

## ANSWERING REVIEWERS

May 18, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 17880-review.doc).

**Title:** Epidemiology of hepatitis C virus in Iran

**Author:** Reza Taherkhani and Fatemeh Farshadpour

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 17880

**The manuscript has been improved according to the suggestions of reviewers and the editor:**

**1 Format has been updated**

**2 Revision has been made according to the suggestions of the reviewer.**

We greatly appreciated the reviewers' comments. The point-to-point response to comments were shown as follows:

### **(1) Reviewer 02528485**

The review manuscript entitled "Epidemiology of hepatitis C virus in Iran" by Reza Taherkhani, Fatemeh Farshadpour is well-presented and comprehensive. In this review, the authors reviewed and discussed the various aspects of epidemiology of HCV in Iran and did present a clear view about current epidemiology of HCV in Iran. Several suggestions:

**Thank you very much for the positive comments.**

1) Please define "HCV infection" in the "Introduction" section. My impression from this review is that any one of the diagnostic tests (e.g., EIA for Ab, NAT for viral RNA) positive means "HCV infection".

**Response: Thank you for your excellent suggestion. A brief description about this topic was added to the introduction section and highlighted in blue color.**

“HCV infection is described by the presence of HCV-RNA and anti-HCV antibodies in serum or plasma. A positive HCV antibody test (ELISA and immunoblot assay) indicates exposure to HCV, however it cannot distinguish between a current or past infection. In general, anti-HCV antibody positive samples can be defined as current HCV infection if HCV RNA test (RT-PCR) is positive.”

(2) Page 5, line 34, 【which is lower than Saudi Arabia (50.49%), Kuwait (43.4%), Jordan (32.51%) and Pakistan (23.7%) [79-82], but higher than Australia (2.3%), United Kingdom (2.7%), Germany (3.9%) and Bahrain (7.4%)】. It is suggested to write as 【which is lower than those of Saudi Arabia (50.49%), Kuwait (43.4%), Jordan (32.51%) and Pakistan (23.7%) [79-82], but higher than those of Australia (2.3%), United Kingdom (2.7%), Germany (3.9%) and Bahrain (7.4%)】. This suggestion is applied to other similar sentences in this article.

**Response: Thank you for the suggestion. The corrections were done, and shown in green color in the manuscript.**

(3) Page 3, line 22, 【the current knowledge about epidemiology of HCV infection merit reviewing】. It is suggested to write as 【the current knowledge about epidemiology of HCV infection merits reviewing】. This suggestion is applied to other similar sentences in this article.

**Response: The corrections were done.**

**English grammatical errors and the style have been revised, and all changes and corrections are shown in green color in the manuscript.**

## **(2) Reviewer 03074707**

The manuscript of Reza Taherkhani et al. reviews the current epidemiology of HCV in Iran, including the prevalence and epidemiology of HCV in different regions and groups such as blood donors, general population, risk groups, patients with immunological disorders or malignancy. Meanwhile, the genotypes distribution of HCV and occult HCV infection in Iran are also been described. The manuscript has several shortcomings:

1. In the abstract and introduction sections, the general information regarding HCV are too long and could be shortened.

**Response: Thank you very much for your review. The abstract and inclusion sections were shortened according to the suggestions of the reviewer. About the introduction section, I wish I could summarize this part too. But the other two reviewers have requested to add some parts to the introduction and even write some parts in more details.**

2. The authors refer a large amount of articles, but the results should be summarized and more focused.

**Response: Thank you very much for your comment. We have restructured and revised the**

**manuscript to get it more focused and concise in a revised form.**

3. There are too much information about the global prevalence of HCV, which could be shortened.

**Response: Thank you very much for your suggestion. The global prevalences of HCV were shortened, and some parts such as the global distribution of HCV genotypes were removed from the text and summarized in a table.**

4. The data appeared in the tables should be shortened in the text.

**Response: According to your comment, the duplicate information was removed from the text.**

5. The manuscript is not properly written. It is unclear and needs a linguistic revision of all sections.

**Response: Thank you.**

**English grammatical errors and the style have been revised, and many corrections have been done on the manuscript, and many parts have been rewritten. All changes and corrections are shown in green color in the manuscript.**

### **(3) Reviewer 03262864**

The current manuscript "Epidemiology of hepatitis C virus in Iran" deals with the prevalence in different patient groups such as general population, risk groups and patients with immunological disorders. The authors compile the results of a large number of studies. There are some aspects which should be revised, presented in more detail or shortened:

1. HCV transmission is transmitted via blood or blood products. Transmission via body fluids or sexual intercourse is widely discussed and not seen as a route of transmission in HCV in contrast to HBV or HIV. Infections by sexual intercourse are mostly related to by mucosal exposure to infectious blood or serum-derived fluids (Alter, 2011) ?

