**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | Kidney transplantation waiting times and risk of cardiovascular events and mortality: a retrospective observational cohort study in Taiwan |
|---------------------|---------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Chen, Hsin-Hung; Chern, Yahn-Bor; Hsu, Chih-Yang; Tang, Pei-Ling; Lai, Chi-Cheng                                                   |

**GENERAL COMMENTS**

Comments to the Author
In the present study, the data show that on a composite endpoint (all-cause mortality, non-fatal myocardial infarction, and non-fatal ischemic stroke) in kidney transplanted (KT) patients, early KT patients were associated with superior long-term clinical and survival outcomes compared to late KT patients in selected end-stage renal disease (ESRD) patients receiving uncomplicated kidney transplantation. It suggests that the primary endpoint is correlated to ESRD vintage, and shorter dialysis vintage is an advantage in relation to the primary endpoint. However, I would like to bring to the Authors' attention few aspects which, in my opinion, deserve a further improvement to increase clarity for the readers. Furthermore, because the relationship between ESRD patients and KT patients in different samples or cohort studies was addressed in the literature many times, from this point of view authors need to explain more information about clinical treatment of this relationship in the introduction and discussion part or provide which aspects were previously not done.

Minor comments
1. Page 2, abstract mark 42. The patients are divided groups 1-4 according to the KT waiting times. Why are only rates of primary endpoint for groups 1-3 given in the abstract?

2. Page 6 mark 12. The concept of ESRD certificate card is introduced. However, it is not clear what this means. The authors should clearly state whether this is equivalent to start of renal replacement therapy or it also could mean Chronic Kidney Disease-5 (CKD-5).

3. Page 6 mark 31. Why KT with complications were excluded?

4. Page 7 mark 10. The authors state that the observation period was 1-17 years. However, the inclusion period was from 1997-2012. (page 5 mark 24, page 8 mark 3, and Figure 1). When did
the observational period end? Was this period in 2013? The descriptions in this text should be consistent.

REVIEWER
Kung, Ming-Hsiang
Kaohsiung Veterans General Hospital, Department of Medical Education and Research

REVIEW RETURNED
09-Nov-2021

GENERAL COMMENTS
Major comments to the Author
The authors conducted an observational cohort study to investigate the effect of different kidney transplantation (KT) waiting times on clinical outcomes in end-stage renal disease (ESRD) patients. Although the methods used were appropriate for answering the questions they asked, there were still some questions needed to be clarified by authors. This study found that early KT was associated with superior long-term clinical and survival outcomes compared to late KT in selected ESRD patients receiving uncomplicated KT, suggesting that an early KT is a better treatment option for ESRD patients who are eligible for transplantation, but whether early KT increased or decreased survival period in (ESRD) is still elusive. Could you give evidence to support your study? Therefore, it should have been fully discussed in this manuscript.

Minor comments:
1. The Primary outcome was a composite outcome. Why make the data composite? All-cause mortality, non-fatal myocardial infarction (MI) and stroke were given the value very differently by patients and clinicians.

2. In Table 2, the major events are all-cause mortality events. What did we know the causes of death? Furthermore, whether these factors were different depending on waiting list time?

3. Why so many young patients waited >6 years for a transplant? The authors should explain why group 4, the youngest with the least co-morbidity, have the longest waiting time.

4. The authors have demonstrated an association between time on the KT waiting list and outcomes, and this is plausible. However, is it the time on the waiting list or the factors making this time longer that lead to adverse outcomes?

5. Figure 1-5: The categories of <1 year, 1-3 years, 4-6 years >6 years should be correctly labelled. ex: KT waiting time <1 year, and so on...

