A prediction model for placenta accreta spectrum: A multicentre external validation study.

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Abstract

Objective: To validate the Weiniger model, a multivariable prediction model for placenta accreta spectrum (PAS). Design: Multicentre external validation study. Setting: Two tertiary care hospitals in the United States. Population: Cohort A included patients with risk factors (prior caesarean delivery, placenta praevia) and/or ultrasound features of PAS (variable risk) presenting to a tertiary care hospital. Cohort B patients were referred to a tertiary care hospital specifically for ultrasound features of PAS (higher risk). Methods: Weiniger model variables (prior caesarean deliveries, placenta praevia and ultrasound features of PAS) were retrospectively collected from both cohorts and predictive performance of the model was evaluated. Main Outcome Measures: Surgical and/or pathological diagnosis of PAS. Results: The model c-statistic in cohorts A and B was 0.728 (95% CI: 0.662, 0.794) and 0.866 (95% CI: 0.754, 0.977) signifying acceptable and excellent discrimination, respectively. Based on calibration curves, the model underestimated average PAS risk in both cohorts. In both cohorts, high risk was overestimated and low risk underestimated. Use of this model compared to a "treat all" strategy had greater net benefit at a threshold probability of > 0.25 in cohort A, but no net benefit in cohort B. Conclusions: This study provides multicentre external validation of the Weiniger model for PAS prediction, making it a useful triaging tool for management of this high-risk obstetric condition. Clinical usefulness of this model is influenced by the incidence of risk factors and PAS ultrasound features, with better performance in a variable-risk population at threshold probability >25%.

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Shortened running Title: External Validation of a PAS Prediction Model.

ABSTRACT

Objective: To validate the Weiniger model, a multivariable prediction model for placenta accreta spectrum (PAS).

Design: Multicentre external validation study.

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Methods: Weiniger model variables (prior caesarean deliveries, placenta praevia and ultrasound features of PAS) were retrospectively collected from both cohorts and predictive performance of the model was evaluated.

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Conclusions: This study provides multicentre external validation of the Weiniger model for PAS prediction, making it a useful triaging tool for management of this high-risk obstetric condition. Clinical usefulness of this model is influenced by the incidence of risk factors and PAS ultrasound features, with better performance in a variable-risk population at threshold probability >25%.

Tweetable abstract: This multi-centre study externally validates a model for prediction of placenta accreta among at-risk women.

Keywords: abnormal placentation, placenta increta, placenta percreta, Weiniger model, ultrasound, caesarean delivery, placenta praevia, placental implantation, invasive placenta, infiltrative placenta.

INTRODUCTION

Placenta accreta spectrum (PAS) describes a range of pathologic placental attachment to and invasion of the uterine myometrium and includes placenta accreta, increta, and percreta.[1] PAS is a leading cause of severe postpartum haemorrhage (PPH) and emergent hysterectomy.[2] Management of PAS and associated maternal morbidity, preterm birth and maternal and neonatal intensive care unit (ICU) admission can be optimised at tertiary level hospitals with specialised multidisciplinary care.[3] Anticipatory planning with recognition of

risk factors for PAS is critical to allow transfer to an appropriate delivery centre, allocate necessary resources and minimise life-threatening PPH and associated complications.[4–6]

Early recognition of suspected PAS is facilitated by identification of risk factors including placenta praevia (praevia), prior caesarean delivery (CD), multiparity, prior uterine surgeries, uterine anomalies,*in vitro* fertilisation and advanced maternal age.[7–11] Diagnostic confirmation of PAS can only happen at delivery, as radiographic evaluation by ultrasound (US) or magnetic resonance imaging (MRI) alone does not reliably predict or refute the presence of PAS.[6,12–14]

A PAS prediction model by Weiniger et al. was derived from analysis of 92 deliveries based on number of prior CDs, presence of praevia, and US features of PAS.[9] The model had good discrimination by area under the curve (AUC) and may be more generalisable, comprehensive, and easier to use than alternative PAS models.[15–23]We aimed to validate this model in two cohorts derived from two tertiary-care hospitals: a variable-risk cohort that included patients with risk factors (prior CD and praevia) and/or US features of PAS (Cohort A) and a higher-risk referral population all of who had US features of PAS and were referred to the PAS service of a tertiary care hospital. Our hypothesis was that this model would demonstrate external validity among the obstetric patients in both tertiary care settings.

