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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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RE: Manuscript Number ONG-21-1375

External validation of the CIPHER prognostic model for pregnant and post-partum women with severe maternal complications during the first 24 hours after admission to the obstetric Intensive Care Unit

Dear Dr. Cecatti:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Sep 17, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

1. This submission represents an esoteric external validation of a prognostic model for pregnant and postpartum women manifesting severe morbidity and complication during the first 24 hours following admission to an Obstetric Intensive Care Unit (ICU) in comparison with an earlier study by the same authors (internal validation) published in 2018 in Critical Care, and referenced in this submission (reference # 9). See Payne B, et al. Development and internal validation of the multivariable CIPHER (Collaborative Integrated Pregnancy High-dependency Estimate of Risk) clinical risk prediction model. 2018 Oct 30;22(1):278. doi: 10.1186/s13054-018-2215-6.

2. I note concerns regarding the study design:
   A. The data collection time spans of the two (external validation) groups appear considerably different. While data was collected at the University of Campinas (UNICAMP) location between the years 2013 through 2015, the IMIP data were obtained between the 10/29/2018 and 9/30/2019.
   B. In addition it appears that these two separate sites likely encounter different patient volumes possibly reflecting distinctly different patient populations with inherently different modalities/mortalities. In the Discussion section (see lines # 277-270), the authors speculate this potential source of the different results.
   C. The likely difference between locations of the external validation study in contrast to the original study (and the inherent difference in the nature of these two groups (external validation versus original study, Obstetrics ICU versus general ICU, respectively), may likely have affected the results, as acknowledged by the authors (see lines # 281-284).
   D. Although detailed in lines 137-146: "Prolonged organ support" without detailed specification which organ was supported (and with what measures), cardiac output (maintenance of blood pressure - vasopressor mediation), respiratory (supplemental oxygen, intubation / ventilation), renal, or blood transfusion, is vague / ill-defined.
   E. Data appear incomplete (see lines 174-179), as PaO2 was replaced "sometimes" by oxygen saturation data SatO2. In the setting of ICU sites and the attempted assignment of prognostic outcome criteria - the is unfortunate.

3. I am unclear regarding the statements (throughout the text) of "live-saving intervention outcome" of hysterectomy. Was
the hysterectomy associated with perinatal complications (hemorrhage / placenta previa/ placental accreta sequence) occurring prior the ICU admission, or alternatively did a patient in the ICU truly require such surgical management (thus representing potential delayed primary surgical management)? That hysterectomy for uncontrollable hemorrhage or infection is associated with increased adverse maternal outcome (see lines # 238-239 and Table 2) is well established prior to this study.

4. Although clearly maternal age is an important variable, it is incorrect to refer to a group of patients in the reproductive age group (even if "older"), as having "declines in reserve capacity and homeostasis making women more vulnerable to the effects of acute disease processes" (see lines # 293-295. I also note that the reference to this unfortunate / incorrect statement regarding Obstetrical patients - reference # 26, refers to "Trends of death among the ELDERLY", which in my assessment, may not be the most appropriate reference for this speculative statement / assumption.

5. Line # 183: Data "were", not "was".

6. While I found this manuscript interesting, respectfully in my assessment I doubt that it would interest the general readership of the Journal, and likely is more appropriate for a Critical Care, Epidemiology, Public or Community Health scientific periodical.

Reviewer #2: The authors are to be congratulated for their external assessment of the CIPHER prognostic model for pregnant and postpartum women admitted to the intensive care unit. As the authors point out in the Background section, numerous models have been developed for prediction of outcomes of ICU patients in general. The CIPHER model was developed specifically for use in ICU patients who are either pregnant or postpartum. However, it has not been externally validated.

The authors collected a large data set from two institutions in Brazil, and assessed performance of the CIPHER model. In contrast to the original publication, the CIPHER model performed poorly in predicting adverse outcomes in their population.

This study was performed in an obstetric icu population. Were obstetric patients also admitted to the general icu? Could the authors include data about the general ICU patients? Could their exclusion have biased the results?

The study population for the CIPHER model development and internal validation, and the authors' study population are very different. As the authors point out, the mortality rate was much higher in the CIPHER population, and numerous additional differences are apparent from comparison of Table 2 of Payne's publication and Table 2 of the authors' manuscript.

