PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cancer Ageing Research Group (CARG) score in older adults undergoing curative intent chemotherapy: A prospective cohort study
AUTHORS	Ostwal, Vikas; Ramaswamy, Anant; Bhargava, Prabhat; Hatkhambkar, Tejaswee; Swami, Rohit; Rastogi, Sameer; Mandavkar, Sarika; Ghosh, Jaya; Bajpai, Jyoti; Gulia, Seema; Srinivas, Sujay; Rath, Sushmita; Gupta, Sudeep

VERSION 1 – REVIEW

REVIEWER	Faisal, Wasek Ballarat Regional Integrated Cancer Centre,, Dept. of Medical Oncology
REVIEW RETURNED	28-Dec-2020

GENERAL COMMENTS	I would like to commend the authors on their efforts in indentifying a relevant research question and attempting to answer this. I would like to make the following comments: 1. There are minor grammatical and linguistic errors throughout the paper (just as an example - page 9/line 43 & page 10/line 9 - these sentences need to be rephrased and corrected grammatically). I would also suggest minimising adjectives and superlatives in the text as much as possible. 2. The particular strength of this study is the study population, all of whom are early-stage compared to 61% in the original Arti Hurria paper who had metastatic disease. However, by this same token, this study population was much healthier than the seminal paper group, and therefore carried a lower baseline risk score. 3. In the methods section, the authors have reported that the treating oncologist was blinded to the CARG score. However, they have not commented if consecutive patients were enrolled into the study. Otherwise, this could have introduced selection bias. 4. 13% patients had a high-risk score at baseline (thereby implying a high risk of adverse events). Given the treating oncologist was blinded to this information, it would be nice to know how this issue was addressed in the protocol and the Ethics approval. 5. Despite a large number of the patients having GI cancer (and 26% being diabetic), it is indeed interesting to see that there was only 1% grade 3-5 Neuropathy in this study. This is much lower than the literature and it would be nice to see the chemotherapy regimens being used in this study. 6. Finally, no information have been provided on subsequent dose modifications in the cohort of patients being studied and it would also be relevant to know if there is an association of CARG score to chemotherapy dose modification(s).

REVIEWER	Gajra, Ajeet Cardinal Health Specialty Solutions, Dublin, Clinical Affairs
REVIEW RETURNED	02-Jan-2021

GENERAL COMMENTS	I would like to congratulate the authors on this excellent work. It is critical to improve care of older adults with cancer. In this prospective longitudinal study their primary objective is to validate the CARG tool in Indian population of older adults albeit treated with curative intent. The manuscript is well written. I have minor suggestions below which are easily addressed. 1. Explain funding by "Intas pharma" 2. Intro: Separate out secondary (AACI/ PS correlation) from exploratory objectives 3. Include neoadjuvant vs adjuvant therapy in pt demographics 4. Include percent of pts treated with Platinum agents (oxaliplatin/ cisplatin; less important but to be included is carboplatin) and taxanes (paclitaxel/ docetaxel/; less important is nab-pac) 5. Study coordinator: What were the qualifications? How was the SC trained? include a statement to highlight physician supervision and approval of the data collected by SC. 6. Typos; Pg 9, line 43- removes word "studies"; Page 11 ln 57 and elsewhere- better to use word laboratory values than "blood values" 7. Describe odds of toxicity for intermediate vs low and then high risk vs low for consistency 8. Pg 16, line 3-4: add that fitter group is due to the fact that compared to CARG study there were no pts with metastatic disease leading to a fitter group. 9. Grade 1 tox is largely meaningless in this population but grade 2 tox can be significant when associated with diminished function e.g. neuropathy. Please add data on grade 2 tox esp if neuropathy data captured. 10. Add a sentence or 2 on how this data may be used in practice at your institution and if any next steps are planned. Thank you for the opportunity to review this work

REVIEWER	Hayashi, Toshinobu Fukuoka University, Pharmaceutical and healthcare management
REVIEW RETURNED	05-Jan-2021

GENERAL COMMENTS	This paper entitled "Prospective validation of the Cancer Ageing Research Group (CARG) score in geriatric patients undergoing curative-intent chemotherapy: A simple assay to predict clinically relevant toxicity in the elderly" by Vikas Ostwal et al. presented the relationship between CARG score in geriatric patients treated with curative intent chemotherapy and grade 3-5 toxicities prospectively. This is an interesting observation that the impact of the CARG score used on Indian patient outcomes was investigated. It is important to validate the prediction scores such as CARG scores in different races and populations. I believe the paper will be of interest to the readership of BMJ Open. I evaluate the work is publishable if the following issues were resolved: comments: 1. Figure 1 is difficult to read accurately because of its small size and obscurity. The authors should improve figure 1 to be clearer according to the submission guideline.