MATERIALS AND METHODS

This manuscript follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[24] The model was previously developed from a prospective cohort (henceforth referred to as the Weiniger development cohort) at the Hadassah Hebrew University Medical Center, a tertiary-care hospital in Israel.[9] Briefly, all women with praevia and/or prior history of CD were screened for US features of PAS (Table S1). Women with both high- and low-risk features were included. Women who had no US features of PAS, but had both praevia and prior CD were also included (Figure 1A).[9] Using the same inclusion criteria, validation cohort A (cohort A) was retrospectively constituted from a database of all deliveries from 2007-2017 at Brigham and Women's Hospital, a tertiary hospital in Boston, MA, United States (Figure 1B). Validation cohort B (cohort B) was retrospectively constituted from a database of patients referred, based on any US features of PAS, to Columbia University Irving Medical Center, a tertiary hospital in New York, NY, United States (Figure 1C).

Data collection

Maternal age, gravidity, parity, number of prior CDs, current praevia, US features of PAS, confirmed PAS at delivery, hysterectomy, and placental pathology reports were retrospectively collected by chart review in both cohorts.

Estimation of risk

PAS risk was estimated from number of prior CDs (N), presence of praevia (R ; 1 = yes, 0 = no) and US features of PAS (H ; 1 = high-risk US features, 0 = low-risk US features). The risk score (probability index, P) was calculated for each woman using the following equation as derived in the model development paper:[9]

$P = \mathrm{e}^{Y} \,/\, (1 + \mathrm{e}^{Y})$

Where Y is log odds of having PAS and is the linear function of the independent risk factors, calculated using the equation:

Y = -8.2862 + (6.5184xR) + (2.3313xN) + (2.7272xH) – (2.1151xN xR).

US features of PAS (H)

US features of PAS were classified as high- or low-risk as defined by Weiniger et al. (Table S1).[9] If PAS could not be ruled out per sonographic report, the patient was classified as "low-risk." Women with no US features but with history of prior CD and current praevia were also classified as low-risk for model input per Weiniger development cohort criteria.

Outcome

The outcome variable was clinical or pathological confirmation of PAS at delivery. Clinical confirmation of PAS was made by the surgeon's report of visible PAS or focal accreta, difficulty creating a plane between the placenta and endometrial wall, or adherence or excessive bleeding with attempted placental removal. If clinical and pathological confirmation of PAS were inconsistent with each other, the diagnosis of PAS was maintained.

Statistical analysis

Magnitude and direction of differences in patient characteristics and outcomes between each validation cohort and the Weiniger development cohort were quantified as standardized differences. For continuous, ordinal categorical, and nominal categorical variables, standardized differences were calculated as the difference in means, ranks, and proportions between groups, respectively, divided by the pooled within-group standard deviation (SD).[25] A standardized difference > 0.1 was used as the threshold for notable difference between groups.[26] We implemented the framework of Debray et al.[27] to determine whether the overall case-mix differences between the Weiniger development and each validation cohort were consistent with reproducibility (model performance in the same target population) or transportability (model performance in different but related populations). C-statistic of membership models, ratio of SD of linear predictor (LP) and estimated difference in mean LP between the Weiniger development and validation cohorts were calculated for this purpose (Appendix S1).

Model performance in each validation sample was evaluated with respect to discrimination,[28,29]calibration,[30] and clinical usefulness[31] which are described in detail in appendix S2. Discrimination was evaluated in each validation cohort by plotting receiver operating characteristic (ROC) curves, estimating the area under ROC curve via c-statistic with 95% Wald confidence intervals (CI),[28] and estimating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at two thresholds presented by Weiniger.[9] Calibration was evaluated by plots of observed versus predicted probability of PAS in each population and the corresponding regression intercepts and slopes[30]. 95% CI for calibration curve intercepts and slopes were estimated using the bias-corrected and accelerated bootstrap method with 1000 bootstraps. Clinical usefulness[31] of the model was assessed via decision curve analysis with plots of net benefit (i.e., net true-positive classification rate) of (1) assuming all patients are low-risk (treat-none) (2) assuming all patients are high-risk (treat-all), and (3) employing the model[32]over a range of threshold probabilities (i.e. the probability of having PAS at which the clinicians would change their management strategy). Visual comparison of these curves indicated the threshold probability at which risk prediction with the model had a greater net benefit than assuming all patients are high risk. Net benefit was also compared between the prediction model and treat-all strategies specifically at 3 predetermined thresholds: 10%, 30%, and 50% predicted risk. 95% CI at thresholds were estimated using the bias-corrected and accelerated bootstrap percentile method with 5000 bootstraps. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria.

