OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

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

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Jul 01, 2019
To: "Robert Edward Bristow" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-864

RE: Manuscript Number ONG-19-864

A Risk-Adjusted Model for Ovarian Cancer Care and Disparities in Access to High Performing Hospitals

Dear Dr. Bristow:

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 Jul 22, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort study evaluating ovarian cancer care in California hospitals, specifically adherence to NCCN guidelines. The study also evaluated sociodemographic characteristics related to disparities in accessing care. The paper is well written. There are parts of the methodology that are confusing and should be better explained. See comments below:

1. As a non-oncologist, it is not clear to me why we don't expect 100% adherence to the NCCN guidelines, that needs to be elucidated more in the introduction. Then you could just compare observed adherence to the actual guidelines to see who was following the guidelines. The creation of the observed to expected ratio is confusing. I am not sure how you are predicting what you would expect the hospital to do given its case mix. You are saying a high observed to expected ratio means the hospital is adhering better than we would expect given what? Why would expectations be low, that is what I don't understand.

2. Results: In the multivariable analysis, the hazard ratios for disease specific survival rates of high O/E compared to Intermediate and Low are very weak (HR of 1.06 and 1.10) even though statistically significant. These conclusions need to be tempered.

3. Discussion: Please explain more why you think the high volume hospitals didn't do well in your ratio.

Reviewer #2: Dear Authors,

This is very well written paper that examines a novel ovarian-cancer specific quality metric measuring the observed to expected ratio for adherence to NCCN guidelines. The study is well designed and is able to show that the O/E ratio is significantly as a reasonable way to stratify hospitals given the differences in overall survival between high, medium and low performing hospitals in a large California database. Further, they clearly identify some disparities in access to those high performing hospitals. There are inherent limitations in what information is available in the larger California database and how they define criteria for adherence of NCAA guidelines from which the O/E score is calculated. Below are a few comments on the paper.

1. Line 104 (Line 136, Line 143) - Standard care for advanced ovarian cancer can include neoadjuvant chemotherapy followed by interval cytoreductive surgery. In these cases, surgical staging is delayed and reported surgical stage may not truly represent original stage as they may have had response to chemotherapy with shrinkage of their disease. (For example, a debulking surgery may reveal a stage IIIB ovarian cancer at time of surgery, but original stage may have been

IIIC or more advanced prior to treatment with chemotherapy). How does the California database code the staging information in neoadjuvant cases? Was the O/E tool built in any way to accommodate for these difficulties with staging in ovarian cancer receiving neoadjuvant chemotherapy. You stage in Line 143 that surgery must have preceded chemotherapy for stage I-IIIB disease to be compliant - does that mean staging was determined pre-operatively in neoadjuvant cases?

2. Line 105-6 - "tumor characteristics, patient characteristics, tumor diagnosis and treatment". This statement is confusing. What is the difference between tumor characteristics and tumor diagnosis.

3. Lin 130 - Are these cases only patients who had surgery? Or do they represent anyone who had an ovarian cancer diagnosis code used during an admission? How was the O/E ratio affected if individual patients received only surgery or only chemotherapy in one hospital and received the remainder of their treatment at another hospital?

4. LINE 138 Stages I-IIIB - standard of care for these stage was considered to be oophorectomy, pelvic and para-aortic lymphadenectomy omentectomy. There is some variation in lymph node dissection in cytoreductive surgeries, particularly if gross evidence of tumor outside of the pelvis. Did you determine how many people with more advanced disease > STAGE I, II did not have LND which may have been reasonable based on their practice in the setting of visible tumor outside of the pelvis.

5. Line 211 (Line 306 on) - DSS 48 v 62 v 73 mos. 2 yrs difference! Very interesting finding and validates that the O/E ratio may be a very good measure of quality of care and the fact this O/E ratio remained significantly associated with survival after multivariate analysis. Nevertheless, there are also likely other social determinants of health that may not be well captured by the database demographic variables confounding this result. As these factors may be fundamentally linked to why certain patients sought care at low O/E institutions and that choice alone is likely not the only reason for the worsened survival. You address this indirectly in Line 306 in the discussion

6. Line 230, 269 - fascinating that only 2/30 high O/E hospitals were high volume - is that the greater than or equal to 20 cases per year? My question again is what does that case volume represent - any admission with ovarian cancer or a surgical admission. My other question is are some high volume hospitals not receiving better O/E scores as patients seek adjuvant therapy closer to home? Was this captured by the database?

7. Tables 2-4: Was a survival analysis run just looking at case volume? Were there any differences? It would reinforce the importance of the more nuanced measure of quality - the O/E ratio - over volume alone if there was no significant differences or less of a robust difference in survival between high, intermediate and low volume hospitals.

