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International Journal of Cancer Management

Article DOI: <https://doi.org/10.5812/ijcm-159609>

Published in: International Journal of Cancer Management: 18(1) ; e159609

Peer Review Report for "Long-Term Impact of HLA Class I Downregulation and Metastasis on Colon Cancer: An Analysis of Defective Models"

Author(s): Maryam Ahmadian, Ahmad Reza Baghestani, Ali Akbar Khadem Maboudi, Ardeshir Qaderi, Ehsan Nazemalhosseini Mojarad

Review Timeline:

Submit Date: 12 Jan 2025

Revised Date: 17 May 2025

Accepted Date: 24 May 2025

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFeree : Reviewer

21 Feb 2025

To AE,

Major Concerns:

- o The paper lacks a clear discussion of the assumptions of the Marshall-Olkin Weibull model and its limitations.
- o How well do the data satisfy the proportional hazards assumption?
- o Were any goodness-of-fit tests performed to evaluate model adequacy?
- o The manuscript mentions that non-CRC deaths were excluded. However, in a survival analysis, competing risks should be accounted for instead of simple exclusion.
- o Check the confidence intervals for all estimates.

- o The estimated cure fraction (66%) is mentioned but lacks a standard error or confidence interval.
- o The findings are not well-integrated with clinical significance.
- o Consider including a subsection on clinical interpretation, explaining how this research can influence CRC treatment strategies.
- o Some sections contain grammatical errors and awkward phrasing.
- o Suggest a language revision to improve clarity and readability.

REFeree : Associate Editor

2 Mar 2025

Dear EIC,

The manuscript needs revision based on the review comments.

REFeree : EIC

2 Mar 2025

Dear Author,

Please revise the manuscript based on the review comments and resubmit.

Thank You

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Author Reply to the Reviewers' Comments

Dear Editor,

Thank you very much for your kind consideration regarding our manuscript entitled "Long-Term Impact of HLA Class I Downregulation and Metastasis on Colon Cancer: An Analysis of Defective Models", with Manuscript ID 159609.

We have carefully considered all the comments from Reviewer 1 and AI reviewers. the responses are provided here, as follows. Changes in the revised manuscript have also been made and highlighted.

I hope the revised manuscript finds its way to final acceptance. Thank you very much again for your kind consideration.

Yours sincerely,
The Corresponding Author

A. Responses to the comments from Reviewer 1

Comment 1 from Reviewer 1: *The paper lacks a clear discussion of assumptions of the Marshall-Olkin Weibull model and its limitations.*

Response: Thank you for your comment. The Marshall-Olkin Weibull model has no assumptions or limitations. If the data is considered cured, as shown in the text in Figure 1 so we can use the model, such as the defective Marshall-Olkin Weibull model.

Comment 2 from Reviewer 1: *How well do the data satisfy the proportional hazards assumption?*

Response: Thank you for your comment. In these models, the proportional hazards assumption is not upheld. However, the Odds Ratio for the cure rate was calculated and is presented in Table 1, as shown below:

With consider $r(x) = \exp(-x\beta)$

$$\text{Odds Cure} = \frac{\text{cure rate}}{\text{not cure rate}} = \frac{\frac{r}{r-1}}{1 - \frac{r}{r-1}} = -r = -\exp(-x\beta)$$

Changed manuscript text/figure and location:

Comment 3 from Reviewer 1: *Were any goodness-of-fit tests performed to evaluate model adequacy?*

Response: Thank you for your comment. We assessed the variables using AIC and the Wald test, and we included the best variable in the model based on AIC. The Marshal-Olkin defective model is presented in the 17th reference and is suitable for data with cure.

Comment 4 from Reviewer 1: *The manuscript mentions that non-CRC deaths were excluded. However, in a survival analysis, competing risks should be accounted for instead of simple exclusion.*

Response: Thank you for the comment. Because defective models have not been published in the world considering competitive risks and in follow up patients

Comment 5 from Reviewer 1: *Check the confidence intervals for all estimates.*

Response: Thank you for the comment. Done. It is mentioned in the revised manuscript.

