

Pre-dialysis care and access type are associated with transplant referral, evaluation, and waitlisting

Corresponding Author: Dr Jessica Harding

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #2

(Remarks to the Author)

Thank you for inviting us to review this manuscript by Harding, et. al. In this manuscript, the group conducted a retrospective cohort study for adult ESKD patients in the Southeast US who started dialysis between 1/1/2015 and 12/31/2019, identified through USRDS, to understand the association between pre-dialysis care/access type and transplant referral/evaluation. The exposure of interest was pre-dialysis care. Primary outcome was referral to transplant center within 12 months of dialysis initiation and other outcomes included evaluation start within 6 months of first referral, and waitlisting through end of follow up date on Dec 31, 2021. Overall, this is a patient-centered and thoughtful research study addressing the association of pre-dialysis care patterns on the navigation of the transplant care continuum, with a goal to help improve access to transplantation. While there are several strengths, including the thoughtful methodological approach and the policy-relevant discussion section, we have a few questions and suggestions that we hope will strengthen the manuscript. We have organized these thoughts into three major comments and several minor comments.

Major comments:

1. Categorization of optimal starts: Line 136 to 145: The categorization of optimal starts was very interesting, but also left us with several questions about how to define an optimal start, and how to differentiate between sup-optimal and non-optimal starts, particularly from a clinical and policy perspective.
 - o What was the rationale for how the researchers defined optimal start and what guidelines informed this? One definition of Optimal ESRD starts from the National Quality Forum #2594 (which is adopted in current kidney payment models, such as the Kidney Care Choices Model), defines optimal starts as: Optimal ESRD Starts CBE #2594 - Percentage of new patients with ESRD aged 18 years and over who initiate renal replacement therapy in a 12-month measurement period with an optimal ESRD therapy, which includes preemptive kidney transplant, home dialysis (PD or home hemodialysis), or outpatient in-center hemodialysis via AV fistula or AV graft. In contrast, the definition of an optimal start/pre-dialysis nephrology care in the current manuscript does not characterize the distinction between initiating hemodialysis in the outpatient versus inpatient setting, and does not account for home hemodialysis. Please consider accounting for outpatient initiation of dialysis and home hemodialysis.
2. Justifying the rationale for suboptimal and non-optimal groups. What is the rationale and potential clinical significance of defining suboptimal and non-optimal groups? We questioned whether it might be simpler to collapse this into one category of 'suboptimal,' particularly given the challenges around defining whether an AVA is a metric of pre-nephrology care (for example, with a growing aging ESRD population, there are several clinical examples of instances where patients may not benefit from the creation of an AVA).

Current categorization:

- o Optimal: initiate PD/HD with mature AVF + pre HD care
- o Sub optimal: initiate HD with catheter and with maturing AVA + preHD care

- o Non optimal: HD with catheter w/o maturing AVA + preHD care

- o Crash: start HD w/catheter – pre HD care

Why not categorize as below:

- o Optimal: initiate PD/HD with mature AVF + pre HD care

- o Sub optimal: initiate HD with catheter with or without maturing AVA + preHD care

- o Crash: start HD w/catheter, no pre HD care

3. Influence of pre-emptive transplant referral on results: Line 154 to 155: In the methods, the researchers classified preemptive transplant referral/evaluation as “pre-dialysis care”, which falls into either the optimal, suboptimal, or non-optimal groups. It would be helpful to understand whether/how this categorization of pre-emptive transplant evaluation influences the primary outcome. For example, with pre-emptive transplant referrals, follow up time was defined as 1 day, which could disproportionately influence the results for days to referral. Please consider expanding on this with a sensitivity analysis that excludes patients with a preemptive referral and evaluation.

Minor comments:

Abstract:

1. Line 53-56: The wording of the ‘primary exposure’ in the abstract is a bit confusing. At first glance, it was not clear if the primary exposure was ‘pre-dialysis care and optimal, suboptimal, non-optimal, and crash starts.’ It seemed like the exposure was a composite of various definitions of pre-dialysis care. Please consider rephrasing this section to be a bit clearer, for example, as “the primary exposure was pre-dialysis care, which was categorized as optimal, supoptimal, non-optimal, or crash start based on a composite of outcomes related to pre-dialysis nephrology visits, dialysis type, and access.”

Intro:

2. The authors state that “Despite this, most patients who progress to ESKD in the U.S. initiate dialysis in a less than ideal setting without pre-dialysis nephrology care or vascular access in place, although contemporary and comprehensive data are lacking to quantify this burden.” Consider specifying that this section refers to in-center hemodialysis (where vascular access is relevant), or broaden this to talk about pre-emptive transplant, home dialysis (which does not necessarily require vascular access if patients choose peritoneal dialysis), and conservative kidney management.

Methods:

3. Line 204: Readers may not understand why percentage of black residents was used as a neighborhood factor. Consider providing rationale for using percentage of Black residents over other measures of social deprivation index or segregation indices

4. In the measure of pre-dialysis nephrology care, home hemodialysis is not mentioned. While home hemodialysis represents a small proportion of patients, it would still be helpful to point out whether the investigators included/excluded home hemodialysis from the study.

5. Is the classification of obesity accurate, particularly for class II and III? Shouldn't it be underweight < 18.5, normal 18.5 to 24.9, overweight 25-29.9, class I obesity 30-34.9, class II 35 to 39.9, class III > 40?

Discussion:

6. Could the researchers speculate further on what post-dialysis initiation factors may continue to drive more delayed median time to follow up for transplant referral and evaluation start for crash starters vs. the other groups? Even though patients are engaged with nephrology care after dialysis start, why might there still such a lag in time to getting referred and evaluation among these three groups?

7. Please expand further on what future studies or directions might be warranted as a result of your findings.

8. The first sentence seems to assume that the only modality of dialysis is in-center hemodialysis. Perhaps this could be reframed as either i) 56% of adults initiating hemodialysis for ESKD did so with no AVA in place, or ii) 56 of adults initiating dialysis for ESKD did so with no AVA in place or no home dialysis (depending on which statement is more reflective of the results).

9. The second paragraph notes how results from this study align with another study by Raffray et al. However, several authors from the current study were involved in that study (including the first author of this paper, who was senior author on that prior paper). Even if this was not the intent, it feels a bit misleading to refer to the Raffray et al paper as if it were an independent study. Please consider reframing this section. For example, “our results align with and extend findings from a recent national study our team conducted which, using similar approaches, demonstrated...”

Tables and Figures:

10. Table S1 legend: spelling error: “columns”

Reviewer #3

(Remarks to the Author)

Summary:

This is a USRDS study that examines the association between the “quality” of dialysis initiation (as defined by responses on the Medical Evidence Form about pre-nephrology and pre-existing vascular access and then categorized into four categories of optimal, sub or non-optimal and crash start) and referral, evaluation and subsequent waitlisting for kidney transplant. It found that patients with optimal starts ended up having better outcomes with respect to transplant access than non and sub-optimal patients, who in turn had better outcomes than crash starts.

Overall impression:

Although the findings are as one would expect and this question has been asked before (as the authors note when they cite

the Raffray et al. paper), there is additional value to this analysis, especially in terms of methodology (linking USRDS data at the patient level with data from 9 southeastern transplant centers) which then allowed for a richer study by including a wider variety of transplant access related outcomes (not just referrals but also evaluations and waitlisting). I also think this is good information for a non-nephrology audience who might question the utility of early nephrology referral, especially as this study shows in detail that even some amount of nephrology care is associated with better access to transplant care, and that a longer duration of time under nephrology care yields even better outcomes. Although I have several questions about the analysis and do think some changes and/or additional analyses would be of benefit, I think it's overall a well-done study.

