Manuscript WJH number 27841

Dear Editors

We thank to the reviewers for the insightful comments. We answered all the comments, and the modifications are tracked in the text and pointed below.

We hope this meets the reviewers' expectations in regard to the questions, and we appreciate your time in reading the document again.

Sincerely, the authors.

Reviewer 02518868

1. The manuscript needs to edit English.

Answer: An English native speaker reviewed and corrected the manuscript.

2. Methods should be described more exactly. There are not any experimental methods in this manuscript such as PCR, Real time PCR, NGS, ...

Answer: the methods are correctly described in section "Methods". The study is an analisys of the European HCV database and the sequences deposited there are publicly available. The sequencing method used for those sequences, according to the information provided in the European HCV database, was Sanger sequencing, as described in line 244. Sanger is a well-described sequencing tool, therefore the authors considered that it is not necessary to describe it in the manuscript, especially because they did not perform sequencing in this study.

3. Discussion should not be as individual parts. In addition, it was poorly compared with other studies.

Answer: This was corrected in the text (section Discussion) and other studies were cited.

Reviewer 00032726

1. To ensure the quality of the analysis, sequences with stop codons in the NS5B gene or with ambiguities consisting of more than 2 bases per nucleotide position or more than 2 ambiguities per codon at individual drug resistance-associated position were also excluded, I don't know why that was?

Answer: The reason for this is that ambiguities will confound the results. Some ambiguities are found after a Sanger sequencing, but when we correlate these positions with resistance they can be a bias in the results. So, we decided to exclude these sequences to ensure a high

quality of results so that the resistance mutations reported in the study in fact exist and are not an artifact of the method used.

2. Mutations were included only positions that have been described in previous studies to be associated in vivo with treatment failure and/or have been shown in vitro phenotypic assays to confer a more than 2-fold change in replication in comparison to the wildtype reference strain. Why not use other positions?

A lot of data was generated when analyzing the European HCV database. In almost all positions of the HCV genome, a polymorphisms can be found. So, the authors aimed to analyze the positions with any clinical relevance and correlations with resistance to the DAAs currently recommended by the international guidelines.

3.The format of the chart in the article was incorrect.

Answer: This was corrected in the text.

4.The content of DISCUSSION was too verbose. Please delete some duplicate content.

Answer: This was corrected in the text.

Reviewer 00054275

1. Table 1, 2 and 3 are complicated and difficult to be immediately understood: they should be modified and simplified.

Answer: the tables had been simplified and only positions that are clinically significant were included in the charts.

2. Q80K resulted very common in 1a patients (in Italy, and in other european countries) in every day experience, it appears much less frequent: this should be discussed

Answer: There are two references cited in the discussion about Q80K where Q80K was observed in 34.7% and 2.1% of subtype 1a and 1b patients, respectively. This was added to the text.

3. What does mean the acronym "SPV" reported in discussion? Simeprevir?

Answer: It was a typing error, which was corrected to SMP (line 496).

4. In table 4 data from data base of Los Alamos are reported: who did study this Data Base? This is no reported in the text...

Answer: This study is reference 11 and is cited in line 437. To be clearer, this reference was added again in this line.

5. The real impact of these constitutive RAV on the possibility of SVR with DAA remains unclear and undefined. Some of these RAV apparently do soon disappear after therapy (NS3/NS4 RAV) while others do not (NS5 RAV)... Globally, clinical significance of these constitutive RAV remains obscure: this should be discussed.

Answer: This was added to the text in line 543.

Reviewer 03262371

I have no comments. The article is appropriate for publishing.