In the Discussion section:

Could the authors contrast the objectives and performance of the CIPHER model with the WHO near miss tool?

Lines 303-306 seems to be at odds with 307-309. Please clarify.

In lines 314-319, the authors comment on the difference between the high AUROC from the original study and the low AUROC in their validation study. The explanations offered were (1) most mortalities in the original study were from Pakistan, and (2) it is possible that many characteristics of this clinical setting differed from the present setting in Brazil.

Could the authors suggest additional possibilities? For example
1. Could a lower or higher threshold for ICU admission affect the predictive value of the model?

2. Could a difference in patient populations (e.g. chronic underlying medical conditions, smoking, etc) affect the predictive value of the model?

3. Could differences in hospital resources (blood bank, interventional radiology, etc) affect the predictive value of the model?

The authors propose that the model be recalibrated for public hospitals in LMICs. Is their own data set of sufficient size to recalibrate the model, using the same techniques as Payne and colleagues employed in the original development?

Also, Payne and colleagues commented: "A reduction in overall performance is evident when we compare performance seen in the high- and low- or middle-income country subgroups. In both settings, performance is maintained above the threshold for an adequate prognostic model (AUROC >0.7) but CIPHER is better at discriminating between women with and without outcomes in the low- or middle-income population, where the majority of outcomes occurred." This seems to conflict with the current article's assertion that the model needs to be calibrated for LMIC countries. Please explain.
The original purpose of the CIPHER model was to develop a statistical tool with international applicability. The internal validation set suggested that the model was applicable to countries with all income levels, pending external validation. From the current article, in this first test of the model, CIPHER has failed. Are we truly looking at the wrong coefficients in the right model, or the wrong model?

The last sentence of the Conclusion section begins "When external validation is completed...". Why are the authors confident that external validation will be completed? Should this sentence not begin IF rather than WHEN?

Reviewer #3: Thank you for the opportunity to review this manuscript on an important topic area. The purpose of the paper was to externally validate the CIPHER prognostic model for pregnant and postpartum women admitted to the intensive care unit. This study was conducted at 2 tertiary centers in Brazil. One site utilized a retrospective design and the other a prospective design. Overall, the manuscript was well written and easy to follow. I have specific comments and questions regarding each section below.

Abstract: Appropriate, results consistent

Lines 50-52. Can you please clarify this statement? Comparisons were made in the discussions but from my understanding of the paper, this doesn't seem like what was completed in the study.

Lines 61-63 This conclusion works in the paper because we have the perspective of what individual variables in the CIPHER was strongly associated with the composite outcome and differences in the populations (internal and external validation). However, in the abstract, it does not completely fit and I would suggest revising.

Background: Concise and study rationale introduced.

A little more information on the importance of this work would be good. The specific results details results from reference 9 does not seem necessary in the introduction. Also, please revise the last sentence to be a clear study objective or provide a hypothesis.

Methods: Clearly written

Eligibility criteria, sample size calculation, and detailed information on included variables provided.

Please include information on IRB approval and consenting process for the prospective portion of the study.

How did you determine the control variables to include?

Can you provide a rationale of why a retrospective design in one center and a prospective in the other? Also, please explain the differences in timeline at the different centers.

Regarding data collection, there are gaps regarding the process.

Lines 159-161, How was RedCap used to identify retrospective participants for the study?

Was the database built for a different purpose and this previously obtained data was then utilized for this new study?

Was the data collected manually and then entered into redcap?

Lines 171-173 - 100% reviewed for completion, accuracy? What did the random evaluation of medical records entail?

Moving up some content from paragraph 3 on page 7 (lines 180-186) to follow paragraph 1 on page 7 may help with flow and immediately provide answers to questions that arise regarding data collection and verification.

Composite outcome described twice (variable section and statistical analysis). One description is adequate.

Results: well described and easy to follow

How was the cut-off of 11.6% determined?

Discussion:

Lines 277-278: I don't think speculations are necessary since this study and the internal validation study both collected information on obstetric indications.

"Other variables such as aPTT, potassium, sodium, creatinine and bilirubin were poorly associated with the outcome, which again suggests that the hysterectomy protected from others organ dysfunctions". I am not sure if this can be solely
attributed as the reason for this.

