Author’s response to reviews

Title: Incident Gout and Chronic Kidney Disease: Healthcare Utilization and Survival

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Version: 1 Date: 30 Dec 2018

Author’s response to reviews:

We submit the below for review, but request an additional week so that all of the authors can review the responses. Due to the holiday season, we were unable to reach all of the authors and we did not hear back regarding our request to the journal for a delay.

Thank you for the comments from the reviewers for the manuscript, "Incident Gout and Chronic Kidney Disease: Healthcare Utilization and Survival." Below are the responses to each of the reviewers' comments and the updated manuscript has revisions in track changes.
Reviewer #1:

The populations of patients with and without CKD and of different age levels largely differ in terms of baseline condition and the differences can explain the outcome and cannot entirely modified by adjustment - A propensity analysis score for patients differing only for age or CKD should be included

We agree with the reviewer that there are substantial differences in the gout populations examined. There is much debate in the literature regarding the utility of propensity scores versus multivariable adjustment (see Shah et al J Clin Epidemiol. 2005 Jun;58(6):550-9). For this study, we chose to use multivariable regression and adjust for the confounding variables in order to monitor the effect of the confounding variables on the results. This approach, although not shown, provided face validity to the observed outcomes.

The abstract text should better summaries the results of the study

The abstract has now been updated with numbers describing the cohort and specific results.

The use of resources in obviously higher in older patients with CKD and again the analysis should be limited to more comparable sub-populations where it should be possible to assess the primary role of the two main co variates.

We agree with this thesis and as such, stratified the analysis according to age group as well as adjusted for age in each group. In addition, we examined general HRU and gout-specific HRU. Interestingly, as baseline, younger adults with CKD had on average more tests performed for serum uric acid than in the other groups. After controlling for other factors, there were differences among the older gout patients for allopurinol purchases by CKD status, whereas there were decreased allopurinol use over time for younger gout patients, but this did not differ by CKD status (see Discussion).

The proportion of lost to follow-up is remarkable as it is the number of patients lacking of some data.

We note in the Results section that "During the 5 years of follow-up from index date, 3421 patients died (26.4%) and 233 (1.8%) left Clalit." The loss to follow-up due to their unknown status (<2%) is considerably small and well documented in the healthcare system in Israel.
Furthermore, we used Cox proportional hazard models to account for the right-censoring of these patients and those who died.

The same is true for gout medications that is not equally distributed and this could have affected the outcome. In addition the dose of ULT and the control of serum uric acid is expected to be different and this could affect the clinical outcome.

We agree that the purchase and dose of gout medications is not equally distributed across groups. We have now added a discussion of this to the limitations’ section in the Discussion.

It is hard to identify a role for gout, since the conclusions could apply to any population by dividing the patients according to age and renal function.

The use of gout-specific HRU is intended to show the unique impact of these groups within the gout population. The intent of the research is not to implicate gout as the cause, rather to differentiate and highlight those at-risk subgroups. The role of gout compared to other non-gout populations is the focus of further research. This point is now added to the Discussion.

The real interesting issue would be if there is any additional impact of gout over age and CKD, but in this case the control population should include patients without gout.

We agree that the next steps are to now examine similar age groups within the population: (a) without gout and with CKD and (b) without either gout or CKD. We used this initial study so examine gout-related HRU. Further studies would look only at overall HRU.

Reviewer #2:

Throughout the manuscript would replace "serum uric acid" for "serum urate" as described in the recently published gout nomenclature.

Thank you for this comment. We have now replaced all references to "serum urate" with "serum uric acid"

The background section fails to build the narrative towards the objective of the study. I do not see a link between gout/treatment of gout/poor gout care/gout and CKD into health care utilization in gout and CKD. I think a link could be that health care utilization in gout is high
(there is data on this) and that is expected that it will be higher in gout/CKD but there are no studies, the authors would be trying to fill in this gap. Probably some other aspects of the introduction could be shortened or eliminated.

Thank you for this important comment. We have now added a paragraph to the discussion describing the link and the gap in understanding of the contribution of age and CKD to the burden of gout on HRU and therefore, cost.

Page 8, line 174 "pseudo" should be "pseudogout", I think

You are correct that we used this prefix "pseudo" to find pseudogout, however, we used the free-text prefix to cover and examine a broader range of possible pseudo-diagnoses.

I fail to grasp the healthcare resource utilization calculation and results. I see is the average per patient of the different measures (GP visits, specialist visits, etc) but cannot understand the final unit change in healthcare utilization. I think this deserves further explanation. Is this a standards process to analyze health care utilization. If so, the authors might want to provide a reference.

We have now clarified the use of total number of visits per patient per year (Methods) and added a reference for the use of this metric to represent utilization. For example, within the gout literature, Singh et al (2016) uses total number of visits and examines trends over time, Robinson et al (2015) looks at the average number of testing and allopurinol purchase in the last year of follow-up or Rothenbacher et al (2011) who uses average number of flares per year. These references have now been added to the Methods.

