Author's response to reviews

Title: Characterizing pre-dialysis care in the era of eGFR reporting: a cohort study

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Author's response to reviews: see over
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Timothy Shipley, PhD
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Dear Dr. Shipley,

We want to thank the reviewers, Drs. Stevens and Sood, for the time and effort taken to provide these helpful comments. We have addressed each point in detail and revised the manuscript using each of the critiques. We feel that these changes have significantly improved the manuscript and hope that this report is now satisfactory for publication in BMC Nephrology.

**Referee 1: Dr. Paul Stevens:**
We want to thank Dr. Stevens for his careful critique of our manuscript including concerns regarding how CKD patients were identified, lack of creatinine calibration, and the unlikelihood of observing improvement in primary care physicians’ (PCP) CKD care following eGFR implementation alone. We have addressed these points as presented below and we believe these changes have significantly improved the manuscript.

1. *It appears that both pre- and post-reporting cohorts were retrospectively selected from secondary care, not primary care.*

   We agree with the reviewer that in order to characterize PCP care of CKD patients accurately, CKD patients should be identified by a chart review/abstraction from the primary care setting. Indeed, this is the approach we used for this study, examining all patients cared for by PCPs in the general internal medicine department of our institution. We have clarified this in the manuscript by altering Figure 1 (study flow diagram) to include the characterization “seen by PCP between...” to more clearly indicate how patients were initially identified. In addition, in the abstract methods section and in the manuscript introduction and methods sections, we have reinforced this by using the term “PCP” or “primary care” when describing the clinical setting from which the patients were identified. For example, in the abstract method’s section, “We conducted a retrospective cohort study of patients with CKD 3b-4 (eGFR < 45) seen at a university-based, outpatient primary care clinic.” We believe these terms should minimize ambiguity for non-US readers who may be less familiar with general internal medicine (GIM).

2. *The authors acknowledge a number of limitations, which should also include the lack of creatinine calibration... and the relatively low numbers of patients included in the cohorts for a study such as this.*

   We agree with the reviewer that the lack of creatinine calibration and limited study size are important limitations of our study. We now acknowledge this in our discussion, “Third, serum creatinine assays were not standardized during the study period,” and, “Finally, we studied a relatively small sample.”
3. *The authors state that no educational activities were undertaken prior to eGFR reporting, what about after? I don’t believe it is reasonable to expect PCP performance in CKD management to improve purely through introduction of automated eGFR reporting, this needs to be accompanied by academic detailing.*

We agree with the reviewer regarding the ambiguity in our statement. Concerning activities undertaken following eGFR implementation, we have clarified in the manuscript, “No systematic educational activities regarding eGFR reporting were undertaken at the university hospital prior to or following eGFR implementation as of 5/31/2008,” (i.e., the close of the post-eGFR cohort).

We also fully agree with Dr. Stevens on the need for additional systematic interventions to improve CKD care delivery by PCPs and nephrologists. We appreciate the reviewer’s interest and expertise in this area and believe these issues warrant further mention within the manuscript and have now expanded our Conclusions section.

As the reviewer is aware, multiple interventions have been studied in an effort to optimize physician performance. This includes traditional didactics (unfortunately, generally ineffective), academic detailing (often effective, but labor intensive and may be difficult to carry out on a wide scale across the US), clinical decision support systems within the electronic health record (can be effective when well designed, well delivered and when paired with other interventions), as well as additional interventions (e.g., audit and feedback). However, prior to implementing these interventions, a needs assessment is useful to confirm and further characterize the local deficiencies and to justify the investment of resources to address these deficiencies. The literature characterizing the quality of CKD care delivery following eGFR implementation can be viewed as global and local needs assessments. This study, with its acknowledged limitations, corroborates the need for further systematic interventions beyond eGFR to improve CKD care delivery. Further, this study identifies not only PCP care as suboptimal, but also reinforces prior documented shortcomings in nephrology care, even in an academic setting following eGFR implementation, KDOQI/KDIGO guideline development, and growing awareness of CKD. The implications of these findings are now further highlighted in the conclusions section:

“This study identifies not only PCP care as suboptimal, but also reinforces prior documented shortcomings in nephrology care [1-5]. Such deficiencies despite the presence of CKD guidelines and eGFR reporting, especially in an academic setting where patient visits are generally longer and providers less hurried, highlight the need to employ a conceptual model of suboptimal CKD care delivery by providers to direct the evaluation of further interventions that may improve care delivery. Such a model should identify the numerous hurdles including perceptual and interpretive errors that may have been addressed by eGFR reporting. It should also identify additional barriers including gaps in knowledge and cognitive burdens not addressed by eGFR reporting but that will need to be overcome to incrementally enhance CKD care. Further studies are needed to explore the role of systematic interventions in addressing these barriers and optimizing the care of pre-dialysis CKD patients.”

