Authors' Responses to the Reviewers' Comments

Authors' response: We thank the editor and the reviewers for their kind comments, constructive criticisms and useful suggestions which we have used to improve the quality of this manuscript. We have responded to the issues raised by the editor and reviewers. Changes within the manuscript text are shown in red (here) and in track changes in the manuscript.

1) Response to Reviewer 1 Comments

ALL COMMENTS BY REVIEWER 1 TO AUTHORS

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The manuscript is very well written in clear language. The study addresses an important issue which the use of generic DAAs especially in low income countries. There are some points that need to be clarified: 1. Was this a retrospective or a prospective study. 2. Was HBV excluded 3. The criteria used to select patients to either generic or brand DAAs. 4. Was there any drop outs , what are the adverse effects encountered. 5. A more detailed history of previous antiviral drugs used and causes of previous treatment failures. 6. An explanation of the difference in SVR between generic and brand DAAs.

Reviewer comment: The manuscript is very well written in clear language. The study addresses an important issue which the use of generic DAAs especially in low income countries. There are some points that need to be clarified:
Authors' response: Thanks for the suggestion. We have made all necessary changes in accordance with the suggestions of this reviewer

Reviewer comment: 1. Was this a retrospective or a prospective study.
Authors' response: Thanks for the suggestion. We have included that this was a retrospective study in our design

Reviewer comment: 2. Was HBV excluded

Authors' response: We thank the reviewer for the comments. In our study objective, we clearly stated that:

"*the objective of this study was to compare the efficacy and safety of generic compared to the original brand DAAs for hepatitis C treatment in Bahrain*."

In the Methods section under study participants, we also clearly stated that:

"*All patients who were 18 years old or more with a diagnosis of chronic liver disease from HCV infection (based on the presence of HCV RNA) were included in the study*."

In accordance with concerns of the reviewers shared we have now modified this to read:
"*This was a retrospective observational study involving 289 patients with a real time reverse transcriptase-polymerase chain reaction (real-time RT-PCR) diagnosis of chronic HCV infection (i.e., for over 6 months) who qualified for antiviral treatment."*

"*All patients who were 18 years old or more with a real-time RT-PCR diagnosis of chronic liver disease from HCV infection (based on the presence of HCV RNA) for over 6 months were included in the study*."

Reviewer comment: 3) The criteria used to select patients to either generic or brand DAAs.
Authors' response: We than the reviewer for the comments. This was a non-randomised observational clinical study. All the patients treated with DAAs irrespective of the type qualified for treatment according to The European Association for the Study of the Liver (EASL) guidelines, 2016 and 2018.

However, whether they received brand or generic DAAs is based on three factors: physicians' interest in treating the greatest number of patients, the best available medication at the time of diagnosis and whether the patient could afford the cost of treatment. These were highlighted in the Limitations paragraph of the manuscript. It reads:

"*In our study, the choice of DAA regimen used was physician driven i.e., based on the physicians' interest in treating the greatest number of patients effectively considering the best available evidence as well as the most effective medications according to the patients' profile at a reduced cost."*

Reviewer comment: 4. Was there any drop outs ,
Authors' response: We than the reviewer for the comments. In our Methods and Results section we indicated we collected information on drop outs.

In the Methods section, it reads:

"*We also assessed the proportion of patients who abandoned treatment due to adverse effects of the antiviral therapy*."

In the Results section, we reported that:

"*In patients who received generic medications, not achieving SVR at 12 weeks post treatment was due to treatment failure 6 (4.3%), while for patients treated with brand medications, not achieving SVR was due to their abandoning treatment due to adverse effects 7 (4.7%) and treatment failure 5 (3.4%)*"

Reviewer comment: 5. what are the adverse effects encountered.
Authors' response: We thank the reviewer for the comments. As this was a retrospective study, data on the specific adverse effects reported by the patients were not available at the time of data collection.

However, data on patients who dropped out of treatment due to severe adverse effects of the DAA medications was collected and reported.

Reviewer comment: 6 A more detailed history of previous antiviral drugs used and causes of previous treatment failures.
Authors' response: We thank the reviewer for the comments and we are not quite sure what he/she meant here or what s/he wants us to do. We do not have data on any previous treatment or previos treatment failures the reviewer is requesting for.