One major overall thought- there's very little difference in outcomes between the 'sub-optimal' and 'non-optimal' start groups. Yet the authors persist in treating a small, statistically indistinguishable difference in likelihood of referral as evidence of a "dose-response". There is evidence of a "dose-response" in terms of the differences between optimal start vs. sub-optimal/non-optimal and then between those groups and the crash starts, but it's clear that there is not a major difference in outcomes between the sub- and non- optimal groups. Because the sub-and the non-group are differentiated by the presence or absence of a maturing vascular access, I wonder to what extent the presence or absence of vascular access drives the outcomes of interest. It seems possible that the exposure that drives outcomes is receipt of pre-dialysis nephrology care or no, and the duration of this receipt (enough time to ensure a mature vascular access or PD catheter start or probably not enough time to do that). An analysis where you looked at no pre-dialysis nephrology care, less than 12 months of pre-dialysis nephrology care, and more than 12 months of nephrology care (or whatever time cut-offs the authors think appropriate), with the same outcomes, and didn't consider the vascular access situation of the patients, could simplify the association and make it more powerful for readers, and should be considered.

Specific Questions/thoughts with line numbers

Abstract

Line 51—53 This is not a pure USRDS study, and one of its strengths is its linkage with the Early Steps to Transplant database. This should be made clear in the abstract as it also makes it clear why only the southeastern US is being studied.

Line 71- again, I think the difference between "sub-" and "non-" for the outcome of referrals is overstated and references to it should be removed, especially given the wide overlap in confidence intervals.

Line 77- I would rephrase in conjunction with the previous note- you indirectly posit a "dose-response" here for the outcome of evaluation, which immediately contradicts what you wrote at line 71.

Introduction

Line 84- "managing care progression" is a confusing and unclear phrase. Do you mean managing the transition of care from pre-dialysis CKD to dialysis? Moreover, it seems like there should be a citation here- I don't think it's self-evident that managing this transition well results in improved quality of life, for example.

Line 85- the sentence that begins with "Despite This..." seems misleading. The USRDS annual data report from 2024 shows that 22% of patients initiate dialysis with no pre-existing nephrology care, a fraction that increases to about 40% if you include individuals with unknown pre-ESRD care. (see figure 1.12 in Chapter 1 of the ESRD section of the annual data report from 2024) So "most patients" who initiate dialysis in the US do have some pre-dialysis nephrology care. It would be better to say something like "Despite this....less than a third of patients who progress to ESKD in the US experience an optimal start (define the term) when they initiate dialysis" and cite the annual data report (actual number something like 30%)

Methods

Line 135- please explain how patients who started dialysis with an HD catheter but also had a PD catheter in place were defined- it does occur that a surgeon or interventional nephrologist will place both accesses and HD will be started while the PD catheter site heals.

Line 161- to what extent is initiation of transplant evaluation influenced by patient specific factors as opposed to transplant center specific-factors? It seems possible that this outcome could be greatly influenced by center-specific factors like how far out they are scheduling (although I am not an expert in this area). Furthermore, it seems like the transplant database they are using would allow the authors to adjust for which center the patients used so that center specific factors were accounted for, but I can't see that this was done.

Line 184- I think two additional, easily available covariates from the 2728 could be useful to include, at least for the initial outcome of referral. I think baseline serum albumin could have an influence on how quickly patients receive transplant referrals- i.e a malnourished hypoalbuminemic patient could be less likely to receive an expeditious referral. Moreover, about 5% of patients in the USRDS report either difficulty with transfers, difficulty with activities of daily living, or inability to ambulate on Form 2728. These patients may have delayed referrals to transplant centers because of these conditions and so a covariate that incorporates these questions should be considered.

Results

Line 281- Again, I would remove reference to the "dose-response", especially here in the results, as it seems editorializing, especially as the results for the "sub-" and "non-" groups are nearly indistinguishable.

Line 289- again, please see comment for 281 and previous comments- there is no clear "dose-response" pattern for the outcomes of referral or evaluation between the "sub-" and "non-groups"

Line 303- could consider providing more information about why cumulative incidences of wait-listing were so close between all the "less optimal" groups but why adjusted incidences were significantly different. What covariates caused this difference?

Line 307- it should be noted in that in table S2 the wait-listing differences between the crash group and the sub-optimal group because statistically indistinguishable, so there was a difference found in that sensitivity analysis.

Discussion

Line 325- remove the word "less" here

Line 362- I think missing-ness of data (9.7%, as discussed in the methods section) with respect to ESRD pre-nephrology care is a problem and should be considered a limitation and discussed as such, especially since there were (minor) differences in outcomes depending on how people with missing data were handled.

Reviewer #4

(Remarks to the Author)

The study of Harding et al aimed at assessing the association between pre-dialysis care (as ascertained through the degree of preparation to dialysis) and three aspects of preparation for kidney transplantation: referral, evaluation, waitlisting. It is based on USRDS data (Southeast USA, 2015-2021) and its linkage with the E-STAR database, the later bringing information about early transplant care. Authors report increasing probability of transplant preparation with increasing dialysis preparation – which is not a new finding and rather logical – with the main novelty of the study involving the analysis step-by-step of the transplant preparation pathway.

The main concern for the study internal validity relies on the fact that groups: optimal, sub-optimal, non-optimal, and unprepared start (<https://doi.org/10.1016/j.kint.2019.01.017>, I would avoid the term “crash start”) do not share the same study time of origin. As such, authors had to displace the outcome onset – i.e., participants who were referred, evaluated or waitlisted before starting KRT had their event onset set on day 1 of follow-up, Line 181. Also, the event was part of the exposure definition – i.e., “(...) patients were deemed to have pre-dialysis nephrology care if they (...) had been preemptively referred, evaluated, or waitlisted (e.g., prior to dialysis initiation), regardless of their original pre-dialysis nephrology care categorization”, Lines 153-156).

While I understand that considering only patients at risk of transplant preparation can also lead to [selection] bias, I think one cannot claim to estimate time-to-event measures within this framework. However, one can argue that estimating time-fixed relative risks (for instance, relative risks of being prepared to kidney transplant at 6-, 12-months after dialysis initiation) may be useful.

Specific comments:

Please, consider revising “causal” terms such “how pre-dialysis nephrology care and dialysis access type impacts access to pre-waitlisting” to better reflect what is being assessed in your study.

Methods: could authors develop on how or in what the E-Star database is novel?

It is not clear whether the fact of considering only the first transplant referral/evaluation (Line 178) can lead to misclassification of the outcome. In particular, could patients who were not first evaluated in the studied center have been evaluated in other centers not participating in the database?

In “(...) conducted multiple imputation for all missing values in the full cohort (n=39,794, 81.1%)”, Lines 239 and 240, is 39,794 (81%) the number (fraction) of participants with missing data for any of the covariates? If so, 5 imputed datasets seem not enough to deal with Monte Carlo error (see 10.1002/sim.4067)

How many studied patients have been referred/evaluated/waitlisted before KRT and thus had their event onset displaced?

One cannot directly interpret the effect size of a sub-distribution hazard model, i.e. a sd-HR of 0.72 does not mean that patients are 28% less likely to be referred, it just means that these patients are less likely to be referred, but not at the same extent that patients with sd-HR of 0.69 or 0.43. Please see doi: 10.1093/ndt/gft355 for a wide-audience accessible explanation of subdistribution hazard ratios.

Despite model adjustment, one cannot exclude that the level of preparation for dialysis is a proxy of more intensive/ longer pre-dialysis care. Even more importantly, in participants who were prepared to kidney transplantation before KRT initiation, assessment of covariates are posterior to event onset which, along with inherent disease misclassification, may lead to confounding of the association by health status. This could explain why patients with non-optimal dialysis start were more likely to be prepared to kidney transplantation than patients with sub-optimal dialysis start.