8. Final comments - several changes to ovarian cancer care are on the horizon and some already being incorporated into standard care, such as use of maintenance therapy with PARP inhibitors for select patients. These are novel and expensive treatments, require genetic testing and sometimes somatic testing of the tumor. Can the O/E ratio be modified to include adherence to guidelines in genetic testing and appropriate use of PARP inhibitors? How easy is this metric to adapt to changing treatment paradigms?

Reviewer #3: Title: A Risk-Adjusted Model for Ovarian Cancer Care and Disparities in Access to High Performing Hospitals

General Comments:

This is a retrospective population based study, using data from a state-wide registry to validate a quality metric that was previously reported by this same group in 2015. The strengths of this manuscript include data from a large cancer registry with high rates of case reporting and follow-up and it was well written. Tables and figures were clear and helpful. Weaknesses include the retrospective nature of the data collection as well as potential confounding factors. Details of the review are as follows:

1. Materials and Methods: Lines 130-133 "Hospital volume was calculated based on the average annual number of ovarian cancer cases that were admitted in that hospital. Hospitals with ≥20 cases per year were classified as high-volume and hospitals with <20 cases per year were considered low-volume." Based on the statement in the introduction (Lines 83-85 "While high-volume hospital care (>20 cases/year) correlates with adherence to NCCN treatment guidelines, crude case volume alone is an imprecise measure of quality care, and there are relatively few centers with the required caseload.") as well as the results showing the low numbers of hospitals with case volumes >20, what was the rationale for using 20 as a measure of high or low volume in this quality metric?

2. Results: Lines 203-205: "High-O/E hospitals were significantly more likely to deliver NCCN guideline adherent care (53.3%) compared to Intermediate-O/E (37.8%) 205 and Low-O/E (27.5%) hospitals." Since high O/E hospitals had less minority, low SES and insured patients, how does this influence the results above?

3. Discussion: Lines 256-258: "The reasons behind this trend are multifactorial and include medical comorbidities precluding surgery or chemotherapy, limited availability of or access to high volume specialty providers, and barriers to care associated with sociodemographic and geographic characteristics" Please expound on how the confounding factors

influence the classification of O/E status for hospitals and if you were able to account for these in the modeling?

4. Discussion: Lines 289-290 "care policy administrators, professional societies, advocacy organizations, and payers to concentrate ovarian cancer care in high-performing centers is warranted" How would concentrating care in high-performing centers affect access to care, especially for those most vulnerable and already have barriers to high performing centers?

5. Discussion: Lines 327-329 "Second, access to high-performing hospitals is currently limited, and marked disparities exist for specific vulnerable populations in their ability to access High-O/E hospitals. Finally, improving access to High-O/E hospitals through a performance-based triage strategy for patients with suspected ovarian cancer may be one of the most expedient means available to directly improve outcomes and progress toward true healthy equity in ovarian cancer care hospitals." Wouldn't concentrating care to high-access hospitals potentially make it harder for vulnerable patients to receive care in and around their communities, thus increasing health disparities?

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: Need units for age at diagnosis

2. Table 2: The reason given to include hospitals with < 5 annual cases was that the variability was unstable, therefore those hospitals were grouped with the lowest O/E quartile group. However, in this Table, Hospital volume for < 2 cases and for 2-4.99 cases total 159+134 = 293 hospitals, while the total for lowest O/E score or < 5 cases was 304, so how many of the 304 were in that category based on O/E score and how many based on volume < 5 cases?

3. Tables 3, 5: Need to include a column of unadjusted HR to contrast with aHR. Could consolidate HR with its CI intor one column. p-values could be indicated by footnotes, thus omitting a column. Need to indicate which variables were retained in the final model. Need to clarify for Table 5 whether age at dx refers to age per year or in strata and is year of diagnosis referenced to earliest year?

4. Table 4: According to Table 2, > 20 cases comprised only 14 hospitals (3.3%) and 6342 cases (21.1%). Seems like an arbitrary cutpoint. The O/E ratios were divided into lowest quartile, middle 2 quartiles and highest quartiles. A similar analysis would be more informative to show the relationship of volume strata to O/E category.

5. Table 5: While "predictor" is a useful term in modeling, it has other connotations. This study design can only evaluate associations.

6. Table 5, Fig 3: The geographic location of the hospital vs patient's home is not included as a variable in the model. To what extent are race, SES and insurance type actually a function of neighborhood and distance to high O/E hospital?

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. Please add some variance to the methods section. We do understand that there will be overlap in this section; however, there is a large amount of self-plagiarism in this section.

5. 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.

6. 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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

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

* All financial support of the study must be acknowledged.
* 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).

8. 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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

9. 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.

