

To the Editors
Artificial Intelligence in Gastroenterology

March 31, 2023
Islamabad

Dear Ladies and Gentlemen,

Manuscript ID: 82283

Dear Ladies and Gentleman,

Thank you for your email of March 29, 2023. We have followed your instructions and changed the manuscript accordingly. On behalf of my co-authors, I would like to resubmit the revised version of research article entitled

“Risk factor profiles for gastric cancer prediction with respect to *Helicobacter pylori*: A study of a tertiary care hospital in Pakistan”

Shahid Aziz, Simone König, Muhammad Umer, Tayyab Saeed Akhter, Shafqat Iqbal, Maryum Ibrar, Tofeeq ur Rehman, Tanvir Ahmad, Alfizah Hanafia, Rabaab Zahra, and Faisal Rasheed

To be considered for publication in Artificial Intelligence in Gastroenterology. In this manuscript, Gastric cancer risk factors were incorporated into a computer model to predict the likelihood of developing gastric cancer with high sensitivity and specificity which may reduce unnecessary endoscopic procedures and will be helpful to reduce the infections associated with invasive procedures.

Yours Sincerely,

Corresponding author

Dr Shahid Aziz



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Reviewer #1

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors studied risk factor profiles for gastric cancer prediction with respect to *Helicobacter pylori* and constructed a computer model to predict the likelihood of developing GC. There is some novelty in the present study; however, there are some serious problems concerning the data and the results.

Reviewer's comments: The original data provided is inconsistent with the results.

2. The title does not cohere with the content. The research focused on risk factors associated with gastric cancer (GC), but there were only 28 GC samples. Most of the samples (262, 77%) were about gastroduodenal diseases (GDD), which was not closely related to the purpose of the study. Are the results of machine learning obtained from such a small sample size reliable?

Author's Response: During this research study, primary data was collected. The patients of gastric cancer were less because to its less prevalence in Pakistan. During sampling and data collection, the imbalanced data of various diseases was collected which is a common problem in population of patients. This problem severely affects the performance of machine learning models during training which results in biased decisions. To avoid this problem we used SMOTE (Synthetic Minority Oversampling Technique) approach to digitally make synthetic copies of minority classes to make results more reliable and accurate.

Reviewer's comments: Some of the statistical methods are not appropriate. For example, in Table 1, the author used Chi-Square (X^2) tests to calculate the p value for the Medication factor, but 4 (26.7%) of the cell counts in the 5×3 table is less than 5, in which circumstance the Fisher's test should be used.

Author's Response: The values in the table belong to observed counts rather than expected counts. However expected counts have been rechecked and where they were less than 5, p values obtained from Fisher's exact test are given according to reviewer's comments.

Reviewer's comments: Sodium intake in Table 6 is divided into four categories with accuracy to a milligram (mg) which are difficult to be accurately defined during the questionnaire.

Author's Response: Thank you for your valuable comments, but before start of this study, the accuracy of salt in milligrams was determined and then this variable was added in order to collect information of salt intake by patients.

Reviewer's comments: In the regression analysis, it is necessary to ensure that there is no correlation between all factors, but the education level and the income level in Table 2 are obviously correlated.

Author's Response: All the variables were checked for correlation before running the analysis. Values in the table 2 are counts and percentages instead of correlation coefficient.

Reviewer's comments: The necessity of this study is not stated in the Background section of the abstract.

Authors Response: The background has been updated according to reviewer's comments in the abstract section.

Reviewer's comments: The authors stated that they constructed a computer model to predict the likelihood of developing GC with high sensitivity and specificity, but the validation of the sensitivity and specificity of the model was not shown.

Author's Response: The validation phase of this research study will be carried out in future research studies and it has been mentioned in the conclusion section of the abstract.

Reviewer's comments: Several minor points. 1) Table 6 appeared before Table 1. 2) Many abbreviations, such as PAN, RUT, and HPE, were not defined at first mention. 3) Language inaccuracy, e.g. 'little sleeps'.

Author's Response: The manuscript has been updated according to reviewer's comments. The table numbers and language inaccuracy have been corrected and abbreviations have been defined according to the suggestions of reviewer.

Reviewer #2

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This manuscript is an original article that retrospectively reported the prevalence of *H. pylori* infection in Pakistan along with its association with various risk factors related to gastroduodenal diseases, and incorporated the risk factors into a dynamic computer tool for the prediction of gastric cancer (GC). The authors identified that age, income level, vomiting, bloating and medication had significant association with gastroduodenal disorders and GC. In addition, the authors developed a dynamic RF GC-predictive model with >80% test accuracy. As the authors analyzed various risk factors, endoscopic and histopathological findings in detail, the results contain informative knowledge, which will be of interest to researchers and clinicians in the field.

