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Title: Recent advances in artificial intelligence for pancreatic ductal adenocarcinoma

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2 Peer-review report

Reviewer #1: Dear Authors, I read very carefully your paper in which you managed to summon all the recent progresses that have been made in using AI in pancreatic ductal adenocarcinoma and I think the article is excellent

[Thank you for your careful review. We appreciate your time to review our manuscript.](#)

Reviewer #2: The authors are dealing with the Artificial Intelligence in pancreatic ductal adenocarcinoma (PDAC). In this paper, Hayashi et al. conduct a comprehensive review of the recent advances of AI in PDAC for clinicians. The topic is interesting because PDAC is a lethal type of cancer and this manuscript shows the ability of Artificial Intelligence to fight against this disease. In addition, the authors discuss advances in the disease from different approaches. I found the review work with the tables to be very appropriate and clear. It is a good selection of key studies in literature. The work is complete and up to date. The manuscript is very interesting. The motivation and justification are appropriate. The paper is well written in correct English.

Now I include some typographical errors in References: In Keywords: For: machine learning read: machine learning In Reference n. 76: Remove: “following competing interests: L. Cozzi acts as Scientific Advisor to Varian Medical Systems and is Clinical Research Scientist at Humanitas Cancer Center. All other co-authors declare that they have no conflict interests. A. Chiti received speaker honoraria from General Electric and Sirtex Medical System; acted as scientific advisor for Blue Earth Diagnostics and Advanced Accelerator Applications; benefited from an unconditional grant from Sanofi to Humanitas University. All honoraria and grants are outside the scope of the submitted work. This does not alter our adherence to PLOS ONE policies on sharing data and materials.”

Thank you for pointing out these errors. We have corrected the keyword and reference 76.

Reviewer #3: The entitled paper “Recent advances in artificial intelligence for pancreatic ductal adenocarcinoma” shed the light on early diagnosing Pancreatic ductal adenocarcinoma using different artificial intelligent (AI) approaches. This kind of cancer is very dangerous and the early detection of it could help doctors to treat the patients and prolong their life for as long as possible. Moreover, early and accurate detection could also important for researchers in the future to fight this deadly disease. The authors reviewed several AI models used in the medical sector. The paper is good and written in an interesting language and however, several notes should be taken into considerations before publishing this paper.

1. In the introduction section, the authors mentioned the application of AI in handling big data. Please provide some examples.

In accordance with your valuable suggestion, we have added examples regarding the utility of AI approaches (page 4, lines 1-5).

2. In “PDAC risk prediction by AI section”, the authors presented some AI-based prediction models. Please provide some details about those models such as model type (SVR, ANN, deep learning, and so on). Moreover, as you reviewed several studies, please conclude this section and focus on which models provided more accurate results.

Thank you for your comments, in response to which we have added descriptive information about AI models as a supplementary file.

Unfortunately, it is currently difficult to conclude which models yield more reliable predictions of PDAC risk’, because patient characteristics and input clinical variables differ considerably among the studies. As an example: Cai et al. [29] developed a PDAC risk prediction rule by studying 138 chronic pancreatitis patients with focal mass lesions, whereas Hsieh et al. [30] predicted PDAC in patients with type 2 diabetes using ICD-9 code data.

3. I can see in some sections of your study that you just mention AI model, or machine learning approach. It is very important to give some details about the model. At least mention the type of AI model that should be mentioned in your manuscript.

We have added the type of AI model at appropriate locations throughout the manuscript.

4. Please conclude the obtained accuracy of adopted models in the Detection of early PDAC by biomarkers using AI. Which model is the best among the reviewed models developed by several studies? ... In all sections of your paper, as long as you reviewed several models, please conclude this section to help the researchers to focus on the robust models.

Thank you for this comment. As mentioned above in our response to Q2, it is difficult at present to conclude which models are superior for predicting PDAC risk, because the biological samples (tissue sample or blood sample) and input gene signatures vary between the AI models adopted in these studies.

5. As this paper is a review paper, please suggest scientific recommendations for future researches. The recommendations include but are not limited to the main variables that could help improve the accuracy of diagnosis using AI approaches. Moreover, discuss unfamiliar factors that may have a major impact in improving diagnostic accuracy to help researchers in the future.

Thank you for this valuable suggestion. In response to your comment, we have now included a discussion of limitations and future perspectives as a separate closing section.

6. 7. Other observations should be addressed regarding AI models:

In table 1, the backward stepwise approach is an approach used for feature selection not used for classification or regression purposes (it is not like ANN, CNN, deep learning, and so on). please take full information from the mentioned source (Boursi et al. [23], 2021).

Thank you for this important comment.