From line 273: do authors mean “Median follow-up to referral (...) in line 267, (...) to evaluation in line 273? As stated in the overall comment above, it may be misleading trying to interpret time to events in this setting of left truncated data.

Please, comply with KDIGO consensus on nomenclature for kidney function and disease, e.g. kidney failure, instead of ESKD.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #2

(Remarks to the Author)

Thank you for the revisions based on our previous feedback. The authors have addressed all of our major concerns, which we hope have improved the clarity and strength of the manuscript. We have one residual minor comment below.

Cumulative Incidence of Referral and evaluation start: The authors write the following in the same paragraph.

“The cumulative incidence of death was 8.1%, 14.2%, 18.6%, and 21.2% in highly, moderately, minimally, and non-optimal

dialysis starts, respectively (Figure 3A).

"The cumulative incidence of death was 2.1%, 3.5%, 4.2%, and 3.9% in highly, moderately, minimally, and non-optimal dialysis starts, respectively, (Figure 3B)."

We suspect it would be helpful to reviewers to clarify within each sentence that these refer to the 1-year cumulative incidence of death and the 6-month cumulative incidence of death, respectively.

Reviewer #3

(Remarks to the Author)

Thank you for your responses to the reviewer comments, and I gladly accept most of them.

Although in general I continue to believe this study has significant merit, I think the authors should consider the suggestions from two of their reviewers to simplify their categorization strategy, and I endorse the strategy presented by Reviewer #2, which would allow them to retain many of their findings and discussion points. Although some of the points that the authors raised in their rebuttal to this idea are valid, I do note that the authors pointed to an interpretation of figure 3 that doesn't seem quite right. The authors stated that Figure 3 shows that "moderately optimal starters had higher rates of transplant referral than minimally optimal starters, lower rates of evaluation and death, and similar rates of waitlisting once evaluated." Doesn't figure 3 show similar rates of referral and evaluation between the moderate and minimal groups, and that minimally optimal patients are more likely to be waitlisted at 5 years than moderately optimal patients? I think that the fact that even the authors and reviewers who are closely reading this material are having trouble accurately differentiating the outcomes for these categories may point to the need for simplification of the categorization scheme. I also think that the three category model proposed demands less from readers in terms of keeping these categorical differences in mind while preserving most of the value of the analysis and discussion.

I will also note that USRDS does include data about the duration of pre-dialysis nephrology care that is received by patients prior to initiation, contrary to the assertion of the authors that "We also note that the amount of nephrology care prior to dialysis initiation is not available in the USRDS dataset" Below are the relevant data files captured by the Medical evidence form, as it may be useful for the authors to consider for a future analysis:

NEPHCARE Num 8 YN9FMT. "(17.b 2018 form; 18.b 2015/2005 form) Was patient under care of a nephrologist?"

"NEPHCARERANG

E" Num 8 RANGE. "(17.b 2018 form; 18.b 2015 form) If Yes, answer: <6, 6-12 or >12 months; (18.b 2005 form) If Yes, answer: 6-12 or >12 months"

Reviewer #4

(Remarks to the Author)

I thank the authors for addressing the comments; I believe that the manuscript is suitable for publication.

Version 2:

Reviewer comments:

Reviewer #3

(Remarks to the Author)

Thank you so much for taking the time to undertake a new analysis and a new revision for the manuscript in light of my suggestions. Given the additional findings and the revisions to the manuscript, I do not have further major concerns. I want to note a couple of minor, likely typographical errors in the revised section of the discussion. My suggested edits are in parentheses:

We also found that 15.5% of patients started dialysis in a moderately optimal way, with pre-dialysis care and an AVF or AVG graft maturing at time of HD initiation, and a further 31.0% with (this should read "without", correct?) maturing graft present at the time of HD initiation despite receiving some pre-dialysis nephrology care. (remove additional period). Despite the substantial difference in the number of patients who do and do not have a maturing graft in place, their access to transplant referral and evaluation was similar (comma) suggesting that being in the care of a nephrologist prior to initiating dialysis may be the more important indicator of dialysis readiness and subsequent transplant access. It is also possible that having a maturing graft in place is simply a function of longer pre-dialysis nephrology care, as suggested in Table Sx (S6, correct?)

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Dear Communications Medicine editorial committee,

Here, we provide reviewer comments from our initial submission of this manuscript, entitled **'Pre-dialysis care and access type are associated with transplant referral, evaluation, and waitlisting – evidence from a multi-regional US cohort study'**. We have provided a response to each of these comments, and in several instances, enacted changes to improve the manuscript. We have included each reviewer comment below, with our response/changes in blue. Where changes have been enacted, we have indicated where on the corresponding tracked document.

We hope you will agree this manuscript is greatly improved and fills an important knowledge gap in what we know of how dialysis context can predict future transplant access in the US, and will be of interest to the broader Communications Medicine readership.

Kind regards

Jessica Harding, on behalf of all co-authors

Referee expertise:

Referee #1: Co-reviewer/ Career researcher (ECR)

Referee #2: Nephrologist; implementation scientist

Referee #3: ESKD; clinical epidemiology

Referee #4: Kidney Epidemiology; Kidney transplant

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Medicine initiative to facilitate training in peer review and to provide appropriate recognition for Career Researchers who co-review manuscripts.

Reviewer #2 (Remarks to the Author):

Overall comments:

Comment: Thank you for inviting us to review this manuscript by Harding, et. al. In this manuscript, the group conducted a retrospective cohort study for adult ESKD patients in the Southeast US who started dialysis between 1/1/2015 and 12/31/2019, identified through USRDS, to understand the association between pre-dialysis care/access type and transplant referral/evaluation. The exposure of interest was pre-dialysis care. Primary outcome was referral to transplant center within 12 months of dialysis initiation and other outcomes included evaluation start within 6 months of first referral, and waitlisting through end of follow up date on Dec 31, 2021. Overall, this is a patient-centered and thoughtful research study addressing the association of pre-dialysis care patterns on the navigation of the transplant care continuum, with a goal to help improve access to transplantation. While there are several strengths, including the thoughtful methodological approach and the policy-relevant discussion section, we have a few questions and suggestions that we hope will strengthen the manuscript. We have organized these thoughts into three major comments and several minor comments.

Response: Thank you to the reviewer for their thoughtful, thorough, and overall positive assessment of our work

Major comments:

Comment: Categorization of optimal starts: Line 136 to 145: The categorization of optimal starts was very interesting, but also left us with several questions about how to define an optimal start, and how to differentiate between sup-optimal and non-optimal starts, particularly from a clinical and policy perspective. What was the rationale for how the researchers defined optimal start and what guidelines informed this? One definition of Optimal ESRD starts from the National Quality Forum #2594 (which is adopted in current kidney payment models, such as the Kidney Care Choices Model), defines optimal starts as: Optimal ESRD Starts CBE #2594 - Percentage of new patients with ESRD aged 18 years and over who initiate renal replacement therapy in a 12-month measurement period with an optimal ESRD therapy, which includes preemptive

kidney transplant, home dialysis (PD or home hemodialysis), or outpatient in-center hemodialysis via AV fistula or AV graft. In contrast, the definition of an optimal start/pre-dialysis nephrology care in the current manuscript does not characterize the distinction between initiating hemodialysis in the outpatient versus inpatient setting, and does not account for home hemodialysis. Please consider accounting for outpatient initiation of dialysis and home hemodialysis.

Response: We agree that defining optimal vs. non optimal is both difficult and a critical element of this paper. In our dataset, we are unable to determine if PD or HD initiation occurs in an inpatient or outpatient setting. We have added a line acknowledging this limitation in our discussion, page, 15, as follows: “... we were unable to determine if PD or HD initiation occurred in an inpatient or outpatient setting, or if a PD catheter was in place for those initiating HD which would have provided additional context for dialysis preparedness.”