However, the following major and minor issues require clarification:

Major

Reviewer's comments: The definitions in the severity of gastritis (mild, moderate, marked) and ulcer (moderate, marked) are unclear and less objectivity.

Author's Response: The severity of gastritis has been cleared in the manuscript in the inclusion and exclusion criteria of material and methods according to reviewers comments.

Minor

Reviewer's comments: Study period should be provided.

Author's Response: The duration of the research study has been mentioned in materials and methods section under the heading of "Ethical approval and study population".

Reviewer's comments: Was *H. pylori* status proven using all provided modalities (RUT, UBT, biopsy, HPE) or one of them? Please describe in detail.

Author's Response: All the modalities were used to diagnose *H. pylori* infection with an exception of some cases because biopsy specimens were not available for all the patients to diagnose infection. Instead the ¹³C Urea Breath Test was used for the entire enrolled subject for infection status. The details has been added in material and methods under

the heading of 'Diagnosis of *H. pylori* infection' of for all the manuscript has been updated according to reviewer's comments.

Reviewer's comments: Were the patients after *H. pylori* eradication included in the study?

Author's Response: In this research study, we didn't include the patients after treatment with *H. pylori* eradication therapies.

Reviewer's comments: Unabbreviated words with abbreviation should be provided at the first appearance (NGM, GDD, RUT, HPE, et al).

Author's Response: the unabbreviated words with abbreviation have been provided at the first appearance in the manuscript in section of abstract under heading of 'methods' and section material and methods under heading of 'inclusion and exclusion criteria', diagnosis of *H. pylori* infection', and results section under heading of 'General characteristics of study participants'.

Reviewer's comments: As the authors use many abbreviations, a list of abbreviations should be provided.

Author's Response: The list of abbreviations has been added in the manuscript after conflict of interest according to author's instructions.

Reviewer's comments: (Figure 1) why did the authors select cross-correlation bar charts with respect to gender, age and *H. pylori* infection status based on RUT.

Author's Response: We found this visualization type useful to understand the composition of the study cohort.

Reviewer's comments: Conclusion should be more summarized. Especially, the content in the second paragraph should be described in Discussion section.

Author's Response: We do not agree with this suggestion. We find the Conclusion quite compact as it is and would rather not change it.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I have now reviewed your paper and recognize the importance of your research question. Manuscript NO. 82283 aimed to identify and incorporate Gastric Cancer (GC) risk factors into a computer model to predict the likelihood of GC development. The main and short titles accurately reflect the major topic and content of the study.

Reviewer's comments: However, there is no clear delineation of the study's main objective in the Abstract. This section highlights only the incorporation of GC risk factors into a dynamic computer tool for the prediction of GC in the "BACKGROUND" subsection. The BACKGROUND and AIM subsections should be separate and the study's AIM should be clearly stated. It is also necessary to better contextualize the research motivation in the "BACKGROUND" subsection. The "RESULTS" subsection should provide detailed important data from the research findings. Finally, the "CONCLUSION" subsection of the Abstract should further explore the limitations of the study and future prospects in the research field.

Author's Response: The abstract has been updated according to reviewer's comments.

Reviewer's comments: The INTRODUCTION should be improved. It is recommended to structure the risk factors for CG in a more cohesive way. The justification for building prediction models - i.e., avoiding unnecessary exposure of patients to invasive procedures - is well stated. Nevertheless, the "state-of-the-art" application of machine learning models in gastroenterology and gastrointestinal oncology should be further explored. It is very interesting that one of the motivations for the construction of the tool was the perception of an overload in referrals to endoscopic procedures in your institution.

Author's Response: The introduction has been improved according to reviewer's comments.

Reviewer's comments: The MATERIALS AND METHODS are not sufficiently described. The ethics-related aspects of the research are no problem. However, there is no sufficiently detailed description of the inclusion criteria for the study.

Author's Response: The inclusion criterion has been improved according to reviewer's comments.

Reviewer's comments: There is also no justification for the exclusion criteria.

Author's Response: The justifications for the exclusion criteria have been added according to reviewer's comments.

Reviewer's comments: Methods for assessing H. pylori infection status are detailed. But what are the "symptoms suggestive of upper gastroduodenal endoscopy"? This should be explained in detail.