**Response: Thank you for the reviewer's comments.**

**Revision has been made according to the suggestion of the reviewer. Changes are highlighted in yellow in the introduction section.**

"HCV is mostly transmitted by parenteral risk to blood and blood products. Blood transfusion, intravenous drug using, sexual intercourse, surgery and tattooing are the some possible ways for spreading HCV infections. Among these, HCV transmission by sexual intercourse is less common, and includes those that lead to mucosal exposure to infectious blood or blood-derived body fluids and is related to the presence of mucosal tears and genital ulcerative disease."

**According to the mentioned references and the accumulated epidemiologic evidence, HCV can also be transmitted sexually; however, this mode is less common.**

**Body fluids mean blood-derived body fluids.**

2. Patients developing liver cirrhosis or HCC may be much higher than 3-11% (page 3) and HCC usually occurs only in patients with liver cirrhosis or advanced fibrosis. Recent reviews on natural course provide up to date information (Westbrook & Dusheiko 2014). Detailed information on cirrhosis development are provided by a meta-analysis by Thein et al., 2008. ?

**Response: Thank you for introducing these valuable studies and up to date information. The corresponding data has been updated and highlighted in yellow in the introduction section.**

“About 75% to 85% of those acutely infected slowly progress to chronic infection, approximately 10-20% of the chronic infected individuals are at the risk of developing liver cirrhosis within 20 to 30 years, and of those with cirrhosis, 1–5% per year will develop HCC”

3. On page 3 is stated that prevention is a major objective. There is no information on treatments available in Iran. Due to recent improvements in HCV therapy information on available therapies should be added. ?

**Response: Thank you for your recommendation. Additional data regarding the recent advances in HCV therapy has been included in the introduction section and highlighted in yellow color.**

“The recent advances in HCV therapy have led to the development of new antiviral drugs for treatment of HCV infection, including the protease inhibitors telaprevir, simeprevir, boceprevir and paritaprevir, NS5A inhibitors ledipasvir, daclatasvir and ombitasvir, the nucleotide analog NS5B polymerase inhibitor sofosbuvir, and the non-nucleotide polymerase inhibitor dasabuvir. These new therapies are well-tolerated, safer and much more effective than the previous therapies pegylated interferon/Ribavirin. Despite these advantages, pegylated interferon- $\alpha$  in combination with ribavirin is recommended as the standard treatment for HCV infection in Iran. The reasons for this include the high cost and the restricted availability of the new medications in low- and middle-income countries.”

4. Spelling of numbers should be consistent in text and tables (thousands separators, number of decimal places) ?

**Response: Revision has been made according to the suggestion of the reviewer.**

5. I assume that prevalence figures are based on antibody prevalence and not confirmed HCV-RNA. This should be mentioned. ?

**Response: Thank you for your comments**

**Revision has been made according to the suggestions of the reviewer. However, the type of test in each study has been mentioned in the tables.**

6. Data on worldwide prevalence figures should be checked as stated numbers for UK and Scandinavia seem very low (page 4, 0.01-0.1%). A recent report by Public Health England assumes a prevalence of 0.4% in the UK. Prevalence figures for international comparison should be based on general population estimates.

([https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/337115/HCV\\_in\\_the\\_UK\\_2014\\_24\\_July.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/337115/HCV_in_the_UK_2014_24_July.pdf)) ?

**Response: Thank you.**

**According to the report provided by the reviewer (Hepatitis C in the UK: 2014 report), the prevalence of HCV is 0.4% in England, and this 0.4% prevalence includes the overall prevalence among all groups even high-risk groups. On the other hand, 0.4% is the prevalence of HCV in England, not UK. While, based on studies among blood donors (Wasley and Alter, 2000), the lowest prevalence of anti-HCV antibodies (0.01-0.1%) is in the United Kingdom and Scandinavia.**

**\*\*\*\* Wasley A, Alter MJ (2000). Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis* 20:1-16.**

**In addition, many papers have also indicated this issue:**

**\*\*\*\* Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; 13(17): 2436-2441 [PMID: 17552026] doi: [10.3748/wjg.v13.i17.2436](https://doi.org/10.3748/wjg.v13.i17.2436)**

**\*\*\*\* Dehesa-Violante M, Nunez-Nateras R. Epidemiology of hepatitis virus B and C. *Arch Med Res* 2007; 38(6): 606-611 [PMID: 17613351]**

**\*\*\*\* Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis* 2010; 14(1): 1-21**

**\*\*\*\* Viral Hepatitis Infections in Chronic Kidney Disease Patients and Renal Transplant Recipients. *Kidney Blood Press Res* 2012;35:454-467. DOI: [10.1159/000338309](https://doi.org/10.1159/000338309)**

