Author's response to reviews

**Title:** Comparison of Quality-of-Care Measures in Patients with End-Stage Renal Disease Secondary to Lupus Nephritis vs. Other Causes

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**Author's response to reviews:** see over
Dear Dr. Weisbord:

We are pleased to submit a revision of our original article, entitled “Comparison of Quality-of-Care Measures in Patients with End-Stage Renal Disease” (manuscript no. 818020291525330), for consideration by *BMC Nephrology*. We appreciate the thoughtful reviews by the editor and reviewers, and we have made several changes to the manuscript based upon their comments:

1. We have updated the original figures as suggested by the reviewers for clarity and ease of interpretation.
2. We have added a new figure (Figure 3) that highlights permanent vascular access placement by attributed cause of ESRD and salient patient characteristics.
3. We have performed further sensitivity analyses, as suggested by reviewers, which are presented in Table 4 and in the Results.
4. We have added discussion of further limitations and references, as suggested by reviewers.
5. We have performed a thorough edit of the manuscript.

We believe these changes have substantially improved the manuscript. Point-by-point responses follow and the revised manuscript and updated figures are included with this submission. We appreciate the opportunity to revised and resubmit our work for consideration, and we look forward to the review of this revision.

Sincerely,
Laura Plantinga, PhD
Point-by-Point Responses

Reviewer 1 (Kelly Liang)

This is a well-written manuscript describing a retrospective cohort study analyzing quality of care among patients with end-stage renal disease (ESRD) due to lupus nephritis (LN-ESRD) vs. ESRD due to other glomerulonephritides (GN) and ESRD due to other causes using the United States Renal Data System (USRDS) database from July 2005 to September 2011. This study found that LN-ESRD patients were more likely than other ESRD patients to receive pre-ESRD care and be placed on the transplant waitlist in the first year, but less likely to have a permanent vascular access (arteriovenous fistula or graft) in place at dialysis start. The authors suggest that better pre-ESRD care is seen in LN-ESRN patients possibly due to the co-management of these patients by both nephrologists and rheumatologists. They suggest that further studies are warranted to examine barriers to permanent vascular access placement, as well as associated morbidity and mortality associated with temporary access, in the LN-ESRD population. The question posed by the authors is well defined. The methods are appropriate and well described. The data are generally sound, but there are limitations to the findings and conclusions that may be drawn from this study due to the use of the USRDS CMS-2728 forms and diagnoses defined by International Classification of Diseases (ICD)-9 codes. As acknowledged by the authors, reliance on this CMS-2728 form may lead to selection bias due to missing data in analyses of pre-ESRD care and misclassification of quality of care data due to variability in provider knowledge about patients. The figures appear to be genuine, i.e. without evidence of manipulation. The manuscript adheres to the relevant standards for reporting and data deposition. The discussion and conclusions are fairly well balanced and adequately supported by the data, though some of the statements made in the discussion and conclusions are more speculative than conclusive, due to the nature of this retrospective cohort study. The limitations of the work are clearly stated. The authors clearly acknowledge any work upon which they are building, both published and unpublished. The title and abstract accurately convey what has been found, but the title does not reveal anything about the findings. The writing is acceptable overall, with only minor editorial errors and ambiguities. The manuscript would be strengthened by addressing some issues and minor errors, which are outlined below.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. Page 10, lines 10-21, Results, Association of Attributed Cause of ESRD with Quality-of-Care Measures, Permanent Vascular Access: These reported findings do not seem to be summarized in any Tables or Figures. Is that true? If not, I would suggest creating an additional Table or Figure to summarize some of these findings, perhaps as supplementary material if there is no room for it in the manuscript.

Response. Thank you for this suggestion. It is true that these findings were not reported with the other sensitivity analyses in Table 4, since they were specific to permanent vascular access. Thus, we have created a new figure (Figure 3; legend on p. 30, line 12)
that shows the percentages of patients with permanent vascular access by characteristics of interest—namely, recovery of renal function, early transplant status, and sex—to further emphasize these results as well as streamline the text (p. 10, lines 21-23; p. 11, lines 1-6).

