November 4, 2022

Dear Editors of *World Journal of Transplantation*,

We sincerely appreciate your thoughtful comments and positive feedback by the editorial board and reviewers on our manuscript entitled "***Influence of Donor and Recipient Hepatitis C Virus Infection on Outcomes after Kidney Transplantation, a Propensity Score Matched National Study across 25 years***" After addressing all your comments point-by-point below, we now present you an enhanced manuscript that is stronger than the original with additional data.

Particularly, as recommended by Reviewer #2, we changed the manuscript title to "***Analysis of publicly available data on kidney transplantation in US 1994-2019 to examine the influence of hepatitis c virus on recipient and donor",*** as discussed below in the point-by-point replies to the editors and reviewers' comments**.**

On behalf of my co-authors, thank you very much for your time and consideration.

Sincerely,
Qing Yuan

Reviewer(s)' Comments to Author:
Reviewer: 1

Overall comments to the Author
Authors generated a very important data by analyzing data of 177,937 renal transplant patients according to HCV treatment with DAA for patient and graft survival. They found that donor positivity had more untoward effect than recipient positivity. The decrease in patient and graft survival due to HCV infection were eliminated by DAA, except for dual positive group.

We thank reviewer #1 for the kind remarks.

1. Abstract: This sentence should be rephrased; "Pre-DAA, donor HCV+ decreased PS by 0.28-fold in HCV+ and 0.55-fold in uninfected recipients, and decreased DCGS by 0.22-fold in HCV+ and 0.64-fold in uninfected recipients. However, recipient HCV+ impaired PS (0.25-fold) and DCGS (0.31-fold) only with uninfected donors." or should be replaced by "Pre-DAA, the HCV+ recipients, receiving an HCV+ kidney was associated with 1.28-fold higher mortality (HR 1.151.281.42) and 1.22-fold higher DCGF (HR 1.081.221.39) compared to receiving an HCV- kidney and the absolute risk difference (aRD) was 3.3% (95%CI, 1.8%, 4.7%) for PS and 3.1% (95%CI, 1.2%, 5%) for DCGS at 3 years."

We thank *reviewer #1 for this wonderful idea. We have revised the abstract as you suggested:*
"Pre-DAA, for HCV+ recipients, receiving an HCV+ kidney was associated with 1.28-fold higher mortality (HR $_{1.15}$1.28$_{1.42}$) and 1.22-fold higher DCGS (HR $_{1.08}$1.22$_{1.39}$) compared to receiving an HCV- kidney and the absolute risk difference (aRD) was 3.3% (95% CI 1.8%-4.7%) for PS and 3.1% (95% CI 1.2%-5%) for DCGS at 3 years."

2. Introduction, Page 9: "…based on KDPI thresholds, …" KDPI should be corrected as KDRI.

We thank reviewer #1 for this great suggestion. We have corrected KDPI as KDRI as you suggested.

3. Table 1a, b, c should be respectively combined with Table 2a, b, c.
Table 3a should be combined with Table 3b.

We thank reviewer #1 for this great suggestion. We have combined Table 1a with Table 2a (Table 1), combined Table 1b with Table 2b (Table 2), combined Table 1c with Table 2c (Table 3) and combined Table 3a with Table 3b (Table 4) as your suggestion. We have also changed number of tables in the text.

4. The abbreviations at the tables should be explained as footnote.

We thank reviewer #1 for this kindly reminder. We have added the footnote abbreviations of each table as you suggested.

5. There is no other attached separate documents for Supplemental Tables. As far as I understood from the titles of tables, Supp.Table 2 and 3 are same/similar to Table 1 and 2, respectively.

We thank Reviewer #1 for picking up this detail. Supplemental Tables were resubmitted as attached files. We have corrected titles of Supp.Table 2 and 3 to differentiate with Table 1, 2 and 3, respectively, as follow:

"Supp.Table 2a Other Characteristics of Donors and Donation Procedures in the pre DAA era

Supp.Table 2b Other Characteristics of Recipients in the pre DAA era

Supp.Table 2c Other Characteristics of Transplantation in the pre DAA era

Supp.Table 3a Other Characteristics of Donors and Donation Procedures in the post DAA era

Supp.Table 3b Other Characteristics of Recipients in the post DAA era

Supp.Table 3c Other Characteristics of Transplantation in the post DAA era "

6. Figure 3 should be converted to cumulative graphic.

We thank Reviewer #1 for this suggestion. In our study, survival rates were presented as Kaplan-Meier curves and analyzed by log-rank tests. Kaplan-Meier estimates are used to assess the effect of HCV (+/-) on the kidney recipients' survival over a period of time. Cumulative graphics are instead more appropriate for presenting the frequency of one incident. Therefore, we don't believe that a cumulative graphic is suitable for this section.