**\*\*\*\* Marco Carrozzo, Kara Scally. Oral manifestations of hepatitis C virus infection. *World J Gastroenterol* 2014 June 28; 20(24): 7534-7543. DOI: [10.3748/wjg.v20.i24.7534](https://doi.org/10.3748/wjg.v20.i24.7534).**

**\*\*\*\* Petrik J, Hewitt P, Barbara J, Allain J: Large scale HCV RNA screening in first time blood donors; the first step towards genomic screening of blood donations. HCV RNA screening study group. *Vox Sang*; 1999; 76: 159-162**

**Even this sentence has been written in books:**

**BOOK=\*\*\*\* Mitchell L. Shiffman. *Chronic Hepatitis C Virus, Advances in Treatment, Promise for the Future*. 2012. Springer New York Dordrecht Heidelberg London. DOI [10.1007/978-1-4614-1192-5](https://doi.org/10.1007/978-1-4614-1192-5).**

**In a study among blood donors in UK (Soldan et al., 2005), the prevalence of anti-HCV per 100 000 donations during 1996-2003 was approximately 41, which is 0.04% and is in the**

**mentioned range (0.01-0.1%):**

**\*\*\*\* K Soldan, K Davison, B Dow. Estimates Of The Frequency Of HBV, HCV, And HIV Infectious Donations Entering The Blood Supply In The United Kingdom , 1996 TO 2003. Euro Surveill 2005;10(2):17-19.**

**Moreover, this sentence has been written in the blood donor section, where it has been compared with prevalence of HCV among blood donors in Iran.**

7. Prevalence rates have an enormous variability in the different studies which are presented. For better comprehensibility authors should mention the reasons for these differences. Main focus should be on large studies. These studies could be presented in more details.

**Response: Thank you for the suggestion. Revision has been made according to the suggestions of the reviewer. This part was added to the manuscript and highlighted in yellow color.**

“In Iran, the prevalence of HCV infection among blood donors in different studies varies considerably (Table 1), depending on the study population, studied sample sizes, study periods, the geographic regions, risk factors and the methods and type of kits used to determine HCV”

“These variations in the prevalence of HCV might be due to the differences in the quality of public health services, lifestyles, habits and rates of high-risk behaviors in different geographic regions of Iran.”

8. Not all studies have to be mentioned in the text as they appear in the tables.

**Response: Thank you for your suggestion.**

**According to your comment, the duplicate information was removed from the text.**

9. Further, explanations for differences such as non-collected or unadjusted co-factors should be mentioned which could distort study results. ?

**Response: This review is based on a comprehensive search of full text articles in English or Persian language reporting on epidemiology of HCV in Iran. However, papers with incomplete data, overlapping place and time of sample collection, unknown sample origins were excluded from the study. Irrelevant articles and papers with insufficient data that did not report HCV prevalence clearly were also excluded.**

10. Some parts include too much general information (HCV in immunological disorders, genotype distribution, occult HCV infection) and should be shortened.

**Response: Thank you for your comment.**

**The mentioned sections (HCV in immunological disorders, genotype distribution, occult HCV infection) were shortened, and some information was removed from the text according to the suggestion of the reviewer.**

11. Comparison of genotype distribution with other countries could be summarized in a table or figure. ?

**Response: Thank you for your excellent suggestion.**

**According to your comments, a new table regarding the global distribution of HCV genotypes has been included in the manuscript.**

12. Further, I would recommend a linguistic revision of the manuscript by a native speaker as some parts do not read very well.

**Response: Thank you for your comment.**

**Following the reviewer's comments, English grammatical errors have been revised and the sentence structure has been improved by professor Makvandi at Ahvaz Jundishapur University of Medical Sciences. Many corrections were done on the manuscript, and some parts were rewritten. Changes and corrections are shown in green.**

1. Please provide the postcode. Thank you!

**Response: The postcode has been provided.**

2. A copy of signed statement should be provided to the BPG in PDF format.

**Response: Conflict-of-interest statement is signed and provided in PDF format.**

3. Audio Core Tip

**Response: Audio-Video attached**

4. Don't need blank space between reference number and the before words.

**Response: References have been revised.**

5. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted.

**Response: PMID and DOI have been added.**

**Some references are in Persian, and only abstracts are in English. Therefore, we only provided a printed copy of the abstracts.**

**Even for some references, the abstract in English was not attached to the full text and thus we found it in the SID database (Scientific Information Database).**

**In addition, the references were provided in EndNote format.**

6. Tables shouldn't be images, but as word or excel format so that I can edit them easily. Thank you!

**Response: Format has been updated is word doc formart.**

**3 References and typesetting were corrected**

**Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.**

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'fateh', with a long, sweeping underline that extends to the left.

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