Notably, since the completion of this study, we have collaborated with the general internal medicine department to provide brief, pertinent didactics on CKD management along with
electronic health record clinical decision support in the setting of a randomized controlled trial to attempt to improve CKD care. We look forward to reporting these findings in the near future.

4. **Whilst ACE/ARB usage is of interest the key questions for ACE/ARB prescribing are:** a) was prescribing appropriate (i.e., were ACE/ARBs used where indicated) and b) was prescribing appropriately monitored.

We agree with the reviewer that these are further important questions that our data was not able to fully address. We did not abstract values for microalbuminuria or proteinuria to help determine whether patients who are most likely to benefit from ACEI/ARB therapy were receiving these treatments. However, we were able to determine that approximately 30-40% of patients had received neither a proteinuria screen nor ACEI/ARB therapy. The failure to either screen for proteinuria or prescribe an ACEI/ARB in the setting of CKD should generally be considered suboptimal care. While contraindications to ACEI/ARB therapy may preclude their use (e.g., hyperkalemia, angioedema, hypersensitivity), these are expected in only a minority of CKD patients. For example, in the RRI-CKD prospective cohort study of greater than 800 non-dialysis dependent CKD 3-5 patients (with initial eGFR<50ml/min/1.73m$^2$) [6], between 5-12% of patients on ACEI or ARB demonstrated hyperkalemia, and only 4% not on an ACEI/ARB demonstrated hyperkalemia. Similarly, in our study, only XXXX had significant hyperkalemia (K+>5.5) during the cohort periods.

We have now revised figure 3 of the manuscript to present the data on absence of both proteinuria screen and ACEI/ARB therapy in each of the cohort groups and briefly review these findings in the results section. We also discuss these issues more fully in the manuscript:

Discussion paragraph 3: “Although we did not examine clinical outcomes in this study, it is notable that ACEI/ARB use and lack of both albuminuria screening and ACEI/ARB therapy were unaffected by eGFR reporting.”

Discussion paragraph 4: Our findings are similar to previous studies reporting minimal or no improvement in ACEI/ARB use following eGFR implementation [28, 29]. In addition, approximately 1/3 of our CKD cohort received neither an albuminuria screen nor ACEI/ARB therapy. Hence, providers did not know whether a significant number of their CKD patients possessed characteristics making them likely to benefit from ACEI/ARB therapy nor were they presumptively treating such patients. Although contraindications to ACEI/ARB therapy (e.g., angioedema, hyperkalemia) may have precluded their use, it should be noted that published rates of hyperkalemia in a recent non-dialysis dependent CKD 3-5 cohort were approximately 5-12% [44] and the approximate rate of hyperkalemia (K>5.5) for outpatients with CKD 3b-5 at our medical center is 17.1% in the previous 12 months (unpublished data). Hence, contraindications to ACEI/ARB are unlikely to explain these shortcomings in care fully.

We did not attempt to ascertain whether serum creatinine and potassium levels were appropriately monitored following initiation or dose increases in ACEI/ARBs. We now raise this limitation within the discussion, “Fourth, there were additional important process of care outcomes that we did not assess including appropriate lab monitoring following the initiation of ACEI/ARB therapy.”
5. Reference 2 is used to support a statement that the incidence of obesity, diabetes and hypertension is increasing. The reference is from nearly 2 decades ago and is therefore of questionable relevance.

We apologize for this oversight. We now reference more recent literature supporting an increase in the rates of obesity, diabetes, and hypertension in the US.


Referee 2: Manish Sood

We want to thank Dr. Sood for his thoughtful comments including the request to conduct a sensitivity analysis to clarify our tables and figures. We have addressed each of his points in detail as presented below. We believe these changes further strengthen the manuscript.

1. Inclusion criteria was a minimum of 1 eGFR measurement: the results mention how many had greater then 2 (94%). Its possible more stable CKD patients would have more measurements over time due to slow progression of CKD. Consider a sensitivity analysis including/excluding patients with different numbers of eGFR measurements.

We agree with the reviewer that patients with multiple serum creatinine/eGFR measures may have substantively differed from patients with fewer creatinine/eGFR readings. For the sensitivity analyses, we excluded patients from both cohorts (pre-eGFR and post-eGFR) with only 1 creatinine value (~21% of the pre-eGFR cohort and 6% of the post-eGFR cohort). These exclusions did not substantively change our findings. We then excluded patients with fewer than 3 serum creatinines values (~60% of the pre-eGFR cohort and 48% of the post-eGFR cohort were excluded). While absolute values showed modest changes, overall the data were qualitatively unchanged. For example, examining only patients with 3 or more serum creatinine assays resulted in a prevalence of co-management of 35% in the pre-eGFR cohort (n=37 of 106) vs. 65% in the post-eGFR cohort (n=90 of 139, P<0.0001). Similarly, the incidence of renal referral for PCP managed patients during the respective cohort periods was 10.4% pre-eGFR vs. 25.8% post-eGFR (P=0.03). Changes in ACEI/ARB use were also similar; PCP managed Pre-
eGFR use 68.8% vs. PCP managed Post-eGFR use 63.6% (P=0.5); Co-managed Pre-eGFR 55.2% vs. Co-managed Post-eGFR 64.4% (P=0.4). Comparison of ACEI/ARB use between PCP and Co-managed patients remained non-significant (P=0.2, P=0.9 in the pre-eGFR and post-eGFR periods, respectively). We did not conduct sensitivity analyses requiring >3 serum creatinine assays as this would have restricted our sample size severely and limited the utility of any comparisons.