Conclusions:
Lines 330-333: This conclusion doesn't fully support current data and external validation completed in this study. Maybe consider including as future studies and goals.

Tables easy to understand

Figure 1 can be a supplemental

Figure 3 may be a difficult figure/caption for readers to follow

Tripod checklist not completed

STATISTICAL EDITOR COMMENTS:
The Statistical Editor makes the following points that need to be addressed:

Table 3: For this cohort, the input variables were significantly associated with the composite outcome for only 5 of 10 patient characteristics in the CIPHER model, perhaps a harbinger of the model's poor performance for this validation cohort.

Table 4: The PPV and NPV columns should be omitted, since they are dependent on the prevalence of the outcome, which varied by center. Instead, should cite the sens, spec, LR(-) and LR(+) with respective CIs, since those are invariant test characteristics. Also, in terms of model utility, the specificities are good, but the sensitivities, which arguably are paramount for prospective identification of the at risk group, were quite poor.

Fig 2: The cutoff for the model seems irrelevant, the model performance is no better than a random coin flip.

Fig 3: The calibration plot is not relevant, since the overall model performed so poorly.

General: Should re-word the abstract and discussion. This cohort did not validate the CIPHER model, rather it did not perform well at all. Should develop a model from this cohort with internal validation to evaluate whether a different model would perform better for this population.

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics & Gynecology. If you opt to submit a revision for consideration, would recommend changing the title to: Prognostic Value of the Collaborative Integrated Pregnancy High Dependency Estimate of Risk (CIPHER) Model in Critically Ill Obstetric Patients in Brazil (or something similar).

2. Per the comments of the statistical editor, please simply report that the model performed poorly and could not be validated rather than trying to establish a new cut off of interest for a model that did not work in your population.

3. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with 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. 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:
   A. OPT-IN: Yes, please publish my point-by-point response letter.
   B. OPT-OUT: No, please do not publish my point-by-point response letter.

4. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
   * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
   * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
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6. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

7. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

8. Please submit a filled in checklist with your revision. The one that was uploaded is blank.

9. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

10. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

11. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

12. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

13. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's...
conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

14. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

15. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

16. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

17. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%)

18. Line 86: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

19. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

20. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

21. Figures

Figure 1: Please convert this into a box.

Figure 2: Please submit the current file.

Figure 3: Please cite Figure 3 within the manuscript text.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and

* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors’ comments.

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 14 days from the date of this letter. If we have not heard from you by Sep 17, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri Metz, MD, MS
Associate Editor for Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.
External validation of the CIPHER prognostic model for pregnant and post-partum women with severe maternal complications during the first 24 hours after admission to the obstetric Intensive Care Unit

Dear Dr. Cecatti:

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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.

Thank you for the careful review and the opportunity.

REVIEWER COMMENTS:

Reviewer #1:

1. This submission represents an esoteric external validation of a prognostic model for pregnant and postparturn women manifesting severe morbidity and complication during the first 24 hours following admission to an Obstetric Intensive Care Unit (ICU) in comparison with an earlier study by the same authors (internal validation) published in 2018 in Critical Care, and referenced in this submission (reference # 9). See Payne B, et al. Development and internal validation of the multivariable CIPHER (Collaborative Integrated Pregnancy High-dependency Estimate of Risk) clinical risk prediction model. 2018 Oct 30;22(1):278. doi: 10.1186/s13054-018-2215-6.

That is OK.

2. I note concerns regarding the study design:
   A. The data collection time spans of the two (external validation) groups appear considerably different. While data was collected at the University of Campinas (UNICAMP) location between the years 2013 through 2015, the IMIP data were obtained between the 10/29/2018 and 9/30/2019.

   That is right. It was judged that increasing the number cases, including another obstetric ICU from other different region and enlarging the time period would be important for increasing the external validity of the study.

   B. In addition, it appears that these two separate sites likely encounter different patient volumes possibly reflecting distinctly different patient populations with inherently different modalities/mortalities. In the Discussion section (see lines # 277-270), the authors speculate this potential source of the different results.

   That is right. Each site is from distinct regions of the country in terms of HDI and populations.

