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Predictive score for postpartum hemorrhage in vaginal deliveries following frozen embryo transfer

Dondurulmuş embriyo transferini takiben vajinal doğumlarda postpartum kanama için tahmin skoru

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Abstract

Objective: To develop a predictive score for life-threatening severe postpartum hemorrhage in vaginal deliveries following frozen embryo transfer.

Materials and Methods: We conducted a retrospective cohort study of 315 singleton vaginal deliveries following frozen embryo transfer from 2017 to 2022. Severe postpartum hemorrhage was defined as hemorrhage exceeding 1500 mL. A predictive score was generated from maternal characteristics and obstetric complications before delivery. We performed multivariable logistic regression analysis using 2017-2020 data and assigned points to identified risk factors. The predictive score's accuracy was evaluated using 2021-2022 data.

Results: A large baby (birth weight ≥3500 g), pre-delivery maternal body mass index ≥25 kg/m^2, marginal or velamentous umbilical cord insertion, and history of postpartum hemorrhage were identified as risk factors. We assigned one point to a large baby, a pre-delivery maternal body mass index ≥25 kg/m^2, and marginal or velamentous umbilical cord insertion, and two points to a history of postpartum hemorrhage. The sum of the points was defined as the predictive score. The cut-off was set at two points, with a score ≥2 points being the high-risk group and a score ≤1 point being the low-risk group. The predictive score demonstrated a sensitivity of 47.8%, specificity of 85.4%, positive predictive value of 45.8%, and negative predictive value of 86.4% in the 2021-2022 validation cohort.

Conclusion: The predictive score identified severe postpartum hemorrhage in approximately half of the high-risk cases. Implementing measures such as autologous blood storage may facilitate rapid response during heavy bleeding and improve maternal prognosis.

Keywords: Postpartum hemorrhage, reproductive techniques, assisted, embryo transfer, risk factors

Öz

Amaç: Bu çalışmanın amacı dondurulmuş embriyo transferini takiben vajinal doğumlarda yaşamı tehdit eden ciddi pospartum kanama için öngörücü bir skor geliştirmektir.

Gereç ve Yöntemler: 2017'den 2022'ye kadar donmuş embriyo transferini takiben 315 tekil vajinal doğumun dahil edildiği retrospektif bir kohort çalışması gerçekleştirdik. Postpartum ciddi kanama, 1,500 mL'yi aşan kanama olarak tanımlandı. Doğumdan önce annenin özelliklerinden ve obstetrik komplikasyonlardan tahmin skoru oluşturuldu. 2017-2020 verilerini kullanarak çok değişkenli lojistik regresyon analizi yaptık ve belirlenen risk faktörlerine puan verdik. Tahmin puanının doğruluğu 2021-2022 verileri kullanılarak değerlendirildi.

Bulgular: Bebeğin iri olması (doğum ağırlığı ≥3,500 g), doğum öncesi annenin vücut kitle indeksinin ≥25 kg/m^2 olması, marjinal veya velamentöz göbek kordonu takılması ve postpartum kanama öyküsünün olması risk faktörleri olarak belirlendi. İri bebeğe, doğum öncesi annenin vücut kitle indeksinin ≥25 kg/m^2 olmasına ve marjinal veya velamentöz göbek kordonu takılmasına birer puan, postpartum kanama öyküsüne ise iki puan verdik. Puanların toplamı tahmin puanı olarak tanımlandı. Kesme noktası olarak iki puan olarak belirlendi ve alınan puana göre iki grup oluşturuldu: ≥2 puan yüksek riskli grup, ≤1 puan ise düşük riskli grup. Tahmin skoru, 2021-2022 doğrulama kohortunda %47,8 duyarlılık, %85,4 özgüllük, %45,8 pozitif prediktif değer ve %86,4 negatif prediktif değer gösterdi.

PRECIS: This study developed a score predicting over 1500 mL hemorrhage in vaginal deliveries after frozen embryo transfer with 47.8% sensitivity and 45.8% positive predictive value.