REVIEWER
Keddis, Mira
Mayo Clinic Research Arizona

REVIEW RETURNED
28-Jan-2022

GENERAL COMMENTS
I applaud the authors for addressing a critical concern and using their work to help raise awareness about the need for more kidney transplantation.
I have a few comments for the authors:
1. In the methods, it is indicated that the waiting time was calculated from time of dialysis to time of transplant. This does not take into account time from dialysis to transplant referral. Can the authors comment from their experiences and experiences in
Taiwan in general regarding transplant referral practices and average time from development of ESRD to referral to transplant?
2. How was the grouping for KT waiting times determined?
3. Can you clarify if the analysis for the composite outcome was performed as time to first event?
4. Can the authors elaborate on what the transplant allocation process is in Taiwan and how that may have influenced patient characteristics of those who waited longer than 1 year versus those who waited < 1 year?
5. The authors acknowledge the existing literature that supports that time on dialysis is a critical determinant of CV events and mortality. The study cannot differentiate whether wait time independent of dialysis is associated with increased CV events and mortality or not because everyone in the study was on dialysis so in essence the wait times were directly correlated with dialysis duration. I think it would be important to acknowledge this in the discussion and limitations as well.

**VERSION 1 – AUTHOR RESPONSE**

Reviewers’ comments to Authors:
Reviewer: 1 Miss I-Tzu Chen

Comments to the Author:
In the present study, the data show that on a composite endpoint (all-cause mortality, non-fatal myocardial infarction, and non-fatal ischemic stroke) in kidney transplanted (KT) patients, early KT patients were associated with superior long-term clinical and survival outcomes compared to late KT patients in selected end-stage renal disease (ESRD) patients receiving uncomplicated kidney transplantation. It suggests that the primary endpoint is correlated to ESRD vintage, and shorter dialysis vintage is an advantage in relation to the primary endpoint. However, I would like to bring to the Authors’ attention few aspects which, in my opinion, deserve a further improvement to increase clarity for the readers. Furthermore, because the relationship between ESRD patients and KT patients in different samples or cohort studies was addressed in the literature many times, from this point of view authors need to explain more information about clinical treatment of this relationship in the introduction and discussion part or provide which aspects were previously not done.

Reply to R1: I heartily appreciate you for the professional comments. I completely agree with your viewpoints. We thus explained and described more information about clinical treatment of the relationship between ESRD patients and KT patients in the Introduction and Discussion parts as the followings.

In the Introduction, we added the description marked in the blue color “Patients with ESRD must receive renal replacement therapy (RRT) including kidney transplantation (KT), hemodialysis (HD) treatments, and/or peritoneal dialysis (PD) treatments. RRT dependent patients who need to receive dialysis treatments.” (line 12-15, page 4)

In the Discussion, I also added and revised the descriptions marked in the blue color “The adjusted mortality risk was considerably augmented by 69% in Group 2 during the long-term observational period. RRT dependent patients who waited for KT needed to receive dialysis treatments. This finding may be explained by the fact that delayed KT requires a longer pre-KT dialysis duration; that is, the prolonged duration of dialysis while awaiting KT may worsen the prognosis.” (line 12-15, page 11).

I additionally described “We therefore conducted a large scale retrospective observational study with an exclusion of KT complications to analyze a 17-year sample from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the relationship between KT timing and long-term cardiovascular outcomes;” (line 3-6, page 5)

Minor comments:
**Question R1-1**: Page 2, abstract mark 42. The patients are divided groups 1-4 according to the KT waiting times. Why are only rates of primary endpoint for groups 1-3 given in the abstract?

**Reply to Q R1-1**: I apologize this to confuse you. We did not present the rates of the group 4 (KT waiting time >6 years) because no case in group 4 at the follow-up of 10 years and the lack of relevant data for presentation. (line 48 page 2, and Table 2)

**Question R1-2**: Page 6 mark 12. The concept of ESRD certificate card is introduced. However, it is not clear what this means. The authors should clearly state whether this is equivalent to start of renal replacement therapy or it also could mean Chronic Kidney Disease-5 (CKD-5).