However, as stated in the Methods section of the paper:

"*This was a retrospective observational study involving 289 patients with a diagnosis of chronic HCV infection (i.e., for over 6 months) who qualified for antiviral treatment. The patients were enrolled from the hepatology clinic of Salmaniya Medical Complex, Bahrain during January 2016 to December 2018.*

Patients' enrolment in the study was in accordance with The European Association for the Study of the Liver (EASL) guidelines, 2016 and 2018 [22-23]. All patients who were 18 years old or more with a diagnosis of chronic liver disease from HCV infection (based on the presence of HCV RNA) were included in the study."

Also, in the Limitations section of the paper we stated that:

"*The type DAA medication given to the patients was based on the EASL guidelines at the time of enrolment [22-23]. Another important limitation is that although the majority of our patients were treatment naïve, we do not have data on the proportion of previously treated hepatitis C patients included in this analysis which might have affected the treatment outcomes [16-18].*"

Reviewer comment: An explanation of the difference in SVR between generic and brand DAAs.
Authors' response: We thank the reviewer for the comments. The SVR definition was the same irrespective of the treatment regimen given. We have now modified/indicated this in our manuscript text.

It reads:
"*Treatment failure was defined as the presence of HCV-RNA above detectable limits in patients after 12 weeks of having completed therapy irrespective of the type DAA received*."

Thanks for the comments on language polishing. We have reviewed the text and performed all other grammatical corrections as necessary.

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2) Response to Reviewer 2 Comments

ALL COMMENTS BY REVIEWER 2 TO AUTHORS

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: As regard the article entitled (Effectiveness and safety of generic and brand direct acting antivirals for the treatment of chronic hepatitis C) although it is not novel but important in the field of viral eradication of HCV as it compare between generic and brand DAAs in treatment of HCV as one of the main barriers in low income countries is the cost of treatment. but some comments to be considered: - patients and methods defenition of chronic HCV must be positive PCRHCV for more than 6 months - The groups must be classified into Cirrhotic and non cirrhotic and every group must be further classified into naive and experienced patients because each group has specific line of treatment and so the response will be diffidently differ so theses data must be presented in tables

Reviewer comment: As regard the article entitled (Effectiveness and safety of generic and brand direct acting antivirals for the treatment of chronic hepatitis C) although it is not novel but important in the field of viral eradication of HCV as it compare between generic and brand DAAs in treatment of HCV as one of the main barriers in low income countries is the cost of treatment. but some comments to be considered:
Authors' response: We thank the reviewer for their kind comments, constructive criticisms and useful suggestions which we have used to improve the quality of this manuscript. We

have responded to the issues raised by the editor and reviewers. Changes within the manuscript text are shown in red.

Reviewer comment: 1)- patients and methods defenition of chronic HCV must be positive PCRHCV for more than 6 months
Authors' response: We thank the reviewer for the comments. We agree with the reviewer that "the definition of chronic HCV must be positive PCRHCV for more than 6 months".

In the Methods section, we clearly noted that:
"*This was a retrospective observational study involving 289 patients with a diagnosis of chronic HCV infection (i.e., for over 6 months) who qualified for antiviral treatment*."

Under study participants, we also indicated that:
"*All patients who were 18 years old or more with a diagnosis of chronic liver disease from HCV infection (based on the presence of HCV RNA) were included in the study."*

In order to address the concerns of the reviewer, we have modified these two sentences in the paper. They now read:

In the Methods section, it reads:
"*This was a retrospective observational study involving 289 patients with a real time reverse transcriptase-polymerase chain reaction (real-time RT-PCR) diagnosis of chronic HCV infection (i.e., for over 6 months) who qualified for antiviral treatment."*

Under study participants, we also indicated that:
"*All patients who were 18 years old or more with a real-time RT-PCR diagnosis of chronic liver disease from HCV infection (based on the presence of HCV RNA) for over 6 months were included in the study*."

Reviewer comment: The groups must be classified into Cirrhotic and non cirrhotic and every group must be further classified into naive and experienced patients because each group has specific line of treatment and so the response will be diffidently differ so theses data must be presented in tables
Authors' response: We thank the reviewer for the comments. We presented the number and proportion of the patients in each group that were cirrhotic and non-cirrhotic in accordance with the reviewers suggestions (Please see Tables 1 to 3). For example, in Table 1, we showed that among the patients who received generic DAAs 27 (19.3%) were cirrhotic (had ultrasound-diagnosed cirrhosis) and 113 (80.7%) were non-cirrhotic. Also, among those who received brand DAAs, 60 (40.3%) were cirrhotic and 59.7% were non-cirrhotic.

