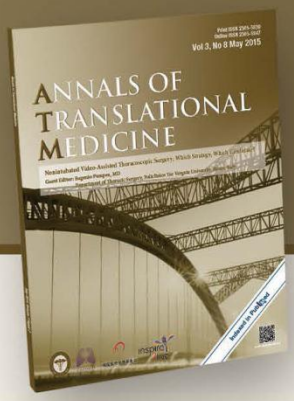
ANNALS OF TRANSLATIONAL MEDICINE



Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-5160.

Reviewer A

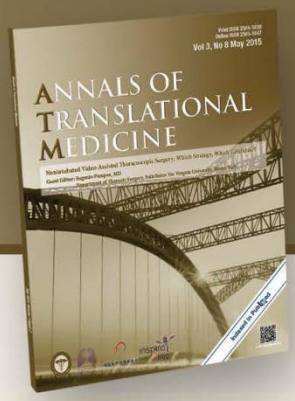
Comments: This manuscript is about predicting blood loss in placenta previa and increta and percreta. The efforts of the authors are appreciated.

Response: Thank you very much for your positive comments. We have revised our manuscript according to your kind suggestion and comments. Please find the detailed responses as following.

Comment 1: Placenta increta and percreta are well known to cause massive bleeding. And the predicting factors found by the authors including vascular lacunae within the placenta, hypervasuclarity of uterine-placental margin, hypervascularity of uterine serosa-bladder wall interface and hypervasuclarity of cervix are the diagnostic ultrasound features for PAS. Using their own diagnostic ultrasound features to predict the risk of bleeding >=2500 ml is not clinically helpful.

Reply 1: Thank you very much for your comments. Although those ultrasound features are typical characteristics of PAS, the purpose of our study was to further assess the relationship between ultrasound features and the severity of PAS. Therefore, we used the combination of patient clinical characteristics and ultrasound features to predict the amount of bleeding during cesarean section. The established risk prediction model can help obstetricians to identify high-risk patients (massive blood loss), develop treatment strategies to reduce the incidence of intraoperative massive blood loss, and further improve prognosis in patients with placenta previa with increta or percreta.

Changes in the text: None.



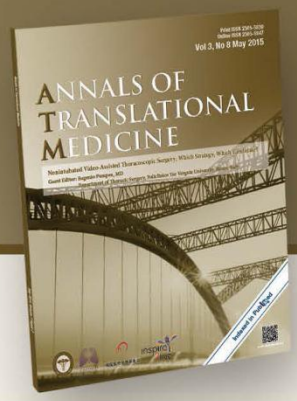
Comment 2: Why placenta accreta is being excluded in this study? Placenta accreta is part of the PAS, it is clinically difficult to differentiate placenta accreta from placenta increta based on USG findings. And placenta accreta can also lead to massive bleeding and the management of placenta accreta and increta are very similar. Placenta accreta should also be included in this study.

Reply 2: Thank you very much for your comments. Placenta increta and percreta are well known to cause massive bleeding during cesarean section, and the purpose of our study was to assess the severe types of PAS. Therefore, at the beginning of the study, we did not include patients with placenta creta (to avoid the double meaning of “placenta accreta”, we have changed all instances of "placenta accreta" in the manuscript to "placenta creta"). It is undeniable that our research has certain limitations. In subsequent PAS-related studies, we will further analyze the prognosis of PAS, including placenta creta. The limitation analysis has been added to the last part of the Discussion. Thank you again for your comment.

Changes in the text: (Page 4 and 11, Line 72 and 258-261)

Comment 3: I don't know the uses or benefit to compare model A with model B. Model B has all the items in model A. And model B has only extra 2 items compare with model A. And the item of preoperative BPAA in model B is not clinically helpful. Pre-operative BPAA can be used as a measure to reduce blood loss in PAS. But as a clinical predictive model to predict blood loss before operation is not helpful. Because in a useful predictive model, is to find those highrisk bleeding case to have pre-operative BPAA, while those low risks not to have pre-operative BPAA.