**Reply to Q R1-2**: I am so sorry that the meaning of ESRD certificate card is not clear enough. I thus added some description marked in the blue color as “Patients with ESRD certificate cards (labeled by the ICD-9-CM code number 585) indicating RRT dependent patients, who had received KT, defined as the ICD-9-CM code number V42.0, were eligible for inclusion.” (line 15-17, page 6)

**Question R1-3**: Page 6 mark 31. Why KT with complications were excluded?

**Reply to Q R1-3**: Thanks very much for your critical question. In brief, KT with complications were excluded to reduce the confounders. If we included the patients with complicated KT including graft rejection, infection and failure, the confounders should be increased and the interpretation should be more complicated (eg. perioperative MI, stroke, and death; partial contributions to primary endpoint, second KT, third KT, etc). For example, the contribution to Cardiovascular events and deaths might be influenced by KT complications. The question may be raised about how to identify the impact of KT waiting times and KT complications on the cardiovascular events and deaths. In addition, a patient receiving KT suffered from acute KT complication leading to cardiovascular event. It seems difficult to differentiate the association of the event with KT waiting time or with KT complication. According to the concern, we finally decided to exclude the patients who had KT complications. The explanation is highly expected to help you understand the reason to exclude patients who had KT complications.

**Question R1-4**: Page 7 mark 10. The authors state that the observation period was 1-17 years. However, the inclusion period was from 1997-2012. (page 5 mark 24, page 8 mark 3, and Figure 1). When did the observational period end? Was this period in 2013? The descriptions in this text should be consistent.

**Reply to Q R1-4**: I deeply appreciate you for the critical comment. As you mentioned, the observation period ended in 2013. I thus added the description as “…The observation period ended in 2013.” (line 31, page 5).

Reviewer: 2 Dr. Ming-Hsiang Kung, Kaohsiung Veterans General Hospital

**Major Comments to the Author**:

The authors conducted an observational cohort study to investigate the effect of different kidney transplantation (KT) waiting times on clinical outcomes in end-stage renal disease (ESRD) patients. Although the methods used were appropriate for answering the questions they asked, there were still some questions needed to be clarified by authors. This study found that early KT was associated with superior long-term clinical and survival outcomes compared to late KT in selected ESRD patients receiving uncomplicated KT, suggesting that an early KT is a better treatment option for ESRD patients who are eligible for transplantation, but whether early KT increased or decreased survival period in (ESRD) is still elusive. Could you give evidence to support your study? Therefore, it should have been fully discussed in this manuscript.

**Reply to R2**: I greatly appreciate you for the crucial comments. I guess you perhaps consider the evidence should be insufficient to support the study. We indeed focus on the discussion of the relationship between KT timing and all-cause mortality in the third paragraph of the Discussion "Consistent results obtained from several studies have exhibited that pre-KT and post-
KT dialysis durations are reversely associated with the survival outcome.\textsuperscript{21-25} Furthermore, an 11-year retrospective cohort study on KT recipients (n = 4,654) revealed a marginal increase in mortality in patients with a delay of >1 year, as well as bridge pre-KT HD treatments, compared with patients without delay (HR: 1.36; 95% CI: 1.01–1.81; P = 0.04).\textsuperscript{25} Moreover, the documented preemptive KT was associated with a 45% reduction in the hazard of the dialysis or re-KT (HR: 0.55; 95% CI: 0.47–0.64; P <0.001), and a 40% reduction in the hazard of death with a functioning graft (HR: 0.60; 95% CI: 0.50–0.71; P <0.001).\textsuperscript{27} In addition, young adults (11–30 year-old) with ESRD who were not listed for KT within five years and received dialysis treatments were 16.6 times more at risk of mortality than those who received transplantation, according to the report of UK renal registry data between 1999 and 2008.\textsuperscript{26} Together, the findings strongly support that KT waiting time is an independent predictor for primary events, as well as all-cause mortality, while early KT generates more favorable clinical outcomes." (line 19-50 page 11) In this paragraph, we intend to provide the sufficient data to support the study, and to discuss the survival issue you concerned.

Minor comments:

Question R2-1: The Primary outcome was a composite outcome. Why make the data composite? All-cause mortality, non-fatal myocardial infarction (MI) and stroke were given the value very differently by patients and clinicians.