Also, Figure 1A to 1G shows the treatment outcome of patients who received the DAAs among those who are cirrhotic only and those who are non-cirrhotic only. [Please, see: **Figure 1: Virologic response among patients (A) Percentage of all patients. (B) Percentage of all patients without cirrhosis. (C) Percentage of all patients with cirrhosis**

Also, the reviewer recommended that e further classify the patients as “treatment-naïve” and “experienced” patients. We wish to point out that we do not have any record of ay previous treatment of the patients and did not specifically collect this information because during the time of this study, approaches to treating both “treatment-naïve” and “experienced” HCV patients or even cirrhotic/non-cirrhotic were essentially the same. However, we have highlighted in our limitations this concern of the reviewer. It reads:

“*Another important limitation is that although the majority of our patients were treatment naïve, we do not have data on the proportion of previously treated hepatitis C patients included in this analysis which might have affected the treatment outcomes [16-18*”

Thanks for the comments on language polishing. We have reviewed the text and performed all other grammatical corrections as necessary.

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3) Response to Reviewer 3 Comments

Specific Comments to Authors: I have reviewed the article entitled "Effectiveness and safety of generic and brand direct acting antivirals for the treatment of chronic hepatitis C". The article has many weak points and flaws. The literature is full of articles discussing the same points with huge number of cases. Also, the retrospective nature of the study carries many biases, and the cases were already treated 5 years ago!!. I can't see any benefits from publishing the results of this work.

Reviewer comment: 1) 1) I have reviewed the article entitled "Effectiveness and safety of generic and brand direct acting antivirals for the treatment of chronic hepatitis C". The article has many weak points and flaws. .
Authors’ response: We thank the reviewer for their kind comments, constructive criticisms and useful suggestions which we have used to improve the quality of this manuscript. We have responded to the issues raised by the editor and reviewers. Changes within the manuscript text are shown in red.

Below is the point-by-point response to the comments given by this reviewer.

Reviewer comment: The literature is full of articles discussing the same points with huge number of cases.
Authors' response: We thank the reviewer for the comments. However, we disagree with his or her suggestions. We believe our paper adds to the literature in this important topic as it is the first study that provides evidence on the evolution and use of DAAs for patients with HCV in the Kingdom of Bahrain

Reviewer comment: Also, the retrospective nature of the study carries many biases, and the cases were already treated 5 years ago!!. I can't see any benefits from publishing the results of this work.
Authors' response: We thank the reviewer for the comments. However, we disagree with his or her suggestions. We agree that the retrospective nature of this article carries some biases which has been highlighted in the limitations. The reviewer argued that the cases were treated 5 years ago. Given that the HCV condition require at lest six months of infection to be diagnosed and about one year or more for treatment, coupled with the challenges occasioned by the Covid-19 pandemic, we believe that the data for this study is still very useful and important for the scientific world.

Thanks for the comments on language polishing. We have reviewed the text and performed all other grammatical corrections as necessary.

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4) Response to Reviewer 4 Comments

Specific Comments to Authors: This study intended to compare the efficacy and safety of generic versus brand DAAs for hepatitis C treatment in Bahrain. They found that treatment of chronic hepatitis C patients with generic and brand DAAs demonstrated comparable effectiveness and safety. Several suggestions: 1. In the [study design], please write down the certificate number after [approval for the study was received from the Institutional Review Board of the hospital]. 2. In the [Treatment groupings], please mention what are the generic DAAs, for example, the different generic sofobuvir(s) used in reference 16 were written. 3. In the [Measurements], please change [real time polymerase chain reaction (PCR)] to [real time reverse transcriptase-polymerase chain reaction (real-time RT-PCR)]. 4. In Table 1, [original] may change to [brand]. 5. Please check ref. 17 and 18, I could not find them in PubMed.

Reviewer comment: 1) This study intended to compare the efficacy and safety of generic versus brand DAAs for hepatitis C treatment in Bahrain. They found that treatment of

chronic hepatitis C patients with generic and brand DAAs demonstrated comparable effectiveness and safety. Several suggestions.
Authors' response: We thank the reviewer for their kind comments, constructive criticisms and useful suggestions which we have used to improve the quality of this manuscript. We have responded to the issues raised by the editor and reviewers. Changes within the manuscript text are shown in red/track changes.

Below is the point-by-point response to the comments given by this reviewer.