2. **Page 29, Figure 1:** Please include explanation of what the numbers with negative signs in front of them represent, shown beside the arrows. It is not clear what these numbers mean, presumably the exclusion of certain populations, e.g. patients with unknown pre-ESRD care status, patients with pre-emptive transplant, etc.

**Response.** We apologize for the confusion. These negative numbers do indeed represent the numbers of excluded individuals. We have added the following to the figure legend for clarity: “Numbers by arrows represent the numbers of patients excluded by indicated criteria; numbers in boxes represent those remaining after prior exclusions” (p. 30, lines 4-6). Additionally, we have updated the figure to show only the total number excluded, rather than numbers excluded by cause, per another reviewer’s request, which provides further clarity.

**Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**

1. **Page 2, line 18, Abstract, Conclusions:** In the first sentence of the Conclusions, change the dashes “—” to commas so it reads, “LN-ESRD patients are more likely to receive pre-ESRD care and have better access to transplant, but are less likely to have a permanent vascular access for dialysis, than other ESRD patients.”

**Response.** This change has been made (p. 2, line 18).

2. **Page 3, line 22, Background:** In the last full sentence on the page, add “as” so it reads, “Translation of quality-of-care measures should be as good as, or better, in patient populations treated by multiple specialty providers,…”

**Response.** Thank you for catching this omission, this change has been made (p. 3, line 19).

3. **Page 6, line 8, Patients and Methods, Quality-of-Care Measures:** Delete the space between “CMS” and “-2728” so it reads “CMS-2728 item 26.”

**Response.** Thank you. The extra space has been deleted (p. 6, line 6).

4. **Page 9, line 3, Results, Association of Attributed Cause of ESRD with Quality-of-Care Measures, Access to Transplant:** Add “(p=0.07)” so it reads, “…although the trend was marginally statistically significant for LN-ESRD patients (p=0.07).”

**Response.** The p-value has been added as suggested (p. 9, line 9).

5. **Page 9, line 4, Results, Association of Attributed Cause of ESRD with Quality-of-Care Measures:** Change the reference “CMS-2728 item 26” to “CMS-2728 item 24.”

**Response.** Corrected (p. 9, line 4).
Measures, Access to Transplant: Are the percentages of 10% and 19% actually supposed to be 11% and 20% based on Table 4, which shows the risk ratios for “informed of transplant options” among patients who never recovered renal function to be 1.11 and 1.20 for LN and other GN, respectively? If so, please correct these numbers.

Response. We apologize for the confusion. These numbers were based on those in the entire population, which are presented in Table 3, last column. We have added a reference to Table 3 after this sentence on p. 9, line 11.

6. Page 9, line 11, Results, Association of Attributed Cause of ESRD with Quality-of-Care Measures, Access to Transplant: Add “(p=0.07)” so it reads, “...although the trend was marginally statistically significant for LN-ESRD patients (p=0.07) (Table 2).”

Response. We have moved the reference to Table 2 after the p-value we added at the end of this sentence (see #4).

7. Page 10, line 8, Results, Association of Attributed Cause of ESRD with Quality-of-Care Measures, Permanent Vascular Access: Delete “was” so it reads, “Results were similar in sensitivity analyses (Table 4), with placement of permanent access less common among LN-ESRD patients…”

Response. Thank you. This sentence has been split and rewritten for clarity (p. 10, lines 19-21).

8. Page 14, line 1, Discussion: Insert “to” so it reads, “...population to receive pre-ESRD care.”

Response. This has been corrected (p. 14, line 15).

9. Page 16, line 1, Competing Interests: Correct the spelling of “competing” (not “completing”).

Response. Thank you, this has been fixed (p. 16, line 23).

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. Page 5, line 8, Patients and Methods, Study Population and Data Sources: In the last sentence of this section, include “(UNOS)” after “United Network for Organ Sharing” since the abbreviation UNOS is used later in the manuscript.

Response. The abbreviation UNOS has now been introduced on p. 5, line 5.