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Sonuç: Tahmin skoru, yüksek riskli olguların yaklaşık yarısında şiddetli postpartum kanamayı öngörebildi. Otolog kan depolama gibi önlemlerin uygulanması, ağır kanama sırasında hızlı müdahaleyi kolaylaştırabilir ve annenin prognozunu iyileştirebilir.

Anahtar Kelimeler: Postpartum kanama, üreme teknikleri, yardımlı, embriyo transferi, risk faktörleri

Introduction

Postpartum hemorrhage (PPH) is a significant global health concern because severe PPH remains one of the primary causes of maternal mortality[1-3]. Timely intervention is crucialbecause a delayed response can lead to increased mortality rates[4]. By predicting severe PPH in advance, appropriate preparations can be made, such as autologous blood storage.

Although developed countries have observed a decline in severe PPH-related maternal deaths, the overall incidence of PPH is reportedly on the rise[5,6]. This increase has been attributed to the growing number of pregnant women with PPH risk factors, including advanced maternal age, nulliparity, placenta previa, placenta accreta spectrum, and pregnancies achieved by assisted reproductive technology (ART)[7-14]. Several studies have examined the relationship between ART and PPH, with some focusing on the incidence of PPH in frozen embryo transfers compared with fresh embryo transfers[13,14].

Our previous research uncovered a notably high incidence of PPH in vaginal deliveries resulting from pregnancies achieved by frozen embryo transfer[15]. In that study, PPH in vaginal deliveries of singleton fetuses was defined as blood loss of 800 mL or more, based on the 90th percentile of blood loss[15]. Approximately half of the vaginal deliveries following frozen embryo transfers met this definition although blood loss of 800 mL rarely necessitates special intervention. Predicting transfusion-requiring blood loss could improve maternal outcomes.

To date, while research has been conducted to assess PPH risk using three-tiered systems, such as the California Maternal Quality Care Collaborative (CMQCC) admission hemorrhage risk score, there has been limited investigation into predictive scores specifically for severe PPH[16]. In this study, we aimed to develop a predictive score capable of identifying a high-risk population, namely those at risk of experiencing hemorrhage of 1500 mL or more in singleton vaginal deliveries following frozen embryo transfer.

Materials and Methods

Data Extraction

We conducted a retrospective cohort study using data from women who underwent vaginal delivery following pregnancies achieved by frozen embryo transfer. This included both embryo transfers in a natural cycle and those in a hormone replacement therapy cycle. Data were collected from delivery records at Kitano Hospital between January 1, 2017, and December 31, 2022. The hospital serves as a regional perinatal center, with approximately 700 deliveries annually and a cesarean section rate of approximately 25%. All singleton pregnancies achieved using the aforementioned methods and delivered vaginally after 22 weeks of gestation were included in the study, totaling 315 cases.

Outcome Definition

Severe PPH was defined as hemorrhage exceeding 1500 mL, which corresponds to stage 3 of the CMQCC staging system[16]. The actual amount of blood loss during vaginal delivery was determined by collecting blood with gauze immediately after delivery of the baby until 2 h post-placenta delivery and subsequently measuring the weight of the gauze.

Selection and Definition of Potential Risk Factors

A literature review and hypothesis generation guided the selection of potential risk factors for severe PPH, which were then subjected to statistical analysis. Factors known or predictable before delivery included large baby (birth weight over 3500 g), gestational diabetes mellitus or overt diabetes mellitus during pregnancy, hypertensive disorder of pregnancy, complication of leiomyoma, marginal or velamentous umbilical cord insertion, body mass index (BMI) of 25 kg/m^2 or higher just before delivery, advanced maternal age (over 35), history of uterine surgery, nulliparity, and history of PPH. Additional complications, such as clinical chorioamnionitis, premature rupture of the membrane, induction of labor, and placenta accreta spectrum (PAS), were also considered but excluded from predictive score calculations because they were only known immediately before or after delivery.