10. 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.

11. 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.

12. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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 Jul 22, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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Obstetrics and Gynecology
Editorial Office

August 28, 2019

Dear Editors:

Please find attached a revised manuscript entitled **A Risk-Adjusted Model for Ovarian Cancer Care and Disparities in Access to High-Performing Hospitals** that we are re-submitting as an original research article soley to the *Obstetrics & Gynecology*. The Reviewers comments, queries, and suggestions were very insightful. We have addressed them in a point-by-point fashion below. As requested, a number of cosmetic linguistic changes have been made to the Methods section to address the issue of self-plagiarism. With resepect to verification of database input: the California Department of Public Health and ten regional cancer registries operate The California Cancer Registry (CCR). Since 1988, all cancer professionals and facilities responsible for treating or diagnosing patients with cancer are required to report demographic, diagnostic, and treatment data to the CCR by law (Health and Safety Code, Section 103885). Hospital cancer registrars, physicians, pathologists, or other professional report the data using standardized data collection and quality control procedures. Master case listing files are created to allow reporting facility or CCR regional staff to verify and validate all cases received from a reporting source for a defined reporting period. Case reporting is estimated to be 99% for the entire state of California, with follow-up completion rates exceeding 95% (website reference: https://www.ccrcal.org/submit-data/). All authors have contributed to this manuscript, approved this submission, and there are no potential conflicts of interest. As lead author, I affirm 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. If the manuscript is ultimately accepted for publication, we elect to **OPT IN** (Yes, please publish our point-by-point response letter). Thank you in advance for considering our revised manuscript.

Sincerely,

Robert E. Bristow, MD, MBA

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REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort study evaluating ovarian cancer care in California hospitals, specifically adherence to NCCN guidelines. The study also evaluated sociodemographic characteristics related to disparities in accessing care. The paper is well written. There are parts of the methodology that are confusing and should be better explained. See comments below:

1. As a non-oncologist, it is not clear to me why we don't expect 100% adherence to the NCCN guidelines, that needs to be elucidated more in the introduction. Then you could just compare observed adherence to the actual guidelines to see who was following the guidelines. The creation of the observed to expected ratio is confusing. I am not sure how you are predicting what you would expect the hospital to do given its case mix. You are saying a high observed to expected ratio means the hospital is adhering better than we would expect given what? Why would expectations be low, that is what I don't understand.

We thank Reviewer #1 for comments and query. Addressing this point has improved the clarity of the manuscript. No contemporary study has demonstrated that 100% adherence to treatment guidelines is feasible in an unselected patient population. There are numerous factors that contribute to this observation, most notably patient-related factors (e.g. age, medical comorbidities, inability to travel, insufficient financial resources, intolerance of side effects etc) that are not within the control of the treating physicians or hospital. We assume that many, but probably not all, of these factors are reflected in the clinical and demographic variables that comprise a hospital's case mix. The O/E ratio attempts to adjust for these non-modifiable factors to arrive at an "expected" rate of adherence for each hospital, given the relative proportions of these non-modifiable factors in the specific hospital patient population. Actual hospital performance (i.e. the "observed" rate of guideline adherence) is then compared to determine whether the hospital is under-performing, over-performing, or at the expected level. To address the Reviewers point, the following passage has been added to the Introduction (pp5-6, lines 93-96): "*There are multiple patient- and disease-related factors that preclude 100% adherence to ovarian cancer treatment guidelines. The O/E instrument accounts for differences in case-mix complexity between hospitals and provides a measure of guideline adherence adjusted for these confounding factors*."

2. Results: In the multivariable analysis, the hazard ratios for disease specific

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survival rates of high O/E compared to Intermediate and Low are very weak (HR of 1.06 and 1.10) even though statistically significant. These conclusions need to be tempered.

We thank Reviewer #1 for their comments. We agree that although the High-O/E association was not the strongest among all variables, it remained significantly associated with survival in the multivariate analysis with a magnitude comparable to other variables that are considered clinical meaningful like Charlson comorbidity score and gradations in SES and payer. We also see a trend in HR at different O/E categories (1.06 for Intermediate vs. high, 1.10 for low vs high. This clearly shows the "dose-response" effect of O/E ratio. Unlike other variables (Charlson comorbidity score and SES) that are beyond the capacity of the health care delivery system to modify, where a patient is treated (e.g. the O/E of their chosen hospital) may be much more readily modified. We respectfully submit that we believe our conclusions as originally written are appropriately tempered given the observed effect on multivariate analysis.