Reply to Q R2-1: I heartily appreciate you for the crucial question. The composite cardiovascular outcome including all-cause mortality, nonfatal MI and nonfatal stroke has been popularly used as a primary cardiovascular endpoint in cardiovascular researches, despite of different values in each for pa. We decided to design the cardiovascular composite endpoint as the primary outcome in the beginning of the study.

Question R2-2: In Table 2, the major events are all-cause mortality events. What did we know the causes of death? Furthermore, whether these factors were different depending on waiting list time? Is there a national body that matches organs to recipients?

Reply to Q R2-2: Thank you a lot for the critical question. Actually, the causes of death were unknown by definition in the study. That is, I did not know the causes of death in each individual. The death was defined as withdrawal from the NHI system. (line 10, page 7) Withdrawal from the NHI system was one of necessarily administrative processes after a person's death. Therefore, I also did not know whether the causes of death were different depending on KT waiting time. A national institute so-called Taiwan Organ Registry and Sharing Center (TORSC) has been responsible to match organs to recipients in Taiwan. We described that in the second paragraphf the Discussion “The key problem of delayed KT is lack of kidney donors in Taiwan. A cultural concept of keeping completely intact body has limited organ donation. The organization of Taiwan Organ Registry and Sharing Center has been responsible to manage the organ donation, matching and sharing.” (line 6, page 10) I strongly expect these explanations may answer you clearly.

Question R2-3: Why so many young patients waited >6 years for a transplant? The authors should explain why group 4, the youngest with the least co-morbidity, have the longest waiting time.

Reply to Q R2-3: Thanks very much for the critical question. I try to explain the reasons that the young ESRD patients had longer life span to wait for KT and had relatively few aging-related comorbidities. The young ESRD patients had relatively high annual survival rate, and thus they had relatively long life span to wait for KT as long as exceeding 6 years. Additionally, they should have the more willing to receive KT because they needed to work for living. Time required dialysis treatments seemed not convenient for work.

In contrast, the older ESRD patients with more comorbidities might have higher annual death rate and possibly died early. It seemed inappropriate to receive KT in very aged patients. We thus acknowledge the potential selection bias mentioned in the Discussion and added description marked in red color (line 8-13, page 12) “First, the patient selection bias and the
baseline heterogeneity should have been considered in the present study. Patients in Group 4 who were younger, presented with fewer comorbidities, and received late uncomplicated KT had an approximately 3-fold higher clinical risk than patients in Group 1 receiving early uncomplicated KT. We explained the finding that younger patients in Group 4 were with possibly more detrimental factors to result in earlier development of ESRD and need longer dialysis treatments, which might lead to poorer clinical outcomes.

Question R2-4: The authors have demonstrated an association between time on the KT waiting list and outcomes, and this is plausible. However, is it the time on the waiting list or the factors making this time longer that lead to adverse outcomes?
Reply to Q R2-4: I deeply appreciate you for the critical comment. I agree with your viewpoint. I consider the key factor making the waiting time longer was the extreme shortage of domestic kidney donors, and whereas my answer to your question is certainly “Yes”. For example, the factors of acute illness and unstably clinical conditions made the waiting time longer and potentially led to adverse clinical outcomes. I have to acknowledge the presence of some unmeasured factors and variables which made the waiting time longer and potentially affect outcomes, and even were likely to lead to adverse outcomes. As mentioned in the limitations of the Discussion, we highlighted this “As conducting a randomized and controlled trial with randomization according to the KT waiting times is challenging and against ethics, this retrospective observational study provides long-term, real-world data; nevertheless, inherently, it has several limitations. First, some crucial variables and confounders were not totally considered, as the NHIRD did not contain laboratory details and all patients’ characteristics, and as factors affecting waitlisting. The baseline heterogeneity and the unmeasured confounders may have affected the outcomes, despite the use of statistically adjusted analyses. Second,…” (line 40-54 page 12) I strongly expect the explanation may convince you to realize the inherent limitations in the study.

