

Peer Review File

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Reviewer A

Comment 1: There is no such consensus as to what defines an AI. I suggest including an operational definition of AI -- it looks like authors have considered machine learning and not all AI.

Reply 1: We thank the reviewer for this observation. According to the reviewer's comments, we revised the title and Abstract to clarify that our manuscript reviewed machine learning. We also pointed out that our review does not cover all AI topics as a limitation in the Discussion.

Changes in the text: We made the following changes: Title (see Page 1, line 1), Abstract (see Page 3, lines 43 and 53) and title of 4.2 (see Page 14, line 235), and the Discussion (see pages 20-22, lines 356-386)

Comment 2. Elaborating on the motivation of the study will help. Why is it important to review the topic?

Reply 2: According to the reviewer's comment, we revised the abstract and the end of the introduction to clarify the motivation.

Changes in the text: The background section of Abstract (see pages 3-4, lines 40-57) and the last paragraph of Introduction were revised (see Page 7, lines 109-112).

Comment 3. Authors claim to review the recent literature but have not included some of the most recent publications in relevant fields. For instance, <https://content.iospress.com/articles/technology-and-health-care/thc202226>

Reply 3: According to the reviewer's comment, we added this reference.

Changes in the text: The fourth paragraph of the introduction was revised (see Pages 6, lines 103).

Comment 4. In the discussion section, the authors have identified some flaws such as multicollinearity and model parameters but have not discussed them in detail. Publications including but not limited to (a)

https://medinform.jmir.org/2020/7/e18599/?utm_source=TrendMD&utm_medium=cpc&utm_campaign=JMIR_TrendMD_0

(b) <https://academic.oup.com/jamiaopen/article/3/3/459/5919218?login=true>

(c) [https://www.thelancet.com/journals/landig/article/PIIS2589-7500\(19\)30123-2/fulltext](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(19)30123-2/fulltext)

have already identified ML/ deep learning flaws most of which apply to breast cancer models as well. It is highly recommended to cite these studies and build upon their discussion.

Reply 4: According to the reviewer's comments, we added these references in the introduction and added a new paragraph to discuss these references.

Changes in the text: The fourth paragraph of the Introduction was revised (see Page 6, lines 103) and the third paragraph of the Discussion was newly added (see pages 20-21, lines 356-369)

Comment 5. What is the contribution of this review? I believed addressing point 4 shall help. Besides, including a section for "clinical relevance" is encouraged.

Reply 5: According to the reviewer's comments, we added a paragraph at the end of the Discussion to describe the clinical relevance.

Changes in the text: The last paragraph of the Discussion was added (see pages 21-22, lines 370-386)

Comment 6. Please include a future recommendation section. Now that we know the problem of multicollinearity (which is a piece of common knowledge) how can we address it?

Reply 6: According to the reviewer's comments, we added a paragraph at the end of section 4.3 Other quantitative omics data to describe how we can address the multicollinearity.
Changes in the text: The last paragraph of 4.3 Other quantitative omics data was added (see pages 18-19, lines 323-329)

Reviewer B

Comment 1. The references should be adjusted properly. Only relevant references should be provided.
Reply 1: We thank the reviewer for this observation. We exchanged the cited references with the appropriate ones.

Changes in the text: The first paragraph of the Introduction was revised (see Page 6, line 103). The first paragraph of 4.2. Multi-gene assay with ML was revised (see page 16, lines 274).

Comment 2. Full names of any abbreviations should be used for the first time.

Reply 15: We thank the reviewer for this observation. We defined full names for abbreviations.

Changes in the text: The fourth paragraph of the Introduction (see page 6, lines 102) and the section 3.2 Nomogram were revised (see page 9, lines 146-147). The first paragraph of section 4.1. Commercially available gene expression analyses was revised (see page 12, lines 207-209). The second paragraph of section 4.3. Other quantitative omics data was revised (see page 18, lines 305).

Comment 3. Figures should be upgraded and should be referred, properly.