RESULTS

Baseline characteristics and outcomes:

The Weiniger development cohort, cohort A, and cohort B included 92, 253, and 99 patients respectively (Figure 1). No data were missing for model outcomes or predictors.

In Weiniger development cohort, 56.5% (n = 52 of 92) of suspected cases were confirmed to have PAS at delivery. Similarly, 51.8% of suspected cases (n = 131 of 253) in cohort A were confirmed to have PAS. Of the 131 patients with confirmed PAS in cohort A, 126 (96.2%) were diagnosed by clinical criteria of which 98 (77.7%) were confirmed by pathology. Five cases without a clinical diagnosis in cohort A were confirmed by histopathology to have PAS. In contrast, 93.9% of suspected cases (n = 93 of 99) in cohort B were confirmed to have PAS at delivery (Table 1). Eighty-two of these cases (88.2%) were confirmed pathologically. None of the cases in cohort B had positive pathology in absence of PAS by clinical diagnosis.

Compared to the Weiniger development cohort, median gravidity and parity were lower in both validation cohorts, mean age was higher, and hysterectomy with confirmed PAS was higher in cohort B and lower in cohort A (Table 1). The distribution of individual model predictors in cohort A was similar to the Weiniger development cohort except for median number of prior CDs, which was lower in cohort A. Cohort B had higher prevalence of high-risk US features compared to the Weiniger development cohort but had similar distribution of other model predictors (Table 1).

Relatedness of the development and validation cohorts:

Membership model c-statistics for cohorts A and B vs. the Weiniger development cohort were 0.845 (95% CI: 0.793, 0.897) and 0.883 (95% CI: 0.835, 0.931), respectively (Table 2). This indicated that patients in each validation cohort can be strongly discriminated from the Weiniger development cohort based on patient characteristics and observed PAS outcome. The mean ± SD LP was 0.23 ± 1.96 in Weiniger development cohort, -0.60 ± 2.09 in cohort A, and 0.80 ± 1.37 in cohort B. The ratio (95% CI) of the LP SD between cohort A and Weiniger development cohort was 1.07 (0.99, 1.47), indicating a similar degree of case-mix heterogeneity. In contrast, the ratio of the LP SD between cohort B and Weiniger development cohort indicated less case-mix heterogeneity in cohort B vs. Weiniger development cohort (ratio [95% CI]: 0.71 [0.36, 0.78]). The difference (95% CI) in LP mean between cohort A and Weiniger development cohort was -0.83 (-1.32, -0.34), indicating a lower average predicted risk of PAS in cohort A. In contrast, the difference in LP mean between cohort B and Weiniger development cohort indicated a higher average predicted risk in cohort B (difference in means [95% CI]: 0.57 [0.09, 1.06]). These overall differences in the patient case mix between the two validation cohorts and Weiniger development cohort indicated that validation of the model in these external samples is assessing transportability.

Model performance

Discrimination

ROC curves for the Weiniger development and both validation cohorts are shown in Figure 2. A model c-statistic of 0.846 (95% CI 0.758, 0.933) was observed in the Weiniger development dataset, corresponding with excellent discrimination. A c-statistic of 0.728 (95% CI: 0.662, 0.794) was observed when the model was applied to cohort A, corresponding with acceptable discrimination. A c-statistic of 0.866 (95% CI: 0.754, 0.977) was observed in cohort B, corresponding with excellent discrimination (Table 3).

Calibration

Plots of predicted versus observed probability of PAS for all cohorts are shown in Figure 3. Table 3 presents intercepts and slopes for these calibration curves. Model calibration was optimal in the development sample, as demonstrated by an intercept of 0 (95% CI: -0.589, 0.646) and a slope of 1.000 (95% CI: 0.629, 1.428). In contrast, the intercepts for cohort A (0.266; 95% CI: 0.004, 0.506) and B (2.636; 95% CI: 1.733, 3.741), both > 0, indicated that risks were underestimated on average in these external samples as described in appendix S2. The slopes for cohort A (0.342; 95% CI: 0.170, 0.532) and B (0.604; 95% CI: -0.166, 1.221), both <1 indicated overfitting of the model for both validation cohorts, which translates to overestimation of high risk and underestimation of low risk (Appendix S2).

