS 19.0 software. For normally distributed data, one-way ANOVA analysis was used to compare the multiple groups, Tukey's *post-hoc* test was used to compare the intergroup comparisons. Data of platelet indices were expressed as average values with the standard deviation (SD). Logistic regression analysis was tested to evaluate the association of platelet indices with PPH. The visibility graphs were shown as box and whiskers by Graph Pad Software 6.0. For statistically significant was defined as $P<0.05$.

Results

After excluding the outliers, a total of 379 women, including 260 NP child-bearing aged women (aged 18–45 years), 50 HP women, and 69 women with PPCs were enrolled in our study (*Figure 1*).

The CBC and TEG-related platelet indices data are presented in *Table 1*. The ANOVA test indicated that except for the PDW, the values of the platelet indices differed significantly between the 3 groups ($P<0.05$). The graphs are shown as box and whiskers in *Figure 2*.

Of the 119 pregnant women, 22 did not give birth at our hospital, 5 had abortions (in the PPC group), and 42 were not diagnosed with PPH. The results of the analysis of the 50 PPH women are shown in *Table 2*. The pregnant women who suffered PPCs, and a decreased MPV was significantly associated with a high risk of PPH [odds ratio (OR) =0.012, P=0.003; OR =0.331, P=0.047].

Discussion

A total of 379 women treated from 2019 to 2021 were enrolled in this retrospective study, which sought to evaluate the use of platelet indices in the description of pregnancy pathological complications and the prediction of PPH. In this study, we first found that all the above-mentioned

Table 1 Platelet parameter analysis of the study participants

Indics	NP (n=260)	HP (n=50)	PPC (n=69)	P	P^a	P^b	P^c
Age [years]	41 [26–49]	31 [24–40]	33 [24–53]	<0.001	<0.001	>0.157	<0.001
Angle (°) (mean ± SD)	67.5±5.7	70.7 ± 5.5	68.8±5.8	<0.001	<0.001	0.089	0.088
MA (mm) (mean ± SD)	64.4±4.1	69.2 ± 4.5	68.1±5.1	<0.001	<0.001	0.146	<0.001
PC (10^9/L) (mean ± SD)	244±53	221±50	198±67	<0.001	0.007	0.027	<0.001
Pct (%) (mean ± SD)	0.26±0.05	0.24±0.05	0.21±0.06	<0.001	0.001	0.004	<0.001
PDW (%) (mean ± SD)	10.9±0.9	10.9±1.2	10.8±1.5	>0.05	0.840	0.951	0.753
MPV (fl) (mean ± SD)	12.9±2.0	13.7±3.1	15.3±2.5	<0.001	0.029	<0.001	<0.001
PC/MPV (mean ± SD)	19.67±6.25	17.38±6.54	13.58±6.00	<0.001	0.018	0.001	<0.001
Pct/MPV (mean ± SD)	0.021±0.005	0.018±0.006	0.014±0.005	<0.001	0.001	<0.001	<0.001

Ages are presented as median [range]. P^a: NP *vs.* HP; P^b: HP *vs.* PPC; P^c: NP *vs.* PPC. MA, maximum amplitude; PC, platelet counts; Pct, plateletcrit; PDW, platelet distribution width; MPV, mean platelet volume; SD, standard deviation.