In response to your suggestion, we have expanded the information about algorithm types in the revised version of Table 1.

Define every approach/ technique, the method mentioned in the tables.

We have described the modality and types of AI used in each study in the revised version of Table 1.

establish a new section in your manuscript about the model evaluation (or you can conclude them in a table). This section provides information about the statistical parameters used in evaluating the prediction accuracy such as AUC, F1-score, RMSE, and so on.

Thank you for this valuable suggestion. We have added a simple overview of AI types and information about their prediction accuracy as a supplementary file, because this review is mainly targeting clinical gastroenterologists and surgeons as the readers.

Discuss briefly the reviewed models by providing a general introduction about the used approaches.

We have added relevant sentences in the Introduction and, as noted above, provided a simple overview of AI types in a new supplementary file.

Provide more information about the pre-processing data. It is very important in obtaining reliable models. This process includes clean the data, outlier handling, normalization, noise removing. In some cases, many input parameters reduce the prediction accuracy. Therefore, it is important to use PCA method to reduce these inputs and remove the correlations between them.

Thank you for your this comment. We have added sentences about the PCA method in the above-mentioned supplementary file, because the current review is mainly addressed to clinical gastroenterologists and surgeons.

Provide general assessment about the reviewed models in terms of accuracy, sort of model, used input.

As noted above, we have added an overview of AI types in the new supplementary file.

Nowadays, deep learning models are well-known for dealing with big data. Please

discuss that approach.

Thank you for this valuable suggestion. We have included the sentences in the 'Introduction' section (Page 3, line 22–Page 4, line 5).

Reviewer #4: The submitted manuscript entitled “Recent advances in artificial intelligence for pancreatic ductal adenocarcinoma” by Hayashi and co-authors focuses on recent advancements in the use of artificial intelligence (AI) approaches in pancreatic ductal adenocarcinoma (PDAC) diagnosis, prognosis and prediction of treatment response. The topic of the manuscript is very important and is somewhat comprehensively discussed. The manuscript is well-organized and is of good quality. However, there are some concerns and recommendations. They are as follows:

- (1) The authors often referred to early review papers instead of recent original research papers or meta-analyses. For example, (i) Ref [27] was not found. Instead, the authors would discuss the following paper “Appelbaum L, Cambronero JP, Stevens JP, Horng S, Pollick K, Silva G, Haneuse S, Piatkowski G, Benhaga N, Duey S, Stevenson MA, Mamon H, Kaplan ID, Rinard MC. Development and validation of a pancreatic cancer risk model for the general population using electronic health records: An observational study. *Eur J Cancer*. 2021 Jan;143:19–30. doi: 10.1016/j.ejca.2020.10.019. PMID: 33278770” ;

In response to this important comment, we have replaced the older paper and added a discussion about the paper by Appelbaum et al (Page 5, lines 18–27).

(ii) Ref. [45] is an old review article. It should be replaced by more recent meta-analysis study: 45a. Rahman MIO, Chan BPH, Far PM, Mbuagbaw L, Thabane L, Yaghoobi M. Endoscopic ultrasound versus computed tomography in determining the resectability of pancreatic cancer: A diagnostic test accuracy meta-analysis. *Saudi J Gastroenterol*. 2020 May–Jun;26(3):113–119. doi: 10.4103/sjg.SJG_39_20. PMID: 32436866; PMCID: PMC7392294.

We carefully checked the meta-analysis cited by the reviewer. Their study showed that EUS and CT were comparable in determining the resectability of pancreatic cancer. It provides important findings, but is not suitable as a replacement for the other review cited in our original text. Instead, we have added new sentences that refer to Rahman et al.’s review.

- (2) Explanations of many abbreviations were missed, and this led to repeated usage of full names and/or abbreviations or both. For example: in section “PDAC risk prediction by AI”, the authors wrote “HbA1C, cholesterol, hemoglobin,

creatinine..." , however HbA1C is hemoglobin A1C.

Thank you for your perceptive comment; we have corrected the term.

(3) A section "AI in response to chemotherapy" is poorly discussed.

We have added new sentences to improve this discussion.

(4) Title of a section "Prognosis prediction" is not good. It is better to change it for example for "Survival prediction" . Additionally, patient' s survival is often assessed using imaging or in response of cancer treatment. Therefore, this section can be combined with some other sections.

We agree thsat this section heading was unsuitable. Additionally, we have now combined the section entitled "AI in response to chemotherapy" with the section on survival prediction, giving the new section "AI in survival prediction and response to chemotherapy" .

(5) Grammar should be checked, for example, "learning" , etc.

We have checked the grammar by conducting English proofreading again.