We were, however, able to incorporate home HD into our definition, a good suggestion. This was relevant for 169 patients overall in our dataset (<0.3% of total population), and these patients have now been categorized as group 1 (renamed ‘highly optimal’) (see revised flowchart, Figure 2). All results have now been updated to reflect this change, but note this has not materially influenced any of our effect estimates or study conclusions.

Comment: Justifying the rationale for suboptimal and non-optimal groups. What is the rationale and potential clinical significance of defining suboptimal and non-optimal groups? We questioned whether it might be simpler to collapse this into one category of ‘suboptimal,’ particularly given the challenges around defining whether an AVA is a metric of pre-nephrology care (for example, with a growing aging ESRD population, there are several clinical examples of instances where patients may not benefit from the creation of an AVA).

Current categorization:

- Optimal: initiate PD/HD with mature AVF + pre HD care
- Sub optimal: initiate HD with catheter and with maturing AVA + preHD care
- Non optimal: HD with catheter w/o maturing AVA + preHD care
- Crash: start HD w/catheter – pre HD care

Why not categorize as below:

- Optimal: initiate PD/HD with mature AVF + pre HD care
- Sub optimal: initiate HD with catheter with or without maturing AVA + preHD care
- Crash: start HD w/catheter, no pre HD care

Response: Our rationale for the current definitions was to provide as much granularity as possible when combining information on dialysis type, vascular access, and pre-nephrology care to delineate specific information about dialysis preparedness. We argue that having a mature AVF in place (vs. starting with a catheter) among people receiving pre-dialysis nephrology care does imply different levels of preparedness, acknowledging this is not true for all patients, including the elderly. Interestingly, when you compare the two ‘sub-optimal’ groups, there are little differences in baseline characteristics (see **Table 1**), including age, suggesting there are other factors at play in the placement (or not) of AVA.

Though it is possible to collapse sub-optimal and non-optimal groups into one category (since renamed moderately and minimally optimal, respectively), we believe we would lose significant information in doing so. For example, a much larger proportion of patients were classified as

minimally optimal (31.0%) than moderately optimal (15.5%) highlighting that even with pre-nephrology care, a very large proportion of patients are starting dialysis without vascular access. Further, as depicted in Figure 3, moderately optimal starters had higher rates of transplant referral than minimally optimal starters, lower rates of evaluation and death, and similar rates of waitlisting once evaluated, an important finding.

We have also added a comment in our discussion alluding to the policy-relevant information that can be gained from examining these two groups separately, page 14-15, as follows:

“Importantly, we found that a significant proportion of individuals (24.8%) initiated dialysis with no reported pre-dialysis nephrology care, and another 31.0% had no AVA present at the time of HD initiation despite receiving pre-dialysis nephrology care, signifying immense opportunity for intervention. Transition to dialysis and then navigating the transplant care continuum requires ample time for thorough, patient-centered discussions with providers, a process that hinges on adequate transplant education, health literacy, and efficient care transitions between dialysis facilities and transplant centers.^{22,35} Introducing innovative clinical decision support systems (e.g., electronic alerts, practice facilitation strategies, audit and feedback reports) may give clinicians and patients additional time and structure for planning the shift to and from dialysis.^{36,37}”

Comment: Influence of pre-emptive transplant referral on results: Line 154 to 155: In the methods, the researchers classified preemptive transplant referral/evaluation as “pre-dialysis care”, which falls into either the optimal, suboptimal, or non-optimal groups. It would be helpful to understand whether/how this categorization of pre-emptive transplant evaluation influences the primary outcome. For example, with pre-emptive transplant referrals, follow up time was defined as 1 day, which could disproportionately influence the results for days to referral. Please consider expanding on this with a sensitivity analysis that excludes patients with a preemptive referral and evaluation.

Response: We have now included a sensitivity analyses excluding all patients pre-emptively referred (n=6,844), evaluated (n=3), or waitlisted (n=718), i.e., those who were referred, evaluated, or waitlisted prior to the need to initiate dialysis (n_{total}=7,565). This is now included as **Table S4** in the Supplement. This did not change key findings, which have now been mentioned in the results, page 13, as follows:

“Findings were also similar when we 1) restricted to individuals without missing pre-dialysis nephrology care or AVF/AVG status (Table S2), and 2) conducted multiple imputation for all missing covariates in the full cohort (Table S3), 3) excluding individuals with pre-emptive access with the exception of waitlisting where there was no difference in sub distribution of hazards between highly, minimally, and moderately optimal dialysis starters (Table S4); and 4) accounting for additional covariates of hypoalbuminemia and functional impairment (Table S5).”

Minor comments:

Comment: Abstract, Line 53-56: The wording of the ‘primary exposure’ in the abstract is a bit confusing. At first glance, it was not clear if the primary exposure was ‘pre-dialysis care and optimal, suboptimal, non-optimal, and crash starts.’ It seemed like the exposure was a composite of various definitions of pre-dialysis care. Please consider rephrasing this section to be a bit clearer, for example, as “the primary exposure was pre-dialysis care, which was categorized as optimal, sub-optimal, non-optimal, or crash start based on a composite of outcomes related to pre-dialysis nephrology visits, dialysis type, and access.”

[Response](#): Revised as suggested.

Comment: Intro: The authors state that “Despite this, most patients who progress to ESKD in the U.S. initiate dialysis in a less than ideal setting without pre-dialysis nephrology care or vascular access in place, although contemporary and comprehensive data are lacking to quantify this burden.” Consider specifying that this section refers to in-center hemodialysis (where vascular access is relevant), or broaden this to talk about pre-emptive transplant, home dialysis (which does not necessarily require vascular access if patients choose peritoneal dialysis), and conservative kidney management.

[Response](#): Nice suggestion. Revised as follows: “Despite this, most patients who progress to kidney failure in the U.S. and initiate do so in a less than ideal setting without pre-dialysis nephrology care or vascular access in place, *without pre-emptive transplant, or home dialysis*, although contemporary and comprehensive data are lacking to quantify this burden”

Comment: Methods, Line 204: Readers may not understand why percentage of black residents was used as a neighborhood factor. Consider providing rationale for using percentage of Black residents over other measures of social deprivation index or segregation indices

[Response](#): Revised as follows: “Neighborhood-level characteristics, *used as proxies for area-level socioeconomic status*, included poverty (percentage of residents living in a ZIP code where $\geq 20\%$ of residents live below the federal poverty line), percentage of Black residents, and percentage of residents with a high school degree”

Comment: Methods: In the measure of pre-dialysis nephrology care, home hemodialysis is not mentioned. While home hemodialysis represents a small proportion of patients, it would still be helpful to point out whether the investigators included/excluded home hemodialysis from the study.

[Response](#): We have now incorporated home HD into our definition (see revised flowchart, Figure 2). This was relevant for 169 patients overall in our dataset ($<0.3\%$ of total population), and these patients have now been categorized as group 1 (renamed ‘highly optimal’). All results have now been updated to reflect this change.

Comment: Methods: Is the classification of obesity accurate, particularly for class II and III? Shouldn't it be underweight < 18.5 , normal 18.5 to 24.9 , overweight $25-29.9$, class I obesity $30-34.9$, class II 35 to 39.9 , class III > 40 ?

[Response](#): Thank you for picking up this error. Indeed, these were the categories used and the text has been updated to reflect this.

Comment: Methods: Could the researchers speculate further on what post-dialysis initiation factors may continue to drive more delayed median time to follow up for transplant referral and evaluation start for crash starters vs. the other groups? Even though patients are engaged with nephrology care after dialysis start, why might there still such a lag in time to getting referred and evaluation among these three groups?

