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ORIGINAL RESEARCH

Values of Caprini Risk Assessment Scale and D-Dimer for Predicting Venous Thromboembolism During Puerperium

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Purpose: To evaluate the predictive value of the combination of the Caprini risk assessment model (RAM) and D-dimer for venous thromboembolism (VTE) during puerperium.

Patients and Methods: This was a retrospective case–control study. Thirty-one puerperium patients with VTE were included as cases, and 279 puerperium women without VTE were matched to cases according to age, number of fetuses, birth day and delivery mode at the ratio of 9:1. Demographic data, clinical data and laboratory parameters within postpartum 24 h were collected. Multivariate analysis, employing the forward stepwise model, was conducted to identify independent factors associated with VTE during puerperium. The predictive values of Caprini RAM, D-dimer and their combination were evaluated using receiver operating characteristic (ROC) curve, and the area under curve (AUC) was compared using *Z* test.

Results: Univariate analysis demonstrated that there were significant differences in D-dimer levels, Caprini score, scarred uterus, adherent placenta, postpartum hemorrhage and intrauterine infection between cases and controls ($P<0.05$). Multivariate analysis demonstrated that D-dimer levels (*OR*: 1.754, 95% *CI*: 1.237–3.182), Caprini score (*OR*: 1.209, 95% *CI*: 1.058–2.280), scarred uterus (*OR*: 1.978, 95% *CI*: 1.258–3.794), postpartum hemorrhage (*OR*: 2.276, 95% *CI*: 1.334–4.347) and intrauterine infection (*OR*: 2.575, 95% *CI*: 1.463–4.618) were independently associated with VTE during puerperium with adjustment for adherent placenta and fetal birth weight. The AUCs of D-dimer levels, Caprini score and their combination were 0.748 (*SE*: 0.030, 95% *CI*: 0.688–0.807), 0.647 (*SE*: 0.035, 95% *CI*: 0.578–0.716) and 0.840 (*SE*: 0.025, 95% *CI*: 0.791–0.888). Combination prediction had a higher AUC compared with that of independent prediction (0.840 *vs* 0.748, $Z=2.356$, $P=0.009$; 0.840 vs 0.647, $Z=4.487$, $P<0.001$) with a sensitivity of 83.9% and specificity of 80.3%.

Conclusion: The combination of the Caprini RAM and D-dimer could significantly elevate the predictive value for VTE during puerperium, and this new tool had the potential in the prediction of VTE during puerperium.

Keywords: venous thromboembolism, puerperium, caprini risk assessment model, D-dimer, prediction

Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a severe maternal complication around delivery.[1] Its incidence during pregnancy and puerperium is 1.0 to 1.8/1000,[2] significantly higher than that of nonpregnant women.[3–5] Although the absolute risk of VTE associated with pregnancy was low, it has gradually become one of the major causes of maternal death instead of postpartum hemorrhage.[6] Accurate prediction of VTE risk during pregnancy and puerperium is therefore crucial for its prevention and treatment.

The Caprini risk assessment model (RAM) has been extensively validated in VTE risk identification of different patients.[7–12] However, its application to VTE risk identification during peripartum showed a limited performance.[13]

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D-dimer levels upregulate gradually during pregnancy and peaked at the first day after delivery.[14] Most of healthy pregnant women demonstrate higher D-dimer levels compared with the normal reference range.[15] A recent study found that abnormally high levels of D-dimer (≥3.70 mg/L) was independently correlated with VTE during puerperium and could serve as an independent predictor.[16] Thus, the combination of the Caprini risk assessment model and D-dimer was used to predict VTE during puerperium in order to improve predictive performance in this study, and the aim was to provide a new tool for the prediction of VTE during puerperium.

