Prediction of Clinical Outcomes in Women with Placenta Accreta Spectrum Using Machine Learning Models: An International Multicenter Study

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Abstract

Objective: To establish a prediction model of clinical outcomes in women with placenta accreta spectrum (PAS) Design: Retrospective cohort study Setting: International multicenter study (PAS-ID); 11 centers from 9 countries Population: Women

who were diagnosed with PAS and were managed in recruiting centers between January 1st, 2010 and December 31st, 2019. Methods: Data were collected using a standardized sheet, which included baseline information, medical and obstetric history, diagnosis, disease characteristics, management, and outcomes. Analysis of association between these variables and primary outcome was first conducted using conventional logistic regression. Data were reanalyzed using machine learning (ML) models, and 2 models were created to predict outcomes using antepartum and perioperative features. Main Outcome Measures: Massive PAS-associated perioperative blood loss (intraoperative blood loss [?] 2500 ml, triggering massive transfusion protocol, or complicated by disseminated intravascular coagulopathy). Other outcomes include prolonged hospitalization $>$ 7 days and admission to intensive care unit (ICU). Results: 727 women with PAS were included. Area under curve (AUC) for ML antepartum prediction model was 0.84, 0.81, and 0.82 for massive blood loss, prolonged hospitalization, and admission to ICU, respectively. Significant contributors to this model were parity, placental site, method of diagnosis and antepartum hemoglobin. Combing baseline and perioperative variables, ML model performed at 0.86, 0.90, and 0.86 for study outcomes, respectively. This model was most contributed by ethnicity, pelvic invasion, and uterine incision. Conclusions: ML models may be used to calculate individualized risk of morbidity in women with PAS, which may assist to outline management plan in priori

Introduction

Placenta accreta spectrum (PAS) refers to a group of placentation disorders that are characterized by trophoblastic invasion beyond the physiologic decidual–myometrial junction zone (1). PAS is identified as one of the most serious pregnancy-related disorders because it is associated with substantial risk of massive obstetric hemorrhage, blood transfusion, surgical injuries, and thereby high risk of maternal intensive care unit (ICU) admission, reoperation, and prolonged hospitalization (2). Unfortunately, burden of PAS morbidity has been significantly aggravated as a result of the rising trend of cesarean section delivery (CS) among contemporary population (2).

To date, the most widely supported approach in management is PAS is cesarean hysterectomy without trying to separate placenta (placenta in-situ) (3). Although this approach may be associated with improved maternal outcomes, uterine preservation is routinely offered as an alternative or even considered as the primary approach in several regions of the world (4). Interventional radiology (IR) is another option that may reduce peripartum bleeding regardless of management approach (5). Despite being widely adopted, uterine preserving procedures are generally not robustly supported by evidence and data on clinical outcomes of these procedures are limited (6). Given the seriousness of PAS and presence of several proposed interventions, calculation of individualized probability of intrapartum and postpartum serious morbidity based on patient demographics, disease characteristics, and different treatment options may facilitate treatment decision and proper use of resources.

Machine learning (ML) is a subset of artificial intelligence, where a computer gains cumulative experience from an existing database, to be capable of making accurate predictions of studied outcomes (7). Generally, ML may provide more accurate prediction, reveal more complex relations between features and outcomes, and provide a scalable and readily applicable clinical tool compared to traditional statistics (7). The current study presents an international multicenter center of women with PAS who were managed conservatively or by cesarean hysterectomy. The study aimed at creating antepartum and peripartum prediction models of peripartum clinical outcomes, using ML technology, to enhance decision making with regard to PAS.

Materials and methods

Study Population The "Placenta Accreta Spectrum International Database (PAS-ID)" is an international database that was launched by Middle-East Obstetrics and Gynaecology Graduate Education (MOGGE) Foundation to conduct the current study (ClinicalTrials.gov identifier: NCT04384510). The database was created on January 21st, 2020 and received contribution from a consortium of 11 tertiary centers located in 9 countries that represent 3 continents. These centers are referral centers for complex PAS cases and they all offer both cesarean hysterectomy and uterine preservation procedures. Data of all patients with PAS who were managed in these centers between January 1st, 2010 and December 31st, 2019 were retrospectively collected. Patients were considered eligible if they received clinical and histopathological diagnosis of PAS