[Response](#): We have included the following thoughts to our discussion, page 15, as follows: “The adverse outcomes associated with non-optimal dialysis starts *even once in the care of a nephrologist* likely reflect broader barriers to healthcare access including financial constraints, rural location, limited health literacy, and weak social support networks.³³ *Transition to dialysis*

and then navigating the transplant care continuum requires ample time for thorough, patient-centered discussions with providers, a process that hinges on adequate transplant education, health literacy, and efficient care transitions between dialysis facilities and transplant centers.^{21,34}

Please note in response to reviewer #4, we have removed specific reporting of median time to event due to our data being left truncated in primary analyses.

Comment: Discussion: Please expand further on what future studies or directions might be warranted as a result of your findings.

Response: We have included the following, page 15, as follows: “The 2022 Kidney Care Choices model⁸ aims to include optimal dialysis start as a utilization quality metric. *While it is still too early to know if this model has improved dialysis transitions, this initiative underscores the need for continued national surveillance and research to better understand the downstream impact of an ideal dialysis start during the transition to transplant. Additional research using appropriate longitudinal datasets that are able to follow patients from a CKD diagnosis through to dialysis initiation would also shed light on pre-dialysis factors contributing to non-optimal starts.*”

Comment: Discussion: The first sentence seems to assume that the only modality of dialysis is in-center hemodialysis. Perhaps this could be reframed as either i) 56% of adults initiating hemodialysis for ESKD did so with no AVA in place, or ii) 56 of adults initiating dialysis for ESKD did so with no AVA in place or no home dialysis (depending on which statement is more reflective of the results).

Response: Revised as follows: “In this multi-regional US cohort study, we found that more than half of adults initiating dialysis (*in-center or home HD and PD*) for kidney failure did so with no AVA in place or without any pre-dialysis nephrology care.”

Comment: Discussion: The second paragraph notes how results from this study align with another study by Raffray et al. However, several authors from the current study were involved in that study (including the first author of this paper, who was senior author on that prior paper). Even if this was not the intent, it feels a bit misleading to refer to the Raffray et al paper as if it were an independent study. Please consider reframing this section. For example, “our results align with and extend findings from a recent national study our team conducted which, using similar approaches, demonstrated...”

Response: We agree with this sentiment and have revised our language throughout to demonstrate the two studies are from the same research group.

Comment: Table S1 legend: spelling error: “columns”

Response: Corrected

Reviewer #3 (Remarks to the Author):

Overall comments:

Comment: This is a USRDS study that examines the association between the "quality" of dialysis initiation (as defined by responses on the Medical Evidence Form about pre-nephrology

and pre-existing vascular access and then categorized into four categories of optimal, sub or non-optimal and crash start) and referral, evaluation and subsequent waitlisting for kidney transplant. It found that patients with optimal starts ended up having better outcomes with respect to transplant access than non and sub-optimal patients, who in turn had better outcomes than crash starts. Although the findings are as one would expect and this question has been asked before (as the authors note when they cite the Raffray et al. paper), there is additional value to this analysis, especially in terms of methodology (linking USRDS data at the patient level with data from 9 southeastern transplant centers) which then allowed for a richer study by including a wider variety of transplant access related outcomes (not just referrals but also evaluations and waitlisting). I also think this is good information for a non-nephrology audience who might question the utility of nephrology referral, especially as this study shows in detail that even some amount of nephrology care is associated with better access to transplant care, and that a longer duration of time under nephrology care yields even better outcomes. Although I have several questions about the analysis and do think some changes and/or additional analyses would be of benefit, I think it's overall a well-done study.

[Response:](#) We appreciate the positive assessment of our work, and the time spent by the reviewer to improve it.

Major comments:

One major overall thought- there's very little difference in outcomes between the 'sub-optimal' and 'non-optimal' start groups. Yet the authors persist in treating a small, statistically indistinguishable difference in likelihood of referral as evidence of a "dose-response". There is evidence of a "dose-response" in terms of the differences between optimal start vs. sub-optimal/non-optimal and then between those groups and the crash starts, but it's clear that there is not a major difference in outcomes between the sub- and non- optimal groups. Because the sub- and the non-group are differentiated by the presence or absence of a maturing vascular access, I wonder to what extent the presence or absence of vascular access drives the outcomes of interest. It seems possible that the exposure that drives outcomes is receipt of pre-dialysis nephrology care or no, and the duration of this receipt (enough time to ensure a mature vascular access or PD catheter start or probably not enough time to do that). An analysis where you looked at no pre-dialysis nephrology care, less than 12 months of pre-dialysis nephrology care, and more than 12 months of nephrology care (or whatever time cut-offs the authors think appropriate), with the same outcomes, and didn't consider the vascular access situation of the patients, could simplify the association and make it more powerful for readers, and should be considered.

[Response:](#) Reviewer #2 raised the same question regarding the two 'intermediate groups' of pre-dialysis care preparedness. Please see our response to the first comment above. We also note that the amount of pre-nephrology care prior to dialysis initiation is not available in the USRDS dataset, but is included as an important future direction, page 15 as follows: "Additional research using appropriate longitudinal datasets that are able to follow patients from a CKD diagnosis through to dialysis initiation would also shed light on pre-dialysis factors contributing to non-optimal starts." We have also toned down our comments regarding dose-response relationships throughout the manuscript, specific comments to this point are included below.

Minor comments:

Comment: Abstract, Line 51—53 This is not a pure USRDS study, and one of its strengths is its

linkage with the Steps to Transplant database. This should be made clear in the abstract as it also makes it clear why only the southeastern US is being studied.

Response: Revised as follows: “Adults initiating dialysis treatment for kidney failure in the Southeast U.S., from 1/1/2015 to 12/31/2019 were identified from the United States Renal Data System, linked to the Early Steps to Transplant Access Registry, and followed through 12/31/2021.”

Comment: Line 71- again, I think the difference between “sub-“ and “non-“ for the outcome of referrals is overstated and references to it should be removed, especially given the wide overlap in confidence intervals. Line 77- I would rephrase in conjunction with the previous note- you indirectly posit a “dose-response” here for the outcome of evaluation, which immediately contradicts what you wrote at line 71.

Response: We have removed any dose-response phrasing as suggested (in abstract, results, and conclusions). This is reflected in our abstract text as follows: “*Those who had a non-optimal start were also 37% less likely to start the evaluation after being referred (0.63, [0.59–0.66]) as compared with highly optimal dialysis starters, while all other groups had a similar likelihood.*” Nonetheless, we take the point that the effect size in these two groups is similar and our manuscript now reflects this observation.

Comment: Introduction, Line 84- “managing care progression” is a confusing and unclear phrase. Do you mean managing the transition of care from pre-dialysis CKD to dialysis? Moreover, it seems like there should be a citation here- I don’t think it’s self-evident that managing this transition well results in improved quality of life, for example.

Response: Sentence has been revised, and citation included as follows: “Managing care needs as patients transition from pre-dialysis CKD to kidney failure, including the timing and modality of dialysis initiation, is of utmost importance to improve outcomes and quality of life.”⁴

Ref#4: Caskey FJ, Wordsworth S, Ben T, et al. Early referral and planned initiation of dialysis: what impact on quality of life? *Nephrol Dial Transplant.* 2003;18(7):1330-1338.

Comment: Line 85- the sentence that begins with “Despite This...” seems misleading. The USRDS annual data report from 2024 shows that 22% of patients initiate dialysis with no pre-existing nephrology care, a fraction that increases to about 40% if you include individuals with unknown pre-ESRD care. (see figure 1.12 in Chapter 1 of the ESRD section of the annual data report from 2024) So “most patients” who initiate dialysis in the US do have some pre-dialysis nephrology care. It would be better to say something like “Despite this....less than a third of patients who progress to ESKD in the US experience an optimal start (define the term) when they initiate dialysis” and cite the annual data report (actual number something like 30%).

Response: We have opted to exclude this sentence entirely since the information the reviewer suggests to incorporate is included in the following paragraph.