3. Discussion: Please explain more why you think the high volume hospitals didn't do well in your ratio.

Reviewer #1 may be referring to why not more high volume hospitals in the high O/E category? As indicated by the Wright paper, both hospital case volume and adherence to accepted treatment standards appear to be important in determining survival outcome for patients with ovarian cancer. Our findings underscore this observation. In other words, case volume alone is a relatively crude measure of survival outcome and a high case volume does not necessarily predict delivery of guideline adherent care. We did include a minimum volume criterion in that hospitals had to have a case volume of at least 5 cases per year to be categorized as Intermediate or High O/E. It is possible that there are other, unmeasured, non-modifiable factors not captured by current clinical and demographic characteristics influencing the observed rate of guideline adherence (the components that comprise the O/E ratio) and that these unknown factors are disproportionately distributed among high volume hospitals, although this premise seems unlikely.

Reviewer #2: Dear Authors,

This is very well written paper that examines a novel ovarian-cancer specific quality metric measuring the observed to expected ratio for adherence to NCCN guidelines. The study is well designed and is able to show that the O/E ratio is significantly as a reasonable way to stratify hospitals given the differences in overall survival between high, medium and low performing hospitals in a large California database. Further, they clearly identify some disparities in access to those high performing hospitals. There are inherent limitations in what

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We thank Reviewer #2 for their kind comments and query. Regarding staging, the CCR extracts information about the cancer case after the case is done with all treatments, so they are able to consolidate information from different sources including an assigned clinical stage if surgery was delayed until after chemotherapy or indeed if no surgery was performed at all. In other words, for CCR data the stage of an ovarian cancer case is not necessarily determined at surgical staging. We do not have the ability to verify how the final stage of disease was assigned in all cases, but presumably the answer to the Reviewer's question is yes, in cases in which chemotherapy preceded surgery, the clinical stage of disease would have been assigned using all available means (imaging, biopsy, cytology etc).

2. Line 105-6 - "tumor characteristics, patient characteristics, tumor diagnosis and treatment". This statement is confusing. What is the difference between tumor characteristics and tumor diagnosis.

We agree with Reviewer #2 that this terminology is confusing. The phrase "tumor diagnosis" has been omitted.

3. Lin 130 - Are these cases only patients who had surgery? Or do they represent anyone who had an ovarian cancer diagnosis code used during an admission? How was the O/E ratio affected if individual patients received only surgery or only chemotherapy in one hospital and received the remainder of their treatment at another hospital?

We thank Reviewer #2 for their queries. The case volumes include every ovarian cancer case diagnosed regardless of surgery. The Hospital field in CCR data is defined

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as the first treating hospital. There is the potential for some patients to have been switching hospitals, and we acknowledge this in the study limitations.

4. LINE 138 Stages I-IIIB - standard of care for these stage was considered to be oophorectomy, pelvic and para-aortic lymphadenectomy omentectomy. There is some variation in lymph node dissection in cytoreductive surgeries, particularly if gross evidence of tumor outside of the pelvis. Did you determine how many people with more advanced disease > STAGE I, II did not have LND which may have been reasonable based on their practice in the setting of visible tumor outside of the pelvis.

Reviewer #2 raises a good point here, but unfortunately we do not have the descriptive detail of surgical findings for any of these population-based database patients in order to construct the type of analysis that the Reviewer suggests.

5. Line 211 (Line 306 on) - DSS 48 v 62 v 73 mos. 2 yrs difference! Very interesting finding and validates that the O/E ratio may be a very good measure of quality of care and the fact this O/E ratio remained significantly associated with survival after multivariate analysis. Nevertheless, there are also likely other social determinants of health that may not be well captured by the database demographic variables confounding this result. As these factors may be fundamentally linked to why certain patients sought care at low O/E institutions and that choice alone is likely not the only reason for the worsened survival. You address this indirectly in Line 306 in the discussion.

We wholeheartedly agree with Reviewer #2 on this point. To make this point more clearly, we have added the phrase "to actually obtaining such care" to the passage immediately succeeding the sentence the Reviewer references above (p 15 lines 311-316) so that it now reads as follows: "*If the fundamental goal is health care equity, all segments of the population should not only have equal access to high-quality care but resources must be directed toward remediating the underlying barriers to actually obtaining such care for underserved populations. This will require a more detailed understanding of the specific barriers (e.g. financial, geographic, cultural, health literacy) affecting the populations most vulnerable to disparities in access to expert care* [17, 36, 48]."

6. Line 230, 269 - fascinating that only 2/30 high O/E hospitals were high volume - is that the greater than or equal to 20 cases per year? My question again is what does that case volume represent - any admission with ovarian cancer or a surgical admission. My other question is are some high volume hospitals not receiving better O/E scores as patients seek adjuvant therapy closer to home? Was this captured by the database?