   C. The likely difference between locations of the external validation study in contrast to the original study (and the inherent difference in the nature of these two groups (external validation versus original study, Obstetrics ICU versus general ICU, respectively), may likely have affected the results, as acknowledged by the authors (see lines # 281-284).

   We also do believe so.

   D. Although detailed in lines 137-146: “Prolonged organ support” without detailed specification which organ was supported (and with what measures), cardiac output (maintenance of blood pressure - vasopressor mediation), respiratory (supplemental oxygen, intubation / ventilation), renal, or blood transfusion, is vague / ill-defined.

In this part of the text (lines 149-161) there is only explanation of methods, describing the organs/systems with examples of this defined outcome. Detailed information is available in the Results session, in table 2.
E. Data appear incomplete (see lines 174-179), as PaO2 was replaced “sometimes” by oxygen saturation data SatO2. In the setting of ICU sites and the attempted assignment of prognostic outcome criteria - the is unfortunate. 

As recommended by literature (reference 14), PaO2 can be replaced by SatO2 to calculate oxygenation index. However, as the CIPHER doesn’t have got this variable, then we excluded this information (lines 194-196).

3. I am unclear regarding the statements (throughout the text) of “live-saving intervention outcome” of hysterectomy. Was the hysterectomy associated with perinatal complications (hemorrhage / placenta previa/ placental accreta sequence) occurring prior the ICU admission, or alternatively did a patient in the ICU truly require such surgical management (thus representing potential delayed primary surgical management)? That hysterectomy for uncontrollable hemorrhage or infection is associated with increased adverse maternal outcome (see lines # 238-239 and Table 2) is well established prior to this study.

Hysterectomy for hemorrhage or infection was the most common life-saving intervention which occurred before the admission to the ICU or during the ICU stay. This information was added to the text (lines 270-271).

4. Although clearly maternal age is an important variable, it is incorrect to refer to a group of patients in the reproductive age group (even if “older”), as having “declines in reserve capacity and homeostasis making women more vulnerable to the effects of acute disease processes” (see lines # 293-295. I also note that the reference to this unfortunate / incorrect statement regarding Obstetrical patients - reference # 26, refers to “Trends of death among the ELDERLY”, which in my assessment, may not be the most appropriate reference for this speculative statement / assumption. OK, we agree and the explanation was excluded (lines 325-327).

5. Line # 183: Data "were", not "was". OK, corrected on line 203)

6. While I found this manuscript interesting, respectfully in my assessment I doubt that it would interest the general readership of the Journal, and likely is more appropriate for a Critical Care, Epidemiology, Public or Community Health scientific periodical.

We do understand the reviewer point, however we still think that appropriate management for critically ill women during or soon after pregnancy is a matter of interest for obstetricians that should be part of the team responsible for the care of these specific population of women, considering the differences in physiologic parameters during pregnancy.

Reviewer #2: The authors are to be congratulated for their external assessment of the CIPHER prognostic model for pregnant and postpartum women admitted to the intensive care unit. As the authors point out in the Background section, numerous models have been developed for prediction of outcomes of ICU patients in general. The CIPHER model was developed specifically for use in ICU patients who are either pregnant or postpartum. However, it has not been externally validated. The authors collected a large data set from two institutions in Brazil, and assessed performance of the CIPHER model. In contrast to the original publication, the CIPHER model performed poorly in predicting adverse outcomes in their population.

The study population for the CIPHER model development and internal validation, and the authors’ study population are very different. As the authors point out, the mortality rate was much higher in the CIPHER population, and numerous additional differences are apparent from comparison of Table 2 of
Payne’s publication and Table 2 of the authors’ manuscript.

You are right. They are different in fact.