Clinical usefulness

Figure 4 shows plots of net benefit at various threshold probabilities for the strategies of (1) assuming all patients are low-risk (treat-none), (2) assuming all patients are high-risk (treat-all), and (3) using the model. In the Weiniger development cohort, use of the model corresponded with net benefit equal to or greater than the treat-all strategy across all threshold probabilities (Figure 4A). In cohort A, using the model corresponded with higher net benefit than the treat-all strategy starting at a threshold probability of 0.25 (Figure 4B). In cohort B, the treat-all strategy had a greater net benefit than using the model across all threshold probabilities (Figure 4C; Table 4).

DISCUSSION:

Main findings:

This study provides external validation of the Weiniger model for PAS prediction in two distinct patient populations. The Weiniger model performed well in both cohorts A and B with acceptable and excellent discrimination, respectively, suggesting reliability to identify women with PAS in both populations, transportability and generalizability, and applicability to populations that meet criteria for PAS suspicion but are otherwise different from the development cohort.

The clinical usefulness of the model to identify women with PAS is dependent on the risk of the population, with more utility in a variable-risk, heterogenous population of patients with prior CD, current praevia, and/or presence of US features of PAS (Cohort A, Figure 4B) compared to a higher-risk, homogenous population in which all patients had US features of PAS (Cohort B, Figure 4C). Model performance was enhanced when at-risk patients without US findings were included, compared to only including women with US risk factors for PAS. Since there were differences between cohorts A and B in the proportion of women with confirmed PAS (52% vs 94%), baseline characteristics, distribution of model predictors (Table 1) and membership model performance (Table 2), a combined analysis was not undertaken.

In cohort A, the net benefit depended on the probability threshold of the clinician for determining delivery timing, location and multidisciplinary planning. The model became more useful than a treat-all strategy above a probability threshold of 25%; if a likelihood of having PAS > 1 in every 4 patients would prompt the clinician to change their management, prediction of PAS using the model was more beneficial. However, if the threshold for a particular decision or intervention was $< 10\%$ (for example, the threshold to refer a patient with suspected PAS to a high-resource setting), it was more reasonable to treat every patient with the model risk factors as if they had PAS.

Strengths and limitations:

There are some advantages of the Weiniger model when compared to other models (Table S2). The Weiniger model utilizes US as opposed to MRI.[19–21] US is more readily available, and the superiority of MRI over US for diagnosis of PAS has not been established.[33–36] Risk of PAS increases with each CD, with a 10-fold increase of concurrent PAS with 5 vs. 2 prior CDs.[37] The Weiniger model accounts for this by integrating the total number of prior CDs as a predictor, rather than having a cut off (e.g. [?]2 or 3) for scoring CDs.[15–18,21] The Weiniger model was developed using a comparatively lower-risk population compared to several other models (Table S2),[15,17–21,23] which may make it more generalizable, as confirmed by the current study. Of note, a model developed and internally validated by Yang et al[22] in a large cohort of over 8000 patients had high discrimination of 0.93 and was based solely on clinical characteristics (prior CD, vaginal bleeding, medications during pregnancy, praevia). Although the Yang model may be useful in community settings, it does not include US features of PAS which can be reliably assessed in high-resource settings.

Another strength of this study is that it is a large multi-centre analysis to externally validate a PAS prediction model in two cohorts that were dissimilar to the Weiniger development cohort and to each other. The results suggest good external validity. The study not only evaluated the calibration, discrimination, sensitivity and specificity, but also the clinical usefulness of the model in the form of a decision curve analysis. We further derived the net benefit at different probability thresholds to establish a user-friendly tool for practical management and decision-making based on available resources. We specifically demonstrated that the model is most useful above a threshold probability of 25% in a variable-risk population.