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We thank Reviewer #2 for their comment. Case volume includes every ovarian cancer cases diagnosed regardless of surgery. In order to better clarify this point, the following passage has been added (p 7 lines 136-7): “Hospital volume was calculated based on the average annual number of ovarian cancer cases that were admitted in that hospital *and included both surgical and non-surgical cases*.”

7. Tables 2-4: Was a survival analysis run just looking at case volume? Were there any differences? It would reinforce the importance of the more nuanced measure of quality - the O/E ratio - over volume alone if there was no significant differences or less of a robust difference in survival between high, intermediate and low volume hospitals.

We thank Reviewer #2 for their comments. We did not perform a parallel analysis of case volume alone for the reasons alluded to in the introduction and in specific reference to the Wright paper, which conclusively demonstrated that survival outcomes were dependent on both case volume and adherence to treatment guidelines simultaneously. In our initial paper on the O/E ratio (reference #8) we did find that increasing annual case volume was positively correlated with an increasing O/E ratio. Based on those data, the O/E ratio as currently constructed includes a basic criterion for case volume (< or > 5 cases per year), but this is included to provide stability for the model rather than directly account for any survival effect of case volume alone. The Reviewer raises an excellent point, however, and analyses of annual case volume as a continuous variable relative to O/E are ongoing.

8. Final comments - several changes to ovarian cancer care are on the horizon and some already being incorporated into standard care, such as use of maintenance therapy with PARP inhibitors for select patients. These are novel and expensive treatments, require genetic testing and sometimes somatic testing of the tumor. Can the O/E ratio be modified to include adherence to guidelines in genetic testing and appropriate use of PARP inhibitors? How easy is this metric to adapt to changing treatment paradigms?

We thank Reviewer #2 for their comments and insightful thoughts. Using a population-based dataset such as the CCR currently does not allow for inclusion of variables such as those outlined by the Reviewer. In order to incorporate such variables into the O/E ratio, they would need to be accessible from whatever data source is used to generate the data input. Ideally, this would be done using a prospectively designed dataset. Absent that, the most likely means of assessing the utility of and adherence to some of these changes to ovarian cancer treatment would be through a claims-based dataset such as SEER-Medicare, which would necessarily limit the scope of the population under study.

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Reviewer #3: Title: A Risk-Adjusted Model for Ovarian Cancer Care and Disparities in Access to High Performing Hospitals

General Comments:

This is a retrospective population based study, using data from a state-wide registry to validate a quality metric that was previously reported by this same group in 2015. The strengths of this manuscript include data from a large cancer registry with high rates of case reporting and follow-up and it was well written. Tables and figures were clear and helpful. Weaknesses include the retrospective nature of the data collection as well as potential confounding factors. Details of the review are as follows:

1. Materials and Methods: Lines 130-133 "Hospital volume was calculated based on the average annual number of ovarian cancer cases that were admitted in that hospital. Hospitals with ≥20 cases per year were classified as high-volume and hospitals with <20 cases per year were considered low-volume." Based on the statement in the introduction (Lines 83-85 "While high-volume hospital care (>20 cases/year) correlates with adherence to NCCN treatment guidelines, crude case volume alone is an imprecise measure of quality care, and there are relatively few centers with the required caseload.") as well as the results showing the low numbers of hospitals with case volumes >20, what was the rationale for using 20 as a measure of high or low volume in this quality metric?

We thank Reviewer #3 for their comments and query. An average annual case volume of 20 or more ovarian cancer cases is the standard criterion for a high-volume hospital that has been validated by numerous retrospective and population-based studies over the past 12-15 years. That said, intuitively, it seems that a round number cut off such as 20 is rather arbitrary, as the number of surgical vs non-surgical cases as well as the number (and identity) of the operating surgeons could fluctuate largely within this “catch-all” measure. Relative to this comment and those of Reviewer 2, analyses of case volume as a continuous measure relative to O/E are currently underway to try and lend more clarity to the demonstrable effect of case volume as a stand alone variable and/or combined with O/E.

2. Results: Lines 203-205: "High-O/E hospitals were significantly more likely to deliver NCCN guideline adherent care (53.3%) compared to Intermediate-O/E (37.8%) 205 and Low-O/E (27.5%) hospitals." Since high O/E hospitals had less minority, low SES and insured patients, how does this influence the results above?

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We thank Reviewer #3 for their query. The O/E ratio adjusts for these variables, so the impact of more or fewer minority or low SES or insured patients is accounted for in the calculation of the O/E ratio for each hospital based on its case mix.

3. Discussion: Lines 256-258: "The reasons behind this trend are multifactorial and include medical comorbidities precluding surgery or chemotherapy, limited availability of or access to high volume specialty providers, and barriers to care associated with sociodemographic and geographic characteristics" Please expound on how the confounding factors influence the classification of O/E status for hospitals and if you were able to account for these in the modeling?