Patients and Methods

Patients

This was a retrospective case–control study, including all puerperium patients with DVT or PE meeting inclusion and exclusion criteria in The First Affiliated Hospital of Shihezi University and Bingtuan Sishi Hospital between March 2012 and December 2022. The inclusion criteria included ①puerperium patients with DVT or PE, ②complete medical records, and ③having D-dimer testing results. The exclusion criteria included ①a previous history of VTE, ②superficial VTE, and ③other cardiovascular diseases or any malignant tumor. The diagnosis of PE was objectively confirmed with computed tomography pulmonary angiography, and the diagnosis of DVT was confirmed with Doppler ultrasound and/or computed tomographic (CT) venography.

Controls, defined as women without VTE during puerperium, were randomly sampled from women who had delivered in The First Affiliated Hospital of Shihezi University and Bingtuan Sishi Hospital between March 2012 and December 2022. They were matched to cases according to age, number of fetuses, birth day and delivery mode at the ratio of 9:1.

This study received the approval of the Ethics Committee of The First Affiliated Hospital of Shihezi University and was performed according to the guidelines of the Declaration of Helsinki, and all participants provided informed consents.

Data Collection

Demographic data, clinical data and laboratory parameters within postpartum 24 h were collected, including age, height, weight, gestational age at delivery, fetal birth weight, previous obstetric history, parity, in vitro fertilization, scarred uterus, placenta previa, adherent placenta, premature birth, postpartum hemorrhage, pregnancy complications, D-dimer, platelet, and fibrinogen.

Caprini score was evaluated for all participants before delivery and within postpartum 24 h, and the highest score was chosen in this study. Supplementary Table 1 provided the raw scores and D-dimer results of each of the patients who developed VTE. Supplementary Table 2 provided a complete list of all the questions that were asked and the number of positive and negative responses for each specific question in those with and without thrombosis.

Statistical Analysis

The SPSS version 22.0 (SPSS Inc., USA) was employed to conduct statistical analysis, and statistical significance was set at two-sided $P< 0.05$. Continuous variables were evaluated for normality using Kolmogorov–Smirnov test. Variables with normal distribution were compared for intergroup differences using Student's t test, and variables without normal distribution were compared for intergroup differences using Mann–Whitney U-test. Categorical variables were compared for intergroup differences using Chi-square test or Fisher exact test. Multivariate analysis, employing the forward stepwise model, was conducted for the variables with two-sided $P<0.10$ in univariate analysis. The predictive values of Caprini RAM, D-dimer and their combination were evaluated using receiver operating characteristic (ROC) curve, and the area under curve (AUC) was compared using Z test.

Results

Univariate Analysis Between the Case Group with Control Group

In this study, 31 puerperium patients with VTE were included according to the inclusion and exclusion criteria, and 279 puerperium women without VTE were matched to cases according to age, number of fetuses, birth day and delivery mode. Univariate analysis results (Table 1) demonstrated that there were significant differences in D-dimer levels,