For conciseness, we now broadly state within the results section, “In sensitivity analyses examining patients with at least 2 or at least 3 serum creatinine values, findings did not substantially differ.”

2) Was cause of CKD collected? This is important as GN vs. Diabetic Nephropathy vs hypertensive nephropathy vary greatly in illness severity and progression to ESRD.

We agree with the reviewer that severity and subsequent care of CKD may vary considerably depending on the underlying etiology. Unfortunately, due to concerns regarding the lack of documentation and the questionable accuracy of inferring the cause of CKD from electronic health record documentation, we did not attempt to evaluate cause of CKD or examine subgroups by (inferred) underlying CKD etiology. For example, patients with diabetes and hypertension often simply have CKD, diabetes, and hypertension on their problem list without a clear indication of which is the most likely etiology of the CKD (assuming this is known). In addition, for many patients further details regarding CKD are only captured in the provider’s free text documentation, which would require either more advanced natural language processing capabilities or a complete chart review to capture. We recognize this is an important limitation and continue to acknowledge it in the discussion section, “In addition, there are other critical factors that are likely to contribute to differences in the care delivered to CKD patients that were not controlled for in this study (e.g., patient comorbidities, underlying etiology of CKD).”

3) For Table 3, please clarify the referent
We agree that clarifying the labeling in table 3 would benefit the readers. We now specify “For each variable, the referent is the latter value listed within parentheses.”

4) For Figure 1, please give numbers for subcategories of those excluded
We concur that further specification of the number of patients excluded for various causes would be informative to the reader. We have now updated figure 1 to include this information.

5) Was serum K known?
We agree that abstracting serum potassium would have been useful in assessing for hyperkalemia in patients prescribed or not prescribed an ACEI/ARB. Please also see the response to reviewer 1, comment 4. Unfortunately, we did not obtain individual patient-level potassium data during our data abstraction. We recognize this is important in judging whether rates of ACEI/ARB use are appropriate. To address these concerns, we have referenced rates of hyperkalemia in a recent non-dialysis dependent CKD cohort. We also report hyperkalemia rates for all CKD 3b-5 outpatients at our medical center over the past year and we report these within the discussion. We believe the approximate rates of hyperkalemia in CKD (either from the published literature or from our medical center) are not high enough to completely explain the
lack of ACEI/ARB use in a significant portion of our cohort. We now state this within the discussion. “Although contraindications to ACEI/ARB therapy (e.g., angioedema, hyperkalemia) may have precluded their use, it should be noted that published rates of hyperkalemia in a recent non-dialysis dependent CKD 3-5 cohort were approximately 5-12% [44] and the approximate rate of hyperkalemia (K>5.5) for outpatients with CKD 3b-5 at our medical center is 17.1% in the previous 12 months (unpublished data). Hence, contraindications to ACEI/ARB are unlikely to explain these shortcomings in care fully.”

6) It seems the authors may have missed an interesting study opportunity with choosing the later assessment period for their post-eGFR data collection. It is reasonable to assume that with the eGFR reporting, an increase in education and awareness in kidney disease occurred. This would have resulted in (hopefully) an increase in interventions, better care etc. It would have been interesting to see the immediate impact in care after eGFR reporting.

We agree with the reviewer that it would be interesting to note whether implementation of eGFR reporting resulted in any immediate changes in provider behavior regarding CKD management. However, during discussions with general internal medicine faculty, it was felt that provider perception and use of eGFR did not truly coincide with automated reporting of eGFR. Therefore, we were concerned that CKD care immediately after eGFR reporting began would not have differed substantially from baseline due to limited familiarity and acceptance of eGFR. We theorized that a latter period would be more reflective of the effects (or lack thereof) of eGFR reporting and that greater provider familiarity and acceptance of eGFR might result in modest improvements in care. It is worth noting, that if eGFR reporting resulted in a robust, marked improvement in awareness and care of CKD, then we would expect those improvements to continue forward into our study period. The lack of such robust improvements in our study suggests that either a) they were never realized or b) they transiently occurred following eGFR implementation but decayed in a relatively short interval. While there are subtle but important differences between these two states, in either scenario we assert that further systematic interventions will be needed to optimize CKD care.

References


5. Filipineri MD, Rocca Rey LA, Schnitzler MA, Abbott KC, Brennan DC, Takemoto SK, Buchanan PM, Burroughs TE, Willoughby LM, Lentine KL: Delivery patterns of