	I hope that my comment is very useful for the improvement of the article.

REVIEWER	DeAngelis, Carlo Sunnybrook Health Sciences Centre, Pharmacy
REVIEW RETURNED	05-Jan-2021

GENERAL COMMENTS	Overall I found the paper interesting and well written. I have the following suggestions: Page 11 – Lines 45- 49 - sentence: “Patients were followed from beginning till the end of chemotherapy course.” Please clarify that this means patients were followed over multiple cycles. Related to this issue please indicate whether patients were counted as experiencing Grade 3-4 toxicity only once. That is once a Grade 3-4 event occurred in an earlier cycle the occurrence of a Grade 3-5 event in a subsequent cycle was not counted? Page 11 – Lines 57-58 and Page 12 –Lines 3-6 – the sentence: “Blood values were captured as grade 1 to 5 toxicity if they met the criteria on the date of scheduled chemotherapy or at the time the patient was seeking attention because of chemotherapy related toxicities.” Is the same sentence verbatim used in the original Hurria paper (J Clin Oncol 2011;29:3457-3465). See page 3459 top left hand column, last sentence before statistical analysis. Your sentence “Patients were followed from beginning till the end of chemotherapy course.” (see above) is also verbatim to the sentence that opens the paragraph in the left hand column on page 3459. Please rewrite these sentences so that they are not identical to the sentences in the Hurria paper. Page 12 – Lines 37-50 – re: sample size calculation. The variable used to calculate sample size (difference in rate of Grade 3-5 toxicity between ECOG 0/1 and ECOG 2 patients) is not the primary objective of the study. In addition in the results section this outcome is not mentioned. Please justify the use of this variable to estimate the study sample size. Page 18 – Lines 10-15 – Sentence beginning “Additionally, while information . . . “ . I found the application of the CARG to predicting the occurrence of Grade 1/2 toxicity interesting. However, the outcome could have been predicted, given (as you point out in your discussion) that virtually everyone develops some form of Grade 1/2 toxicity. The rates of Grade 1/2 you report in the three CARG risk categories are virtually identical. This is not an issue of power/sample size. In my mind the issue is that the CARG was not developed to identify patients at risk for lower grade toxicities. A more appropriate comment would be indicate this in your discussion, not raise the issue of power. Other comments Page 9 – Lines 42-44 – Sentence - “The CARG risk score has been studies validated in other countries and in specific tumor sites to varying degrees.” It seems the word “studies” is out of place. Did you mean to write: “The CARG risk score has been validated in other countries and in specific tumor sites to varying degrees.” Please clarify/correct.

	Page 10 – Lines 8-9 Sentence – “With this background, the investigators conductive a longitudinal prospective study . . . “ Should “conductive” be “conducted”? Please clarify/correct. Page 16 – Lines 10-11 – “in validated” did you mean to say “invalidated” or “validated”? Please clarify/correct. Figure 1 is difficult to see/read

VERSION 1 – AUTHOR RESPONSE

Reviewer Comment	**Replies and change in manuscript**
Reviewer 1	
There are minor grammatical and linguistic errors throughout the paper (just as an example - page 9/line 43 & page 10/line 9 - these sentences need to be rephrased and corrected grammatically). I would also suggest minimising adjectives and superlatives in the text as much as possible.	We have rechecked the grammar and hope the corrections satisfy the reviewer
The particular strength of this study is the study population, all of whom are early-stage compared to 61% in the original Arti Hurria paper who had metastatic disease. However, by this same token, this study population was much healthier than the seminal paper group, and therefore carried a lower baseline risk score.	We agree with the reviewer and have mentioned this under the “Discussion” section. However, despite the variance in population, there was a similar incidence of grade 3-5 toxicities in each risk group when compared to the original study.
In the methods section, the authors have reported that the treating oncologist was blinded to the CARG score. However, they have not commented if consecutive patients were enrolled into the study. Otherwise, this could have introduced selection bias.	We agree with the reviewer. We have now mentioned this in the materials and methods section.
13% patients had a high-risk score at baseline (thereby implying a high risk of adverse events). Given the treating oncologist was blinded to this information, it would be nice to know how this issue was addressed in the protocol and the Ethics approval.	The reviewer has raised a valid point. The acceptance of the CARG risk score is not universal in clinical practice. Additionally, this is the first Indian study which has prospectively evaluated whether the CARG score is valid in the Indian scenario. In this study, patients were treated with curative intent and standard of care