In relation to the term "large baby", macrosomia is traditionally defined as a birth weight over 4000 g. However, there has been a notable decline in birth weight in Japan in recent years[17]. Consistent with this trend, our study data revealed a limited number of cases that met the standard definition of macrosomia. To effectively identify cases with an elevated risk of severe PPH, we established a criterion for "large baby" as a birth weight over 3500 g.

Consistent with our prior study, a history of PPH was defined as a previous hemorrhage exceeding the 90th percentile of blood loss per mode of delivery and number of fetuses, according to the Perinatal Committee of the Japanese Society of Obstetrics and Gynecology report[18]. The 90th percentile of blood loss for vaginal delivery was 800 mL for singleton and 1500 mL for twin deliveries. No cases of vaginal birth after cesarean section were recorded. In instances where previous deliveries occurred at other hospital and blood loss data were unavailable, histories of PPH were assumed to exist when blood transfusions were performed. PAS cases included those clinically or pathologically diagnosed.

Ethical Considerations

The study received approval from the Ethics Committee of Kitano Hospital (date: 5/16/2023, number: 2205005) and was conducted in adherence to the Declaration of Helsinki and other pertinent Japanese laws and regulations. Written informed consent was obtained.

Statistical Analysis

Statistical analyses were performed using R version 4.1.1 and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[19]. EZR is a modified version of the R commander, specifically designed to incorporate frequently used biostatistical functions.

Initially, maternal characteristics and obstetric complications were stratified by the presence or absence of severe PPH in the 2017-2020 and 2021-2022 datasets, respectively. Subsequently, using the 2017-2020 dataset from our previous study, a multivariate logistic regression analysis was conducted with potential risk factors to predict severe PPH before delivery. Variables were meticulously selected on the basis of analysis results and clinical relevance. The selected risk factors were assigned points according to their odd ratios, and a predictive score was calculated.

The accuracy of the score in predicting severe PPH was first assessed in the 2017-2020 dataset, and its predictive accuracy was then validated using the 2021-2022 dataset.

We used the strengthening the reporting of observational studies in epidemiology statement in reporting this study[20].

Results

First, maternal characteristics and obstetric complications were stratified by the presence or absence of severe PPH in the 2017-2020 and 2021-2022 datasets, respectively. The incidence of severe PPH was 15.3% in the 2017-2020 data and 20.5% in the 2021-2022 data. Although p-values were not calculated to avoid multiple testing, a trend emerged where cases with severe PPH in both the 2017-2020 and 2021-2022 datasets were more likely to have a large baby, marginal or velamentous insertion of the umbilical cord, a pre-delivery maternal BMI over 25, and a history of PPH (Table 1).

The patient analysis flow is depicted in Figure 1. A multivariate logistic regression analysis was conducted on the 2017-2020 data, focusing on factors known or predictable before delivery to identify risk factors for severe PPH (Table 2). Consistent with the univariate analysis, a large baby, marginal or velamentous insertion of the umbilical cord, pre-delivery maternal BMI over 25, and history of PPH appeared to correlate with severe PPH. Considering the odds ratio, we assigned two points to the history of PPH and one point to the other factors. The predictive score was defined as the sum of these points. To ensure robustness, we also performed a multivariate logistic regression analysis for all cases in the 2017-2022 period, which revealed the same trend as the 2017-2020 data (Supplementary Table 1).

The distribution of the predictive score in the 2017-2020 cohort is shown in Table 3. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.713. The cut-off was set at two points, with a score ≥2 points being the high-risk group and a score ≤1 point being the low-risk group. Sensitivity was 46.4%, specificity was 89.0%, positive predictive value was 43.2%, and negative predictive value was 90.2%.

