PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pattern of Cardiac Surveillance Among Lymphoma Patients Receiving Anthracycline-Based Chemotherapy
AUTHORS	Hung, Olivia; Brown, Jennifer; Dai, Tian; Easley, Kirk; Flowers, Christopher; Parashar, Susmita

VERSION 1 - REVIEW

REVIEWER	Anne Blaes University of Minnesota, USA
REVIEW RETURNED	20-May-2015

GENERAL COMMENTS	Overall, I find the paper and review an interesting subject and topic, and a well thought out study design. I however have a quite a few reservations about the paper, and suggestions about ways to improve it: Major: - It is clear how the study was designed. However, in the tables, the numbers do not match up. For example, if n=24, the columns only tally 22. This needs explained or clarified. The numbers are not correct in table 1 and table 3. It is unclear to me then if this affects the statistical conclusions. - The sensitivity of echo and MUGA should be defined at the institution at that time. For example, what is the variability of echo with each reader's interpretation. This should be clearly explained in the methods section. - Explain why a p value of 0.20 was used. - how was coronary artery disease defined? Was this a chart check in the medical record? a cath? ICD 9 code? - Line 22 on page 10; it is unclear to me how long the follow up was. This statement says the mean follow up was 6.9 years. However, in the tables, it says the mean time on study is 2.99 years. This is not a study. It is a retrospective review. I'm confused by the terminology "time on study." From my understanding, these numbers should be the same, not reported differently. - Consider adding a table for therapies used for those with AC_CMP i.e. last paragraph on page 10 of the results. - the overall manuscripts cited are old. There are many updated papers on the topic of cardiooncology that I would suggest citing i.e. papers by Lenihan, Cardinale, etc Minor: WHO definition is non-Hodgkin lymphoma, not non-Hodgkin's lymphoma. I would suggest correcting this. I really like the flow diagram. I would suggest adding an explanation of LVEF < 45% and > 45%. Is this post treatment that their EF was <

	45%? The figure should be self-explanatory, and in its current format, it is unclear. Overall, I really liked the paper and found it easy to read and understand. I am mostly concerned about correcting the numbers and if this influences the statistical conclusions.

REVIEWER	Daniel Lenihan Vanderbilt University USA
REVIEW RETURNED	24-May-2015

GENERAL COMMENTS	This is an important and interesting manuscript that is well written. The authors present a careful retrospective analysis and display the data in a clear and concise format. There are obvious limitations of any such study but the authors have either addressed them well or acknowledged them.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Overall, I find the paper and review an interesting subject and topic, and a well thought out study design. I however have a quite a few reservations about the paper, and suggestions about ways to improve it. Overall, I really liked the paper and found it easy to read and understand. I am mostly concerned about correcting the numbers and if this influences the statistical conclusions.
We thank the reviewer for her constructive suggestions. Please find our responses and edits below in a point-by-point fashion.

1. It is clear how the study was designed. However, in the tables, the numbers do not match up. For example, if n=24, the columns only tally 22. This needs explained or clarified. The numbers are not correct in table 1 and table 3. It is unclear to me then if this affects the statistical conclusions.
The numerical discrepancies within a subgroup in Table 1 (page 15) and Table 3 (page 17) reflect unknown (missing) patient data that could not be elicited despite comprehensive chart review. As there was only 1 subject with incomplete information, the missing proportions are small. All statistical analyses were originally performed on the subset of patients with the available data on each characteristic reported in Tables 1 and 3. None of analyses have changed and the conclusions remain as originally stated.
We have revised Tables 1 and 3 by adding a table footnote to clarify the 'missing' data concern, and adding 'Unknown' to Smoking History, where there is >1 subject without clearly documented information, in order to be consistent with the Race data.

