Apr 14, 2019

Dr. Fang-Fang Ji

Science Editor

World Journal of Clinical Cases

Re: WJCC 47026

Dear Editor Fang-Fang Ji,

Thanks for your letter on Mar 27, 2019 regarding our article titled as: **Anti-HCV therapy in chronic kidney disease patients improves long-term renal and patient survivals**. We've learned a lot from your valuable advice. According to your suggestion, we make some revisions marked as red words in the manuscript. More clear details are described as the follows.

Reply to Editor

1. We submit all related documents to WJCC.

Reply to Reviewer 1 (00503536)

1. Response to "1. The association between the results of interferon-based therapy (SVR vs. non-SVR) and the prognosis of renal and patient survival is unclear."

There was the lack of laboratory data in the NHIRD, thus the association between the SVR and prognosis of renal and patient survival failed to be clarified. We had listed this point as a limitation (page 16, line 7).

2. Response to "2. Genotype distribution of HCV should be shown."

There was the lack of laboratory data in the NHIRD, thus the association between the HCV genotypes and prognosis of renal and patient survival failed to be clarified. We had listed this point as a limitation (page 16, line 7).

3. Response to "Were there any patients who had been treated with both IFN and ribavirin? Ribavirin is contraindicated in most patients with CKD."

In our CKD cohort, including treated cohort, there were no patients receiving ribavirin. We added this in the revised manuscript (page 7, lines 19-20).

Reply to Reviewer 2 (02476570)

1. Response to "Although the subjects with CKD having prevalent HCV infection and had appropriated HCV treatment had a 1.31-fold high risk of death compared to the risk in non-HCV infected subjects,..."

This is misinterpretation! In our Table 4, the subjects with CKD having prevalent HCV infection and **not receiving** HCV treatment (ie. the untreated HCV-infected cohort) had a 1.31-fold high risk of death compared to the risk in non-HCV infected subjects.

2. Response to "Although the subjects with CKD having prevalent HCV infection and had appropriated HCV treatment..., they had a surprisingly low risk of ESRD compared to the risk in non-HCV infected subjects."

Our finding was similar to one previous research by Wu et al. (Ref 22) that diabetic patients with HCV who underwent HCV treatment had lower risk of ESRD compared to the risk in diabetic patients without HCV infection. The efficacy of anti-HCV therapy in alleviating insulin resistance (IR), which has been convincingly

demonstrated in previous research (Ref 45), may account for our finding. IR is a prevalent feature in CKD [Ref 46] and diabetes (Ref 47). The clinical impacts of IR includes endothelial dysfunction and initiation and progression of CKD (Ref 46). This is why IR may be a therapeutic target in the attempt to improve clinical outcomes of CKD (Ref 46) and diabetic vascular complications (Ref 48). The mechanism through which antiviral therapy ameliorates IR was most likely mediated via viral clearance, instead of direct pharmacological effects of IBT (Ref 22). Conjeevaram et al. (Ref 45) reported that successful viral eradication was central to sustain the beneficial effects in insulin resistance. We believe that our finding should result from viral elimination in the treated patients, although this study could not directly measure SVR because of no laboratory information in the NHIRD. Future research is warranted to better understand the pathological mechanism underlying this association. We added this in the revised manuscript (page 14, lines 27-29; page 15, lines 1-15).

3. Response to "Since whether adequate HCV treatment contributes to decreases in the risk of death and incident ESRD in CKD patients with HCV infection has not been elucidated, there is a significant value to examine whether HCV treatment contributes to decreases in the risk of death and incident ESRD in CKD patients with HCV."

In Tables 4 and 5, we demonstrated that HCV treatment, especially complete treatment, contributes to decrease the risks of death and incident ESRD in CKD patients with HCV.

4. Response to "Why did CKD patients with HCV who underwent HCV treatment have a very low risk of ESRD compared to the risk in CKD patients without HCV infection? A lack of biological feasibility certainly makes quality of this study worse."

Our finding was similar to one previous research by Wu et al. (Ref 22) that diabetic patients with HCV who underwent HCV treatment had lower risk of ESRD compared to the risk in diabetic patients without HCV infection. The efficacy of anti-HCV therapy in alleviating insulin resistance (IR), which has been convincingly demonstrated in previous research (Ref 45), may account for our finding. IR is a prevalent feature in CKD [Ref 46] and diabetes (Ref 47). The clinical impacts of IR includes endothelial dysfunction and initiation and progression of CKD (Ref 46). This is why IR may be a therapeutic target in the attempt to improve clinical outcomes of CKD (Ref 46) and diabetic vascular complications (Ref 48). The mechanism through which antiviral therapy ameliorates IR was most likely mediated via viral clearance, instead of direct pharmacological effects of IBT (Ref 22). Conjeevaram et al. (Ref 45) reported that successful viral eradication was central to sustain the beneficial effects in insulin resistance. We believe that our finding should result from viral elimination in the treated patients, although this study could not directly measure SVR because of no laboratory information in the NHIRD. Future research is warranted to better understand the pathological mechanism underlying this association. We added this in the revised manuscript (page 14, lines 27-29; page 15, lines 1-15).

5. Response to "I supposed that the study failed to match the baseline characteristics between the groups. ...Thus, never do multivariate-adjusted analysis using a strong risk factor as one of the explanatory variables, or never do analysis using propensity score using a strong risk factor as one of the constitutive factors for generating propensity score."

In the treated vs. untreated cohorts: we matched one treated patient with four untreated patients by propensity score and same year. The propensity score model was reliable (Hosmer–Lemeshow test $P>0.05$) and provided fair discrimination between

the cohorts (c-index >0.6) (Ref 35) every year. We added this in the revised manuscript (page 7, lines 24-26).

Year	C-index	Hosmer–Lemeshow test *P*
1997	0.929	0.167
1998	0.794	0.693
1999	0.973	1
2001	0.946	1
2002	0.842	1
2003	0.78	0.1
2004	0.607	0.784
2005	0.672	0.967
2006	0.668	0.9
2007	0.728	0.792
2008	0.661	0.886
2009	0.655	0.897
2010	0.674	0.809
2011	0.698	0.98
2012	0.744	0.909

In the untreated vs. uninfected cohorts: we matched one untreated patient with two uninfected patients by propensity score. The propensity score model was reliable (Hosmer–Lemeshow test *P*=0.999) and provided fair discrimination between the cohorts (c-index, 0.686). We added this in the revised manuscript (page 7, line 9; page 8, lines 1-2).

6. Response to "I would like to make a suggestion that a complete matching of distribution of the CKD stage between the groups should be done at first and other factors should be used as explanatory variables in the multivariate-adjusted model or used for the factors of the propensity score."

There was the lack of laboratory data in the NHIRD, thus the CKD stage failed to be clarified. We had added this (page 7, lines 9-10) and listed this point as a limitation

(page 16, line 7).

Thank you heartily for your invaluable opinions on this paper. We are deeply honored by the time and efforts that you had spent in reviewing and revising this manuscript. By incessantly reviewing and revising our texts, we are spurred to read more and learn more from your comments.

Yours sincerely,

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