Table 1. Background characteristics and complications of eligible patients

	2017-2020		2021-2022	
	Severe PPH Yes (n=31)	No (n=172)	Severe PPH Yes (n=23)	No (n=89)
Large baby, n (%)	10 (32.3)	26 (15.1)	7 (30.4)	12 (13.5)
GDM, n (%)	2 (6.5)	12 (7.0)	2 (8.7)	5 (5.6)
HDP, n (%)	2 (6.5)	7 (4.1)	3 (13.0)	5 (5.6)
ICSI, n (%)	15 (48.4)	79 (45.9)	12 (52.2)	57 (64.0)
Complication of leiomyoma, n (%)	6 (19.4)	21 (12.2)	2 (8.7)	10 (11.2)
Marginal cord insertion, n (%)	7 (25.0)	19 (11.0)	6 (26.1)	10 (11.2)
Advanced maternal age, n (%)	23 (74.2)	130 (75.6)	17 (73.9)	68 (76.4)
History of PPH, n (%)	3 (9.7)	1 (0.6)	6 (26.1)	8 (9.0)
History of uterine surgery, n (%)	3 (9.7)	15 (8.7)	6 (26.1)	22 (24.7)
Nulliparity, n (%)	19 (61.3)	116 (67.4)	15 (65.2)	58 (65.2)
Induction of labor, n (%)	22 (71.0)	90 (52.3)	18 (78.3)	45 (50.6)
Placenta accreta spectrum, n (%)	11 (35.5)	3 (1.7)	8 (34.8)	3 (3.4)
Pre-delivery maternal BMI ≥25, n (%)	18 (58.1)	55 (32.0)	14 (60.9)	30 (33.7)
PROM, n (%)	10 (33.3)	67 (39.0)	9 (39.1)	25 (28.1)

GDM: Gestational diabetes mellitus, HDP: Hypertensive disorder of pregnancy, ICSI: Intracytoplasmic sperm injection, PPH: Postpartum hemorrhage, BMI: Body mass index, PROM: Premature rupture of membranes, Large baby: Birth weight ≥3500 g, GDM: Gestational diabetes mellitus or overt diabetes mellitus during pregnancy, Marginal cord insertion: Marginal or velamentous insertion of the umbilical cord, Advanced maternal age: ≥35 years old at the time of delivery, History of PPH: ≥800 mL for singleton vaginal delivery or ≥1500 mL for twins

The accuracy of the predictive scores was validated using the 2021-2022 data, yielding the following results (Table 4). The distribution of the predictive score was similar to that of the 2017-2020 data. The AUC of the ROC curve was 0.751, with a sensitivity of 47.8%, specificity of 85.4%, positive predictive value of 45.8%, and negative predictive value of 86.4%.

The distribution of hemorrhage according to the predictive score was expressed as a box and whisker plot for the 2017-2020 and 2021-2022 datasets, respectively (Figure 2). In each dataset, the high-risk group with a score of two or more tended to have a larger bleeding volume. However, even in the low-risk group with a score of 0 or 1, there were often outliers with a substantial amount of bleeding.

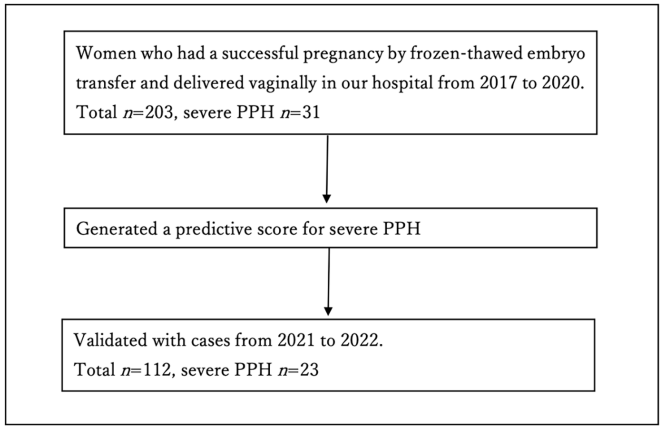

Figure 1. Patient analysis flow chart. Patients were analyzed as this flow

PPH: Postpartum hemorrhage

Discussion

We found that cases of severe PPH were more likely to have a large baby, marginal or velamentous insertion of the umbilical cord, pre-delivery maternal BMI over 25, and a history of PPH, with these associations remaining after adjusting for other factors. A predictive score was developed and validated using a validation cohort, achieving a sensitivity of 47.8% and a positive predictive value of 45.8%.