Reply 3: Thank you very much for your comments. Model B was mainly established to evaluate the effect of BPAA on the control of intraoperative blood loss. For example, if a patient is predicted to be at risk of intraoperative massive blood loss by Model A, then we can use Model B to further assess whether the use of BPAA can reduce the risk of massive blood loss. Therefore, models A and B are complementary. In addition, in our study, only 25.4% (66/260) of the patients accepted BPAA before surgery, and the remaining high-risk patients did not



undergo BPAA due to emergency surgery, economic factors, or other factors. Therefore, the use of BPAA in this study does not entirely depend on the severity of PAS. The combined use of models A and B can further help clinicians to predict the risk of massive blood loss and the necessity of using BPAA, allowing them to formulate surgical methods more accurately.

Changes in the text: None.

Comment 4: P value <0.05 should be enrolled in the logistic regression analysis instead of using P-value <0.1

Reply 4: Thank you very much for your comments. P-value <0.05 is considered statistically significant. However, using P-value <0.05 as inclusion criteria for influencing factors enrolled in the multivariate logistic regression could have resulted in the loss of clinically significant influencing factors, so we relaxed the inclusion criteria to P-value <0.1.

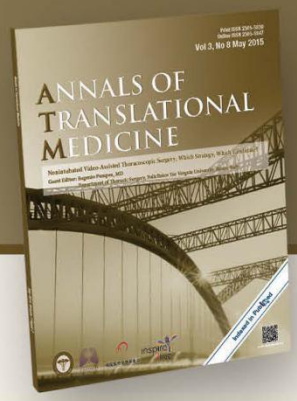
Changes in the text: None.

Reviewer B

Comments: To authors, the theme is important. I have some advice.

Response: Thank you very much for your positive comments. We have revised our manuscript according to your kind suggestion and comments. Please find the detailed responses as following.

Comment 1: Your study target is unclear. First, PAS is subdivided into “creta”, increta, and percreta. (NOT “accreta”). As you cited Jauniaux’s article several times, the one of the main reasons why new terminology PAS was introduced was “to avoid double meaning of placenta accreta”. And thus FIGO introduced this terminology PAS. I admit that the term “creta” is not so widely used but using “placenta accreta” is very confusing. Second, please remember that PAS has two categories; with previa or without previa. Thus, your target is (my understanding is): placenta previa with placenta increta or percreta, and excluding placenta “creta”. In short,



your target was severe type of PAS with previa, right? You wrote this meaning in the following parts:

Line 104: This was a retrospective study of all placenta increta and percreta patients who attended or were referred to the Department of Obstetrics, Qilu Hospital of Shandong University, (author; then you did not have PAS without previa during the time??)

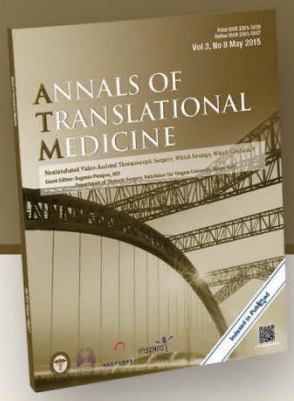
Line 155: All patients had at least one previous cesarean section, and with placenta previa. Exclusion criteria were: 1) placenta accreta. (Author, no terminology of placenta accreta)

Please read the new definition of PAS and use appropriate term. Title should also be changed according this.

Reply 1: Thank you very much for your comments. For the classification of PAS, we have changed all instances of "placenta accreta" in the manuscript to "placenta creta", including in the title. Placenta increta and percreta are well known to cause massive bleeding during cesarean section, and the purpose of our study was to assess the severe types of PAS. Therefore, at the beginning of the study, we did not include patients with placenta creta. It is undeniable that our research has certain limitations. In subsequent PAS-related studies, we will further analyze the prognosis of PAS, including placenta creta. The limitation analysis has been added to the last part of the Discussion. Thanks again for your comment.