Comment: Methods, Line 135- please explain how patients who started dialysis with an HD catheter but also had a PD catheter in place were defined- it does occur that a surgeon or interventional nephrologist will place both accesses and HD will be started while the PD catheter site heals.

Response: We were unable to know from our data if a PD catheter was in place among HD patients. We have acknowledged this limitation in our discussion, page 16, as follows: *"In particular, we were unable to determine if PD or HD initiation occurred in an inpatient or outpatient setting, or if a PD catheter was in place for those initiating HD which would have provided additional context for dialysis preparedness."*

Comment: Methods, Line 161- to what extent is initiation of transplant evaluation influenced by patient specific factors as opposed to transplant center specific-factors? It seems possible that this outcome could be greatly influenced by center-specific factors like how far out they are scheduling (although I am not an expert in this area). Furthermore, it seems like the transplant database they are using would allow the authors to adjust for which center the patients used so that center specific factors were accounted for, but I can't see that this was done.

Response: Great point. Unfortunately, transplant centers are de-identified in E-STAR and thus we have no information on center characteristics to examine the center-level factors the reviewer alludes to. We have acknowledged this limitation, page 17, as follows: *"Our data is also unable to account for different transplant center factors that may influence patient access such as BMI thresholds for transplant."*

Comment: Methods, Line 184- I think two additional, easily available covariates from the 2728 could be useful to include, at least for the initial outcome of referral. I think baseline serum albumin could have an influence on how quickly patients receive transplant referrals- I.e a malnourished hypoalbuminemic patient could be less likely to receive an expeditious referral. Moreover, about 5% of patients in the USRDS report either difficulty with transfers, difficulty with activities of daily living, or inability to ambulate on Form 2728. These patients may have delayed referrals to transplant centers because of these conditions and so a covariate that incorporates these questions should be considered.

Response: Nice suggestion. We have conducted a sensitivity analyses adjusting for these two factors (hypoalbuminemia and functional impairment), now included as **Table S5**. We also include these in our baseline characteristics table (**Table 1**). Note there is a high amount of missing in these variables so these were not retained in primary models. Nonetheless, adjustment for these factors did not change our conclusions.

Comment: Results, Line 281- Again, I would remove reference to the "dose-response", especially here in the results, as it seems editorializing, especially as the results for the "sub-" and "non-" groups are nearly indistinguishable.

Response: Agreed, removed.

Comment: Results, Line 289- again, please see comment for 281 and previous comments- there is no clear "dose-response" pattern for the outcomes of referral or evaluation between the "sub-" and "non-groups"

Response: Agreed, removed throughout.

Comment: Results, Line 303- could consider providing more information about why cumulative incidences of wait-listing were so close between all the "less optimal" groups but why adjusted incidences were significantly different. What covariates caused this difference?

[Response:](#) Patterns between cumulative incidence, crude and adjusted sub distribution hazards of waitlisting are in fact similar, see **Table** below. Note that HRs compare each ‘less optimal’ group to the highly optimal group.

Table. Comparison of crude incidence and sub distribution hazards model for the secondary outcome of waitlisting				
Dialysis preparedness	Cumulative incidence over 6 yrs	Crude	Partially adjusted¹	Fully adjusted²
Highly optimal	65.3%	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Moderately optimal	48.2%	0.57 (0.53, 0.62)	0.63 (0.58, 0.69)	0.68 (0.62, 0.73)
Minimally optimal	53.8%	0.70 (0.66, 0.74)	0.75 (0.71, 0.80)	0.78 (0.73, 0.83)
Non-optimal	47.8%	0.56 (0.53, 0.60)	0.52 (0.49, 0.56)	0.57 (0.52, 0.61)
¹ Partially adjusted for age, obesity status, comorbidities, and primary cause of end-stage kidney disease; ² Fully adjusted for the covariates in the partially adjusted model plus sex, race/ethnicity, patients being informed of transplant options, insurance status, neighborhood-level, and facility-level covariates				

[Comment:](#) Results, Line 307- it should be noted in that in table S2 the wait-listing differences between the crash group and the sub-optimal group because statistically indistinguishable, so there was a difference found in that sensitivity analysis.

[Response:](#) Below, we show the primary analysis for waitlisting, and the sensitivity analysis in **Table S2** which excludes those who are missing data on pre-nephrology care. In both analyses, those with non-optimal starts have significantly lower waitlisting than the minimally optimal group. The ‘No difference’ described in our results pertains to the difference between primary and sensitivity results, not the difference between subgroups.

	Primary analyses	Excluding missing data
Highly optimal	<i>Ref</i>	<i>Ref</i>
Moderately optimal	0.68 (0.62, 0.73)	0.68 (0.62, 0.73)
Minimally optimal (former sub)	0.78 (0.73, 0.83)	0.78 (0.73, 0.83)
Non-optimal (former crash)	0.57 (0.52, 0.61)	0.61 (0.56, 0.67)
Fully adjusted for age, obesity status, comorbidities, primary cause of end-stage kidney disease, sex, race/ethnicity, patients being informed of transplant options, insurance status, neighborhood-level, and dialysis facility-level covariates		

[Comment:](#) Discussion, Line 325- remove the word “less” here

[Response:](#) Removed.

[Comment:](#) Discussion, Line 362- I think missing-ness of data (9.7%, as discussed in the methods section) with respect to ESRD pre-nephrology care is a problem and should be considered a limitation and discussed as such, especially since there were (minor) differences in outcomes depending on how people with missing data were handled.

[Response:](#) Limitation acknowledged, page 16, as follows: “High levels of missing data for pre-

dialysis nephrology care (~10%) is also likely to lead to misclassification, though scenarios excluding missing data or with multiple imputation showed similar results.

Reviewer #4 (Remarks to the Author):

Overall comments:

Comment: The study of Harding et al aimed at assessing the association between pre-dialysis care (as ascertained through the degree of preparation to dialysis) and three aspects of preparation for kidney transplantation: referral, evaluation, waitlisting. It is based on USRDS data (Southeast USA, 2015-2021) and its linkage with the E-STAR database, the later bringing information about early transplant care. Authors report increasing probability of transplant preparation with increasing dialysis preparation – which is not a new finding and rather logical – with the main novelty of the study involving the analysis step-by-step of the transplant preparation pathway.

Response: Thank you for taking the time to review this paper and to provide guidance on how to meaningfully improve upon our first submission.

Major comments:

The main concern for the study internal validity relies on the fact that groups: optimal, sub-optimal, non-optimal, and unprepared start (<https://doi.org/10.1016/kint.2019.01.017>, I would avoid the term “crash start”) do not share the same study time of origin. As such, authors had to displace the outcome onset – i.e., participants who were referred, evaluated or waitlisted before starting KRT had their event onset set on day 1 of follow-up, Line 181. Also, the event was part of the exposure definition – i.e., “(...) patients were deemed to have pre-dialysis nephrology care if they (...) had been preemptively referred, evaluated, or waitlisted (e.g., prior to dialysis initiation), regardless of their original pre-dialysis nephrology care categorization”, Lines 153-156).

While I understand that considering only patients at risk of transplant preparation can also lead to [selection] bias, I think one cannot claim to estimate time-to-event measures within this framework. However, one can argue that estimating time-fixed relative risks (for instance, relative risks of being prepared to kidney transplant at 6-, 12-months after dialysis initiation) may be useful.

Response: We acknowledge the issue the reviewer refers to. To address this, we have conducted a sensitivity analysis excluding those preemptive patients (n=7,565; 15.4%) who have event dates prior to dialysis start, a common approach employed by other similar studies with the same issue. This has been described in the methods and results, and findings presented in **Table S4**. There were no substantial differences between this sensitivity analyses and primary results with the exception of waitlisting where there was no difference in sub distribution of hazards between highly, minimally, and moderately optimal dialysis starters.