and were managed, delivered, and followed-up for 6 weeks postpartum by their respective study site. Exclusion of candidates was made if relevant documented information and follow-up was deficient (e.g. single antenatal visit) or if no authorization to use anonymous patient data was provided for research purposes. Data were collected using a standardized spreadsheet, which included 57 variables that comprise patient baseline information *(e.g. age, parity, body mass index "BMI", ethnicity, smoking status)*, obstetric and gynaecologic data*(e.g. obstetric complications, previous CS, prior gynaecologic surgeries)*, medical history, antepartum and intrapartum disease characteristics *(e.g. PAS type, complete versus focal uterine wall invasion, bladder invasion, parametrial invasion, placental location)*, diagnosis *(antepartum versus intrapartum diagnosis, imaging modality, and gestational age at diagnosis)*, antepartum hemoglobin level, intraoperative details *(e.g. hysterectomy versus uterine preservation, uterus preserving procedures used either surgical or IR-related, success of uterine preservation, use of preoperative or intraoperative sonographic assessment, type of uterine incision and its relation to the placenta, intraoperative blood loss, transfused blood products, surgical complications)*, maternal outcomes *(success of uterine preservation, length of hospital stay, admission to intensive care unit [ICU], postoperative complications),* and neonatal outcome*(APGAR score at 1 and 5 minutes, admission to NICU, need for respiratory support, neonatal morbidity and mortality).* Data collection was completed on June 15^{th}, 2020. Institutional review board (IRB) approval was obtained from all participating centers. Study Outcomes Primary outcome of this study was massive PAS-associated blood loss, which we defined as intraoperative blood loss [?] 2500 ml, blood loss that required massive blood transfusion (transfusion of [?] 10 units of packed red blood cells [RBCs] within 24 hours), or blood loss that was complicated by intraoperative disseminated intravascular coagulopathy (DIC). Secondary outcomes included maternal admission to ICU and prolonged hospital stay (postpartum hospital stay for more than 7 days). Prediction models PAS-ID was used to establish an antepartum prediction model to calculate a score that presents probability of peripartum massive PAS-associated blood loss, admission to ICU and prolonged hospital stay. "MOGGE placenta accreta risk-antepartum score" or "MOGGE PAR-A score" aims at predicting these outcomes once PAS diagnosis is made antenatally. "MOGGE placenta accreta risk-peripartum score" or "MOGGE PAR-P score" is a second scoring system that was created to predict the same outcomes using baseline features in conjugation with disease- and surgery-related peripartum variables. This score is designed to calculate probability of unfavorable outcomes of a management strategy and clinical scenario(s) in priori, and would, thereby, assist designation of management. Statistical analysis *Conventional statistics* Variables were described as means and standard deviations for continuous variables, and numbers (percentages) for categorical variables. Missing data were generally less than 5% in all variables. For reason of comparison, a prediction model of the primary outcome was created using conventional statistics. Data were randomly split into a model development group and model validation group in a 4:1 ratio. Within model development group, each independent variable was tested using univariable logistic regression. Results were expressed in unadjusted odds ratio (OR) and 95% confidence interval (CI). Variables that exhibited a p-value of less than 0.2 on univariable logistic regression were included in a multivariable logistic regression model and adjusted ORs (aORs) were calculated. The diagnostic performance of prediction model was evaluated using receiver operating characteristic (ROC) curve, which was applied to both model development and validation groups. Statistical analysis for this part was performed using STATA 16 software (StataCorp, College Station, TX).*ML prediction model* ML model was applied using python® programing language (Spyder 3.3.6) with Scikit-learn (ML library package) through Anaconda 3.0 platform. For purpose of training and validation, data were randomly assigned to a train set (0.8) and test set (0.2). The model was developed using the train set and was applied to the test set to assess internal validation. A 'train/test split' technique was considered over k-fold cross-validity because it is associated with unbiased performance regardless of sample size (8). A logistic regression algorithm with gradient descent was performed on a train set using L-BFGS solver with a maximum iteration set to 1000. Algorithms were all successfully converged at less than 10 iterations in all models. Each model was evaluated using Jaccard index, confusion matrix, weighted precision, recall, F1 score, and log loss were calculated. A ROC curve was used to assess diagnostic performance of each model through the test set to assess model validity. Intercept value and coefficients of each model were used to calculate probability of the specific outcome. Range of calculated probability of each outcome among women who did and did not develop this outcome was graphed using a "box and whisker"

plot. The graph was created to provide a reference to facilitate interpretation of calculated probabilities in clinical setting.