Table 1 Univariate Analysis Results Between the Case Group with Control Group

Variables	Case Group (n=31)	Control Group (n=279)	χ^2/Z/t	P
BMI before delivery(Kg/m^2, mean±SD)	26.82±2.94	26.59±3.02	0.649	0.514
Gestational age at delivery(weeks, mean±SD)	37.78±1.92	38.06±2.17	−1.178	0.248
Fetal birth weight(g, mean±SD)	3084.53±551.76	3198.64±567.38	−1.715	0.091
Platelet(10^9/L, mean±SD)	176.54±40.61	184.19±49.68	−1.484	0.146
Fibrinogen(g/L, mean±SD)	4.55±0.92	4.62±0.83	0.651	0.513
D-dimer(mg/L, mean±SD)	5.24±2.06	3.69±1.71	6.543	<0.001
Caprini score	8(5, 10)	4(1, 6)	4.327	<0.001
Previous obstetric history				
0	17(54.8%)	156(55.9%)	0.013	0.909
≥1	14(45.2%)	123(44.1%)		
Parity				
1	28(90.3%)	263(94.3%)		0.419*
≥2	3(9.7%)	16(5.7%)		
IVF				
Yes	2(6.5%)	10(3.6%)		0.342*
No	29(93.5%)	269(96.4%)		
Scarred uterus				
Yes	13(41.9%)	67(24.0%)	4.680	0.031
No	18(50.1%)	212(76.0%)		
Placenta previa				
Yes	2(6.5%)	9(3.2%)		0.303*
No	29(93.5%)	270 (96.8%)		
Adherent placenta				
Yes	5(16.1%)	13(4.7%)		0.024*
No	26(83.9%)	266(95.3%)		
Premature birth				
Yes	4(12.9%)	31(11.1%)		0.765*
No	27(87.1%)	248 (88.9%)		
Postpartum hemorrhage				
Yes	5(16.1%)	11(3.9%)		0.014*
No	26(83.9%)	268 (96.1%)		
Gestational diabetes mellitus				
Yes	5(16.1%)	40(14.3%)		0.789*
No	26(83.9%)	239 (85.7%)		
Hypertensive disorders of pregnancy				
Yes	3(9.7%)	16(5.7%)		0.419*
No	28(90.3%)	263 (94.3%)		
Fetal distress				
Yes	5(16.1%)	50(17.9%)	0.061	0.804
No	26(83.9%)	229 (82.1%)		
Intrauterine infection				
Yes	3(9.7%)	4(1.4%)		0.024*
No	28(90.3%)	275(98.6%)		
Premature rupture of membranes				
Yes	8(25.8%)	62(22.2%)	0.205	0.651
No	23(74.2%)	217 (77.8%)		

Note: *Fisher exact test.
Abbreviations: IVF, in vitro fertilization; BMI, body mass index; SD, standard deviation.

Table 2 Multivariate Analysis Results Between the Case Group with Control Group

Variables	*β*	*SE*	Wald χ^2	OR	95% *CI*	*P*
D-dimer	0.415	0.176	7.378	1.754	1.237–3.182	<0.001
Caprini score	0.359	0.143	6.160	1.209	1.058–2.280	0.012
Intrauterine infection	0.378	0.161	5.371	2.575	1.463–4.618	0.023
Postpartum hemorrhage	0.247	0.092	4.639	2.276	1.334–4.347	0.038
Scarred uterus	0.196	0.074	4.492	1.978	1.258–3.794	0.040
Adherent placenta	0.213	0.087	1.754	2.012	0.775–4.129	0.191
Fetal birth weight	0.162	0.069	0.315	1.014	0.583–1.030	0.617

Abbreviations: β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

Caprini score, scarred uterus, adherent placenta, postpartum hemorrhage and intrauterine infection between the case and control group ($P< 0.05$), and there were no significant differences in the rest variables ($P > 0.05$).

Multivariate Analysis Between the Case Group with Control Group

Multivariate analysis was conducted for D-dimer levels, Caprini score, scarred uterus, adherent placenta, postpartum hemorrhage, intrauterine infection and fetal birth weight. The results demonstrated that D-dimer levels, Caprini score, scarred uterus, postpartum hemorrhage and intrauterine infection were independently associated with VTE during puerperium with adjustment for adherent placenta and fetal birth weight (Table 2).

Predictive Value for VTE During Puerperium

As shown in Figure 1, the AUC of D-dimer levels was 0.748 (*SE*: 0.030, 95% *CI*: 0.688–0.807) when applied in predicting VTE during puerperium and Caprini score was 0.647 (*SE*: 0.035, 95% *CI*: 0.578–0.716). In order to elevate