We have also revised our terminology throughout to: highly optimal, **moderately optimal**, **minimally optimal**, and **non-optimal**, removing the term ‘crash start’.

Minor comments:

Comment: Please, consider revising “causal” terms such “how pre-dialysis nephrology care and dialysis access type impacts access to pre-waitlisting” to better reflect what is being assessed in your study.

Response: We have revised our language throughout.

Comment: could authors develop on how or in what the E-Star database is novel? It is not clear whether the fact of considering only the first transplant referral/evaluation (Line 178) can lead to misclassification of the outcome. In particular, could patients who were not first evaluated in the studied center have been evaluated in other centers not participating in the database?

Response: The novelty of E-STAR has been described in detail previously and is now mentioned in our study, see: “Referral and evaluation start data were obtained via patient-level USRDS linkage to the Early Steps to Transplant Access Registry (E-STAR), *described in detail elsewhere*,²³ the only multi-regional data source that captures early transplant access information from all nine transplant centers across the Southeast U.S. (Georgia (GA), North Carolina (NC), and South Carolina(SC)).”

Citation now included: Kelty C, Buford J, Di M, Drewry K, Urbanski M, Harding JL, Wilk A, Pastan SO, Patzer RE. A Decade of Pre-waitlisting Data Collection for Kidney Transplant: The Early Steps to Transplant Access Registry (E-STAR) dashboard: center-specific reporting on prewaitlisting data to improve access to kidney transplantation. Current Opinion in Organ Transplantation 2025; p130-138 DOI: 10.1097/MOT.0000000000001202

To the reviewer’s second point, it is possible that patients are referred to transplant centers outside GA, SC, or NC and thus not captured in E-STAR. However, previous analysis has shown that this is the case in less than 10% of patients. Nonetheless, we now acknowledge this limitation, page 17, as follows: “*Finally, referral data for patients who may have initiated dialysis in the region but were referred to transplant centers outside of GA, NC, and SC will not be captured in this study. However, based on previous literature, we expect this to be a small proportion of all patients (i.e., <10%).*”²¹

Comment: In “(...) conducted multiple imputation for all missing values in the full cohort (n=39,794, 81.1%)”, Lines 239 and 240, is 39,794 (81%) the number (fraction) of participants with missing data for any of the covariates? If so, 5 imputed datasets seem not enough to deal with Monte Carlo error (see 10.1002/sim.4067)

Response: 81.1% represents the proportion of patients with complete data; there was 18.9% of patients missing data key covariates. Thus 5 mutations are adequate for this amount of missingness. We have revised our description to avoid this confusion, e.g., In sensitivity analyses, we: 2) conducted multiple imputation for missing values (excluding functional impairment and hypoalbuminemia [n=9,263, 18.9%]).

Comment: How many studied patients have been referred/evaluated/waitlisted before KRT and thus had their event onset displaced?

Response: This refers to 7,565 (15.4%) of patients. We have since excluded these in a sensitivity analysis, see response to comment #1 above.

Comment: One cannot directly interpret the effect size of a sub-distribution hazard model, i.e. a sd-HR of 0.72 does not mean that patients are 28% less likely to be referred, it just means that these patients are less likely to be referred, but not at the same extent that patients with sd-HR of 0.69 or 0.43. Please see doi: 10.1093/ndt/gft355 for a wide-audience accessible explanation of subdistribution hazard ratios.

Response: We have revised our language accordingly to reflect the interpretation of a sub distribution hazards ratio. For example, page 12, “In fully adjusted *sub distribution hazard models accounting for the competing risk of death*, patients initiating dialysis in moderately, minimally, and non-optimal ways had 28% (aSHR 0.72 [0.69–0.72]), 31% (0.69 [0.66–0.71]), and 57% (0.43 [0.41–0.44]) *lower sub distribution hazards* of referral over time, respectively, compared with those with highly optimal pre-dialysis care”

Comment: Despite model adjustment, one cannot exclude that the level of preparation for dialysis is a proxy of more intensive/ longer pre-dialysis care. Even more importantly, in participants who were prepared to kidney transplantation before KRT initiation, assessment of covariates are posterior to event onset which, along with inherent disease misclassification, may lead to confounding of the association by health status. This could explain why patients with non-optimal dialysis start were more likely to be prepared to kidney transplantation than patients with sub-optimal dialysis start.

Response: We agree with the sentiment from the reviewer with regards to confounding, and limited information available on pre-dialysis care patterns. These have now been acknowledged in our limitations and in future research directions, page 16 as follows:

“Additional research using appropriate longitudinal datasets that are able to follow patients from a CKD diagnosis through to dialysis initiation would also shed light on pre-dialysis factors contributing to non-optimal starts.”

“As with other registry studies, we lack granular data on the quality, duration, or timing of pre-dialysis nephrology care; patient preferences and clinical contraindications for transplant; and nonclinical factors such as health literacy or social support. Unmeasured confounding may persist, and some misclassification of dialysis initiation context is possible.”

Comment: From line 273: do authors mean “Median follow-up to referral (...) in line 267, (...) to evaluation in line 273? As stated in the overall comment above, it may be misleading trying to interpret time to events in this setting of left truncated data.

Response: We have removed data specific to median follow-up time to avoid misleading readers, as the reviewer points out.

Comment: Please, comply with KDIGO consensus on nomenclature for kidney function and disease, e.g. kidney failure, instead of ESKD.

Response: Revised throughout

Dear Communications Medicine editorial committee,

Here, we provide reviewer comments from our initial submission of this manuscript, entitled **'Pre-dialysis care and access type are associated with transplant referral, evaluation, and waitlisting'**. We have provided a response to each of these comments, and in several instances, enacted changes to improve the manuscript. We have included each reviewer comment below, with our response/changes in blue. Where changes have been enacted, we have indicated where on the corresponding tracked document.

We hope you will agree this manuscript is greatly improved and fills an important knowledge gap in what we know of how dialysis context can predict future transplant access in the US, and will be of interest to the broader Communications Medicine readership.

Kind regards

Jessica Harding, on behalf of all co-authors

Reviewer #2

1. **Comment:** Thank you for the revisions based on our previous feedback. The authors have addressed all of our major concerns, which we hope have improved the clarity and strength of the manuscript. We have one residual minor comment below.

Cumulative Incidence of Referral and evaluation start: The authors write the following in the same paragraph.

"The cumulative incidence of death was 8.1%, 14.2%, 18.6%, and 21.2% in highly, moderately, minimally, and non-optimal dialysis starts, respectively (Figure 3A).

"The cumulative incidence of death was 2.1%, 3.5%, 4.2%, and 3.9% in highly, moderately, minimally, and non-optimal dialysis starts, respectively, (Figure 3B)."

We suspect it would be helpful to reviewers to clarify within each sentence that these refer to the 1-year cumulative incidence of death and the 6-month cumulative incidence of death, respectively.

Response: Thank you for noting this. We have updated as suggested to avoid confusion.

Reviewer #3 (Remarks to the Author):

1. **Comment:** Thank you for your responses to the reviewer comments, and I gladly accept most of them.

Although in general I continue to believe this study has significant merit, I think the authors should consider the suggestions from two of their reviewers to simplify their categorization strategy, and I endorse the strategy presented by Reviewer #2, which would allow them to retain many of their findings and discussion points. Although some of the points that the authors raised in their rebuttal to this idea are valid, I do note that the authors pointed to an interpretation of figure 3 that doesn't seem quite right. The authors stated that Figure 3 shows that "moderately optimal starters had higher rates of transplant referral than minimally optimal starters, lower rates of evaluation and death, and similar rates of waitlisting once evaluated." Doesn't figure 3 show similar rates of referral and evaluation between the moderate and minimal groups, and that minimally optimal patients are more likely to be waitlisted at 5 years than moderately optimal patients? I think that the fact that even the authors and reviewers who are closely reading this material are having trouble accurately differentiating the outcomes for these categories may point to the need for simplification of the categorization scheme. I also think that the three category model proposed demands less from readers in terms of keeping these categorical differences in mind while preserving most of the value of the analysis and discussion.