We thank Reviewer #3 for their request. The passage referred to is in reference to the variability in the observed rates in ovarian cancer guideline adherence by study methodology and institution type. While not able to account for all confounding factors, the stated purpose of the O/E ratio is to provide a calculation of hospital guideline adherence rate adjusted for the effects of many of these confounding factors. For example, medical comorbidities are included in the model, but there are some sociodemographic variables that are beyond the granularity of a population-based dataset that we were not able to include. The effect of geographic location is the subject of ongoing analyses. So, indeed, many of these confounding factors are accounted for in the modeling. To make this point more clearly, we have added the following passage to the Introduction (pp 5-6 lines 93-96): "*There are multiple patient- and disease-related factors that preclude 100% adherence to ovarian cancer treatment guidelines. The O/E instrument accounts for differences in case-mix complexity between hospitals and provides a measure of guideline adherence adjusted for these confounding factors.*"

4. Discussion: Lines 289-290 "care policy administrators, professional societies, advocacy organizations, and payers to concentrate ovarian cancer care in high-performing centers is warranted" How would concentrating care in high-performing centers affect access to care, especially for those most vulnerable and already have barriers to high performing centers?

We thank Reviewer #3 for their query. One of the central messages of the current analysis is that by using the novel measure of the O/E ratio the absolute number of high-performing hospitals (more likely to deliver guideline adherent care and associated with improved survival) more than doubles the number of hospitals that would have been so-designated if based on volume criteria alone (from 14 high volume hospitals to 30 High-O/E hospitals). This is detailed in the Results section (pp 11-12 lines 228-237) as follows: "*The geographic distribution of the 426 hospitals treating ovarian cancer patients, classified according to O/E status and high annual case volume, is shown in Figure 3. The northernmost regions and mid-section of the state*

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were predominantly serviced by Low- and Intermediate-O/E hospitals. The 30 High-O/E hospitals and 14 high volume centers were largely concentrated around population-dense areas in Northern and Southern California. A cross-tabulation by hospital O/E classification and case volume revealed that only 2 of 30 High-O/E hospitals also had high average annual case volume, both located in Northern California (Table 4, Figure 3-top inset). In other words, 93.3% of High-O/E hospitals were not high volume, and only 14.3% of high annual case volume hospitals met the performance-based metric of High-O/E." Admittedly, High-O/E hospitals geographically track with population centers; however, large geographic barriers so not appear to the primary issue for many of the demographically-at-risk patient populations. We believe that by significantly expanding the number of high-performing hospital "options" (admittedly, mostly located within population centers), barriers for vulnerable populations such as payer type and geographic location to traditionally defined high-volume centers could be significantly mitigated.

5. Discussion: Lines 327-329 "Second, access to high-performing hospitals is currently limited, and marked disparities exist for specific vulnerable populations in their ability to access High-O/E hospitals. Finally, improving access to High-O/E hospitals through a performance-based triage strategy for patients with suspected ovarian cancer may be one of the most expedient means available to directly improve outcomes and progress toward true healthy equity in ovarian cancer care hospitals." Wouldn't concentrating care to high-access hospitals potentially make it harder for vulnerable patients to receive care in and around their communities, thus increasing health disparities?

We thank Reviewer #3 for their comment and query. This is a good point and one that addresses our premise head on. Improving ovarian cancer outcomes for all, not only the underserved, can be achieved either by concentrating care in centers that provide superior treatment or by raising the level of performance of all centers that provide ovarian cancer care. State of the art, high-quality ovarian cancer care is a resource intense undertaking, requiring multiple specialist providers and services, such that the "raise all boats" approach noted above is challenging at best. In other cancer types, the concentration of care model has proven more successful. As noted above, the O/E methodology can increase the number of high performing hospitals, improving access to such centers becomes a question for health policy administrators and payers.

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: Need units for age at diagnosis

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TABLE 3. Unadjusted and adjusted hazard ratios for disease-specific survival for socio-demographic variables, tumor characteristics, and hospital classification.