Question R2-5: Figure 1-5: The categories of <1 year, 1-3 years, 4-6 years >6 years should be correctly labelled. ex: KT waiting time <1 year, and so on...
Reply to Q R2-5: I cordially appreciate your professional comment and kind reminding. We revised Figure 1-5 throughout and added “KT waiting time” on the top of the categories of <1 year, 1-3 years, 4-6 years >6 years because of their limited spaces in the figures. We here take Figure 1 and Figure 2 as examples below.
Reviewer: 3 Dr. Mira Keddis, Mayo Clinic Research Arizona

Comments to the Author:
i applaud the authors for addressing a critical concern and using their work to help raise awareness about the need for more kidney transplantation.
Reply to R3: Thank you a lot for the positive feedback which inspires us to go forward on our research work.

I have a few comments for the authors:

Question R3-1: In the methods, it is indicated that the waiting time was calculated from time of dialysis to time of transplant. This does not take into account time from dialysis to transplant referral. Can the authors comment from their experiences and experiences in Taiwan in general regarding transplant referral practices and average time from development of ESRD to referral to transplant?

Reply to Q R3-1: I greatly appreciate you for the professional question. In Taiwan, the organization of "Taiwan Organ Registry and Sharing Center (TORSC)" has been responsible for facilitating the process of KT. The TORSC has operated as a foundation to deal with the organ donation and sharing, and to cooperate with the globe. Because of the extreme short of organ donors, the ESRD patients who intended to receive KT had to be list for candidates for KT after preparation and approval of applications. As mentioned in the Introduction of the text, “A proportionally large number of ESRD patients received late KT due to the shortage of kidney donors. Thus, by early 2017, the KT waitlist in Taiwan exceeded 6,000 patients; nevertheless, only 230–325 patients received KTs per year (between 2005 and 2016).” That is, almost of ESRD patients did not receive KT and received dialysis treatments. The patients still kept waiting for KT when the referrals to KT were well done. Therefore, the average time from development of ESRD to referral to KT seemed not crucial in Taiwan. On the other hand, the average time from development of ESRD to referral to KT was also not available from the NHI database. Moreover, the time of ESRD defined as the time of receiving ESRD certificate card from the NHI system in the study was not absolutely accurate time indicating the cut-point time of development of ESRD. Together, I am very sorry to accurately provide the data regarding the average time from the development of ESRD to referral to KT.

Question R3-2: How was the grouping for KT waiting times determined?

Reply to Q R3-2: I appreciate you for the critical question. The partial authors including me discussed this and finally determined the grouping for KT waiting times in the beginning of designing the study according to the annual rates of cardiovascular events in ESRD patients.

Question R3-3: Can you clarify if the analysis for the composite outcome was performed as time to first event?

Reply to Q R3-3: Thank you very much for your kind suggestion. As mentioned in the Study Design and Relevant Variables of the Method “The analysis was conducted as described to avoid repetitive counting, as the time to the first event involved composite endpoints.” (line 45-47, page 7) I am so sorry about this to misunderstand you. It seems appropriate to move the description to the part of Statistical Analyses. Therefore, I moved the sentence to the part of Statistical Analyses. (line 15, page 7)

Question R3-4: Can the authors elaborate on what the transplant allocation process is in Taiwan and how that may have influenced patient characteristics of those who waited longer than 1 year versus those who waited < 1 year?