Reviewer comment: . In the [study design], please write down the certificate number after [approval for the study was received from the Institutional Review Board of the hospital].
Authors' response: We thank the reviewer for the kind comments. We have added the reference number / certificate number of the approval given by Institutional Review Board of the hospital. It reads:

"*All patients gave a written informed consent before participating in the study, and approval for the study was received from the Secondary Health Care Research Sub Committee (SHCRSC), Ministry of Health, Kingdom of Bahrain (Reference number 22G45-40-01925).*"

Reviewer comment: . In the [Treatment groupings], please mention what are the generic DAAs, for example, the different generic sofobuvir(s) used in reference 16 were written.
Authors' response: We thank he reviewer for the comments. We have added the names of the generic and brand DAAs used. It reads:

"*Most of the patients who were treated with brand name antiviral agents received Ombitasvir / Paritaprevir / Ritonavir ± Dasabuvir ± Ribavirin [Omb/Par/Rit ± Das ± Rib] 44 (44.3%), or Sofosbuvir/Ledipasvir ± Ribavirin [Sof/Lep ± Rib] 55 (36.9%), Sofosbuvir/Declatasvir ± Ribavirin [Sof/Dec ± Rib] 26 (17.4%) and Sofosbuvir ± Ribavirin [Sof ± Rib] 2 (0.7%). These brand name agents included Sovaldi (Sofosbuvir), Harvoni (Sofosbuvir / Ledipasvir), Viekira Pak (Ombitasvir / Paritaprevir / Ritonavir / Dasabuvir), Viekirax (Ombitasvir / Paritaprevir / Ritonavir), Daclinza (Daclatasvir), Rebetol (Ribavirin), respectively. Of patients treated with generic medications, 118 (84.3%), received Sofosbuvir/Daclatasvir ± Ribavirin [Sof/Dec ± Rib] while 22 (15.7%) received Sofosbuvir/Ledipasvir ± Ribavirin [Sof/Lep ± Rib]. These generic agents (all meant for use in Egypt) included Nucleobuvir (Sofosbuvir), Daclavirdine (Daclatasvir), Harvoni (Sofosbuvir/Ledipasvir), and Ribavirin (Ribavirin-Egypt). Note that some of these generic medications used were produced by the same brand-name company at a lower price and for use only in low- and middle-income countries like Egypt.* "

Reviewer comment: 3. In the [Measurements], please change [real time polymerase chain reaction (PCR)] to [real time reverse transcriptase-polymerase chain reaction (real-time RT-PCR)].
Authors' response: We thank he reviewer for the comments. We have made the recommended changes

Reviewer comment: 4. In Table 1, [original] may change to [brand].
Authors' response: We thank he reviewer for the comments. We have made the recommended changes in Table 1. We also made similar change in Table 4 to maintain consistency

Reviewer comment: 5. Please check ref. 17 and 18, I could not find them in PubMed.
Authors' response: We have reviewed the references and we can confirm that both reference 17 and 18 are in PUBMED and are consistent with te manuscript style. Please, see below.

Reference 17: https://pubmed.ncbi.nlm.nih.gov/30077791/
17. Abozeid M, Alsebaey A, Abdelsameea E, Othman W, Elhelbawy M, Rgab A, et al. High efficacy of generic and brand direct acting antivirals in treatment of chronic hepatitis C. Int J Infect Dis. 2018;75:109-114.

Reference 18: https://pubmed.ncbi.nlm.nih.gov/30096091/
18. El-Nahaas SM, Fouad R, Elsharkawy A, Khairy M, Elhossary W, Anwar I, et al. High sustained virologic response rate using generic directly acting antivirals in the treatment of chronic hepatitis C virus Egyptian patients: single-center experience. Eur J Gastroenterol Hepatol. 2018;30(10):1194-1199.

Thanks for the comments on language polishing. We have reviewed the text and performed all other grammatical corrections as necessary.

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5) Response to Science Editor comments

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Editor comment: Language Quality: Grade B (Minor language polishing)
Authors' response: Thanks, we have performed English language editing and provided an English language editing certificate.

6) Response to Company Editor-in-Chief

I recommend the manuscript to be published in the World Journal of Clinical Cases. 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/.

Authors' response: We thank the editor for the advice. Thanks. We have applied the new tool Reference Citation Analysis (RCA) as recommended. We are happy to confirm that most of the references cited in the manuscript all had high impact rank in the RCA,

We were also happy to find one additional paper (reference 31) which is much recent and of high impact which we have used to strengthen our manuscript.

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We thank all the reviewers and editors for their kind comments, constructive criticisms and useful suggestions which we have used to improve the quality of this manuscript. We hope we have addressed all the issues raised by the reviewers. We will be happy to respond to any other issues the reviewers/editors may deem necessary.

Many thanks once again.