In the Discussion section:
Could the authors contrast the objectives and performance of the CIPHER model with the WHO near miss tool?
We contrasted CIPHER objectives with WHO near miss tool objectives (information added to the text on lines 323-324)

Lines 303-306 seems to be at odds with 307-309. Please clarify.
We excluded explanation and the corresponding reference (lines 325-327)

In lines 314-319, the authors comment on the difference between the high AUROC from the original study and the low AUROC in their validation study. The explanations offered were (1) most mortalities in the original study were from Pakistan, and (2) it is possible that many characteristics of this clinical setting differed from the present setting in Brazil.
Could the authors suggest additional possibilities? For example,
1. Could a lower or higher threshold for ICU admission affect the predictive value of the model?
2. Could a difference in patient populations (e.g. chronic underlying medical conditions, smoking, etc) affect the predictive value of the model?
3. Could differences in hospital resources (blood bank, interventional radiology, etc) affect the predictive value of the model?
Support details were added as suggested: such as more septic obstetric patients in ICU admissions in Pakistan. In addition, we cannot exclude the possibility of differences between settings from both studies regarding the threshold for ICU admission, chronic underlying medical conditions and also the availability of hospital resources could interfere in this assessment. This was included in the text on lines 351-355.

The authors propose that the model be recalibrated for public hospitals in LMICs. Is their own data set of sufficient size to recalibrate the model, using the same techniques as Payne and colleagues employed in the original development?

Also, Payne and colleagues commented: "A reduction in overall performance is evident when we compare performance seen in the high- and low- or middle-income country subgroups. In both settings, performance is maintained above the threshold for an adequate prognostic model (AUROC >0.7) but CIPHER is better at discriminating between women with and without outcomes in the low- or middle-income population, where the majority of outcomes occurred.” This seems to conflict with the current article’s assertion that the model needs to be calibrated for LMIC countries. Please explain.

The original purpose of the CIPHER model was to develop a statistical tool with international applicability. The internal validation set suggested that the model was applicable to countries with all income levels, pending external validation. From the current article, in this first test of the model, CIPHER has failed. Are we truly looking at the wrong coefficients in the right model, or the wrong model?
At the best of our knowledge, we believe that it is the right model, but it was developed with a completely different population from our, which can explain the differences between the results. This is the reason why we think the model should be recalibrated for different populations. And yes, we do think that this sample size is enough for such procedure.

The last sentence of the Conclusion section begins “When external validation is completed...”. Why are the authors confident that external validation will be completed? Should this sentence not begin IF rather than WHEN?
We agree and changed accordingly. The word “when” was substituted for “if” in the conclusion.

Reviewer #3: Thank you for the opportunity to review this manuscript on an important topic area. The purpose of the paper was to externally validate the CIPHER prognostic model for pregnant and postpartum women admitted to the intensive care unit. This study was conducted at 2 tertiary centers in Brazil. One site utilized a retrospective design and the other a prospective design. Overall, the
manuscript was well written and easy to follow. I have specific comments and questions regarding each section below.

Abstract: Appropriate, results consistent

Thank you.

Lines 50-52. Can you please clarify this statement? Comparisons were made in the discussions but from my understanding of the paper, this doesn't seem like what was completed in the study. **We mean that we compared the results of the current study with the results of the internal validation.**

Lines 61-63 This conclusion works in the paper because we have the perspective of what individual variables in the CIPHER was strongly associated with the composite outcome and differences in the populations (internal and external validation). However, in the abstract, it does not completely fit and I would suggest revising. **We agree and this phrase was then deleted (lines 67-68).**

Background: Concise and study rationale introduced.

A little more information on the importance of this work would be good. The specific results details results from reference 9 does not seem necessary in the introduction. Also, please revise the last sentence to be a clear study objective or provide a hypothesis. **The importance of this work was highlighted and added to the introduction, lines 97-99. Also, specific results from the internal validation were deleted (lines 95-96). The objective of the study is clearer now in the last paragraph (line 100).**

Methods: Clearly written

Eligibility criteria, sample size calculation, and detailed information on included variables provided.

Please include information on IRB approval and consenting process for the prospective portion of the study. **IRB approval for the prospective portion of the study was included (lines 247-249).**

How did you determine the control variables to include? **We determined the control variables according to those used in the internal validation study to assure consistency.**

Can you provide a rationale of why a retrospective design in one center and a prospective in the other? Also, please explain the differences in timeline at the different centers. **Well noted. This was in fact a long history. Initially the intention was to include all cases from the first component in the first development and internal validation study. However, all the procedures and approvals took so long that the data could not be collected and used, but only a few cases. After the first study came out, we decide to use that data plus those from a prospective design performed to complete the sample size. This information was added to the methods. This is now explained in the text (lines 177-181).**

Regarding data collection, there are gaps regarding the process.