Reply 20: We thank the reviewer for this observation. Figure 3A was revised and the reference for AE was changed to the proper one.

Changes in the text: The first paragraph of 4.2. Multi-gene assay with ML was revised (see page 16, lines 274). Figure 3A and its legends (see page 38, lines 649-652)

Comment 4. The authors should summarize all the mentioned studies in sections 2 and 3, in a new Table. Names of studies, methods used, their outcomes, and their drawbacks should be provided in this table.

Reply 4: We thank the reviewer for this comment. Instead of short descriptions in a table format, we separated the descriptions regarding each model into each paragraph to clarify their relationships. The detailed descriptions for each model were added. We also added a new paragraph to describe the feature selection.

Changes in the text: The second to fourth paragraphs of section 3.3. Machine learning methods (see pages 10-12, lines 173-199) were revised and the last paragraph of the section 4.3. Other quantitative omics data was added (see pages 18-19, lines 323-329).

Comment 5. The word AI is very generic. Thus, it is suggested to use a proper structure for this review article. For instance, feature-based AI methods, feature-based machine learning methodologies, and deep learning approaches.

Reply 1: We thank the reviewer for this observation. We revised the title and Abstract to clarify that our manuscript reviewed machine learning. We also described that our review did not cover all AI topics as a limitation in the discussion.

Changes in the text: Title (see Page 1, line 1), Abstract (see pages 3-4, lines 40-57) and title of 4.2 (see Page 14, line 235), and the Discussion (see page 21, lines 370-372)

Comment 6. Overall, the papers should be structured properly. It can be done by taking into consideration two things: 1) types of data 2) methods.

Reply 6: According to the reviewer's comments, we revised the Abstract and the last paragraph of the Introduction to clarify the structure which was done by taking into consideration of both data and methods.

Changes in the text: The Abstract (see pages 3-4, lines 40-57) and the last paragraph of the Introduction were revised (see Page 7, lines 109-112).

Comment 7. Lastly, how the data/references were collected? Which terminology was used? Which keywords were used? Which database was used for the collection? Which tools were for this process? What is the real motivation behind this review? Why it is different from other review articles carried out recently?

Reply 7: According to the reviewer's comments, we revised the Abstract and this manuscript is not a systematic review but a narrative review.

Changes in the text: Abstract was revised (see pages 3-4, lines 38-59).

Introduction:

Comment 8. The authors should mention the definition of breast and its causes, along with its mortality and morbidity rate among women worldwide.

Reply 8: We thank the reviewer for this observation. We added these issues at the beginning of the introduction.

Changes in the text: The first paragraph of the Introduction was added (see page 4, lines 64-72).

Comment 9. The authors should also provide details about the manual screening of breast cancer, and the need for automatic analysis.

Reply 9: We revised the Introduction to address the reviewer's comments.

Changes in the text: The last sentence in the first paragraph of the Introduction was added (see Page 1, lines 64-72).

Comment 10. References should be adjusted accordingly.

Reply 10: According to the reviewer's comments, we exchanged several references for the appropriate one.

Changes in the text: The first paragraph of the Introduction was revised (see Page 6, line 103).

Comment 11. Why the authors did not mention histology data?

Reply 11: According to the reviewer's comments, we added a sentence to describe histology data.

Changes in the text: The first paragraph of the Introduction was revised (see Page 6, lines 105-106).

Comment 12. The authors should mention a few unsupervised and supervised methods, along with the references, explicitly.

Reply 12: According to the reviewer's comments, we added a sentence to describe unsupervised and supervised methods with a reference.

Changes in the text: The first paragraph of the Introduction was revised (see page 6, line 104-106).

Comment 13. The datasets should be mentioned properly, along with the references.

Reply 13: According to the reviewer's comments, we added a sentence to describe the datasets with a reference.

Changes in the text: The first paragraph of the Introduction was revised (see page 6, line 103-105).