	(dose density /intensity) therapy. Once the treating physician decided the management plan as per standard institutional practice, the patient was consented and enrolled by the coordinator along with unblinded medical oncologists. Based on the results of the current study, we will be using the score as a validated assay in future studies. However, at the time the study was planned, we were not sure whether the CARG score would discriminate similarly in an Indian population as in North American population. Hence, this point was not addressed in the protocol or raised by the Institutional Ethics Committee.
Despite a large number of the patients having GI cancer (and 26% being diabetic), it is indeed interesting to see that there was only 1% grade 3-5 Neuropathy in this study. This is much lower than the literature and it would be nice to see the chemotherapy regimens being used in this study.	We have now added the chemotherapy regimens in supplementary table 3
Finally, no information have been provided on subsequent dose modifications in the cohort of patients being studied and it would also be relevant to know if there is an association of CARG score to chemotherapy dose modification(s).	We have now added this information in the results section as per reviewer comment. We have also added a brief comment on this in the 'Discussion' aspect of the manuscript.
Reviewer 2	
Explain funding by "Intas pharma"	We have expanded on the role of the same.
Intro: Separate out secondary (AACI/ PS correlation) from exploratory objectives	We have separated out the secondary and exploratory objectives as pointed out by the reviewer.
Include neoadjuvant vs adjuvant therapy in pt demographics	We have added this data in table 1.
Include percent of pts treated with Platinum agents (oxaliplatin/ cisplatin; less important but to be included is carboplatin) and taxanes (paclitaxel/ docetaxel/; less important is nab-pac)	We have added this data as part of supplementary table 3

Study coordinator: What were the qualifications? How was the SC trained? include a statement to highlight physician supervision and approval of the data collected by SC.	The study coordinator was a trained medical doctor . For the purpose of the study, she was specifically trained in assessment of geriatric patients using the CARG score by verbal instruction of the score and its measurement by the PI and Co-PI. A Physician oncologist who was not part of the treating team vetted the data entry by the trained medical doctor. We have added this statement in the Materials and methods section.
Typos; Pg 9, line 43- removes word "studies"; Page 11 ln 57 and elsewhere- better to use word laboratory values than "blood values"	We have made the corrections in the errors pointed out by the reviewer
Describe odds of toxicity for intermediate vs low and then high risk vs low for consistency	We have made the changes as required by the reviewer
Pg 16, line 3-4: add that fitter group is due to the fact that compared to CARG study there were no pts with metastatic disease leading to a fitter group.	We have reiterated this aspect in the same paragraph in response to the reviewer's comment.
Grade 1 tox is largely meaningless in this population but grade 2 tox can be significant when associated with diminished function e.g. neuropathy. Please add data on grade 2 tox esp if neuropathy data captured.	Based on the reviewer's comment, we have now provided the incidence of grade 2 neuropathy and grade 2 HFS in the results section. We have presented the data on neuropathy and HFS because these side-effects are particularly associated with diminished function, as pointed out by the reviewer.
Add a sentence or 2 on how this data may be used in practice at your institution and if any next steps are planned.	We have now added a sentence addressing this point under the 'Discussion' heading.
Reviewer 3	
Figure 1 is difficult to read accurately because of its small size and obscurity. The authors should improve figure 1 to be clearer according to the submission guideline.	We have now improved the quality of figure 1.
Reviewer 4	
Page 11 – Lines 45- 49 - sentence: "Patients were followed from beginning till the end of chemotherapy course." Please	We have now clarified this statement. Additionally, the occurrence of a single

clarify that this means patients were followed over multiple cycles. Related to this issue please indicate whether patients were counted as experiencing Grade 3-4 toxicity only once. That is once a Grade 3-4 event occurred in an earlier cycle the occurrence of a Grade 3-5 event in a subsequent cycle was not counted?	grade 3-4 toxicity was counted as an endpoint for the purpose of the study. Once a grade 3-4 toxicity occurred, the occurrence of a subsequent grade 3-4 toxicity was not counted.
Page 11 – Lines 57-58 and Page 12 –Lines 3-6 – the sentence: "Blood values were captured as grade 1 to 5 toxicity if they met the criteria on the date of scheduled chemotherapy or at the time the patient was seeking attention because of chemotherapy related toxicities." Is the same sentence verbatim used in the original Hurria paper (J Clin Oncol 2011;29:3457-3465). See page 3459 top left hand column, last sentence before statistical analysis. Your sentence "Patients were followed from beginning till the end of chemotherapy course." (see above) is also verbatim to the sentence that opens the paragraph in the left hand column on page 3459. Please rewrite these sentences so that they are not identical to the sentences in the Hurria paper.	The sentences are inadvertently similar. We have now modified both statements
Page 12 – Lines 37-50 – re: sample size calculation. The variable used to calculate sample size (difference in rate of Grade 3-5 toxicity between ECOG 0/1 and ECOG 2 patients) is not the primary objective of the study. In addition in the results section this outcome is not mentioned. Please justify the use of this variable to estimate the study sample size.	We agree with the reviewer on his point regarding the assumptions for statistical calculations. However, as now mentioned in the current version of the manuscript, the CARG score was not routinely used in routine clinical practice in our institution. We extrapolated data from an internal audit to calculate the sample size for the study.
Page 18 – Lines 10-15 – Sentence beginning "Additionally, while information . . . " . I found the application of the CARG to predicting the occurrence of Grade 1/2 toxicity interesting. However, the outcome could have been predicted, given (as you point out in your discussion) that virtually everyone develops some form of Grade 1/2 toxicity. The rates of Grade 1/2 you report in the three CARG risk categories are virtually identical. This is not an issue of power/sample size. In my mind the issue is that the CARG was not developed to identify patients at risk for lower grade	We agree with the reviewer's comment. We have now made an addition to the discussion aspect highlighting this aspect.