In our study population, 17.1% of singleton vaginal deliveries following frozen-thawed embryo transfer experienced hemorrhages of 1500 mL or more. The incidence of obstetrical hemorrhage is 13.6% in populations classified as high-risk according to the CMQCC score[21]. In that study, obstetrical hemorrhage was defined as bleeding of 1000 mL or more, regardless of the mode of delivery, according to the American College of Obstetricians and Gynecologists definition. This demonstrates how high-risk the population in our study is, specifically those who achieved pregnancy through frozen-thawed embryo transfer and underwent vaginal delivery. By developing a predictive score within this high-risk population, we achieved a higher positive predictive value for severe PPH occurrence than previously reported.

In addition to the report that frozen-thawed embryo transfers increase PAS, our previous study indicated that minor placental adhesions not diagnosed as PAS may also increase[15,22]. These factors may have contributed to the unusually high incidence of severe PPH in our study population. Patients with a predictive score of two or higher have approximately a 50% risk of experiencing severe PPH, suggesting that precautions such as advanced autologous blood storage should be considered.

Table 2. Risk factors for severe PPH result of multivariable logistic regression analysis with 2017-2020 data and development of the predictive score

Risk factor	Odds ratio	95% CI	p-value	Points
Complication of leiomyoma	1.30	0.38-4.48	0.67	0
Advanced maternal age	0.63	0.21-1.89	0.41	0
GDM	0.90	0.15-5.61	0.91	0
HDP	1.34	0.19-9.39	0.77	0
History of PPH	16.10	1.16-223.00	0.04	2
History of uterine surgery	0.68	0.11-4.05	0.67	0
ICSI	0.94	0.38-2.31	0.89	0
Large baby	2.84	1.02-7.93	0.05	1
Marginal cord insertion	3.33	1.11-10.00	0.03	1
Nulliparity	0.85	0.31-2.33	0.75	0
Pre-delivery maternal BMI ≥25	2.53	0.97-6.61	0.06	1

Predictive score: The sum of the points, GDM: Gestational diabetes mellitus, HDP: Hypertensive disorder of pregnancy, ICSI: Intracytoplasmic sperm injection, PPH: Postpartum hemorrhage, BMI: Body mass index, Large baby: Birth weight ≥3500 g, GDM: Gestational diabetes mellitus or overt diabetes mellitus during pregnancy, Marginal cord insertion: Marginal or velamentous insertion of the umbilical cord, Advanced maternal age: ≥35 years old at the time of delivery, History of PPH: ≥800 mL for singleton vaginal delivery or ≥1500 mL for twins

Table 3. Relationship between predictive score and severe PPH with 2017-2020 data

Predictive score	Severe PPH Yes (n=31)	No (n=172)
0	7	90
1	8	63
2	9	18
3	3	1
4	1	0
5	0	0

AUC of ROC curve: 0.713 (0.602-0.823)
When two points are cut-off;
Sensitivity: 0.464
Specificity: 0.890
Positive predictive value: 0.432
Negative predictive value: 0.902
PPH: Postpartum hemorrhage, AUC: Area under the curve, ROC: Receiver operating characteristic

Table 4. Validation of the predictive score with 2021-2022 data

Predictive score	Severe PPH Yes (n=23)	No (n=89)
0	2	41
1	10	35
2	6	7
3	3	5
4	2	1
5	0	0

AUC of ROC curve: 0.751 (0.65-0.852)
When two points are cut-off;
Sensitivity: 0.478
Specificity: 0.854
Positive predictive value: 0.458
Negative predictive value: 0.864
PPH: Postpartum hemorrhage, AUC: Area under the curve, ROC: Receiver operating characteristic

Study Limitations

Although this predictive score does provide some indication of severe PPH occurrence, it failed to predict over half of the cases that developed into severe PPH. In addition to the risk factors incorporated in this predictive score, other risk factors for PPH known before delivery, such as nulliparity, hypertensive disorder of pregnancy, and advanced maternal age, have been reported[7-9]. Although this was a single-center study, conducting a larger, multicenter study to incorporate these factors into a more comprehensive predictive score may enable more accurate prediction.