2. The sensitivity of echo and MUGA should be defined at the institution at that time. For example, what is the variability of echo with each reader's interpretation. This should be clearly explained in the methods section.
The variability should be minimal because the MUGAs and the echocardiograms were re-interpreted and validated by a single physician (JRB). Any disagreements between the reader and the original report (difference in LVEF >5 absolute points) was solved by consensus reached with subsequent joint evaluation of the images (JRB and SP). Independent reports have suggested a LVEF test re-test variability of 5-7%. The above comment and these references have been added to the manuscript on page 3, lines 15-19.

3. Explain why a p value of 0.20 was used.
Only risk factors that were significant at P < 0.20 in the univariable analyses were included in the multivariable analyses (Cox proportional-hazards regression analysis). The choice of the level to decide between 'significant' and 'non-significant' is a subjective decision. More traditional levels such as 0.05 have been noted to be too stringent and can result in failure to identify risk factors known to be important. Common alpha levels recommended in statistical text books include 0.10, 0.15 and 0.20. Part of the challenge is that risk factors may be thought to be risk factors because they are associated with a small P value, and other factors may be thought not to be risk factors because of larger P values, but both opinions may be erroneous (type I and type II statistical errors, respectively). We used a P value of 0.20 to help ensure we were less likely to reject a possibly important risk factor. When building a survival model, it is better to err on the side of caution, i.e., to include a risk factor rather than exclude it.
We have revised the text as follows on page 4, lines 18-23: "Only risk factors that were significant at P < 0.20 in the univariable analyses were included in the multivariable analyses (Cox proportional-hazards regression analysis). A P value of 0.20 was used as a significance level to help ensure that all potentially important covariates were included in the final multivariable Cox model. The hazard ratio (HR) and its 95% CI were calculated for each factor in the presence of others in the final Cox proportional-hazards regression model."

4. How was coronary artery disease defined? Was this a chart check in the medical record? A cath? ICD 9 code?
Coronary artery disease was defined based on a chart check in the medical record, with either a History & Physical or initial clinic visit note documenting a past medical history of coronary artery disease.

5. Line 22 on page 10; it is unclear to me how long the follow up was. This statement says the mean follow up was 6.9 years. However, in the tables, it says the mean time on study is 2.99 years. This is not a study. It is a retrospective review. I'm confused by the terminology "time on study." From my understanding, these numbers should be the same, not reported differently.
The text reports the mean time on study while the chart reports median time on study. For consistency, we have changed the text in the Results section to report median follow up time on page 6, line 18.
While a retrospective study, we defined "time on study" as the time period from the date of their first anthracycline-based chemotherapy at our institution to the date of their last known clinic visit or date of death. We have added this definition to the Methodology section on page 4, lines 7-9.

6. Consider adding a table for therapies used for those with AC_CMP i.e. last paragraph on page 10 of the results.
Thank you for the suggestion. We have added a Venn diagram as Figure 3 to represent the therapies used for those with AC-CMP.

7. The overall manuscripts cited are old. There are many updated papers on the topic of cardiooncology that I would suggest citing i.e. papers by Lenihan, Cardinale, etc
Thank you for your author suggestions. We have referenced the most recent paper by Cardinale et al (Circulation, June 2015) in our Discussion (page 8, lines 10-12). In addition, we have added updated citations throughout the paper, including those by Lenihan, Drafts, Lerman, and Thavendiranathan.

8. WHO definition is non-Hodgkin lymphoma, not non-Hodgkin's lymphoma. I would suggest correcting this.
This has been changed throughout the manuscript.

9. I really like the flow diagram. I would suggest adding an explanation of LVEF < 45% and > 45%. Is

this post treatment that their EF was < 45%? The figure should be self-explanatory, and in its current format, it is unclear.
Thank you for the suggestion. We have added “post AC” prior to the LVEF in Figure 1.

Reviewer 2
This is an important and interesting manuscript that is well written. The authors present a careful retrospective analysis and display the data in a clear and concise format. There are obvious limitations of any such study but the authors have either addressed them well or acknowledged them.
We thank the reviewer for these kind comments.