Results

Baseline, disease and management characteristics A cohort of 797 patients was recruited in PAS-ID. Of those, 727 women were considered eligible for this current study based on adequate documentation of patient outcomes. Mean age of participants was 33.15 +- 4.93 years, mean parity was 2.20 +- 1.37, and mean BMI was 27.89 +- 4.50 kg/m^2. Prevalence of twin pregnancy was 2.6%. Pregnancy was complicated by gestational diabetes and hypertension in 8.6% and 7.1%, respectively. Participants reported history of obstetric dilation and curettage (D & C) in 26.92% and history of gynaecologic D & C in 14.96% of cases. The placenta was most commonly located centrally over the internal os (35.76%). Mean antepartum hemoglobin level was 11.04 +- 1.43 g/dl. Preoperative ultrasound was performed in 95.32% of cases and 4.13% underwent intraoperative ultrasound. Planned cesarean hysterectomy was performed in 18.7% of patients. Placenta accreta was encountered in 41.68%, followed by placenta increta (31.22%) and percreta (27.10%). Bladder invasion was present in 13.07% of cases. The most commonly performed uterine incision was low transverse (56.03%), followed by high transverse incision (27.88%). Delayed cord clamping was done in 16.69% of all deliveries. Incising through the placenta to deliver the fetus occurred in 28.75% of cases. Among women who were conservatively managed, the most commonly performed procedure was compression sutures (32.88%). Different modalities of IR were used in 9.42% of cases. Incidence of unintentional cystotomy was 10.18%. Patient characteristics, PAS characteristic and management details are summarized in Table 1. Primary and secondary outcomes Massive PAS-associated blood loss was reported in 17.74% of all cases. Mean estimated blood loss was 1786.33 +-1707.74 ml. Patients received a mean of 2.66 +- 4.91 of packed RBCs units, 1.37 +- 2.69 of fresh frozen plasma units, 1.42 +- 6.37 of cryoprecipitate and 0.81 +- 4.45 of platelet unites. Peripartum DIC manifested in 5.78% of patients. After delivery, 26% of all patients were admitted to the ICU. Mean length of hospital admission was 6.16 +- 6.36 days. Mean postoperative hemoglobin was 9.33 +- 1.75 g/dl (Table 1). Prediction model using conventional statistics Among prenatally-determined variables, maternal age (aOR 1.06; 95% CI, 1.001 – 1.12), ethnicity (aOR 0.09; 95% CI, 0.04 – 0.23), previous CS (aOR 5.65; 95% CI, 1.91 – 16.73 for previous 2 CSs), prior gynaecologic D & C (aOR 2.83, 95% CI, 1.37 – 5.80), antepartum hemoglobin level (aOR 0.75; 95% CI, 0.62 – 0.90), and intrauterine fetal death (aOR 6.40; 95% CI, 1.04 – 39.48) were significantly associated with risk of massive blood loss. AUC of antepartum model performance was 0.84 and 0.81 among development and validation groups, respectively (Table S1). Adding peripartum variables to the model, variables that exhibited significant association with massive blood loss included ethnicity (aOR 0.18; 95% CI, 0.05 – 0.67), Previous 2 CS (aOR 4.92; 95% CI, 1.34 – 18.05), prior gynaecologic D & C (aOR 4.58; 95% CI, 1.76 – 11.93), intrauterine fetal death (aOR 18.36; 95% CI, 1.68 – 200.73) and preoperative hemoglobin (aOR 0.75; 95% CI, 0.61 – 0.93). Significant intraoperative variables were placental bed sewing (aOR 0.17; 95% CI, 0.04 – 0.70), incising through the placenta (aOR 0.31, 95% CI, 0.14 – 0.69), IR (aOR 3.48; 95% CI, 1.23 – 9.78), complete placental invasion (aOR 3.92; 95% CI, 1.71 - 8.99), and bladder invasion (aOR 5.33; 95% CI, 2.27 – 12.50). AUC for this model was 0.91 for development group and 0.82 for validation group (Table S1). ML prediction models*Antepartum prediction model (MOGGE PAR-A score)*For PAS-associated massive blood loss, diagnostic accuracy of antepartum ML model was 0.84 for both train and test sets (Figure 1A). Model evaluation is summarized in Table 2. The most contributing factors to this model were parity (12%), previous CSs (12%), Asian ethnicity (12%), and centrally located placenta (9%). Size of contribution of baseline variables in this model is illustrated in Figure 2A. Median and interquartile range (IQR) of calculated probability was 13.0 (9.0 – 19.1) in women who did not have massive blood loss and 22.5 (16.3 – 32.5) in women with massive blood loss (Figure 3A). Antepartum ML model for prediction of prolonged hospitalization was associated with an AUC of 0.80 and 0.81 for train and test sets, respectively (Figure 1B). Asian ethnicity was the most influential variable to this model (14%), followed by central placenta (12%), anterior low placenta (10%), antepartum diagnosis using abdominal sonography and Doppler assessment (9%), and antepartum hemoglobin level (8%) (Figure 2B). Women who were hospitalized for $>$ 7 days had a median probability of 12.1 (8.6 – 18.6) compared to women who were hospitalized for a shorter duration (7.1 [4.9 - 10.0]) (Figure 3B). Diagnostic accuracy of antepartum ML prediction of maternal

