

**Dear Reviewers,**

We have revised the manuscript in accordance with the suggestions, and all changes are highlighted in red color in the main file.

**Response to reviewers' comments**

**Article:** *Brzdęk M et al.: Changes in the characteristics of patients with HCV-related cirrhosis from the beginning of the interferon-free era.*

**Reviewer 1**

The Brzdęk et al conducted an observational study to investigate the changes in patient profile, effectiveness, and safety in the HCV-infected cirrhotic Polish population in the IFN-free era. Overall the study is quiet confusing and need major revision. Some of the comments are given below

1. As the study was conducted on Polish population and the title is not representing the main idea of the study.

*The need to enter the place of examination in the title of the article should only occur if it concerns a local epidemic or endemic disease in a given area. HCV-related cirrhosis is not such a disease, therefore the information about the location of the study in Methods is sufficient. Genetic factors related to liver disease may vary across the human population, but the clinical image of cirrhosis is the same. For this reason, indicating that the study concerned "Polish" cirrhosis is not justified and may even narrow an interest in the article. Our study provides meaningful observations for clinicians in different world parts, not only one country.*

2. In introduction some paragraphs are very short and incomplete.

*Thank you for this suggestion. The paragraphs have been expanded and the Introduction has been rewritten to provide a better background for the study presented.*

3. I am not able to understand the aims of the study.

*We have corrected the paragraph in the Introduction regarding the aim of the study and hope that it is now clearer.*

4. Methodology is poorly written and is very confusing.

*We have examined the methodology description closely and provided some edits. Figure 1, which outline the studied groups, was improved in terms of resolution and readability. The methodology description is divided into subsections, which provide essential information on the studied population of patients, collected data, and statistical analyses, and follows the outline used in over 20 papers that were published based on the Epiter-2 database. All authors agree that in the present form, it is sound and provides all the details necessary to understand how our research was pursued.*

5. You have taken 15161 patients as mentioned in study population. This number is different in results ( Figure 1).

*Thank you very much for this comment. Indeed, this point needed to be improved and it has been done. The number 15161 includes also patients treated with DAA IFN-based triple regimens, the correct number of those treated with IFN-free option is 14801.*

6. Questionnaire was evaluated among CHC patients. So all the patients were recovered from CHC? No death was reported?

*According to the data presented in Table 7 and in "Results" - "Treatment safety", there were a total of 45 deaths in the analyzed population. Patients who died during treatment or in the post-treatment follow-up period without SVR assessment were included in the baseline analysis and intent-to-treat effectiveness analysis, but were not included in the per-protocol effectiveness analysis based on statistical analysis assumptions.*

7. Limitation of the study is not mentioned.

*Thank you for this comment. We presented the limitations in the last paragraph of the Discussion, but indeed they did not exhaust the whole issue and were expanded according*

*to the suggestion. Additionally, we have distinguished the paragraph Limitations in the Discussion for full clarity.*

8. Some of the findings in the results are not clear and vague.

*The presented results of the analysis, in our opinion, correspond to the assumed goals of the therapy. Please identify specific shortcomings that we could improve.*

9. The data may vary due to available patients in a particular year. It should be mentioned as one of the limitation of the study.

*Thank you for this comment. We completed Limitations according to this suggestion, also indicating that our study encompasses the COVID-19 pandemic, during which the availability of diagnostic tests and antiviral therapy was limited.*

10. Graphical presentation of the findings is very poor. It is recommended to use Graphpad prism or any other software.

*Thank you for this valuable comment, indeed, it was necessary to improve the graphical presentation, and as suggested, it was done. According to the Reviewer's suggestion, the graphs were now prepared using GraphPad Prism and saved in high resolution. Figures presenting the number of patients in particular years and divided by sex are now grouped in the panel as Figure 2. Three graphs presenting SVR were now grouped in the panel as Figure 3.*

## **Reviewer 2**

### **SPECIFIC COMMENTS TO AUTHORS**

This manuscript demonstrated clearly the serial changes of profiles in DAAs therapy for CHC with liver cirrhosis in Poland during these seven years. The authors' findings are informative and useful in clinical settings. However, there might be several issues to be solved for further considerations.

Major points:

1. The authors did not collect adherence to DAAs therapy in this study. However, for example, in SOF/LDV regimen, there were previous reports that therapy discontinuation would be unfavorable factors for SVR, especially in elder patients (JGH open. 2018;2:300-6; Hepatol Res 2021;51:417-25). Although the reviewer recognized the authors' excuse of limitations of this study, please add some comments in Discussion.

*Thank you for this comment; we have added the information as suggested.*

2. As for Reference #30, the reviewer believes that it's not appropriate to cite unpublished data. In particular, the authors should avoid the duplicate the data of the same retrospective cohort.

*Thank you for the suggestion. We have removed item number 30 from the References.*

*The cited data from the Polish HCV-infected cohort summarized the first four years of access to DAA therapy and served as a reference point in the current analysis.*

3. The reviewer understands that this manuscript was written in descriptive fashion, however more concise expressions might be desirable in scientific journals.

*Thank you for this comment. We made some changes to shorten the length of the Results, also by combining the figures.*

### **Reviewer 3**

#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript introduces changes in characteristics of HCV patient and IFN free therapy regimens along with their effectiveness and safety profile over 7 years. This observational study with a large sample size is very interesting. However, there were some major issues which need to be addressed.

1. Quality of the writing needs to be improved and introduction section with poor organization is suggested to be rewritten, e.g., gather the first and second paragraphs

together. Moreover, some references were missing in this section. It's hard for me to give more comments on this manuscript due to the lack of line numbers.

*Thank you for this suggestion. The introduction was rewritten to provide better background for the study presented. Additionally, three new references have been added.*

2. The quality of the figures (Figure 2-5) is not satisfactory, e.g., In Figure 2, it is better to gather the Figure 2B-2F to show the findings like Figure 2A.

*According to the Reviewer's suggestion, the graphs were now prepared using GraphPad Prism and saved in high resolution. Figures presenting the number of patients in particular years and divided by sex are now grouped in the panel as Figure 2. Three graphs presenting SVR were now grouped in the panel as Figure 3.*

3. There is a lack of results of statistical analyses in Table 1-4 and Figure 3.

*Thank you for this comment. Table 1-4 and Figure 3 (now Figure 3B) present descriptive data. The univariate and multivariate analysis is detailed in subsequent tables.*

4. I am less clear about what is already known on the topic and what this study adds. How this observational study with HCV infected patients might affect clinical practice?

*During the seven years of access to interferon-free therapy, there have been significant changes in the characteristics of patients receiving antiviral treatment. The aim of our study was to track these changes, as well as to document changes in the therapeutic regimens used at that time, ranging from genotype-specific options, favoring patients infected with GT1, to pangenotypic options, registered in the treatment of patients with all HCV genotypes. In the analysis, we focused only on patients with cirrhosis, which is the novelty of our work. Changes in the characteristics of patients, especially those with cirrhosis, may affect the expected change in the number of patients with liver cancer or at risk of decompensation. This knowledge is important from the point of view of planning the directions of health care development.*

5. Please highlight the limitations of the study.

*Thank you for this comment. We presented the limitations in the last paragraph of the Discussion, but indeed they did not exhaust the whole issue and were expanded according to the suggestion. Additionally, we have distinguished the paragraph Limitations in the Discussion.*