Changed manuscript text/figure and location: Please see Table 2 on Page 7.

Comment 6 from Reviewer 1: *The estimated cure fraction (66%) is mentioned but lacks a standard error or confidence interval.*

Response: Thank you for your comment. Done. It is mentioned in the revised manuscript.

Changed manuscript text/figure and location: Please see the last paragraph on Page 6. It is highlighted.

Comment 7 from Reviewer 1: *The findings are not well-integrated with clinical significance.*

Response: Thank you for the comment. The references numbered 10, 15, and 19-21, as well as 23, indicate that the downregulation of HLA class I is associated with a poor prognosis in patients.

Although there are many studies on this subject, we are unable to include them due to the word count limitations imposed by the journal for the article.

Comment 8 from Reviewer 1: *Consider including a subsection on clinical interpretation, explaining how this research can influence CRC treatment strategies.*

Response: Thank you for the comment. Done. It is mentioned in the revised manuscript.

Changed manuscript text/figure and location: Please see paragraph after discussion on Page 11.

Comment 9 from Reviewer 2: *Some sections contain grammatical errors and awkward phrasing.*

Response: Thank you for your comment. Done. We reviewed the article again and made the necessary edits to the text.

Comment 10 from Reviewer 1: *Suggest a language revision to improve clarity and readability.*

Response: Thank you for your nice suggestion. We reviewed the article again.

B. Responses to the comments from AI Reviewer 1

Major Comment 1 from AI Reviewer: *The study design should be explicitly stated in the abstract.*

Response: Thank you for the comment. It is mentioned in the revised Abstract.

Changed manuscript text/figure and location: Please review the method section in the Abstract and highlight the first sentence.

Major Comment 2 from AI Reviewer: *Details on eligibility criteria, data sources, and statistical methods are lacking.*

Response: Thank you for the comment. It is mentioned in the revised Abstract and main manuscript text.

Changed manuscript text/figure and location: Please review the Method section in the Abstract and highlight the new sentences and the first paragraph of the Method section in the main text.

Major Comment 3 from AI Reviewer: *The abstract does not address potential sources of bias or study limitations.*

Response: Thank you for the comment. It is mentioned in the revised Abstract.

Changed manuscript text/figure and location: Please review the Method section in the Abstract and highlight the new sentences.

Minor Comment 1 from AI Reviewer: *Consider providing more comprehensive participant demographics.*

Response: Thank you for the comment. It is mentioned in the revised manuscript.

Changed manuscript text/figure and location: Please review the Method section in the main manuscript text on Page 4.

Minor Comment 2 from AI Reviewer: *Include information on the generalisability of the findings.*

Response: Thank you for the comment. It is mentioned in the revised manuscript.

Changed manuscript text/figure and location: Please review the Discussion section in the main manuscript and highlight it in the first paragraph on Page 11.

Minor Comment 3 from AI Reviewer: *Mention funding sources if applicable.*

Response: Thank you for the comment. It is mentioned in the revised manuscript.

Changed manuscript text/figure and location: Please review the last main manuscript text on Page 13, which is highlighted.

“It is worth mentioning we have changed and highlighted some parts of the introduction and method of the article for more clarity and transparency to answer some ambiguities observed by the AI reviewer. Summary of key changes made is as below”

1. Introduction:

- Incorporated detailed eligibility criteria and participant demographics.
- Clarified the significance of HLA class I expression in survival outcomes.
- Added objectives directly related to the investigation's purpose.
- Stressing the relevance of the study in clinical practice.

2. Methods:

- Specified a retrospective cohort design in the context of participant selection.

- o Detailed the eligibility criteria, ensuring clarity on participant selection.
- o Defined and clarified relationships among variables impacting overall survival.
- o Enhanced explanation of statistical methods to address potential biases.
- o Explicitly mentioned software used for statistical analysis, supporting reproducibility.

