

07 March 2021

Lian-Sheng Ma, Science Editor, Company Editor-in-Chief

Dear Editor,
Dear Reviewers,

Thank you for your letter dated February 27.

We were pleased to know that our manuscript was rated as potentially acceptable for publication in the *World Journal of Gastroenterology* after appropriate revision. We thank the reviewers for the time and effort they have put into reviewing the previous version of the manuscript.

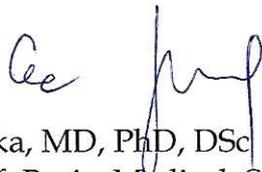
Their suggestions have enabled us to improve our work. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript

Appended to this letter is our point-by-point response to the comments raised by the reviewers and science editor. The comments are reproduced, and our responses are given directly afterward in a different color (blue).

We would also like to thank you for allowing us to resubmit a revised copy of the manuscript.

We hope that the revised manuscript meets the requirements for final acceptance and publication in the *World Journal of Gastroenterology*.

Sincerely,



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Responses to the reviewer's comments:

Reviewer #1:

Specific Comments to Authors: This manuscript took into consideration a considerable number of patients. As the authors themselves write, there are several limitations in their study. In any case, I believe that the manuscript presents a considerable amount of data and that it reaches reasonable conclusions. I only recommend checking the English language.

Response: We thank you for the time and effort that you put into reviewing our manuscript. We really appreciate your comments. The revised manuscript has been re-evaluated by an editing service and linguistically corrected (certificate available in Editorial Manager).

Reviewer #2:

Specific Comments to Authors: This retrospective cohort study, which evaluates the factors affecting the failure of interferon-free treatment for chronic hepatitis C, seems remarkable with its sample size. You can find my comments below: 1. Poland and direct acting antivirals can be added to the article title to highlight the topic 2. The authors identified many differences between the classical analyzes and the machine learning techniques method and stated them in the discussion section. But why there are differences between the results obtained from the two statistical methods is not discussed. Therefore, in the discussion part of the article; After writing the differences between these results of two statistical methods, I think it is necessary to add the authors' comments on these differences.

Response: Thank you for your sincere advice on our manuscript.

1. The information was added to the title that the study was conducted in a Polish patient cohort. According to the guidelines, the limit for a manuscript title is 18 words. Interferon free-treatment is a synonym for direct-acting antivirals and allows us to fit into the word limit after adding information about the Polish origin of the cohort.
2. Part of the analyzed parameters showed a significant impact on the treatment effect in both "traditional" statistics and machine learning. For other parameters, we observed differences in statistical significance between these methods.

Direct comparison is difficult, because the methods involve different aspects of data collected. "Traditional" statistics cannot assess the interaction between many continuous variables and many factors simultaneously. We used "traditional" statistics for univariate analysis only. Machine learning algorithms are a multivariate way to analyze the data. It takes into account interaction between all variables, and this is a reason for inconsistency between results of analyses using "traditional" and ML methods. In our opinion, machine learning algorithms perform better because of the following reasons – the large data frame with more than 11000 observations and a significant disproportion between patients who achieved and did not achieve SVR (97 vs. 3%); ML counts interactions between all variables; the oversampling technique allows us to have equal groups of HCV RNA detectability (in standard statistics, oversampling does not work because multiplication of data may result in biased outcomes). Following your suggestion, we have added a comment on statistical methods in the Discussion.

Reviewer #3:

Specific Comments to Authors: This study summarized the factors of failure of direct-acting antiviral drugs therapy in patients with chronic hepatitis C through a multi center, large sample retrospective cohort study, and proposed that liver cirrhosis and deterioration of liver function are the most important factors of treatment failure. The data is true and reliable, and the predictive model was established by machine learning techniques. The research method is novel and has great reference value. But there are some comments as follows: 1. The research background is too simple to highlight the importance and scientific significance of the research purpose. 2. In the introduction, the author mentioned that the use of direct-acting antiviral drugs in patients with chronic hepatitis C, including liver cirrhosis and renal failure, can achieve good curative effect, but they are also important factors of treatment failure. Are the two contradictory? 3. The author combines the "traditional" analysis with the multivariate analysis, but does not make a detailed comparison between the two analysis results. What are the advantages and disadvantages of the multivariate analysis compared with the "traditional" analysis? Which analysis method is more advantageous for this study? And there is no explanation for the inconsistency between the two analysis results. 4. In the discuss and conclusion, the author proposed to carry out individualization of therapy for patients with advanced liver disease. Since liver cirrhosis and liver failure are the most important factors leading to treatment failure, it is well known

that the treatment of liver cirrhosis and liver failure is more difficult, and the curative effect is not satisfactory. so for patients with chronic hepatitis C, how to prevent the progression of liver disease, formation of cirrhosis, liver function deterioration is more clinical value and significance?