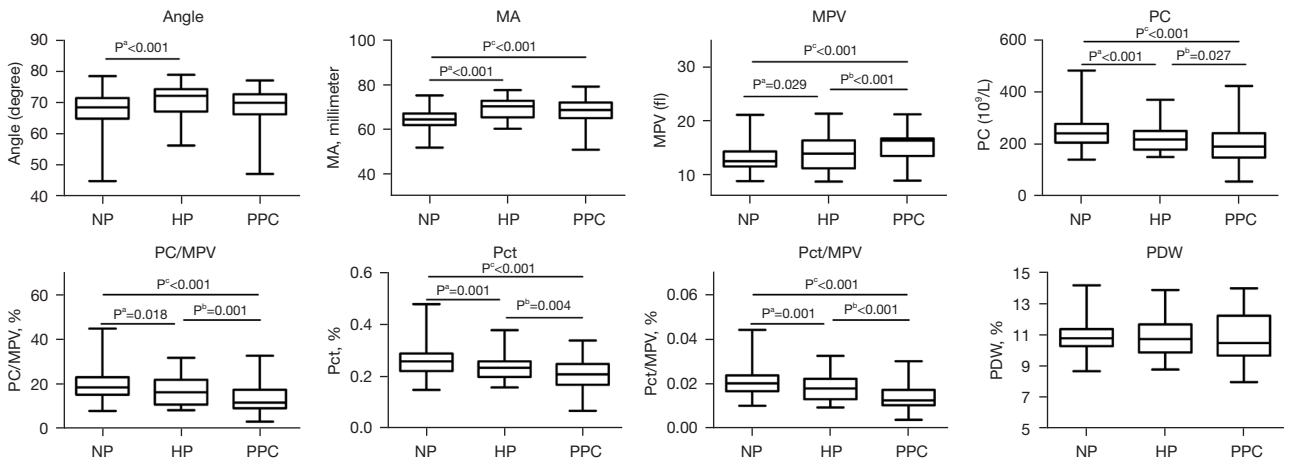

Figure 2 Comparison of the CBC and TEG parameters related to platelets among the NP child-bearing aged women, HP women, and HP women with PPCs. P^a: NP *vs.* HP; P^b: HP *vs.* PPC; P^c: NP *vs.* PPC. MA, maximum amplitude; MPV, mean platelet volume; PC, platelet counts; Pct, plateletcrit; PDW, platelet distribution width; NP, non-pregnant; HP, healthy pregnant women; PPC, pregnancy-related pathological complications; CBC, complete blood count; TEG, thromboelastography.

platelet indices, except for PDW, differed significantly between the 3 groups. For the intergroup analysis, MA, PC, Pct, MPV, PC/MPV, and Pct/MPV differed significantly between the PPC group and the HP and/or NP groups.

Women with PPCs had significantly lower PC, Pct, PC/MPV, and Pct/MPV values, but significantly higher MA and MPV values. In spite of the variations, when a receiver operating characteristic (ROC) curve was drawn, the area under the curve was <75% (data not shown).

Previous studies have classified PPCs as PE, GH, GDM, and so on. Temur *et al.* (16) reported that MPV and the PC/MPV ratio were promising diagnostic parameters in PE prediction. The optimum cut-off value of MPV was 9.15, and a ROC analysis of 257 PE patients showed that it had had a sensitivity of 58.7% and a specificity of 61.7%. Conversely, Xie *et al.* (19) reported that TEG can be used to accurately assess and monitor coagulation function, especially in pregnant women with the complications of GH and PE. The P value of the CBC and TEG-related platelet indices data was significantly decreased and was able to efficiently distinguish between normal pregnancies and GH and PE pregnancies. The MA value was significantly lower in PE patients than

Table 2 Evaluation of the association between diagnosis, age, Angle, MA, PC, Pct, PDW, and MPV in the PPH pregnant women using a logistic regression analysis

Indics	SE	Wald χ^2	P	OR	95% CI
Diagnosis: PPC *vs.* HP	1.508	8.726	0.003	0.012	0.001–0.223
Ages: ≥35 *vs.* <35	1.180	0.009	0.924	1.120	0.111–11.314
Angle	0.181	0.496	0.481	1.136	0.797–1.620
MA	0.065	0.445	0.505	0.044	–0.084–0.171
PC	0.105	1.788	0.181	0.870	0.708–1.067
Pct	29.984	0.179	0.672	–12.688	–71.457–46.080
PDW	1.564	0.077	0.781	1.543	0.72–33.106
MPV	0.558	3.928	0.047	0.331	0.111–0.988

PPC, pregnancy-related pathological complications; HP, healthy pregnant women; MA, maximum amplitude; PC, platelet counts; Pct, plateletcrit; PDW, platelet distribution width; MPV, mean platelet volume; PPH, postpartum hemorrhage; SE, standard error; OR, odds ratio; CI, confidence interval.

HP patients. However, in our study, it was difficult to divide the patients into groups, as 11 patients were diagnosed with GH and PE simultaneously. Further, PE, GH, and GDM are all associated with endothelial damage (20-22), and platelets increase destruction and production as a result of larger and younger platelets being released into the peripheral blood. We did not identify any promising parameters with sufficient diagnostic efficacy; however, the variations, especially in PC, MPV and MA values, were confirmed.

The univariate analysis also showed that a diagnosis of PPC and low MPV values were strongly related to PPH. A retrospective single-center cohort study of 23,205 deliveries reported that a PC of $<50\times10^9$/L and a PDW ≥23% increase the odds of severe postpartum hemorrhage (SPPH) (23). In our study, deliveries were not thrombocytopenic, and we did not distinguish between SPPH from PPH. Further, in many settings, TEG values have been used to assess coagulation status and guide transfusion management in PPH (19,24). The TEG values were not significantly predictive value, though they were first enrolled in the prediction of PPH. Thus, our results are also reliable and have independent research value.

All the indications supported that observational studies should be conducted in clinical trials. In our study, CBC parameters, which can be evaluated as they are easy, fast and inexpensive to obtain, and TEG parameters, which can be evaluated as they are dynamic and complete, were found to be useful in assessing PPC.

Conclusions

In prenatal follow-up, a timely accurate diagnosis and evaluating MPV values may be useful in the prediction of PPH. However, due to the deficiencies of this study, a multicenter, large-scale study urgently needs to be conducted in the near future.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1196/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1196/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1196/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by medical committee board of The First Affiliated Hospital of Soochow University (No. 2022-430). All the patients

enrolled in this study gave informed consent for the research.