ICU admission was 0.85 (train set) and 0.82 (test set) (Figure 1C). Major contributors to the model include European and Asian races (15% and 13%, respectively), central placenta (12%), posterior and anterior low placentas (7%), parity (5%), BMI [?] 30 (5%), previous CSs (5%), antepartum hemoglobin (5%) (Figure 2C). Women who were and were not admitted to ICU had a median probability of 27.6 (17.9 – 39.8) and 11.3 (7.1 – 17.6), respectively (Figure 3C).*Peripartum prediction model (MOGGE PAR-P score)* Peripartum prediction model of massive blood loss yielded an AUC of 0.88 and 0.86 for train and test tests, respectively (Figure 1D). Method of diagnosis of PAS presented a major contribution to this model, including whether ultrasound was combined with Doppler assessment (12%) or magnetic resonance imaging (MRI) (10%), or if diagnosis was first made intrapartum (7%). Other major variables are parametrial invasion (8%), and bladder invasion (5%) (Figure 2D). Median calculated probability among women who had massive blood loss was 27.4 (17.8 – 39.8) and 12.8 (9.4 – 18.3) in women with no massive bleeding (Figure 3D). Regarding prolonged hospitalization, AUC of peripartum model was 0.86 for the train and 0.90 for the test set (Figure 1E). Parametrial invasion contributed the most to this model (12%), followed by high transverse uterine incision (8%), intraoperative ultrasound (7%), bladder invasion (6%) (Figure 2E). Median probability in women who were admitted for longer than 7 days was 10.5 (7.4 – 16.4), while women who were admitted for shorter duration had a median of 6.3 (4.8 – 8.6) (Figure 3E). AUC peripartum prediction model of ICU admission was 0.88 and 0.86 for the train and test sets, respectively. The largest contribution comes from ethnicity (Asian [17%] and European [9%]), delayed cord clamping (7%), complete placental invasion (4%), and internal iliac artery ligation (4%) (Figure 2F). Calculated probability of admission to ICU in women who were or were not admitted to ICU was 11.4 (5.2 – 21.5) and 1.6 (0.5 – 5.2), respectively (Figure 3F).

Discussion

PAS-ID is a multicenter international database that includes data of 797 patients from 11 centers that present 9 countries from Europe, Asia and Africa. The current study was conducted to establish prediction models of different critical outcomes of PAS using emerging ML models. Two prediction models were created to determine risk of adverse maternal outcomes, namely massive PAS-associated peripartum blood loss, admission to ICU and prolonged hospitalization, using antepartum and peripartum inputs. Diagnostic performance of all models ranged between 0.80 and 0.90, which is defined as 'excellent' for a diagnostic test (9). Internal validity was demonstrated by consistency of diagnostic performance between train and test sets in all models.

Although PAS has been one of the most concerningly mounting obstetric complications in contemporary practice, evidence-based recommendations on management of PAS are limited and mostly represent level 3, 4 or good practice point recommendations (10). Cesarean hysterectomy seems to be the most acceptable approach whenever possible (3, 10). However, if cesarean hysterectomy is rejected by the patient, practice recommendations are generally less determinate. Of conservative options, leaving the placenta in situ was considered by the Royal College of Obstetricians and Gynaecologists (RCOG) in women who are highly motivated to preserve the uteri (10). This approach was considered investigational by the American College of Obstetricians and Gynaecologists (ACOG) and no recommendations were made in its regard (3). This practice does not seem to be prevalent though (4). Other uterine preserving techniques were less endorsed.