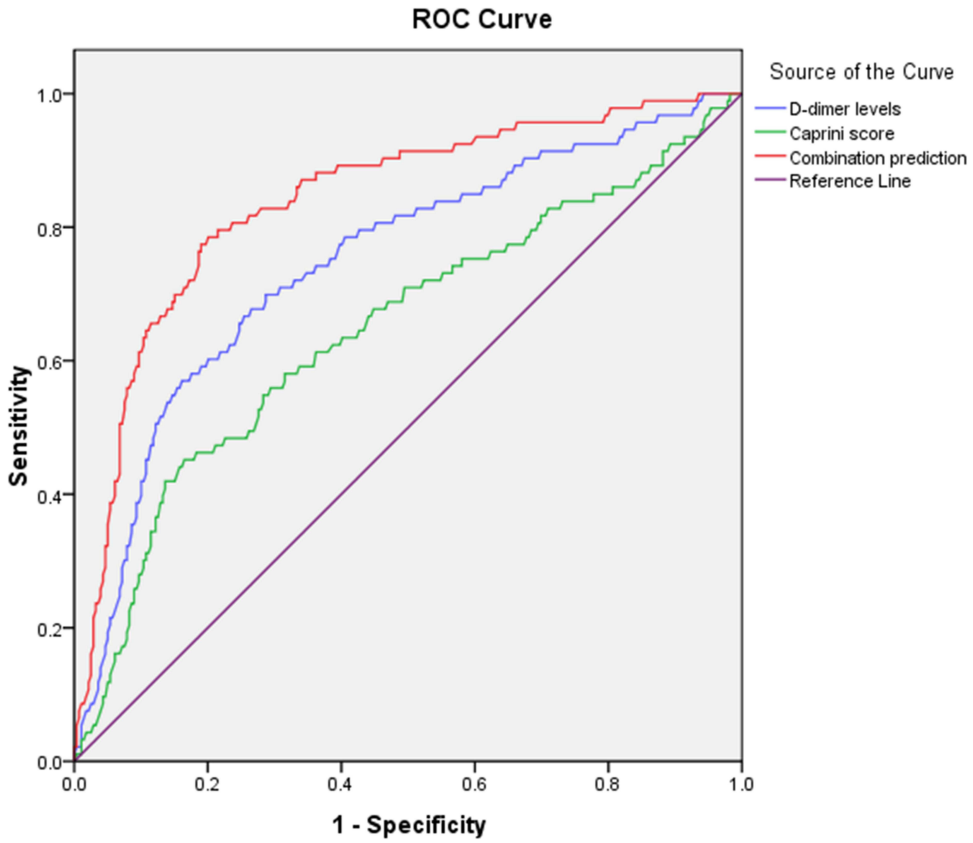

Figure 1 ROC curves of D-dimer levels, Caprini score and their combination in predicting VTE during puerperium.
Abbreviations: ROC, receiver-operating characteristic; VTE, venous thromboembolism.

Table 3 Clinical Utility Indexes of D-Dimer Levels, Caprini Score and Combination Prediction for VTE During Puerperium

	Best Cut-Off	Sensitivity	Specificity	Accuracy	FPR	FNR	PPV	NPV	Youden Index
D-dimer	4.02 mg/L	71.0%	74.2%	73.9%	76.6%	4.2%	23.4%	95.8%	0.45
Caprini score	6	67.7%	59.1%	60.0%	84.4%	5.7%	15.6%	94.3%	0.27
Combination prediction		83.9%	80.3%	80.6%	67.9%	2.2%	32.1%	97.8%	0.64

Abbreviations: VTE, venous thromboembolism; FPR, false-positive rate; FNR, false negative rate; PPV, positive predictive value; NPV, negative predictive value.

the predictive value for VTE during puerperium, the combination of D-dimer levels and Caprini score was used in this study. The results showed that the AUC of combination prediction was up to 0.840 (*SE*: 0.025, 95% *CI*: 0.791–0.888), which was significantly higher than that of independent prediction (0.840 vs 0.748, Z=2.356, P=0.009; 0.840 vs 0.647, Z=4.487, P<0.001). Clinical utility indexes of D-dimer levels, Caprini score and combination prediction for VTE during puerperium are shown in Table 3.

