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Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
RE: Manuscript Number ONG-19-189

Factors associated with maternal ICU admission: developing a predictive model for women at increased risk for ICU admission.

Dear Dr. Rossi:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Comments to the author:

This is a population-based cohort study looking at prenatal risk factors for maternal ICU admission between 20-44 weeks. A predictive model was then developed and externally validated on a different cohort of deliveries. The authors should be applauded for addressing a critical need to reduce maternal morbidity and mortality. In addition to implementing safety bundles a big focus of the AIMs project is to reduce maternal mortality by regionalization of care. This type of tool could be used to assess appropriate risk referral.

Abstract:

Well written and concise. The objectives are clear. The results and conclusion are consistent and stand alone.

Introduction:

1. This is a very good review of the problem and history. Perhaps discuss more about the collaboration Alliance for Innovation on Maternal Health (AIM) with specific goals of reducing maternal mortality by 1,000 and severe maternal morbidity by 100,000.

Materials and methods:

2. Line 143 Why were the date ranges 2012-1016 chosen? The specific time period for AIM intervention with safety bundles started in 2014-2018 which may make SMM and mortality different on the National level for these ranges.

3. Line 170 The statement does not make sense. "Livebirths delivered at that less than 20 0/7 weeks of gestation"

4. Line 178-179 Looking at weight as a continuous variable and categorical is clinically important when looking at any prediction models.

Results:

5. Table 1 The table is easy to read and understand with legend and title.

6. Table 2 Was the association of inter pregnancy time controlled for maternal age? Other data on adverse outcomes
seems to suggest short interval pregnancy is associated with adverse outcomes, some of which may be associated with ICU admission.

7. Table 3 The biggest thing that stands out is the significantly greater risk of aOR for scheduled cesarean sections for having an ICU admission. Was there further assessment of this risk?

8. Figure 2 and 3 suggest a good fit for this predictive model with external validation. My only concerns are the dates chosen for the Ohio cohort 2006-2011. Were there any changes with data collection, birth certificates or active participation with AIM goals before or after this time period?

Discussion:

9. The authors do a good job of putting the findings into clinical context with explanations for the up to 5% predictive model. The limitations were acknowledged. Although the cesarean sections in labor were excluded this may actually be a strength since this cannot be predicted vs. scheduled cesarean sections which was one of the biggest drivers for ICU admission.

Reviewer #2: I think this work is very important as an aid to decreasing maternal morbidity and mortality in the USA. I believe this information will be helpful to all practitioners of Obstetrics but especially those practicing in rural areas or in facilities with limited capability to care for patients requiring intensive care.

The statistics are very sophisticated and may be difficult for many practitioners. Perhaps a paragraph outlining the author's thoughts on the use of this information would be helpful.

Reviewer #3: The authors have utilized an administrative data set to assess risk factors for maternal morbidity, which they defined as ICU admission. The topic of maternal morbidity is important and relevant. I have several questions/points of clarification for the authors.

Precis: Consider the definition of an "independent" risk factor: this statistical definition (i.e. statistically significant when included in a model) is dependent on the other variables included and does not reflect causality. Consider omitting.

Overall: ICU admission can be problematic as an outcome given the differences in local policies regarding indication for ICU admission: in other words, the level of "illness" or "morbidity" of a patient admitted to the ICU at one institution is not the same as another institution. Attention to this issue in the discussion at a minimum would be helpful.

Abstract and throughout: Consider whether the list of risk factors is antenatal: scheduled cesarean, induction of labor, birthweight, and VBAC do not seem to fit this categorization.

Abstract and throughout: Is the goal to use this predictive model as a tool for patient care? In that case, presentation of more information/discussion regarding the tradeoffs between sensitivity and specificity, rather than solely focusing on the AUC, would be appropriate. Even with an AUC as demonstrated, due to the low prevalence of the outcome, a particular cutoff may fail to identify many women at risk or have an acceptably low PPV in order to be used clinically. In addition, given the type of predictors included (scheduled CD, race, insurance, chronic medical conditions) what would be the anticipated intervention to improve outcome in these populations? The references below may be helpful in framing the goals and the discussion.