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Revision (1)

REFeree : Reviewer

7 Apr 2025

This study entitled: Long-Term Impact of HLA Class I Downregulation and Metastasis on Colon Cancer: An Analysis of Defective Models that examines the impact of HLA class 1 expression on colon cancer survival using the Marshall Olkin Weibull model. It finds that low HLA expression and metastasis significantly reduce cure rates with patients having normal HLA expression showing a 4.75 times higher cure rate. The study suggests that targeting HLA expression could improve treatment outcomes and patient survival. Moreover, below comments could be helpful:

- In abstract: "CRC" is not introduced for the first time.
- Please present mean plus SD for followup time. And it is better to report median with IQR.
- There are two abstracts with different materials and p values. Please make a correction.
- The text needs a grammatical and spelling English writing by a native, such as:
 - in lines 81-82. the sentence is incomplete and needs "who are" to make it grammatically correct.
- In line 91, the sentence should start with "This" instead of "his".
- The verbs should come in a correct tense (mostly past tense such as line 84).
- Using the defective Marshall-Olkin Weibull (MOeW) model to estimate the cure rate is a relatively new and suitable approach for survival data. "suitable approach" is not clear and professional. Please mention the advantages of the MOeW model. Please mention how you find this model has a decent fit to the studied data. It is highly recommended to illustrate the hazard function
- It is highly recommended to present a comparison with other survival models specially other parametric models, if possible. And mention the "Competitive advantage" of MOeW model, i.e. it would be better if the authors explained how this study goes beyond previous research.
- How the authors think about validation and goodness of fit of the MOeW model, in comparison to alternative survival models.
- What the authors think about the interaction effects between variables. In particular, the interaction between HLA and metastasis could be important?
- There is no comparison with previous studies. How do your results align with or differ from previous findings in this field?
- Please discuss whether the relationship between HLA and patient survival is causal or merely correlational.
- The methodological limitations are not discussed. Please mention the limitations of the MOeW model and the data, if there is. Could data quality, data censoring, or the sample size (n=226) have affected the results?
- Please explain your variable selection strategy for modeling.

- Please mention the R package was used to implement the defective Marshall-Olkin Weibull (MOeW) model in your analysis. Or present your written codes for readers.
- References are old (older than 2021), just one 2023 and one 2024 {only in medical area}. Please find and refer more new studies in your advanced statistical model area.

REFEREE : Reviewer

3 May 2025

To AE,

The authors addressed all comments, and the revision in this form is acceptable.

REFEREE : Associate Editor

4 May 2025

Dear EIC,

The manuscript needs minor revision according to the comments of the reviewer.

REFEREE : EIC

4 May 2025

Dear Author,

Please revise the manuscript according to the comment and resubmit,

Thank you

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Author Reply to the Reviewers' Comments

Dear Editor,

Thank you very much for your kind consideration regarding our manuscript entitled "Long-Term Impact of HLA Class I Downregulation and Metastasis on Colon Cancer: An Analysis of Defective Models", with Manuscript ID 159609.

We have carefully considered all the comments from Reviewer 2. The responses are provided here, as follows. Changes in the revised manuscript have also been made and highlighted.

I hope the revised manuscript finds its way to final acceptance. Thank you very much again for your kind consideration.

Yours sincerely,
The Corresponding Author

A. Responses to the comments from Reviewer 2

Comment 1 from Reviewer 2: *In abstract: "CRC" is not introduced for the first time.*

Response: Thank you for your comment. I did it in first line on abstract

Comment 2 from Reviewer 2: *Please present mean plus SD for follow-up time. And it is better to report median with IQR.*

Response: Thank you for your comment. We presented mean plus SD.

Changed manuscript text/figure and location: it is considered in 119 and 120 lines.

Comment 3 from Reviewer 2: *There are two abstracts with different materials and p values. Please make a correction.*

Response: Thank you for your comment. I checked it.

Comment 4 from Reviewer 2: *The text needs a grammatical and spelling English writing by a native, such as:*

- in lines 81-82. the sentence is incomplete and needs "who are" to make it grammatically correct.

Response: Thank you for your comment. In the revised manuscript, we checked the text again and revised text grammatically.