Nevertheless, management of PAS is globally diverse and is not enclosed by these recommendations (4). This may be attributed to paucity of data. Also, most data come from case reports and case studies that lack a study design and selection criteria, and likely reflect a single surgeon or team experience. Conduction of prospective studies, pilot studies, and clinical trials on management of PAS may be restricted by ethical considerations and recruitment difficulties and therefore, conclusions from large retrospective studies may present the first step to support future prospective studies and enhance evidence on current widely adopted management strategies.

To our knowledge, PAS-ID may present the first international multicenter database that investigates clinical outcomes of PAS in centers that offer both cesarean hysterectomy and conservative management. The database is one of the largest databases available on PAS in the literature and it conveys a wide range of practice. The current study applied ML algorithms, which tends to provide accurate prediction and

enclose complex and hidden relations between studied variables and outcomes. Although ML is generally used with large databases to permit model learning, current prediction models seem to perform better that traditional statistics and to yield consistent performance on untested data and excellent internal validity. Clinically, MOGGE PAR-A score can be used to determine high risk group, who may benefit from additional interventions (e.g. prophylactic IR procedures). Similarly, MOGGE PAR-P score may determine women in whom significant bleeding is anticipated. The score may be used to outline intraoperative management in priori, by calculating risk using different scenarios. Specifically, it may help to avoid unnecessary steps, which may not seem to lower risk of these outcomes (e.g. internal iliac artery ligation), to determine whether certain measurements may be helpful (e.g. preoperative or intraoperative ultrasound), and whether some intraoperative steps would be safe to do (e.g. delayed cord clamping).

The current study is limited by the retrospective nature of the study. Although the study was based on an international database, generalizability to some regions of the world, that were not represented in this data, cannot be determined. Although PAS-related research is associated with inherited risk of reflecting a specific team practice, our data were representative of management approaches that are widely recognizable in the literature. Complexity of ML models may present a barrier to their applicability. However, these calculations can be programmed into an application to facilitate their use in clinical practice. For this purpose, a simple tool (MOGGE PAR score, version 1.0) was created to enable use of these models and is available at (https://www.mogge-obgyn.com/clinical-studies) for research purposes (Figure S1).

In conclusion, utilization of ML algorithms may provide an individualized tool to determine women with PAS who are at high risk of significant morbidity and to optimize management plan in priori based on available information. Prospective validation of these scores may permit robust evidence-based recommendations on management of PAS, converge current treatment options, and determine required training and skills that would be deemed satisfactory to manage PAS if uterine preservation is considered.

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Contribution to Authorship:

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References

1. Jauniaux E, Collins S, Burton GJJAjoo, gynaecology. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. 2018;218(1):75-87.

2. Silver RM, Branch DWJNEJoM. Placenta accreta spectrum. 2018;378(16):1529-36.

3. Cahill AG, Beigi R, Heine RP, Silver RM, Wax JR, Obstetricians ACo, et al. Placenta accreta spectrum. 2018;219(6):B2-B16.

4. Cal M, Ayres-de-Campos D, Jauniaux EJIJoG, Obstetrics. International survey of practices used in the diagnosis and management of placenta accreta spectrum disorders. 2018;140(3):307-11.

5. Vinas MT, Chandraharan E, Moneta M, Belli AJCr. The role of interventional radiology in reducing haemorrhage and hysterectomy following caesarean section for morbidly adherent placenta. 2014;69(8):e345-e51.

6. CON-PAS registry. Middle-East Obstetrics and Gynaecology Graduate Education (MOGGE) Foundation. https://www.mogge-obgyn.com/con-pas-registry. Last accessed: July 16th, 2020.

7. Mohri M, Rostamizadeh A, Talwalkar A. Foundations of machine learning: MIT press; 2018.

8. Vabalas A, Gowen E, Poliakoff E, Casson AJJPo. Machine learning algorithm validation with a limited sample size. 2019;14(11):e0224365.