Author's Response: The symptoms and explanation for upper gastroduodenal endoscopy have been added in material methods under heading of inclusion and exclusion criteria according to reviewer's comments.

Reviewer's comments: The elaboration of a scheme for the diagnostic approach would also be interesting.

Author's Response: The scheme for the diagnostic approach using machine learning has been added in manuscript under the section of machine learning algorithms according to reviewer's comments.

Reviewer's comments: The Machine-learning algorithm should be further explored in the METHODS section. But it is well-detailed in the RESULTS alongside Principal components analysis (PCA) and decision trees. The reduction of some categories to 'yes' and 'no' in the Machine-learning algorithm is justifiable but constitutes an important limitation of the study that should be further discussed.

Author's Response: We have added sufficient information about machine-learning algorithms under the heading of "machine learning algorithm". Moreover, it is true that minor details have been eliminated by reducing categories to 'yes' and 'no'. But it is done to reduce the complexity of machine learning model. The extent to which this may affect the results may be further studied in future validation research.

Reviewer's comments: The RESULTS provide sufficient experimental data on GC risk factors. This is a major strength of the manuscript. However, the findings on the accuracy of the computer model are not well presented.

Author's Response: The findings on the accuracy of the computer model have been presented in the section of "machine learning algorithm" in manuscript according to reviewer's comments.

Reviewer's comments: In this sense, the clinical-epidemiological characteristics of the enrolled patients are well approached in the DISCUSSION. The risk factors found are

well-compared to the findings of other studies. The model correctly classified 80% of the cases; 10% of the cases from GC, 98% from GDD, and 30% of the NGM participants. Therefore, this results in >80% test accuracy. Although the model shows high predictive power for GDD, it has a questionable performance in predicting GC itself. These limitations should be clearly addressed.

Author's Response: Yes it's true that we have imbalanced data and all classes of gastric diseases don't have equal number of samples in our research study. And model correctly classified 98% samples from GDD group because of higher number of samples. In comparison, model also correctly classified 10% of GC cases among 12 or 13% samples showing really good accuracy for prediction of GC in suspected patients. And we also mentioned in the manuscript that the test accuracy will be increased with the future validation studies.

Reviewer's comments: In conclusion, this study presents interesting data about the risk factors for the development of gastric cancer and the clinical-epidemiological characteristics of patients affected by GDD. These data constitute the major part of the findings of this manuscript. Although the RF GC-predictive model is an interesting tool, its construction, results, and limitations are not well exposed or discussed.

Author's Response: The details of RF GC-predictive model have been added in the manuscript under the heading of " Machine-learning algorithm" according to reviewer's comments.

Reviewer's comments: The manuscript has language issues and the text construction is somewhat repetitive.

Author's Response: The manuscript has been read by a native speaker and was partially rewritten.

Reviewer's comments: Manuscript formatting should be revised according to BPG guidelines.

Author's Response: Manuscript formatting has been revised according to BPG guidelines after reviewer's comments.

Reviewer's comments: The tool has potential and should be further optimized.

Author's Response: The model is being validated in future studies for further optimization.

Company editor-in-chief:

I recommend the manuscript to be published in the Artificial Intelligence in Gastroenterology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Author's Response: We looked at the RCA tool and found it quite interesting. Some of us will use it, others stick to their established means of literature search including SciFinder and PubMed. We did find relevant papers mentioned below and included them into the manuscript.

1. Differential Proteomics of *Helicobacter pylori* Isolates from Gastritis, Ulcer, and Cancer Patients: First Study from Northwest Pakistan.
2. Shah SAR, Rahman H, Qasim M, Akram MS, Saygideger Y, Puspita N, Saygıdeğer Demir B, Alzahrani KJ, Rehman MFU, Alzahrani FM, Alblihd MA. *Medicina (Kaunas)*. 2022 Aug 28;58(9):1168. doi: 10.3390/medicina58091168.
3. Frequency, distribution and determinants of *Helicobacter pylori* infection in adults and adolescents with gastric symptoms: cross-sectional epidemiological inquiry in district Haripur, Pakistan.
4. Awan UA, Khattak AA, Haq M, Saadia Z, Marwat M, Khalid S, Kamran S, Haseeb A, Ahmed B, Irfani MA, Nadeem MF, Javed F. *Braz J Biol*. 2022 Jun 17;84:e248913. doi: 10.1590/1519-6984.248913. eCollection 2022. PMID: 35730809