I wonder if all health care utilization is equal. For example, frequent visits to GP or specialist, measurements or urate levels, allopurinol refills are not undesirable and might lead to less healthcare utilization related to , most notably, hospitalizations. Frequent visits might be needed to adjust allopurinol doses, educate the patient, or other important features of gout care.

We have now added this point to the Discussion as a limitation of this study. Indeed, the underlying cause of differences between groups or even within groups (and unaccounted for) may be a result of confounding variables such as ULT dose.
Do the authors have access to data on emergency room visits? This is an expensive and undesirable feature of healthcare utilization (along with hospitalizations) that would be interesting to count. If not, I might consider this a limitation

The reviewer makes a valid and important point. Date for ER utilization is incomplete in the database. We will now add this to the limitations section of the Discussion.

The data on mortality is interesting. However, when comparing gout patient mortality with and without CKD my natural question will be: how is this different than the increased mortality in any individual with and without CKD? What I believe would be an interesting calculation would be to obtain a standardized mortality ratio comparing the ratio of gout patients with and without CKD with the ratio in the general population with and without CKD. Them you could argue that is the combination of gout and CKD conferring a particular increase in mortality, that you are not just seeing the effect of CKD -Is there a possibility of misclassification of gout? Would be misclassification be non-differential? I personally think the gout definitions taken by the authors are good, but would compare their definitions with others taken in the epidemiological literature.

We agree with the Reviewer's comments, similar to those above. The use of the non-gout population as a reference for the burden of gout with and without CKD is an essential next step. This will be the focus of the follow-up study.

Reviewer #3

I would like to see more numbers in the abstract. Specifically, how many people were in the CKD and non-CKD groups?

The abstract has now been updated with numbers describing the cohort and specific results.

The Results section is quite muddled up and jumps around a lot. It would help to be clearer.

Thank you for this feedback. We have now revised this section.
Background

There is some terminology that might be best changed. For example, it would be better not to refer to gout "sufferers", and describing those with and without CKD as routine and complex patients is probably unhelpful - I would just say with and without CKD.

Thank you, we have now updated the language in the manuscript.

Study population

I don't understand the sentence on lines 149-150. How can you exclude data from subsequent years, when you don't have this data?

We agree with the reviewer and this statement has now been updated.

Is the SES at the end of follow-up all that is available, as this is technically inappropriate, as it is measured after exposure and so could be consider to be on any causal pathway? I doubt this makes much material difference, but should probably be discussed.

We agree with the Reviewer that our assumption should be discussed. We note that changes in SES, especially among middle-aged and older adults is particularly stable and that the use of the last SES may be more informative for adjustment since it represents the cumulative effect of SES. A brief discussion of this has now been added to the Methods section.

Statistical analysis

The use of GEE models seems reasonable for the question, but I wonder about the use of the Normal distribution for the purchase of allopurinol, is this not count data?

All of the distributions were checked and plotted. The purchase of allopurinol was closest to the normal distribution.

I agree that updating the models for the onset of CKD would change the question, but I wonder if the failure to do so makes the question less clinically relevant? The authors should discuss this more. If the non-CKD people develop CKD then this is likely to bias any association towards the null.
We have now added this to the discussion. Indeed, if the non-CKD group develop CKD, then they would be more similar with regards to outcomes to the CKD group.

There is no mention of testing the proportional hazards assumption. Whilst the Cox model is fairly robust to departures from proportional hazards, this should still be checked.

This has now been added.

Results

I do not understand how sUA can be considered controlled at diagnosis if the person has a new diagnosis of gout (line 268-270).

Apologies for this confusion. One of the inclusion criterion for identifying gout patients were for patients with sUA levels above 6. For the control variable, we used the lowest level during the 12 months prior to index date (see Table 2 footnote).

I thought people with gout-related prescriptions before the index date had been excluded (line 271-272).

Our apologies for this confusion. One of the inclusion criterion for identifying gout patients were for patients with two gout-related prescription purchase in the previous 6 months form index. In the analysis, we examine the percent of patients who had a purchase in the previous year from index.

Rather than fitting separate models for the different age groups, did the authors consider fitting an interaction term? This may have been more appropriate.

This was considered and assessed during our initial research and interaction was significant. However, since the results of these models are often more difficult to interpret and there was a biological basis to stratify the results, we chose the current model.

I am not convinced that the survival findings are necessary if this paper is about health care utilisation.

Editor: Can remove, although other reviewers thought this was a good addition.
Tables

It is not necessary to include mean and median in Table 1.
We have now removed the median values for all variables in Table 1.

I cannot make sense of Table 2. What are the units.
We have now added more detail to the table to reflect the average annual number of visits or purchases per patient.

Figure 1 would be much more informative as a table with confidence intervals.
Figure 1 is the flow chart that is typically used for cohort studies.

I am concerned by the number of people to whom analysis is attributed (line 416).
The analysis and interpretation of the EHR data were undertaken by several data analysts, epidemiologists, biostatisticians and clinicians. All were involved at various time points to assess for example, face validity, determine inclusion and exclusion criteria, and identify appropriate methodological approaches.