This study is not without limitations. Neither the Weiniger development nor validation cohorts included women who had PAS in the absence of risk factors which may constitute $> 50\%$ of PAS in the community, so use of the model should not preclude readiness for unanticipated PAS cases.[38] Second, the validation cohorts spanned a significant duration (11 and 7 years), during which diagnostic and management practices may have changed significantly. Another limitation is the retrospective nature of the validation cohorts. Given that PAS is a rare condition, prospective enrolments of large cohorts would be difficult and time-consuming. However, reliable retrospective data extraction was possible because the features evaluated for cohort inclusion are routinely documented in the medical record. Datasets with a minimum of 100 events

and 100 non-events are recommended for external validation of prediction models developed using logistic regression.[39] Given the rarity of PAS, despite the long duration of data collection, this recommendation was met in cohort A but not in cohort B. Therefore, model performance estimate precision in cohort B may be suboptimal. In our model, US features were scored in a binary fashion. This approach may have lowered the precision of the model for determining the risk of specific features compared to some other models available in the literature.[15–18,23]

Interpretation:

Use of this model for decision-making depends on the ability to escalate resources in response to PAS at the time of CD. In high-resource settings, using the model may allow deployment of treatment modalities at different probability thresholds. For example, while the threshold for alerting interventional radiology (IR) may be low (e.g., 30%), it may be reasonable to have a higher treatment threshold, e.g., 50%, for having IR personnel in the operating room. In contrast, low-resource hospitals may need to use a lower threshold (<25%) for referral to a specialist service or transfer to higher level of maternal care and may benefit by treating all patients with inclusion criteria as high-risk. Similarly, there may be different treatment thresholds for different anaesthetic modalities and types of vascular access (arterial, central and occlusive balloon catheter access).

Conclusions:

This validation study demonstrates that the Weiniger model for PAS prediction successfully identified patients with PAS in two distinct patient populations in the United States. In low resource settings and in referral populations with a high prevalence of PAS, it is likely be beneficial to treat every at-risk patient as having PAS. However, at high resource centres managing general obstetric populations, this model may be helpful to triage patients with variable risk of PAS. Use of this model may refine communication and planning for patients with suspected PAS. Of note, the NPV of this model was 0.722 in cohort A at the optimal cut off. This suggests that 27.8 % of the women predicted to *not*have PAS by the model would actually have PAS, highlighting the importance of having emergency protocols in place. Centres must also recognize the inherent possibility of unanticipated PAS among women with no risk factors and have systems for managing such emergencies.

Although this model can predict the presence of PAS, it cannot predict the degree of invasion or severity of haemorrhage, nor the surgical complexity of an individual case. Thus, research toward models that predict clinically relevant measures including blood loss, ICU requirement, and maternal morbidity are warranted to further refine surgical and anaesthetic planning for patients at risk for PAS is warranted.

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Authors Contributions:

SS: Study design, Data collection at Brigham and Women's Hospital, analysis planning, manuscript preparation.

DC: Data collection at Brigham and Women's Hospital and manuscript preparation.

PW: Data collection at Brigham and Women's Hospital

ERI: Study design and data collection at Columbia University Irving Medical Center.

RL: Study idea and design, data collection at Columbia University Irving Medical Center, manuscript preparation.

KF: Data analysis

CW: Study idea, manuscript preparation

MF: Study idea, design, manuscript preparation.

Details of Ethics Approval: The study was approved by the institutional review board (IRB) of both Brigham and Women's Hospital (IRB number: 2018P003126 ; date of approval: December 24th, 2018) and Columbia University Irving Medical Center (IRB number: AAAD3960; date of approval: July 15th, 2008 and last renewed on April 30th, 2019) with waivers of informed consent.

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Figure legends:

Figure 1: Flowchart showing the constitution patients at risk for placenta accreta spectrum in (A) the Weiniger development cohort, (B) validation cohort A and (C) validation cohort B; HHMC: Hadassah Hebrew University Medical Center; BWH: Brigham and Women's Hospital CUIMC: Columbia University Irving Medical Center; CD: Caesarean Delivery, PAS: Placenta Accreta Spectrum; US: Ultrasound.

Figure 2: Receiver Operating Characteristic curves of showing discrimination of the model in (A) the Weiniger development cohort, (B) validation cohort A and (C) validation cohort B.

Figure 3: Calibration of the model in the (A) Weiniger development cohort, (B) validation cohort A and (C) validation cohort B.

Figure 4: Decision curve analyses showing plots of net benefit vs threshold probability for the (A) Weiniger development cohort, (B) validation cohort A and (C) validation cohort B. Net benefit is the net true positive classification rate (calculation described in Appendix S2). Threshold probability is the minimum predicted probability of the outcome at which the clinician would change the management of a patient (Appendix S2).

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