Changes in the text: (Page 4 and 11, Line 72 and 258-261)

Comment 2: Diagnosis of creta vs increta. As you may know, gold standard of PAS and also its sub-classification (creta, increta, percreta) should be done by “hysterectomized specimen” and not “removed placenta”. You wrote; Line 161: Hysterectomy was performed only in 8 (3.1%). Thus, almost all patients (specimens) were diagnosed as increta or percreta (at least having PAS but not creta) based on “clinical diagnosis”. This is very important. As a 3-decade-carrier PAS specialist, distinction between creta vs increta is not always easy. I well understand that when one used uterus-preserving strategy, one MUST employ “clinical diagnosis” to determine creta, increta, or percreta. Here you intentionally excluded “creta”, and thus distinction of creta vs increta is of paramount importance. Please definitely state how you distinguished these two.



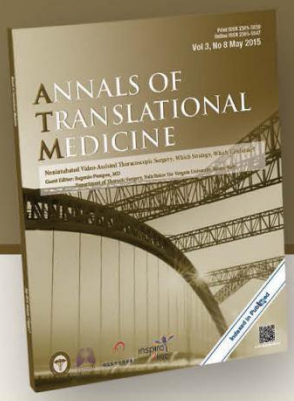
There are many articles by authorities (including Jauniaux) regarding the "clinical or intra-surgical diagnosis of PAS (creta, increta, percreta)". Please just fit it, otherwise, this paper does not stand. 1+2= readers do not understand who was the target and how the diagnoses were made; very severe weak points of this study!

Reply 2: Thank you very much for your comments. As you said, there are some difficulties in the clinical diagnosis of increta and percreta. However, our medical center still tries to classify them according to the intraoperative findings. When no penetration of the placenta close to the serous layer and no or little vascularity of the uterine serosa–bladder wall interface were observed, it was classified as creta. When increased vascularity of the uterine serosa–bladder wall interface, myometrial thinning of the anterior wall, and penetration of the placenta close to the serous layer were observed, it was classified as increta. Based on this, when the placenta penetrated through the uterine surface, even invading into the bladder or other organs, it was classified as percreta. Our diagnostic criteria are consistent with classification criteria proposed by Jauniaux and suggested by FIGO. We found your comments extremely helpful to further improving our study. Thank you again!

Changes in the text: (Page 5-6, Line 106-112)

Comment 3: Balloon occlusion (BO) was made on doctors' preference. If BO was decided in a random manner, incorporating this into predictive model is worthy; however, "do it and plan it intentionally and then incorporate it into predicting factor"; Is this OK? In my opinion, one can use whatever you wish to incorporate into the predictive model; however, its meaning naturally becomes different each other. The data/manuscript has already become completed and thus I only wish you to "touch" this issue.

Reply 3: Thank you very much for your comments. In our study, only 25.4% (66/260) of the patients accepted BPAA before surgery, and the remaining high-risk patients did not undergo BPAA due to emergency surgery, economic factors, or other factors. Therefore, the use of BPAA in this study was not necessarily dependent on the severity of PAS or doctors' preferences. So, we included BAPP and established model B, also to further evaluate the effect



of BAPP on the control of intraoperative bleeding. For example, if a patient is predicted to be at risk of intraoperative massive blood loss by Model A, then we can use Model B to further assess whether the use of BPAA can reduce the risk of massive blood loss. Therefore, models A and B are complementary.

Changes in the text: None.

Comment 4: I made these three advices. If you may agree with me, please incorporate them. In this occasion, please do not expand volume so much. If you do not agree with me, please tell me the rationale.

Reply 4: Thank you very much for your positive comments. We answered your kindly advices and hope to get your approval. Your advices are very helpful for us to further improve our research, thank you again!

Changes in the text: None.