Response: Thank you for your valuable suggestion.

1. More information has been added to the introduction to highlight the scientific significance of the research purpose.
2. In our opinion, there is no inconsistency in the information that DAAs allow to achieve good curative effect in all HCV infected patients, including those with liver cirrhosis and renal failure, and the fact that fibrosis, cirrhosis, and impaired liver function are factors influencing treatment failure. The efficacy of >90% achieved in these difficult-to-treat patients allows for the assessment that these drugs are highly effective.
3. Part of the analyzed parameters showed a significant impact on the treatment effect in both "traditional" statistics and machine learning. For other parameters, we observed differences in statistical significance between these methods. Direct comparison is difficult, because the methods involve different aspects of data collected. "Traditional" statistics cannot assess the interaction between many continuous variables and many factors simultaneously. We use "traditional" statistics for univariate analysis only. Machine learning algorithms are a multivariate way to analyze the data. It takes into account interaction between all variables, and this is a reason for inconsistency between results of analyses using "traditional" and ML methods. In our opinion, machine learning algorithms perform better because of the following reasons - the large data frame with more than 11000 observations and a significant disproportion between patients who achieved and did not achieve SVR (97 vs. 3%); ML counts interactions between all variables; the oversampling technique allows us to have equal groups of HCV RNA detectability (in standard statistics, oversampling does not work because multiplication of data may result in biased outcomes). We have added a comment on statistical methods in the Discussion.

4. In any liver disease, the most effective method of preventing adverse consequences is to eliminate the causative agent (if possible). We know that achieving SVR does not completely exclude the development of complications of cirrhosis, but there are no better methods to prevent the development of liver fibrosis, cirrhosis, liver failure, and HCC in patients with chronic hepatitis C than to eliminate the infection. The group of patients with cirrhosis and/or impaired liver function has the worst treatment results, and any measures that could improve this effectiveness are, in our opinion, important and justified.

Reviewer #4:

Specific Comments to Authors: It is an interesting retrospective cohort study evaluating the factors influencing the failure of interferon-free therapy for chronic hepatitis C in a real-world settings. The study data were extracted from 22 centers in Poland using EpiTer-2 database. The data were statistically analyzed with the standard and machine learning methods. They concluded that patients with advanced liver disease, individualized therapy should be considered to maximize the chance of achieving SVR. Minor changes are required: 1. As the study was performed in Poland, the authors should report this issue in the title for specificity. 2. In the introduction section, the authors should reflect the rationale and hypothesis with great details. 3. In the methodology section the STROBE statement should be considered. 4. A combined flow chart containing laboratory analyses and therapeutic regimens that were performed for those patients is recommended. 5. In the standard statistical method and for continuous data why the authors didn't use the parametric tests, please give the reason in the text. 6. Minor English polishing is required.

Response: Thank you for the valuable suggestions.

- 1) The information was added to the title that the study was conducted in a Polish patient cohort
- 2) In the Introduction, details of the rationale of the research hypothesis have been added

- 3) STROBE declaration was placed as a separate statement on page 5 (according to Guidelines and Requirements for Manuscript Revision). STROBE checklist was also loaded to the submission system as a separate file
- 4) We considered preparing a combined flow chart as proposed. However, information on therapeutic regimens is presented in Figure 2 and the laboratory analyzes in Table 2. This information would therefore be duplicated and a flow-chart with such a large amount of data could become difficult to read. Therefore, we propose to keep the flow chart in its original version
- 5) The parametric tests were not used because of the unequal sample size (SVR n = 11,629; non-SVR n = 309). The use of parametric methods would be burdened with a very large statistical inference error when comparing the SVR and non-SVR groups due to the significant difference in the size of the groups. Therefore, it was better to use other methods.
- 6) The revised manuscript has been re-evaluated by an editing service and linguistically corrected (certificate available in Editorial Manager).

