Author's response to reviews

Title: Timing of preemptive vascular access placement: do we understand the natural history of advanced CKD?: an observational study

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Author's response to reviews: see over
April 12, 2013

Hayley Henderson, MD
Executive Editor
BMC Nephrology

Dear Dr. Henderson:

Thank you for the review of our manuscript, “Timing of preemptive vascular access placement: do we understand the natural history of advanced CKD?” for consideration as a Research Article in BMC Nephrology.

We appreciate the thoughtful comments from the editors and reviewers. We have prepared a point-by-point response below. We believe that the manuscript has been strengthened with these revisions and we hope you find the paper acceptable for publication.

Dr. Bansal is the corresponding author and can be reached by telephone (415-514-1122), fax (415-476-3381), or email (nisha.bansal@ucsf.edu). She has full access to all of the data in this study and takes full responsibility for the data and the accuracy of the data analyses.

Thank you in advance for your time and consideration.

Sincerely,

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**Response to Editors:**

Comment: Please include the full name of the ethical committee that approved the study and upload the Appendix as an Additional File.

Response: The ethical committee that approved the study was the UCSF Human Research Protection Program. This has been added to the manuscript. The Appendix has been uploaded as an additional file.

**Responses to Reviewer #1:**

Major Compulsory revisions:

Comment: Under methods, 2995 charts were reviewed and only 116 patients were eligible for the chart review. What were the reasons the remaining were ineligible? This is concerning mainly because of the zero mortality rate - usually mortality in CKD stage 4-5 patients is quite high. It is indeed quite possible that nephrologist choose patients who are healthy enough to live but with bad renal disease to go on dialysis only - but to achieve such a fantastic survival rate is uncommon. To ensure there is no selection bias, I would recommend using the Strobe guidelines (Report the numbers of individuals at each stage of the study, e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up, and analyzed) Ref: J Clin Epidemiol. 2008 Apr;61(4):344-9. PMID: 18313558

Response: We appreciate the reviewer's in-depth review of our paper and for the Strobe guidelines reference. Of the 2,995 patients potentially eligible for the study, 122 had preemptive vascular access placed. Of these, 6 were lost to follow-up. We have included these results in the methods section. The other patients were ineligible because they did not undergo surgery to create a dialysis access.

We would like to point out though that the chart review component of our study is not to describe outcomes among patients with stage 4-5 CKD. The point is rather to describe outcome among patients whom nephrologists selected to refer for pre-emptive dialysis access placement (and who agreed to undergo surgery). We want to see how patient selected in “real life” by nephrologists fare. So there is no “selection bias” which threatens validity. The fact that there is a low death rate suggest that nephrologists largely succeed in avoiding placement of pre-emptive dialysis access in patients who have high short term mortality. This process of selection is what we seek to understand better with regard to timing of dialysis initiation, especially in the context of nephrologists’ stated goal according to our survey.
Minor Essential revisions:  
None

Discretionary revisions:  

Response: We appreciate the reviewer bringing this review to our attention. We have now referenced this review in the introduction.


Response: Thank you for this citation. We have added it to the introduction.

Comment 3. Some of the nuances of the KDOQI classification - referenced in the discussion have been taken care by the KDIGO staging with CKD stage 5ND and stage 5D stages.

Response: This is a good point. We have added a statement in the discussion to acknowledge this:
This notion may have been enforced by high profile studies which designate estimated GFR <15 ml/min/1.73m² without dialysis as being “untreated” “kidney failure” [20], although recent initiatives by KDIGO have attempted to distinguish between stage 5 requiring dialysis versus stage 5 disease not requiring dialysis [21].

Comment 4. The manuscript takes an eGFR only approach - which is likely to be at the root of some of the problems discussed. Many papers, especially from the Alberta group (Braden Manns, Cello Tonnelli and Brenda Hemmelgarn) have shown that there is a huge difference in progression (and overall mortality) based on the presence or absence of proteinuria.

Response: We agree with the reviewer have acknowledged this in the limitations section:
Our study focused on eGFR thresholds for referral to vascular access placement, however we acknowledge that proteinuria is a very important determinant of renal prognosis.

Comment 5. With the publication of the IDEAL study showing that late initiation of dialysis may be preferable - and definitely non-inferior - access placement perhaps could be done much later than at arbitrary 16 or 18 eGFR thresholds.

Response: This was a very interesting paper and we appreciate the reviewer mentioning it here. We have referenced this study in the discussion.

Responses to Reviewer #2:

Comment 1. Discretionary Revisions: On page 8, paragraph 1: When was the urine albumin quantified in the 67 patients? Since the urine albumin was quantified within one year of outcome in 49 patients perhaps these results are more representative of outcomes? You could add this as another row to Table 3. It is possible that the formula would have given a better prediction if all 116 patients had urine albumin values.

Response: For the N=67 patients, the mean and median times between vascular access surgery and measurement of ACR was 11.2 (17.9) months and 3.3 (IQR 1.3-13.4) months, respectively. We have added this to the results section of the manuscript. Additionally, we have added a row to Table 3 as suggested showing the predicted risk of ESRD among patients who had albuminuria measured within 1 year of vascular access surgery. The updated table is below:

Table 3. Predicted risk of ESRD among patients who did undergo pre-emptive AV access surgery

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis within 1-year of AV access surgery</th>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>N=37</td>
</tr>
<tr>
<td>2-year risk of ESRD by Tangri equation in all patients with measured albuminuria (N=67)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>2-year risk of</td>
<td>N=26</td>
</tr>
</tbody>
</table>
ESRD by Tangri equation in patients with albuminuria measured within 1 year of vascular access surgery (N=49)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61% ± 30%</td>
<td>65% (40%-84%)</td>
</tr>
<tr>
<td></td>
<td>34% ± 22%</td>
<td>28% (19%-38%)</td>
</tr>
</tbody>
</table>

**Comment 2. Reference 3 and 10 is missing.**

Response: Thank you for noting this. We have corrected this.

**Responses to Reviewer #3:**

**Major Compulsory Revisions:**
None

**Minor Essential Revisions:**

**Comment 1. references no 3 and 10 are missing, in the reference no 18 ..et al.. should be omitted**

Response: We have corrected references 3 and 10. We would prefer to retain reference18 (JAMA 307(23): 2507-2515) if allowable by the Editors of BMC Nephrology as it defines any patient with eGFR<15 with “untreated kidney failure,” regardless of clear indications for dialysis and hence pertinent for our Discussion.

**Comment 2. How many AV fistulas and grafts clotted in the first year before having been used and if did what was the rescue approach?**

Response: This is an excellent question but is tangential to our main research focus which is about timing of pre-emptive AV access as observed in clinical practice (compared with nephrologists’ stated goals).