toxicities. A more appropriate comment would be indicate this in your discussion, not raise the issue of power.	
Page 9 – Lines 42-44 – Sentence - “The CARG risk score has been studies validated in other countries and in specific tumor sites to varying degrees.” It seems the word “studies” is out of place. Did you mean to write: “The CARG risk score has been validated in other countries and in specific tumor sites to varying degrees.” Please clarify/correct.	We have now corrected the mentioned error in the current version of the manuscript.
Page 10 – Lines 8-9 Sentence – “With this background, the investigators conductive a longitudinal prospective study . . . “ Should “conductive” be “conducted”? Please clarify/correct.	We have now corrected the mentioned error in the current version of the manuscript.
Page 16 – Lines 10-11 – “in validated” did you mean to say “invalidated” or “validated”? Please clarify/correct.	We have now corrected the mentioned error in the current version of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Faisal, Wasek Ballarat Regional Integrated Cancer Centre,, Dept. of Medical Oncology
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	The authors have adequately addressed the questions/issues raised on my initial review. The revised manuscript is now at a much better quality. This can be considered for publication, pending formal statistical review.

REVIEWER	Gajra, Ajeet Cardinal Health Specialty Solutions, Dublin, Clinical Affairs
REVIEW RETURNED	28-Mar-2021

GENERAL COMMENTS	The authors are commended for their efforts in this vital and understudied area- the present study accomplishes two purposes despite the stated and obvious limitations: 1. It validates use of CARG score in Indian population 2. It validates the use specifically in patients treated with curative intent I hope that the CARG score will be actually utilized in practice to appropriately risk stratify patients for chemotherapy associated toxicity in the curative setting and the study is not simply an academic/ publication exercise. WHen used appropriately, CARG score can be (one of) the measures that can improve outcome sin older adults with cancer undergoing chemotherapy with curative intent.

REVIEWER	DeAngelis, Carlo

	Sunnybrook Health Sciences Centre, Pharmacy
REVIEW RETURNED	06-Apr-2021

GENERAL COMMENTS	Thank you for addressing the reviewer comments in a thorough and thoughtful manne I have no further comments/suggestions

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Wasek Faisal, Ballarat Regional Integrated Cancer Centre,

Comments to the Author:
The authors have adequately addressed the questions/issues raised on my initial review. The revised manuscript is now at a much better quality. This can be considered for publication, pending formal statistical review.

Reply: We thank Dr. Wasek Faisal for the positive comments.

Reviewer: 2
Dr. Ajeet Gajra, Cardinal Health Specialty Solutions, Dublin

Comments to the Author:
The authors are commended for their efforts in this vital and understudied area- the present study accomplishes two purposes despite the stated and obvious limitations:
1. It validates the use of CARG score in the Indian population
2. It validates the use specifically in patients treated with curative intent
I hope that the CARG score will be actually utilized in practice to appropriately risk stratify patients for chemotherapy-associated toxicity in the curative setting and the study is not simply an academic/ publication exercise. When used appropriately, the CARG score can be (one of) the measures that can improve outcomes in older adults with cancer undergoing chemotherapy with curative intent.

Reply: We thank Dr. Ajeet Gajra for the positive comments. We confirm that we have initiated the use of the CARG score in our older adults while planning the chemotherapy treatment. We agree with Dr. Gajra on his view that the use of the score would improve the outcomes in this group of patients.

Reviewer: 4
Dr. Carlo DeAngelis, Sunnybrook Health Sciences Centre, University of Toronto Leslie Dan Faculty of Pharmacy

Comments to the Author:
Thank you for addressing the reviewer comments in a thorough and thoughtful manner

I have no further comments/suggestions

Reply: We thank Dr. Carlo DeAngelis for the positive comments.

We have already included the IEC approval number and IEC name. We have highlighted the same.
Thank you.