This study focused on cases of pregnancies achieved by frozen-thawed embryo transfer with a high probability of severe PPH. However, severe PPH can also occur in natural pregnancies. Future research should develop a prediction score for severe PPH without limiting the study population.

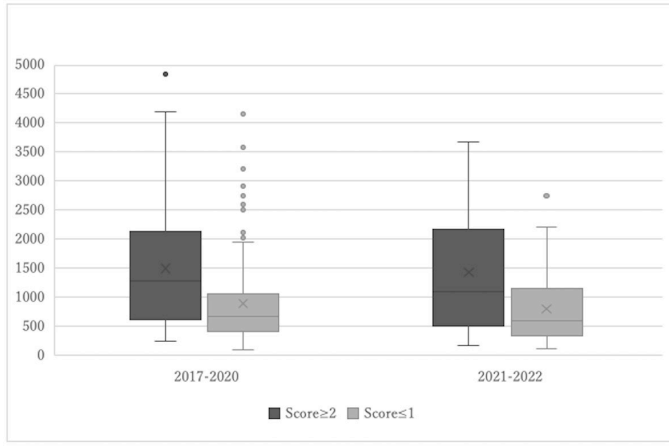

Figure 2. Distribution of hemorrhage by predictive score. Both the 2017-2020 data and the 2021-2022 validation cohort showed a trend toward more bleeding in the high-risk group with a predictive score ≥2 points

Conclusion

In cases of vaginal deliveries following pregnancies achieved by frozen-thawed embryo transfer, nearly half of the patients with a risk score of two or higher experienced severe PPH. Consequently, we recommend that patients with a risk score of two or higher undergo advanced autologous blood storage. Future large-scale, multicenter studies could develop a more generalized risk score for severe PPH, contributing to safer delivery practices.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee of Kitano Hospital (date: 5/16/2023, number: 2205005) and was conducted in adherence to the Declaration of Helsinki and other pertinent Japanese laws and regulations.

Informed Consent: Written informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., A.O., A.A., Y.K., A.M., Y.Ko., K.S., Y.Y., T.H., Concept: A.Y., A.O., T.H., Design: A.Y., A.O., T.H., Data Collection or Processing: A.Y., A.A., Y.K., Analysis or Interpretation: A.Y., A.M., Y.Ko., K.S., Y.Y., T.H., Literature Search: A.Y., A.O., T.H., Writing: A.Y.

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Supplementary Table 1. Result of multivariable logistic regression analysis with 2017-2022 data

Risk factor	Odds ratio	95% CI	p-value
Complication of leiomyoma	1.08	0.42-2.75	0.87
Advanced maternal age	0.72	0.34-1.54	0.39
GDM	0.86	0.25-2.96	0.81
HDP	1.81	0.54-6.07	0.33
History of PPH	6.35	1.95-20.60	<0.01
History of uterine surgery	1.11	0.44-2.76	0.83
ICSI	0.87	0.46-1.67	0.68
Large baby	3.06	1.46-6.42	<0.01
Marginal cord insertion	3.23	1.43-7.29	<0.01
Nulliparity	1.42	0.64-3.14	0.38
Pre-delivery maternal BMI ≥25	2.61	1.34-5.10	<0.01

GDM: Gestational diabetes mellitus, HDP: Hypertensive disorder of pregnancy, ICSI: Intracytoplasmic sperm injection, PPH: Postpartum hemorrhage, BMI: Body mass index, Large baby: Birth weight ≥3500 g, GDM: Gestational diabetes mellitus or overt diabetes mellitus during pregnancy, Marginal cord insertion: Marginal or velamentous insertion of the umbilical cord, Advanced maternal age: ≥35 years old at the time of delivery, History of PPH: ≥800 mL for singleton vaginal delivery or ≥1500 mL for twins