9. Hosmer Jr DW, Lemeshow S, Sturdivant RX. Applied logistic regression: John Wiley & Sons; 2013.

10. Jauniaux E, Alfirevic Z, Bhide A, Belfort M, Burton G, Collins S, et al. Placenta praevia and placenta accreta: Diagnosis and management: Green-top guideline no. 27a. 2019;126(1):e1-e48.

Table 1. Patient demographics, disease characteristics and management detailed of study cohort

Variable	**Description***
Age in years	33.15 ± 4.93
Parity	2.20 ± 1.37
BMI (kg/m^2)	27.89 ± 4.50
Smoking	64 (8.86%)
Ethnicity Asian	299 (41.53%) 67 (9.31%) 354 (49.17%)
White (European)	
Middle Eastern	
Number of previous CS	1.38 ± 1.08
IVF pregnancy	34 (4.71%)
Type of conception Singleton	701 (97.36%) 19 (2.64%)
Twin pregnancy	
Obstetric complications Gestational diabetes	62 (8.60%) 7 (0.97%) 21 (2.91%) 17 (2.36%) 13 (1.80%) 1
Pregestational diabetes	
Gestational hypertension	
Chronic hypertension	
Preeclampsia	
Fetal growth restriction	
Others	
History of gynecologic surgery Obstetric D & C	189 (26.92%) 105 (14.96%) 9 (1.28%) 1 (0.14%) 5 (0.71%
Gynecologic D & C	
Open myomectomy	
Laparoscopic myomectomy	
Hysteroscopic adhesiolysis	
Hysteroscopic septum resection	
Others	
Gestational age at diagnosis in weeks	26.71 ± 6.20
Gestational age at delivery in weeks	35.10 ± 3.19
Method of diagnosis Ultrasound alone	34 (4.72%) 429 (59.58%) 208 (28.89%) 2 (0.28%) 47 (6.53
Ultrasound and Doppler	
Ultrasound confirmed by MRI	
MRI only (inconclusive ultrasound) Intrapartum diagnosis	

Variable	Description*
Placental location Central	260 (35.76%) 233 (32.05%) 185 (25.45%) 15 (2.06%) 18 (
Anterior low	
Posterior low	
High anterior	
High posterior	
Fundal	
Type of invasion Focal	446 (61.52%) 279 (38.48%)
Complete	
Organ invasion No organ involvement	613 (84.32%) 95 (13.07%) 18 (2.48%) 1 (0.14%)
Bladder invasion	
Parametrium invasion	
Others	
Type of CS incision Low transverse	404 (56.03%) 201 (27.88%) 101 (14.01%) 15 (2.08%)
High transverse	
Classic	
Low vertical	
Relation of incision to placenta Incision through the placenta	205 (28.75%) 508 (71.25%)
Incision away from the placenta	
Antenatal steroids Complete course	304 (42.16%) 108 (14.98%) 309 (42.86%)
Incomplete course	
Not indicated	
Indication of delivery Elective (related to accreta)	485 (67.36%) 55 (7.64%) 141 (19.58%) 39 (5.42%)
Elective (not related to accreta)	
Emergency (related to accreta)	
Emergency (not related to accreta)	
Antepartum hemoglobin (g/dl)	11.04 ± 1.43
Preoperative ultrasound	693 (95.32%)
Intraoperative ultrasound	30 (4.13%)
PAS type Placenta accreta	303 (41.68%) 227 (31.22%) 197 (27.10%)
Placenta increta	
Placenta percreta	
Management of PAS Planned hysterectomy	135 (18.70%) 587 (81.30%)
Conservative management	
Outcomes of conservative management Successful	469 (79.90%) 118 (20.10%)
Failed	
Conservative management Local uterine resection	33 (5.62%) 67 (11.41%) 72 (12.27%) 89 (15.16%) 36 (6.13
Intrauterine balloon placement	
Internal iliac artery ligation	
Uterine artery ligation	
Ovarian artery ligation	
Extensive suturing of placental bed	
Compression sutures	
B-Lynch suture	
Nausicaa suture	
Interventional radiology Uterine artery embolization	68 (9.42%) 27 (3.71%) 44 (6.05%) 6 (0.83%)
Common iliac artery balloon	
Internal iliac artery balloon	