Comment 5 from Reviewer 2: *In line 91, the sentence should start with "This" instead of "his".*

- The verbs should come in a correct tense (mostly past tense such as line 84).

Response: Thank you for your comment. we corrected tenses and checked the text again to correct words.

Comment 6 from Reviewer 2:

Using the defective Marshall-Olkin Weibull (MOeW) model to estimate the cure rate is a relatively new and suitable approach for survival data. "suitable approach" is not clear and professional. Please mention the advantages of the MOeW model. Please mention how you find this model has a decent fit to the studied data. It is highly recommended to illustrate the hazard function.

Response: Thank you for your comments.

In the flawed Marshall-Olkin model, the 17th reference suggested that the MOeW model is preferable to parametric models because it does not require additional parameters to estimate the cure rate. instead, cure rate in this model is obtained by considering the limit of the survival function. We fitted hazard function in 133 line and 135 in the manuscript also .

Comment 7 from Reviewer 2: *It is highly recommended to present a comparison with other survival models, specially other parametric models, if possible. And mention the "Competitive advantage" of MOeW model, i.e. it would be better if the authors explained how this study goes beyond previous research.*

Response: Thank you for your comments. We compared it with the mixed model, but because there was no significant difference between the Akaike value of the two models and the presentation of the newer model due to its inherent advantage in obtaining the cure rate, as well as due to the word limit in the journal and the

understanding of medical readers of defective models, we choose this model and presented it in this article.

Comment 8 from Reviewer 2: *How the authors think about validation and goodness of fit of the MOeW model, in comparison to alternative survival models.*

Response: Thank you for your comments. We assessed it with AIC.

Comment 9 from Reviewer 2: *What the authors think about the interaction effects between variables. In particular, the interaction between HLA and metastasis could be important?*

Response: Thank you for your comment. we assessed interaction between HLA and metastasis but it was not significant (p-value = 0.9).

Comment 10 from Reviewer 2: *There is no comparison with previous studies. How do your results align with or differ from previous findings in this field?*

Response: Thank you for your comment. No study has been conducted on such data with the presence of genetic factors in the field of data curation. Only this data has been examined in reference number 10, which introduced the variable downregulation HLA class I as an influential and significant independent factor.

Comment 11 from Reviewer 2: *Please discuss whether the relationship between HLA and patient survival is causal or merely correlational.*

Response: Thank you for your comment. it is casual and in 9,10,15,24,25,26,27 references indicated this subject in this regard. Although we added a section to manuscript named clinical interpretation

Changed manuscript text/figure and location: in 227 to 293 lines, we discussed this subject more.

Comment 12 from Reviewer 2: *The methodological limitations are not discussed. Please mention the limitations of the MOeW model and the data, if there is. Could data quality, data censoring, or the sample size ($n=226$) have affected the results?*

Response: Thank you for your comment.

In 215 to 223 lines, the limitations to study are explained in the revised manuscript.

Comment 13 from Reviewer 2: *Please explain your variable selection strategy for modeling.*

Response: Thank you for your comment.

We assessed the variables using AIC and the Wald test, and we included the best variable in the model based on AIC. The Marshall-Olkin defective model is presented in the 17th reference and is suitable for data with cure.

In explained it in 108 to 110 lines in revised manuscript.

Comment 14 from Reviewer 2: *Please mention the R package was used to implement the defective Marshall-Olkin Weibull (MOeW) model in your analysis. Or present your written codes for readers.*

Response: Thank you for your comment. We described it in 110 line in the revised manuscript.

Comment 15 from Reviewer 2: *References are old (older than 2021), just one 2023 and one 2024 {only in medical area}. Please find and refer more new studies in your advanced statistical model area.*

Response: Thank you for your comment. References 6, 25, and 26 were added to the manuscript for 2022 to 2024 in the medical area, and reference 22 in 2022 demonstrated the application of the

model in medical data, which was added to the manuscript in the area of statistics. We highlight them in reference text.

OPEN PEER REVIEW

Revision (2)

REFEREE : EIC

24 May 2025

Dear Author,

Thank you for submitting your work to IJCM.