2. Page 5, lines 20-23 and page 6, lines 1-2, Patients and Methods, Study Variables: The authors state they chose to include only patients with ESRD attributed to diabetes, hypertension, or large vessel disease representing “typical U.S. ESRD patients” in the
referent group in sensitivity analyses. Although they justify this decision with the fact that “the majority of incident ESRD in the United States is attributed to diabetes or hypertension (72%) or GN (6%) and the remaining attributed causes represent a fairly diverse group of ESRD etiologies such as cystic kidney disease,” I question whether they should have excluded all the other causes of ESRD. If it is possible to include all the remaining causes of ESRD in the “other” group, it would probably be a more accurate representation of the referent group.

Response. We agree, and all remaining causes of ESRD are included in the “other” group for all the primary analyses presented. Results with this restricted referent group are shown in Table 4, column 1, only.
Reviewer 2 (Khaled Abdel-Kader)

This review was performed with the assistance of post-doctoral fellow Rocio Figueroa diaz MD. This is a large, retrospective cohort study comparing quality of care (pre-nephrology care, surrogates for KTx access, perm vasc access at HD initiation) in ESRD LN vs. ESRD other diagnoses. This is a novel study and the authors acknowledge most of the limitations:

Minor essential revisions:

1. limited ability to effectively exclude AKI (~3% of incident ESRD patients based on USRDS) or a very rapidly progressing CKD, AKI on CKD course (e.g., Ohare, AJKD 59:513, >10% with very rapid declines in preceding 24mo in a VA cohort). Inclusion of these patients is likely to lower the rate of achievement of the quality outcomes examined.

Response. We agree that this is a limitation of our analysis that should be acknowledged. On p. 12, lines 6-7, we added “It is also possible that progression to ESRD may be quite rapid among some kidney disease patients [35].” And in the discussion of limitations (p. 15, lines 20-23), we added “We also could not adjust for acute kidney injury status leading to ESRD, which might be a marker of fast progression and provider inability to intervene prior to start of ESRD, although we were able to examine associations among those who never recovered renal function.”

2. a) limited ability to determine suitability for KTx: though authors excluded age>70 and adjusted for CVD, the data available does not offer a granular view re: KTx eligibility which is likely to be higher among the LN cohort (younger, fewer comorbidities). b) KTx provision of information as delineated on 2728 may have limited reliability (see Salter JASN 25: 2871)

Response. We agree that these limitations are important to acknowledge. To address these issues, we have added “…although we excluded patients aged ≥70 and adjusted for CVD in the primary analysis, we do not have specific, more granular data on kidney transplant eligibility, which is likely to be higher among the LN-ESRD patients and could be a confounder of the associations with kidney transplant access measures…” and “Misclassification of quality of care measures on the CMS-2728 is also possible, particularly provision of information about kidney transplant [54]…” (p. 15, lines 10-12).

3. Was age examined in the regression model for non-linear relationship with outcomes? Were interaction terms (e.g., age*sex) examined?

Response. This is a good point. We did not allow for non-linear relationships of age with outcomes or interactions of age with sex in our previous models. We have now performed sensitivity analyses with a squared term for age as well as with an interaction term for age and sex (added to Table 4). Generally, while the quadratic terms for age and the interaction terms were statistically significant, the associations of attributed cause with outcomes were not substantially changed by the addition of these terms.
4. Many of the patient level barriers to permanent vasc access (recently reviewed by Casey AJKD 64:937) would seem to be particularly salient in a younger LN cohort. Additional provider level barriers that could be considered are the increased complexity of these patients (e.g., contraception concerns while on RAAS blockade/MMF, toxicity from IS meds including glucocorticoids, etc) and limited time to discuss multiple concerns and adequately educate and communicate re: the importance of creating a perm vasc access, especially if follow-up visits are inconsistent in this young cohort).