Response: Respectfully, our research aim was to see if different dialysis start context, as defined using the four original groups, was associated with differences in transplant referral and evaluation rates. Reclassifying groups based on study findings, we believe, is not the best scientific approach. Indeed, two groups with different dialysis contexts but similar referral and evaluation rates is an interesting finding in and of itself. In particular, it is interesting that we find 15.5% of patients start in a moderately optimal way (with AVF/AVG graft maturing), but twice as many (i.e., 31.0%) start in a minimally optimally way (without a maturing graft). This suggests that at least for downstream transplant

access, starting with a maturing graft does not make considerable difference, so long as everyone is in the care of a nephrologist prior to initiating dialysis.

Nonetheless, we do note the point the reviewer makes re ensuring we describe the lack of differences between these groups, and we have added the following language, page 15-16, as follows:

"We also found that 15.5% of patients started dialysis in a moderately optimal way, with pre-dialysis care and an AVF or AVG graft maturing at time of HD initiation, and a further 31.0% with no maturing graft present at the time of HD initiation despite receiving pre-dialysis nephrology care. Despite the substantial difference in the number of patients who do and do not have a maturing graft in place, their access to transplant referral and evaluation was similar suggesting that being in the care of a nephrologist prior to initiating dialysis may be the more important indicator of dialysis readiness and subsequent transplant access."

2. **Comment:** I will also note that USRDS does include data about the duration of pre-dialysis nephrology care that is received by patients prior to initiation, contrary to the assertion of the authors that "We also note that the amount of nephrology care prior to dialysis initiation is not available in the USRDS dataset" Below are the relevant data files captured by the Medical evidence form, as it may be useful for the authors to consider for a future analysis:

NEPHCARE Num 8 YN9FMT. "(17.b 2018 form; 18.b 2015/2005 form) Was patient under care of a nephrologist?"

"NEPHCARERANG

E" Num 8 RANGE. "(17.b 2018 form; 18.b 2015 form) If Yes, answer: <6, 6-12 or >12 months; (18.b 2005 form) If Yes, answer: 6-12 or >12 months"

Response: We apologize for this misstep. We have now looked at this and shown that, as expected, those in the minimally optimal group have lower duration of pre-dialysis care than those in the moderately or highly optimal groups, see **Table S6**. There was >10% of dialysis duration data missing for these patients, and this data was not missing at random (i.e., was more likely to be missing in the minimally optimal group). Thus, we are reluctant to reexamine groups considering this additional variable in the current manuscript. However, we do think this is an interesting point to make in our discussion, and have included this, along with the table, page 16, as follows:

*"We also found that 15.5% of patients started dialysis in a moderately optimal way, with pre-dialysis care and an AVF or AVG graft maturing at time of HD initiation, and a further 31.0% with maturing graft present at the time of HD initiation despite receiving some pre-dialysis nephrology care. Despite the substantial difference in the number of patients who do and do not have a maturing graft in place, their access to transplant referral and evaluation was similar suggesting that being in the care of a nephrologist prior to initiating dialysis may be the more important indicator of dialysis readiness and subsequent transplant access. It is also possible that having a maturing graft in place is simply a function of longer pre-dialysis nephrology care, as suggested by our data in **Table S6**."*

We also note that future research should consider quality and duration of pre-dialysis nephrology care, page 17, as follows: “Additional research using appropriate longitudinal datasets that are able to follow patients from a CKD diagnosis through to dialysis initiation would also shed light on pre-dialysis factors, including quality and duration of nephrology care, contributing to non-optimal starts.”

Table S6 Distribution of pre-dialysis duration care across the 3 groups who received some pre-dialysis care

	Pre-Dialysis Care Classification		
	Highly Optimal	Moderately Optimal	Minimally Optimal
<i>A. In all patients</i>			
<6 months	1,605 (12.44)	1,078 (19.58)	4,298 (29.2)
6-12 months	3,572 (27.69)	1,795 (32.59)	4,428 (30.08)
>12 months	7,724 (59.87)	2,634 (47.83)	5,994 (40.72)
<i>B. Excluding pre-emptive patients</i>			
<6 months	1,176 (13.53)	965 (20.41)	4,000 (30.42)
6-12 months	2,487 (28.61)	1,546 (32.7)	3,986 (30.32)
>12 months	5,030 (57.86)	2,217 (46.89)	5,162 (39.26)

Note: >10% of pre-dialysis duration data is missing not at random, and thus we did not include this variable in our final models in primary analyses.

Reviewer #4

1. **Comment:** I thank the authors for addressing the comments; I believe that the manuscript is suitable for publication.

Response: Thank you

Dear Communications Medicine editorial committee,

Here, we provide reviewer comments from our initial submission of this manuscript, entitled **'Pre-dialysis care and access type are associated with transplant referral, evaluation, and waitlisting'**. We have provided a response to each of these comments, and in several instances, enacted changes to improve the manuscript. We have included each reviewer comment below, with our response/changes in blue. Where changes have been enacted, we have indicated where on the corresponding tracked document.

We hope you will agree this manuscript is greatly improved and fills an important knowledge gap in what we know of how dialysis context can predict future transplant access in the US, and will be of interest to the broader Communications Medicine readership.

Kind regards

Jessica Harding, on behalf of all co-authors

From the editor:

Comment: While we understand that raw data cannot be shared due to privacy concerns, we do ask that you share the source data used to generate the main figures (charts, graphs, and shaded maps) in your manuscript, which should not have any protected or identifiable information. Please upload these data in text or excel format as Supplementary Data files, and include a line in your Data Availability statement indicating which files correspond to which figures using text similar to “The source data for Figure X is in Supplementary Data Y”.

Response: This has now been included page 23 as follows: “The source data for Figure 3 and Figure S1 is in Supplementary Data 2”

Reviewer #3:

Comment: Thank you so much for taking the time to undertake a new analysis and a new revision for the manuscript in light of my suggestions. Given the additional findings and the revisions to the manuscript, I do not have further major concerns. I want to note a couple of minor, likely typographical errors in the revised section of the discussion. My suggested edits are in parentheses:

We also found that 15.5% of patients started dialysis in a moderately optimal way, with pre-dialysis care and an AVF or AVG graft maturing at time of HD initiation, and a further 31.0% with (this should read "without", correct?) maturing graft present at the time of HD initiation despite receiving some pre-dialysis nephrology care. (remove additional period). Despite the substantial difference in the number of patients who do and do not have a maturing graft in place, their access to transplant referral and evaluation was similar (comma) suggesting that being in the care of a nephrologist prior to initiating dialysis may be the more important indicator of dialysis readiness and subsequent transplant access. It is also possible that having a maturing graft in place is simply a function of longer pre-dialysis nephrology care, as suggested in Table Sx (S6, correct?)

Response: Thank you for the eye to detail. This section, page 14-15, now reads:

“We also found that 15.5% of patients started dialysis in a moderately optimal way, with pre-dialysis care and an AVF or AVG graft maturing at time of HD initiation, and a further 31.0% without a maturing graft present at the time of HD initiation despite receiving some pre-dialysis nephrology care. Despite the substantial difference in the number of patients who do and do not have a maturing graft in place, their access to transplant referral and evaluation was similar, suggesting that being in the care of a nephrologist prior to initiating dialysis may be the more important indicator of dialysis readiness and subsequent transplant access. It is also possible that having a maturing graft in place is simply a function of longer pre-dialysis nephrology care, as suggested in **Table S6**”