References

1. Ramlakhan KP, Johnson MR, Roos-Hesselink JW. Pregnancy and cardiovascular disease. Nat Rev Cardiol 2020;17:718-31.
2. Thornton P, Douglas J. Coagulation in pregnancy. Best Pract Res Clin Obstet Gynaecol 2010;24:339-52.
3. Simcox LE, Ormesher L, Tower C, et al. Thrombophilia and Pregnancy Complications. Int J Mol Sci 2015;16:28418-28.
4. Brown HL, Smith GN. Pregnancy Complications, Cardiovascular Risk Factors, and Future Heart Disease. Obstet Gynecol Clin North Am 2020;47:487-95.
5. Pinheiro MB, Gomes KB, Dusse LM. Fibrinolytic system in preeclampsia. Clin Chim Acta 2013;416:67-71.
6. Gonzalez-Brown V, Schneider P. Prevention of postpartum hemorrhage. Semin Fetal Neonatal Med 2020;25:101129.
7. Andrikopoulou M, D'Alton ME. Postpartum hemorrhage: early identification challenges. Semin Perinatol 2019;43:11-7.
8. Nyfløt LT, Sandven I, Stray-Pedersen B, et al. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy Childbirth 2017;17:17.
9. Wetta LA, Szychowski JM, Seals S, et al. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. Am J Obstet Gynecol 2013;209:51.e1-6.
10. Koopmans CM, van der Tuuk K, Groen H, et al. Prediction of postpartum hemorrhage in women with gestational hypertension or mild preeclampsia at term. Acta Obstet Gynecol Scand 2014;93:399-407.
11. Lucas IM, Barr ELM, Barzi F, et al. Gestational diabetes is associated with postpartum hemorrhage in Indigenous Australian women in the PANDORA study: A prospective cohort. Int J Gynaecol Obstet 2021;155:296-304.
12. Coban E. Comment on "Mean platelet volume and long-term cardiovascular outcomes in patients with stable coronary artery disease". Atherosclerosis 2019;280:194.
13. Zhu C, Wang B, Xiao L, et al. Mean platelet volume mediated the relationships between heavy metals exposure and atherosclerotic cardiovascular disease risk: A community-based study. Eur J Prev Cardiol 2020;27:830-9.
14. Vardon-Bounes F, Ruiz S, Gratacap MP, et al. Platelets Are Critical Key Players in Sepsis. Int J Mol Sci 2019;20:3494.
15. Zhou Z, Chen H, Ju H, et al. Platelet indices in patients with chronic inflammatory arthritis: a systematic review and meta-analysis. Platelets 2020;31:834-44.
16. Temur M, Taşgöz FN, Çift T, et al. Role of platelet indices in prediction of preeclampsia. Ginekol Pol 2021;92:792-6.
17. Zhou Z, Chen H, Sun M, et al. Mean Platelet Volume and Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Diabetes Res 2018;2018:1985026.
18. Golwala ZM, Shah H, Gupta N, et al. Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet Count and Plateletcrit (PCT) as predictors of in-hospital paediatric mortality: a case-control Study. Afr Health Sci 2016;16:356-62.
19. Xie X, Wang M, Lu Y, et al. Thromboelastography (TEG) in normal pregnancy and its diagnostic efficacy in patients with gestational hypertension, gestational diabetes mellitus, or preeclampsia. J Clin Lab Anal 2021;35:e23623.
20. Lip SV, Boekschoten MV, Hooiveld GJ, et al. Early-onset preeclampsia, plasma microRNAs, and endothelial cell function. Am J Obstet Gynecol 2020;222:497.e1-497.e12.
21. Liu Y, Xiong M, Zhou F, et al. Effect of baicalin on gestational hypertension-induced vascular endothelial cell damage. J Int Med Res 2020;48:300060520934288.
22. Nguyen-Ngo C, Jayabalan N, Salomon C, et al. Molecular pathways disrupted by gestational diabetes mellitus. J Mol Endocrinol 2019;63:R51-72.
23. Shen XM, Xia YY, Lian L, et al. Mean platelet volume provides beneficial diagnostic and prognostic information for patients with resectable gastric cancer. Oncol Lett 2016;12:2501-6.
24. Frigo MG, Agostini V, Brizzi A, et al. Practical approach to transfusion management of post-partum haemorrhage. Transfus Med 2021;31:11-5.

Cite this article as: Zuo Y, Wang J, Zhang X, Gu C, Zhang J. Role of variation in platelet indices in pregnancy-related pathological complications and the prediction of postpartum hemorrhage: a case-control study. Ann Palliat Med 2022;11(12):3712-3717. doi: 10.21037/apm-22-1196