Variable	Description*
Intraoperative surgical complications No complications	643 (88.45%) 74 (10.18%) 5 (0.69%) 5 (0.69%)
Unintentional cystotomy	
Ureteric injury	
Bowel injury	
Cord clamping Immediate cord clamping	604 (83.31%) 121 (16.69%)
Delayed cord clamping (> 30 seconds)	
Intraoperative tranexamic acid	240 (33.01%)
Estimated blood loss in ml	1786.33 ±1707.74
DIC	42 (5.78%)
Transfusion of blood products Number of transfused RBC units	2.66 ± 4.91 0.38 ± 1.63 1.37 ± 2.69 1.42 ± 6.37 0.81 ± 4
Number of transfused whole blood units	
Number of transfused FFP units	
Number of transfused cryoprecipitate units	
Number of transfused platelet units	
Admission to maternal ICU	189 (26.0%)
Duration of admission to ICU in days	0.54 ± 1.20
Duration of maternal hospital stay	6.16 ± 6.36
Postoperative hemoglobin (g/dl)	9.33 ± 1.75
Maternal mortality	1 (0.14%)
IUFD	11 (1.51%)
Postoperative maternal morbidity Acute kidney injury	17 (2.35%) 4 (0.55%) 4 (0.55%) 1 (0.14%) 3 (0.41%) 1 (0
Pulmonary edema	
Ileus	
Femoral/external iliac thrombosis	
Femoral arteriovenous fistula	
Others/unrelated	

BMI, body mass index; CS, cesarean section; IVF, in vitro fertilization; D & C, dilation and curettage; MRI, magnetic resonance imaging; PAS, placenta accreta spectrum; DIC, Disseminated intravascular coagulopathy; RBC, red blood cell; FFP; fresh frozen plasma; IUFD, intrauterine fetal death

* Continuous variables are presented in mean ± standard deviation, categorical variables are presented in numbers and percentages

Table 2. Evaluation of machine learning prediction models

Model	Outcome	AUC (train set)	AUC (test set)	Jaccard index	Precision*
Antepartum model	Massive blood loss	0.84	0.84	0.80	0.64
	Prolonged hospitalization	0.80	0.81	0.82	0.66
	Maternal ICU admission	0.85	0.82	0.74	0.73
Peripartum model	Massive blood loss	0.88	0.86	0.82	0.80
	Prolonged hospitalization	0.86	0.90	0.84	0.86
	Maternal ICU admission	0.88	0.86	0.79	0.80

AUC, area under curve; ICU, intensive care unit

* Reported as weighted average

Figure legends

Figure 1. Receiver operating characteristic (ROC) of machine learning prediction models

Figure 1A: Antepartum prediction of massive PAS-associated blood loss - ROC of train (left) and test sets (right)*Figure 1B:* Antepartum prediction of prolonged hospitalization - ROC of train (left) and test sets (right)*Figure 1C:* Antepartum prediction of admission to intensive care unit - ROC of train (left) and test sets (right)*Figure 1D:* Peripartum prediction of massive PAS-associated blood loss - ROC of train (left) and test sets (right)*Figure 1E:* Peripartum prediction of prolonged hospitalization - ROC of train (left) and test sets (right)*Figure 1F:* Peripartum prediction of admission to intensive care unit - ROC of train (left) and test sets (right)

Figure 2. Size of contribution of baseline, disease, and management variables in antepartum and peripartum prediction models (variables are ordered in a clockwise direction starting from 12 o'clock)

Figure 2A: Antepartum prediction of massive PAS-associated blood loss - ROC of train (left) and test sets (right)*Figure 2B:* Variables contributing to antepartum prediction of prolonged hospitalization*Figure 2C:* Variables contributing to antepartum prediction of admission to intensive care unit*Figure 2D:* Variables contributing to peripartum prediction of massive PAS-associated blood loss*Figure 2E:* Variables contributing to peripartum prediction of prolonged hospitalization*Figure 2F:* Variables contributing to peripartum prediction of admission to intensive care unit

Figure 3. A "box and whisker" graph of calculated probability of adverse outcomes in women

who developed or did not develop these outcomes

Figure 3A: Antepartum probability of massive PAS-associated blood loss*Figure 3B:* Antepartum probability of prolonged hospitalization*Figure 3C:* Antepartum probability of admission to intensive care unit*Figure 3D:* Peripartum probability of massive PAS-associated blood loss*Figure 3E:* Peripartum probability of prolonged hospitalization*Figure 3F:* Peripartum probability of admission to intensive care unit