Comment 14. The last paragraph is a bit confusing. The authors should mention what has been reviewed and what has been missed, and what is the motivation behind this current review.

Reply 14: According to the reviewer's comments, we revised the last paragraph of the introduction to clarify the motivation of this review.

Changes in the text: The last paragraph of the Introduction was revised (see page 7, line 109-112).

2.2 Nomogram

Comment 15. It is better to mention a full name for abbreviation when used for the first time.

Reply 15: We thank the reviewer for this observation. We defined full names for abbreviations.

Changes in the text: The paragraph of the 3.2 Nomogram was revised (see page 9, lines 146-147).

Comment 16. I think the authors should provide details about Immunohistochemistry (IHC) and evaluation of pathological characteristics.

Reply 16: According to the reviewer's comments, we added details about Immunohistochemistry.

Changes in the text: The second paragraph of the section 3.2 Nomogram was revised (see page 9, lines 152-153).

2.3 Machine learning methods

Comment 17. Subsection 2.3 can be improved. The authors should explicitly mention unsupervised and supervised machine learning approaches and their outcomes in terms of prognosis/diagnosis.

Reply 17: According to the reviewer's comments, we added a sentence to clarify which type of machine learning method was used.

Changes in the text: The first and paragraphs of the 2.2 Machine learning methods were revised (see page 10, line 172).

Comment 18. Referring to lines 152-163, the authors mentioned their previous works. However, terms like "we utilized, or we previously utilized" are somehow confusing. The outcomes of any study previous should be mentioned independently.

Reply 18: According to the reviewer's comments, we revised these sentences to eliminate these expressions.

Changes in the text: The second to fourth paragraph of the section 3.2 Machine learning methods were revised (see pages 10-11, lines 176-199).

3.1 Commercially available gene expression analyses

Comment 19. All the commercially available tools should be named, followed by their reference. Full name should be provided before its abbreviation is introduced.

Reply 19: We thank the reviewer for this observation. Full name and references were added.

Changes in the text: The first paragraph of the section 4.1. Commercially available gene expression analyses was revised (see page 12, lines 207-209).

3.2 Multi-gene assay with AI

Comment 20. While referring to convolutional neural networks (CNNs), do the authors mean Figure 3A? The Figure of CNN needs improvement. Currently, it looks more like a multilayer perceptron. Also, Figure 3B about autoencoder (AE) should be referred, properly.

Reply 20: We thank the reviewer for this observation. Figure 3A was revised and the reference for AE was changed to the proper one.

Changes in the text: The first paragraph of the section 4.2. Multi-gene assay with ML was revised (see page 14, lines 239). Figure 3A and its legends (see page 38, lines 648-652)

Comment 21. Why the authors did not elaborate on deep learning approaches?

Reply 21. According to the reviewer's comments, we revised the Abstract and the last paragraph of the introduction to clarify the focus of this review.

Reply 12: The abstract (see pages 3-4, lines 40-55) and the last paragraph of the introduction were revised (see Page 7, lines 109-112).

Comment 22. All the commercially available tools should be named, followed by their reference. Full name should be provided before its abbreviation is introduced.

Reply 22: We thank the reviewer for this observation. Full name and references were added.

Changes in the text: The second paragraph of the section 4.3. Other quantitative omics data was revised (see page 17, lines 305).

4. Discussion

Comment 23. The discussion section weak and is very generic. It needs improvement. Currently, they only focused on the generalization ability of ML methods in a broadway. It is recommended to address this issue for all the methods (feature-based approaches to deep learning approaches) along with possible solutions and references.

Reply 23: According to the reviewer's comment, we added other topics including clinical relevance. The description regarding deep learning approaches was also added. Related to this discussion, we also revised the abstract and the last paragraph of the introduction.

Changes in the text: The third and fourth paragraphs of the discussion were added (see pages 20-22, lines 356-386). The abstract (see pages 3-4, lines 40-55) and the last paragraph of the introduction was revised (see Page 7, lines 109-112).