Response. We agree that there are many other potential barriers to vascular access. On p. 13, lines 14-15, we have added “…and generally increased complexity (e.g., contraception and fertility concerns approaching dialysis)…” to our discussion of the effect of female predominance in lupus. And on p. 14, lines 4-8, we added: “Finally, many barriers to vascular access that have been noted in the overall ESRD population, including fear of needles, issues of coping with thoughts of imminent dialysis, and the threat of potential physical deformity due to vascular access [51], may be particularly salient in the younger LN-ESRD population. Further, follow-up may be less consistent in this population, preventing providers from discussing the importance of creating a permanent vascular access.”

Discretionary revisions:

1. Please consider changing the figure so that the y axis represents proportion of patients wait-listed.

Response. We agree that the cumulative proportion of patients waitlisted (vs. proportion not yet waitlisted) is easier to interpret. We have replaced the Kaplan-Meier curve in Figure 2 with a cumulative incidence curve and updated the legend (p. 30, lines 8-10) accordingly.
Reviewer 3 (Manisha Jhamb)

This is a very interesting manuscript comparing the quality-of-care measures in ESRD due to lupus versus other causes. The manuscript is well-written and addresses an important question. The analyses are well described and tables are comprehensive.

Major compulsory revisions:

1. A large number of patients (~246K) were excluded from the analyses for access to transplant because of age ≥70 years. Given that the population of elderly ESRD patients starting dialysis is rapidly growing and more than 40% of those receiving renal transplant in the recent years are 70 yrs or older (Trends in kidney transplant outcomes in older adults. J Am Geriatr Soc. 2014), it would be important to NOT exclude this group. I would suggest to the authors to re-do this analysis, perhaps by using a higher age cut off.

Response. This is an important point. We agree that transplant has become far more common in older adults and that age restrictions may not be appropriate for studying waitlisting in the overall ESRD population. However, in lupus, the number of patients in this age range is quite small, and the numbers receiving transplants is even smaller. In fact, over our study period, we found that there were only 259 LN-ESRD patients who were aged ≥70 years, and only 11 of these were waitlisted. (Similarly, for GN-ESRD, 11,462 were aged >70 years, and 445 were waitlisted.) This is likely the reason for the nearly identical results for both informed of transplant options and waitlisting when we re-ran our primary analysis without applying the age exclusion; these similar results are now reported in the text (p. 10, lines 11-14; p. 11, lines 3-6). Additionally, the rationale for including these patients has been added on p. 10, lines 11-12: “Estimates were nearly identical when patients aged ≥70 years were included, to account for increasing transplantation among older adults [33]…”

2. Please specify the duration of pre-ESRD care if known

Response. Duration is only known by 6-month intervals and the accuracy of reporting of duration has been questioned. However, given this weakness, we have added the following to the text: “LN- and GN-ESRD patients were also more likely to receive greater duration of pre-ESRD care than other ESRD patients (>12 months, 36% and 35% vs. 27%; >6 months, 57% and 56% vs. 51%; P<0.001 for both; not shown in table)” (p. 9, lines 14-17).

Discretionary revisions:

1. Was there a difference in the outcomes if pre-ESRD care was 6-12 months versus >12 months

Response. The outcomes were similar but of slightly different magnitude when duration of pre-ESRD care was used as an outcome. We have added the following to the text: “The associations were slightly stronger for longer duration [pre-ESRD care ≥12 vs. <12 months]…”
months: LN-ESRD, OR=1.82, (95% CI, 1.70-1.92); GN-ESRD, OR=1.42 (95% CI, 1.39-1.45)] and weaker for shorter duration [pre-ESRD care ≥6 vs. <6 months: LN-ESRD, OR=1.50 (95% CI, 1.42-1.59); GN-ESRD, OR=1.21 (95% CI, 1.18-1.23)]” (p. 8, lines 21-23; p. 9, lines 1-2).

2. Fig 1 is hard to follow, probably because the total numbers in each category described in the text are not stated in the Fig.

Response. We apologize for this confusion. We believe the inclusion of total excluded/included numbers, as well as those by cause, would have made the figure even more difficult to follow. Thus, we have updated the figure to include only the total numbers in each category, rather than excluded numbers by cause, to match the text.