Methods: The stated goal is to include variables available prior to delivery. Consider whether all of the factors included fit that definition.


Methods: What was the reason for choosing 50 iterations for the bootstrap validation? Understanding that this is a large data set, if bootstrap validation is planned, a larger number of trials may be warranted or at least the presentation of the histogram to demonstrate convergence with the number of trials chosen. (Apologies if this is available in the supplementary materials that were not visible).

Methods and Results: There were a number of tables and figures in the supplementary materials. Consider whether any of these should be included in the main manuscript.

Discussion: Additional information is needed in order to understand how the predictive model could be used clinically given the limitations of this administrative data set as well as the issues with ICU admission as an outcome.
Discussion: The fact that ICU admission rates are as expected does not give information about potential underreporting of comorbid conditions. These concepts should be presented separately.

Consideration of these references may help to place this study in context and to improve the manuscript:


STATISTICAL EDITOR’S COMMENTS:

1. lines 101-102: Should include the n(%) of ICU admits among the validation set.

2. lines 111-112: It is true that the AUC was 81%, but that does not "suggest" good predictive accuracy up to 5%. That is, the two statements are unrelated. See later comments re: calibration plot.

3. lines 300-315 and Fig 1: Should add to limitations section that ~ 1,000,000 patient data are missing. If those were not randomly selected, then the cohort both may not be representative and potentially could limit the precision of the estimates for the coefficients of the 15 variables included in the regression equation. Should rank the 15 variables included in the final model in order of importance (eg, by variance reduction or by reduction in goodness of fit statistic as each variable was added to the model, so that the reader can have some appreciation of the relative weight of each variable.)

4. Box 1: Should include this in the supplemental, since it would not be of interest to general readership.

5. Fig. 4: I infer from the CIs that there are few instances of subsets with scores that would predict a risk of 3-4% or 4-5%. Please conform to the the guidelines in the TRIPOD recommendations, esp Fig 8: "Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): Explanation and Elaboration" by K.G.M. Moons, D.G. Altman, J.B. Reitsma, J.P.A. Ionnidis, P. Macaskill, E.W. Steyerberg, A.J. Vickers, D. F. Ransohoff and G. S. Collins, Annals of Internal Medicine 2015:162:W1-W73."

6. In that format, the data are divided (by score) into 10 ~ equal cohorts, so that the reader can view a more representative display of the usual range of observed vs predicted rates, along with CI for each decile. If that process leads to sequestering of most data points at the lowest end (<1%), then suggest having more strata (probably could go to increments of 0.25% risk for the 1st percentage and 0.5% for 1-2% and perhaps centered at 2.5, 3.5 and 4.5% to show more fully the range of observed vs predicted, along with the widening CIs as the risk increased, due to fewer events. (e.g., 0-0.25%, 0.25-0.5%, 0.50-0.75%, .75-1.0%, 1.0-1.25%, 1.25-1.5%, 1.5-2.0%, 2-3%, 3-4%, and 4-5%) realize that these may be contain equal size samples in these cohorts, but a balance should be struck between showing more information along the range of predicted %s, with confidence intervals, rather than the present version of Fig 4, which does not show enough fine-grain observed vs predicted outcomes in the lower range, where most of the scores. No need to emulate the TRIPOD fig 8 in terms of the ICU cases vs non-cases along the x-axis below the figure, that would not work well with a sample of > 800,000.

7. It would be informative to show the reader the scores that correspond to risks of e.g., .25%, .5% etc and the n(%) of scores that were in each increment. On-line maternal ICU calculator: the probability of ICU admission is given to nearest .01%, but there is not context; that is, there are no CIs. Suggest rounding to the nearest 0.1% and should also cite the strata and its CI. For example if the predicted % = .3%, then could cite the CI for the .25-.50%. stratum.

EDITORIAL OFFICE COMMENTS:

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efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

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Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

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The Editors of Obstetrics & Gynecology

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