7. Patient survival and mortality (and also graft survival and failure) data were mixed up throughout the manuscript, that makes the manuscript difficult to understand, repetition of particular result several times, and too much prolonging the manuscript. I strongly recommend to standardly use of either survival and mortality data.

We thank Reviewer #1 for this suggestion. In our study, survival rates were presented in Kaplan-

Meier curves and analyzed by log-rank tests. Absolute and relative risk differences in mortality and death-censored graft failure (DCGF) were estimated using Austin's methods. Survival rates in Kaplan-Meier curves and mortality as an outcome in cox regression models are both standard methods. To present these results, we therefore hope to retain the existing methods and presentation.

Reviewer: 2

Specific Comments to Authors:

1-Title: The title is not clear and misleading. Comment: the tile would be more informative if it is reformatted to "Analysis of publicly available data on kidney transplantation in US 1994-2019 to examine the influence of hepatitis c virus on recipient and donor.

We thank Reviewer #2 for this excellent recommendation, we have modified the title as your recommendation as follow:

"Analysis of publicly available data on kidney transplantation in US 1994-2019 to examine the influence of hepatitis c virus on recipient and donor"

2-Methods: "Data Sources: We used the OPTN Analysis and Research file released in June 2019 based on data collected through March 2019" Comment: please provide the source, website, and permission of use of these data.

We thank Reviewer #2 for this point, we have added the source, website, and permission of use of these data into Disclosure and Date availability statement.

"Disclosure

The data reported here have been supplied by the United Network for Organ Sharing (UNOS) as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US government.

Date availability statement

The data sources for this study are publicly available from the OPTN web site: http://optn.transplant.hrsa.gov."

3- Direct-acting antiviral (DAA) Comment: Please provide the generic name of the DAA, and the drugs that was used before introduction of DAA.

We thank the reviewer #2 for this valuable suggestion. We have added the generic name of the DAAs, and the drugs that were used before the introduction of DAA in the Introduction as follow:

"Since December 2013, direct-acting antivirals (DAA), including NS3/4A inhibitors (boceprevir, telaprevir, simeprevir, asunaprevir, grazoprevir and paritaprevir), NS5A inhibitors (ombitasvir, ledipasvir, daclatasvir, elbasvir and velpatasvir), NS5B inhibitors (sofosbuvir and dasabuvir), have revolutionized HCV treatment by consistently achieving 95% or better sustained virologic responses[6]. Before the introduction of DAAs, a combination of interferon and ribavirin were the standard scheme for HCV treatment."

4- "DAA era": The sentence is better formulated: (before introduction of DAA, after introduction

of DAA).

We thank Reviewer #2 for this suggestion. “DAA era” and “introduction of DAA” were both used many times in published studies. However, considering the brevity and article space, we hope to choose “DAA era” which was used 66 times in the text.

5- Did the immunosuppressant in both groups had the same effect on viral load.
6- Incidence of graft rejection in both groups.

We thank Reviewer #2 for picking up this detail. Immunosuppressant effects on viral load and graft rejection are important to HCV+ kidney transplantation. However, information on immunosuppressant regimes, viral load, and graft rejection was not detailed in this database. We have added this weak point in the limitation section as follow:

“Second, PSM use to eliminate confounders between comparator groups could be biased by unmeasured potential confounders, including HCV genotype, viral load, infection duration and severity, and graft rejection, and immunosuppression intensity, none of which is found in the used registry data.”

7- Discussion: Be precise.

We agree with Reviewer #2 and have refined our discussion in regard to limitation and conclusions as follow:
“Second, PSM use to eliminate confounders between comparator groups could be biased by unmeasured potential confounders, examples including HCV genotype, viral load, infection duration and severity, graft rejection, and immunosuppression intensity, none of which is found in the used registry data.”
“In conclusion, although HCV infection in either KT donors or recipients negatively impacted PS and DCGS pre-DAA, neither donor nor recipient HCV infection appears to portend worse outcomes in the DAA era, supporting increased utilization of HCV+ kidneys as the standard of care. Given comparable outcomes across all four patient cohorts in the DAA era, a new allocation algorithm, eliminating HCV+ kidneys’ negative influence on the KDPI, is urgently needed to improve utilization and allocation of this under-utilized resource.”

8- Conclusion and core message: There is no conclusion, recommendation, or personal opinion.

We thank Reviewer #2 for pointing out this crucial issue. We have added conclusion, recommendation, or personal opinion at the end of article as follow:
“In conclusion, although HCV infection in either KT donors or recipients negatively impacted PS and DCGS pre-DAA, neither donor nor recipient HCV infection appears to portend worse outcomes in the DAA era, supporting increased utilization of HCV+ kidneys as the standard of care. Given comparable outcomes across all four patient cohorts in the DAA era, a new allocation algorithm, eliminating HCV+ kidneys’ negative influence on the KDPI, is urgently needed to improve utilization and allocation of this under-utilized resource.”