Reviewer #5:

Specific Comments to Authors: The authors put forward a retrospective cohort study regarding factors influencing the failure of interferon-free therapy for chronic hepatitis C: Data from the EpiTer-2 cohort study. The authors may correct on the text citation 18 to: Ioannou G instead of Ioannis The authors may also comment on the following articles in the discussion: Starace M, Minichini C, De Pascalis S, Macera M, Occhiello L, Messina V, Sangiovanni V, Adinolfi LE, Claar E, Precone D, Stornaiuolo G, Stanzione M, Ascione T, Caroprese M, Zampino R, Parrilli G, Gentile I, Brancaccio G, Iovinella V, Martini S, Masarone M, Fontanella L, Masiello A, Sagnelli E, Punzi R, Salomone Megna A, Santoro R, Gaeta GB, Coppola N. Virological patterns of HCV patients with failure to interferon-free regimens. *J Med Virol.* 2018 May;90(5):942-950. doi: 10.1002/jmv.25022. Epub 2018 Feb 1. PMID: 29315640. Rial-Crestelo D,

Sepúlveda MA, González-Gasca FJ, Geijo-Martínez P, Martínez-Alfaro E, Barberá JR, Yzusqui M, Casallo S, García M, Muñoz Hornero C, Espinosa-Gimeno A, Torralba M; Grupo de Estudio de Castilla la Manche de enfermedades Infecciosas (GECMEI). Impact of interferon-free therapies in HIV/HCV co-infected patients on real clinical practice: results from a multicenter region-wide cohort study (2014-2018). *Eur J Gastroenterol Hepatol*. 2021 Feb 1;32(2):279-287. doi: 10.1097/MEG.0000000000002012. PMID: 33252415.

Response: Thank you for your valuable comment. Citation No 18 was corrected. The proposed articles were used in the Discussion and were added to the reference list.

LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

The revised manuscript has been re-evaluated by an editing service and linguistically corrected (see attached certificate)

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

- (1) *Science editor*: 1 Scientific quality: The manuscript describes a retrospective cohort study of the factors influencing the failure of interferon-free therapy for chronic hepatitis C. The topic is within the scope of the WJG. (1) Classification: Four Grades B and Grade C; (2) Summary of the Peer-Review Report: It is an interesting retrospective cohort study evaluating the factors influencing the failure of interferon-free therapy for chronic hepatitis C in a real-world settings. The questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 6 figures. A total of 32 references are cited, including 17 references published in the last 3 years. There are 5 self-citations (Ref. 1, 10, 12, 27, 28). The topics of the self-citations are related to this study. 2

Language evaluation: Classification: Grade A and four Grades B. A language editing certificate issued by Editage was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and the written informed consent. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Polish Association of Epidemiologists and Infectiologists. The topic has not previously been published in the WJG. 5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (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; (3) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text; and (4) Authors should always cite references that are relevant to their study. Please check and remove any references that not relevant to this study. 6 Recommendation: Conditional acceptance.

Response:

1. Approval document from the Polish Association of Epidemiologists and Infectiologicsts has been uploaded to the editorial system.
2. Figures have been prepared using PowerPoint
3. The "Article Highlights" section has been added
4. In our opinion, all references are relevant to this study. The self-citations included:
 - pivotal international multicenter clinical trials in which authors of the manuscript were principal investigators and met the criteria for authorship
 - Recommendations for the treatment of hepatitis C issued by Polish Group of Experts for HCV according to which the patients participating in the study were treated
 - the article on the treatment efficacy in Poland at the turn of the interferon and interferon-free era
 - the article on the prevalence of RASs in patients with advanced liver fibrosis. The group of patients partially overlapped the EpiTer-2 group, and the manuscript discusses tests performed, among others, in EpiTer-2 patients

- the article on the prevalence of RASs in patients with advanced liver fibrosis. The group of patients partially overlapped the EpiTer-2 group, and the manuscript discusses tests performed, among others, in tEpiTer-2 patients

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According to the Guidelines and Requirements for Manuscript Revision: Retrospective Cohort Study all authors should sign their names on a single page, in the order that they appear on the title page of the manuscript.

We kindly ask you for permission for another method of signing the form due to the difficult conditions related to the SARS-CoV-2 pandemic. The authors are employed in 22 different centers several hundred kilometers apart, and it is now virtually impossible to obtain signatures on one page. Most of the authors are directly involved in treating COVID-19 patients. Sending the document by post for signature for all authors would take more than the 14 days allotted for manuscript revisions.

Therefore, we send the form with signatures placed on separate pages in the order consistent with the list of authors

Sincerely,
C. J. P.