Reply to Q R3-4: I cordially appreciate you for the critical comment. As mentioned above, in Taiwan, the organization of "Taiwan Organ Registry and Sharing Center (TORSC)" has been responsible for facilitating the process of KT. The TORSC has operated as a foundation to deal with the organ donation and sharing, and to cooperate with the globe. Because of the extreme short of organ donors, the ESRD patients who intended to receive KT have to be list for candidates for KT after preparation and approval of application. I consider the factors of patients’ characteristics influencing the waiting times contained patients’ age, willing for KT, general condition, co-morbidities, matching criteria, etc. For example, the domestic patients who were well prepared early for KT were likely to wait for a long time. Only a small proportion of such patients received KT. Among them, fewer patients were lucky to receive early KT < 1 year. I believe the key factor was the short of kidney donors, as
mentioned in the text. However, some factors about patients’ characteristics were not available from NHI database and in the retrospective cohort study. These limitations were emphasized in the Discussion. (line 40 page 12)

**Question R3-5:** The authors acknowledge the existing literature that supports that time on dialysis is a critical determinant of CV events and mortality. The study cannot differentiate whether wait-time independent of dialysis is associated with increased CV events and mortality or not because everyone in the study was on dialysis so in essence the wait-times were directly correlated with dialysis duration. I think it would be important to acknowledge this in the discussion and limitations as well.

**Reply to Q R3-5:** We cordially appreciate you for the critical comment. We totally agree with your point about this. We described in the text as “Patients with ESRD certificate cards (labeled by the ICD-9-CM code number 585) indicating RRT dependent patients, who had received KT, defined as the ICD-9-CM code number V42.0, were eligible for inclusion….” The waiting time was calculated from the time of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded).” (line 15-17, page 6) We added the description marked in red color to clarify this.

That is, the waiting time for KT was reserved and used to renal replacement therapy dependent patients. In other words, these selected patients needed to receive KT or dialysis treatments as RRT. I acknowledge this in the discussion as “This finding may be explained by the fact that delayed KT requires a longer pre-KT dialysis duration; that is, the prolonged duration of dialysis while awaiting KT may worsen the prognosis. Consistent results obtained from several studies have exhibited that pre-KT and post-KT dialysis durations are inversely associated with the survival outcome.21-25 Furthermore, an 11-year retrospective cohort study on KT recipients (n = 4,654) revealed a marginal increase in mortality in patients with a delay of >1 year, as well as bridge pre-KT HD treatments, compared with patients without delay (HR: 1.36; 95% CI: 1.01–1.81; P = 0.04).25” (line 15-29, page 11)

I also added the description in the limitations of the Discussion (line 3 page 13) as “Fourth, the durations between the KT and ESRD might not be entirely accurate, using the record dates of the medical codes. Dialysis treatments were warranted during the waiting time for KT.” (line 15, page 13)

Finally, on behalf of all co-authors, I have to cordially thank all Editors and Reviewers again for your professional review work and comments to refine the manuscript, and your kind decision to consider the manuscript for publication.

Sincerely

Chi Cheng Lai, M.D. Ph.D.
Chief of Internal Medicine, Kaohsiung Municipal United Hospital, Taiwan
GENERAL COMMENTS

The manuscript had been improved after the revision. I will recommend an acceptance after major revisions.

REVIEWER
Keddis, Mira
Mayo Clinic Research Arizona

REVIEW RETURNED
14-Mar-2022

GENERAL COMMENTS

thank you for addressing concerns/comments raised. I recognize many of the questions raised could not be analyzed because of lack critical variables in the NHIRD database used for this study. thank you for noting this significant limitation.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

Q 1-1: The manuscript has been improved after the revision. I recommend publication of the manuscript.

Reply to Q 1-1: I heartily thank you for your kind recommendation for publication of the manuscript.

Reviewer: 2

Comments to the Author:

Q 2-1: The manuscript had been improved after the revision. I will recommend an acceptance after major revisions.

Reply to Q 2-1: I heartily thank you for your kind recommendation for acceptance of the manuscript.

Reviewer: 3

Comments to the Author:

Q 3-1: thank you for addressing concerns/comments raised. I recognize many of the questions raised could not be analyzed because of lack critical variables in the NHIRD database used for this study. thank you for noting this significant limitation.

Reply to Q 3-1: I heartily thank you for your kind understanding for the limitations of the NHIRD related researches, and your support.

Finally, on behalf of all co-authors, I have to deeply thank all Editors and Reviewers again for your professional review work and comments to refine the manuscript, and your kind decision to consider the manuscript for publication.