

Artificial Intelligence in Medical Imaging

Manuscript NO: 58628

Answering Reviewers

Dear Editor-in-chief,

I responded and answered the issues raised in the peer review report as follows.

Yasunari Miyagi, MD, PhD.

(1) Science editor: Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

Response; As the suggestion, I added "Author contribution" section after authors names at Page #1 shown in red color here as follows:

Author contributions: Miyagi Y, Habara T, R Hirata, and Hayashi N designed and coordinated the study; Miyagi Y and Hayashi N supervised the project; Habara T, and R Hirata acquired and validated data; Miyagi Y developed artificial intelligence software, analyzed and interpreted data, and wrote draft; Hayashi N set up project administration; Miyagi Y, Habara T, R Hirata, and Hayashi N wrote the manuscript; all authors approved the final version of the article.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response; As the suggestion, I submitted figures as a PowerPoint file named "58628-Figures.ppt".

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Response; As the suggestion, I added PMID and DOI numbers as much as I could. There are some papers that have no PMID or DOI numbers including my paper; '6. **Miyagi Y**, Fujiwara K, Oda T, Miyake T, Coleman RL. Development of New Method for the Prediction of Clinical Trial Results Using Compressive Sensing of Artificial Intelligence. *J Biostat Biometric App* 2018, 3 (2), 203'. I would like you to accept those references without PMID or DOI information.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

Response; As the suggestion, I added "Article Highlights" section at the end of the main text shown in red color as follows.

ARTICLE HIGHLIGHTS

Research background

To acquire live births is the goal of assisted reproductive technology. No method has been established in practice to use non-morphological analysis and/or morphological analysis such as conventional morphological evaluations and time-lapse microscopy to predict the live birth of a blastocyst.

Research motivation

Artificial intelligence (AI) classifiers for blastocyst images to predict the live birth has been introduced in reproductive medicine recently.

Research objectives

The present study aimed to develop an AI classifier that combines blastocyst images and the morphological features and clinical information of the conventional embryo evaluation parameters such as maternal age to predict the probability of achieving a live birth.

Research methods

A total of 5,691 images of blastocysts combined with conventional embryo evaluation parameters were used. A system in which the original architecture of the deep learning

neural network was developed to predict the probability of live birth.

Research results

The number of independent clinical information for predicting live birth is 10. The best single AI classifier composed of ten layers of convolutional neural networks and each elementwise layer of ten factors was developed and obtained with 42,792 as the number of training data points and 0.001 as the L2 regularization value. The accuracy, sensitivity, specificity, negative predictive value, positive predictive value, Youden J index, and area under the curve values for predicting live birth were 0.743, 0.638, 0.789, 0.831, 0.573, 0.427, and 0.740, respectively.

Research conclusions

AI classifiers have the potential of predicting live births that humans cannot predict. AI that can be trained by both morphological and non- morphological information may make progress in assisted reproductive technology.

Research perspectives

Due to the development of AI that does not harm the embryo, the embryo can be transferred after making the prediction. AI could bring benefits to the advancement of assisted reproductive technology.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

1) The datasets used to train and validate the machine learning algorithm seems to work better in certain age groups compared to others. Is there any reason for selecting the said age groups? Eg, what was the reason for the age cut offs selected? Is it a biological factor or simply a historical dataset? Do you have the dataset raw numbers in terms of patients numbers?

Response;

The age groups classification due to the OFFICIAL report of the Japan Society of Obstetrics and Gynecology in 2015 that was written in No 13 reference.

It is written as "...for the age categories of <35, 35-37, 38-39, 40-41 and ≥42 years respectively [13]" at the second paragraph in Discussion section. This classification of age category is not universal.

The number of blastocysts were 2265, 1244, 709, 804 and 669 for the age categories of <35, 35-37, 38-39, 40-41 and ≥42 years, respectively. I do not have information of patient basis including the numbers of patients. I had only information of blastocyst basis. I can add not the number of patients but the number of blastocysts along with the age classification. Because this study is for blastocyst incorporated with conventional embryo evaluation parameters, I do not think it is necessary to describe statistic values of patient basis.

2) This algorithm has been trained and validated on a certain patient cohort (Asian/Japanese/certain treatment pathways such as only implanting 1 blastocyst per attempt etc). Would the team be willing to share/release the anonymised datasets for others to attempt to reproduce or validate it with other datasets (other regions, different treatment practices).

Otherwise, the data and this research is very interesting. The issue is will the algorithm be used to select blastocytes for implantation in future (this could lead to other ethical implications which the authors have not addressed - is this ethical to be used clinically, is it even accurate enough to be used?)

Response; The IRB in Futari Clinic did not allow to share/release their datasets for others.

As the reviewer's suggestions, the similar algorithm can be applied to not only prediction of live birth but also prediction of implantation. As far as retrospective study, this research might be worthwhile to investigate. But a prospective study might have ethical problems and achievement of live birth may be more important than implantation for patients.

Therefore, we did not carry on prospective studies.

I think I could collaborate other institutes or clinics with our system and/or algorithm in the future.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. Please supply the technical detail of the routine conventional microscopic observation, such as the magnification ratio, the standard of the blastocyst "large enough"

Response; As the reviewer's suggestion, I revised the explanation in detail shown in red color here as follows.

(before)

As a routine conventional microscopic observation, a single clear image of the blastocyst is captured at about 115 hours after insemination or about 139 hours if the blastocyst is not large enough.

(after)

As a routine conventional microscopic observation **at magnification of 400 times**, a single clear image of the blastocyst is captured at about 115 hours after insemination or about 139 hours if the blastocyst is **less than approximate 120 μm in diameter**.

2. Given the data were obtained from single institution, did the author test the generalization ability of the prediction formula using external data?

Response;

We did not test the generalization ability of the prediction formula using external data.

As the reviewer's suggestion, I added the following sentence in Discussion section shown in red color here as follows;

Since there is theoretically an infinite number of probabilities for the construction of the neural network architecture and numerous combinations of statistical functions, further investigations for patients are worthwhile. By selecting the hyperparameters and setting the random seed value within the program in various ways, the result can be changed, e.g., the prediction accuracy can be a little better or a little worse. Similar statements can be made about the dataset. If one uses the same deep neural network architecture and a different training dataset, for example, provided by a different institute, the prediction accuracy differs. This is one of the aspects of current AI technology.

The AI in this study had not been tested for external data as an institutional joint research to validate the generalization ability. In the field of AI technology, a critical statistical method for evaluating the relative superiority of predictive ability between two classifiers is not well established.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

1 Title. Does the title reflect the main subject/hypothesis of the manuscript? yes

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? yes 3

Key words. Do the key words reflect the focus of the manuscript? yes

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? yes

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? yes

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? yes/ this is the first result in this area

7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? yes

8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? yes/no

9 Biostatistics. Does the manuscript meet the requirements of biostatistics? yes

10 Units. Does the manuscript meet the requirements of use of SI units? yes

11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? Yes/yes-self-cite/no

12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Yes/yes

13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? yes-basic study

14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics?

Response; I think I have to do nothing for the reviewer #3 comments. This study was approved by the IRB of Okayama Couples' Clinic as described in the main text.

I am looking forward to having this manuscript published in your journal.
Thank you.

With My Best Regards,

September 2020

Y Miyagi, MD, PhD.