Lines 159-161, How was RedCap used to identify retrospective participants for the study? **The database was built for the internal validation study, but only a few patients were used in the first study. We think this is clearer now.**

Was the data collected manually and then entered into Redcap? **The data was collected using the Redcap, not manually (line 188).**

Lines 171-173 - 100% reviewed for completion, accuracy? What did the random evaluation of medical records entail? Moving up some content from paragraph 3 on page 7 (lines 180-186) to follow paragraph 1 on page 7 may help with flow and immediately provide answers to questions that arise.
regarding data collection and verification. 

In fact all cases were reviewed. This is clearer now in the text (lines 190-191).

Composite outcome described twice (variable section and statistical analysis). One description is adequate. 

You are right. We deleted the information on lines 215-220.

Results: well described and easy to follow

How was the cut-off of 11.6% determined? 

The cutoff of 11.6% was determined using the ROC curve

Discussion:

Lines 277-278: I don't think speculations are necessary since this study and the internal validation study both collected information on obstetric indications. 

We think this an important topic which help to explain the differences we had between both studies and also taking into account that we performed the study only in obstetric ICU (lines 308-309).

"Other variables such as aPTT, potassium, sodium, creatinine and bilirubin were poorly associated with the outcome, which again suggests that the hysterectomy protected from others organ dysfunctions". I am not sure if this can be solely attributed as the reason for this. 

We agree that this is again a speculation. We tried to soften this in the text (line 330).

Conclusions:

Lines 330-333: This conclusion doesn't fully support current data and external validation completed in this study. Maybe consider including as future studies and goals. 

We agree and changed the text accordingly(lines 366-367.

Tables easy to understand

Figure 1 can be a supplemental

Figure 3 may be a difficult figure/caption for readers to follow

Tripod checklist not completed

Now completed.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Table 3: For this cohort, the input variables were significantly associated with the composite outcome for only 5 of 10 patient characteristics in the CIPHER model, perhaps a harbinger of the model's poor performance for this validation cohort. 

We agree.

Table 4: The PPV and NPV columns should be omitted, since they are dependent on the prevalence of the outcome, which varied by center. Instead, should cite the sens, spec, LR(-) and LR(+) with respective CIs, since those are invariant test characteristics. Also, in terms of model utility, the specificities are good, but the sensitivities, which arguably are paramount for prospective identification of the at-risk group, were quite poor. 

We agree and omitted the columns for PPV and NPV as suggested.

Fig 2: The cut-off for the model seems irrelevant, the model performance is no better than a random coin flip. 

We agree.
Fig 3: The calibration plot is not relevant, since the overall model performed so poorly.

General: Should re-word the abstract and discussion. This cohort did not validate the CIPHER model, rather it did not perform well at all. Should develop a model from this cohort with internal validation to evaluate whether a different model would perform better for this population. Thank you. Now we agree that is better to say that directly as we did in the abstract (lines 71-71) and in the discussion session (lines 364-365)

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics & Gynecology. If you opt to submit a revision for consideration, would recommend changing the title to: Prognostic Value of the Collaborative Integrated Pregnancy High Dependency Estimate of Risk (CIPHER) Model in Critically Ill Obstetric Patients in Brazil (or something similar).
Suggestion accepted. Changed accordingly.

2. Per the comments of the statistical editor, please simply report that the model performed poorly and could not be validated rather than trying to establish a new cut off of interest for a model that did not work in your population.
Again, suggestion accepted.

3. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with 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. 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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* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.
OK, all these points were checked and they are OK.

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OK.

6. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author affirms that this manuscript is an honest, accurate, and transparent account of the
study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

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**OK, done.**

7. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

**OK, done.**

8. Please submit a filled in checklist with your revision. The one that was uploaded is blank.

**OK.**

9. 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 data definitions at [https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions](https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions) and the gynecology data definitions at [https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions](https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions). If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

**OK.**

10. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

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**OK.**

12. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
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13. Provide a précis on the second page, for use in the Table of Contents. The précis is a single
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abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This
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abstract carefully.
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