	Unadjusted hazard ratio and 95% C.I.	Adjusted hazard ratio and 95% C.I.
Patient demographic		
Race		
Non-Hispanic white	1.00	1.00
Non-Hispanic black	1.59 (1.47, 1.71)***	1.28 (1.18, 1.38)***
Hispanic	1.10 (1.05, 1.15)***	0.97 (0.92, 1.02)
Asian/Pacific Islander	0.92 (0.87, 0.98)**	0.99 (0.93, 1.05)
American Indian or unknown	0.88 (0.70, 1.11)	0.86 (0.68, 1.10)
Insurance		
Managed Care	1.00	1.00
Medicare	1.05 (1.01, 1.10)*	0.96 (0.92, 1.01)
Medicaid	1.46 (1.37, 1.55)***	1.14 (1.06, 1.22)***
Other Insurance	0.95 (0.90, 1.01)	0.96 (0.90, 1.02)
Not insured	1.41 (1.27, 1.56)***	1.23 (1.10, 1.38)***
Unknown	1.19 (1.06, 1.35)**	0.94 (0.83, 1.07)
SES		
Highest SES	1.00	1.00
Higher-middle SES	1.08 (1.03, 1.13)**	1.06 (1.004, 1.11)*
Middle SES	1.13 (1.07, 1.18)***	1.10 (1.04, 1.16)***
Lower-middle SES	1.30 (1.24, 1.37)***	1.20 (1.14, 1.27)***
Lowest SES	1.33 (1.25, 1.41)***	1.18 (1.11, 1.26)***
Marital status		
Single or unknown	1.00	1.00
Married	0.88 (0.85, 0.91)***	0.92 (0.89, 0.96)***
Charlson comorbidity score		
'0	1.00	1.00
'1	1.29 (1.24, 1.35)***	1.16 (1.11, 1.21)***
2+	1.21 (1.16, 1.26)***	1.06 (1.01, 1.11)*
Unknown	1.19 (1.10, 1.29)***	1.02 (0.93, 1.11)
Tumor characteristics		
Grade or differentiation of the tumor		
Grade I or well differentiated	1.00	1.00
Grade II or moderately well differentiated	2.41 (2.15, 2.70)***	1.64 (1.46, 1.84)***
Grade III or poorly differentiated	3.95 (3.55, 4.39)***	1.79 (1.60, 2.00)***
Grade IV or undifferentiated/anaplastic	3.86 (3.45, 4.31)***	1.79 (1.59, 2.02)***
Grade and differentiation not stated	5.18 (4.65, 5.76)***	2.24 (2.00, 2.52)***
Stage		
Stage I	1.00	1.00
Stage II	2.44 (2.21, 2.70)***	2.49 (2.25, 2.76)***

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Stage III	6.68 (6.21, 7.18)***	6.57 (6.08, 7.11)***
Stage IV	12.64 (11.73, 13.62)***	10.70 (9.87, 11.60)***
Size		
< 5cm	1.00	1.00
5-10cm	1.08 (1.01, 1.14)*	1.01 (0.95, 1.08)
>10cm	0.86 (0.81, 0.92)***	0.95 (0.89, 1.01)
Unknown	1.61 (1.52, 1.70)***	1.16 (1.10, 1.23)***
Histology		
Serous	1.00	1.00
Mucinous	0.51 (0.47, 0.56)***	1.40 (1.26, 1.54)***
Endometrioid	0.36 (0.34, 0.39)***	0.82 (0.75, 0.88)***
Clear cell	0.57 (0.52, 0.62)***	1.27 (1.16, 1.39)***
Adenocarcinoma, NOS	1.92 (1.82, 2.02)***	1.43 (1.35, 1.51)***
Others	1.11 (1.06, 1.16)***	1.31 (1.25, 1.37)***
Hospital O/E Classification		
O/E category		
Low or <5 cases per year	1.23 (1.17, 1.29)***	1.10 (1.04, 1.16)***
Intermediate	1.06 (1.01, 1.11)*	1.06 (1.01, 1.11)*
High	1.00	1.00

Both unadjusted and adjusted hazard ratios are from Cox models included age at diagnosis in years and year of ovarian cancer diagnosis as strata.

*p<0.05, **p<0.01, ***p<0.001

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TABLE 5. Unadjusted and adjusted odds ratios of access to high-O/E centers