Discussion

Originally, the Caprini RAM was developed for assessing thrombosis risk in both surgical and medical patients.[17] Although many reports have demonstrated its validity in identifying VTE risk among surgical patients,[7–12] its performance in identifying VTE risk during peripartum was limited.[13] Tran et al showed that the Caprini RAM would define a large proportion of pregnant women as high VTE risk during peripartum and was correlated with high the number needed to treat,[13] and the limitation of this study was a small sample size of VTE patients with only three. In our study, 31 women who experienced a VTE event during puerperium were retrospectively enrolled. Through a relatively large sample size, we confirmed that the Caprini RAM was independently associated with VTE during puerperium. We also evaluated the predictive value of the Caprini RAM for VTE during puerperium using the ROC curve, and the results showed that its predictive value was low with an AUC of less than 0.700.

In order to elevate the predictive value for VTE during puerperium, we combined the Caprini RAM with D-dimer for the prediction of VTE during puerperium. As the product of cross-linked fibrin degradation, D-dimer mainly reflects the global coagulation activation and fibrinolysis. D-dimer is one of the most accurate and reliable biomarkers, and the elevation of D-dimer levels has been confirmed an association with the increased risk of VTE.[18–20] The American College of Chest Physicians has recommended that D-dimer can be applied in predicting VTE.[21]

Studies on non-pregnant women have demonstrated that the negative predictive value (NPV) of D-dimer is helpful when employed to exclude PE through the combination with a low Wells score.[22–25] D-dimer levels upregulate gradually during pregnancy and peaked at the first day after delivery,[14] and most of healthy pregnant women demonstrate higher D-dimer levels compared with the normal reference range.[15] Therefore, the "normal range" of non-pregnant women cannot be appropriate for pregnant women.[26,27]

The role of D-dimer in the prediction of VTE associated with pregnancy is still controversial. Hedengran et al demonstrated that the D-dimer level fluctuated by more than 50% among healthy pregnant women, and thus concluded that it might not be valuable for the prediction of VTE during pregnancy.[27] Damodaram et al demonstrated that the sensitivity and specificity of D-dimer in predicting suspected PE among pregnant women was 73% and 15%, respectively, and the negative likelihood ratio was up to 1.8.[28] Therefore, they suggested that a negative D-dimer result should not be used to exclude the diagnosis of PE among pregnant women. O'Connor et al showed that D-dimer was significantly less effective than the modified Wells score in prediction of PE.[29] Hassanin et al showed that the sensitivity of D-dimer for the prediction of PE among postpartum women with symptoms suggestive of PE was up to 100.0%.[30] Hu et al showed that D-dimer ≥3.70 mg/L was independently associated with VTE during puerperium, and the sensitivity and specificity of D-dimer for the prediction of VTE were 73.7% and 75.5%, respectively.[16] These previous studies have been limited by small sample sizes. Our results were consistent with Hu et al. Furthermore, we evaluated the predictive value of the combination of the Caprini RAM and D-dimer for VTE during puerperium, and the ROC curves showed that the AUC of combination prediction was 0.840, significantly higher than individual prediction. The sensitivity and specificity of combination prediction were 83.9% and 80.3%, respectively. Therefore, the combination of the Caprini

RAM and D-dimer could significantly elevate the predictive value for VTE during puerperium, and this new tool had the potential in the prediction of VTE during puerperium.

The main limitation of our study was that the study group represented a highly selected population because we excluded the patients with a history of DVT, superficial venous thrombosis, other cardiovascular diseases or tumors. These excluded complications are quite important in calculating a proper Caprini score and often these questions are not asked in clinical practice. Additionally, our sample size was still small for puerperium patients with VTE, although it was greater than those of previous studies.

Conclusion

The combination of the Caprini RAM and D-dimer could significantly elevate the predictive value for VTE during puerperium, and this new tool had the potential in the prediction of VTE during puerperium.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; agreed on the journal to which the article will be submitted; and agreed to be accountable for all aspects of the work.

Disclosure

All the authors do not have any conflict of interest.

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