	Unadjusted odds ratio and 95% C.I.	Adjusted odds ratio and 95% C.I.
Patient demographic		
Age at diagnosis (year)	0.992 (0.990, 0.994)***	0.995 (0.992, 0.997)***
Year of diagnosis	1.02 (1.01, 1.03)***	1.02 (1.01, 1.03)***
Race		
Non-Hispanic white	1.00	1.00
Non-Hispanic black	0.78 (0.68, 0.91)**	0.91 (0.78, 1.06)
Hispanic	0.79 (0.73, 0.86)***	0.85 (0.78, 0.93)***
Asian/Pacific Islander	1.33 (1.22, 1.45)***	1.21 (1.11, 1.33)***
American Indian or unknown	0.94 (0.65, 1.34)	0.91 (0.63, 1.32)
Insurance		
Managed Care	1.00	1.00
Medicare	0.64 (0.60, 0.69)***	0.74 (0.68, 0.81)***
Medicaid	0.98 (0.88, 1.08)	1.19 (1.07, 1.33)**
Other Insurance	0.76 (0.69, 0.83)***	0.68 (0.62, 0.75)***
Not insured	1.21 (1.03, 1.41)*	1.41 (1.20, 1.66)***
Unknown	1.16 (0.95, 1.40)	1.34 (1.10, 1.63)**
SES		
Highest SES	1.00	1.00
Higher-middle SES	0.80 (0.74, 0.87)***	0.79 (0.73, 0.86)***
Middle SES	0.58 (0.53, 0.63)***	0.58 (0.53, 0.63)***
Lower-middle SES	0.52 (0.47, 0.57)***	0.51 (0.46, 0.56)***
Lowest SES	0.42 (0.38, 0.47)***	0.41 (0.36, 0.46)***
Marital status		
Single or unknown	1.00	1.00
Married	1.03 (0.98, 1.10)	0.94 (0.89, 1.002)
Charlson comorbidity score		
'0	1.00	1.00
'1	0.87 (0.81, 0.94)***	0.95 (0.88, 1.02)
2+	0.74 (0.69, 0.80)***	0.91 (0.83, 0.99)*
Unknown	1.16 (1.04, 1.29)**	1.15 (1.02, 1.29)*
Tumor characteristics		
Grade or differentiation of the tumor		
Grade I or well differentiated	1.00	1.00
Grade II or moderately well differentiated	0.97 (0.85, 1.10)	0.99 (0.87, 1.13)
Grade III or poorly differentiated	0.99 (0.88, 1.11)	0.99 (0.87, 1.12)
Grade IV or undifferentiated/anaplastic	1.03 (0.91, 1.17)	0.95 (0.82, 1.09)
Grade and differentiation not stated	0.83 (0.74, 0.93)**	0.93 (0.81, 1.06)
Stage		

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Stage I	1.00	1.00
Stage II	1.01 (0.90, 1.13)	1.03 (0.91, 1.16)
Stage III	1.06 (0.98, 1.14)	1.14 (1.04, 1.24)**
Stage IV	0.85 (0.78, 0.92)***	1.01 (0.92, 1.12)
Size		
< 5cm	1.00	1.00
5-10cm	1.05 (0.95, 1.16)	1.05 (0.95, 1.17)
>10cm	1.11 (1.01, 1.22)*	1.13 (1.02, 1.24)*
Unknown	0.82 (0.75, 0.90)***	0.90 (0.82, 0.995)*
Histology		
Serous	1.00	1.00
Mucinous	0.91 (0.80, 1.03)	0.90 (0.79, 1.04)
Endometrioid	1.01 (0.91, 1.11)	0.97 (0.87, 1.08)
Clear cell	1.02 (0.90, 1.15)	0.92 (0.81, 1.06)
Adenocarcinoma, NOS	0.81 (0.73, 0.90)***	1.03 (0.92, 1.15)
Others	0.91 (0.84, 0.98)*	0.95 (0.87, 1.03)

*p<0.05, **p<0.01, ***p<0.001

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4. Table 4: According to Table 2, > 20 cases comprised only 14 hospitals (3.3%) and 6342 cases (21.1%). Seems like an arbitrary cutpoint. The O/E ratios were divided into lowest quartile, middle 2 quartiles and highest quartiles. A similar analysis would be more informative to show the relationship of volume strata to O/E category.

We thank the Statistical Reviewer for this comment; we take this to mean to add the corresponding # of cases to Table 4, which has been done.

TABLE 4. Cross-tabulation of hospital O/E classification and annual volume criteria (number of hospital (number of corresponding cases)).

	Low Volume <20 cases/year	High Volume ≥20 cases/year	Total
Low-O/E or <5 cases/year	304 (7068)	0 (0)	304 (7068)
Intermediate-O/E	80 (11919)	12 (5452)	92 (17371)
High-O/E	28 (4722)	2 (890)	30 (5612)
Total	412 (23709)	14 (6342)	426 (30051)

5. Table 5: While "predictor" is a useful term in modeling, it has other connotations. This study design can only evaluate associations.

We thank the Statistical Reviewer for this suggestion. The title has been changed. See revised Table 5.

6. Table 5, Fig 3: The geographic location of the hospital vs patient's home is not included as a variable in the model. To what extent are race, SES and insurance type actually a function of neighborhood and distance to high O/E hospital?

We thank the Statistical Reviewer for this query. The current work is a component of a larger series of studies encapsulated by the NIH finding mechanism. The impact of geographic location of residence and proximity to the different hospital types relative to the likelihood of ovarian cancer treatment guideline adherence and survival are the subjects of separate, but related, investigations within this scope of work.

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