Author's response to reviews

Title: Seroprevalence of Streptococcal Inhibitor of Complement (SIC) suggests association of streptococcal infection with chronic kidney disease.

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Dear Editor,

Thanks you for giving us an opportunity to revise our manuscript entitled “Seroprevalence of Streptococcal Inhibitor of Complement (SIC) suggests association of streptococcal infection with chronic kidney disease.” We have made extensive revision to the manuscript. Please find below our point by point rejoinder to the reviewer’s comments. As shown in here, we have made appropriate amendments to the manuscript.

Claire Turner’s comments:
1. “It is surprising therefore that there is such a high level of seroreactivity to SIC in patients with CKD or ESRD …”

Manifestations of chronic kidney disease and end stage renal disease often take many years. Paucity of SIC-positive strains in a cross-sectional study on strain distribution does not necessarily reflect absence of these strains in the past. Availability of long-lasting immune reaction to one or two specific antigens offers a convenient way to assess whether the population has come in contact with specific strains. This requirement is met by SIC and DRS which are highly immunogenic and their immune reaction are persistent.

Action: The first sentence of the 3rd paragraph in the background clarifies this point.

2. Under minor revisions, the reviewer asked for more details on the distribution of emm types.

Action: We now provide a table (table 2) showing emm types and number of isolates for each type in two cross-sectional data.

3. Under minor revisions, the reviewer asked whether the patients with CKD or ESRD are exposed to or carry GAS.
This is not a routine investigation in the nephrology department of the KEM hospital.

Action: Nil.

4. Under discretionary revisions, the reviewer suggested simplification of figure 1.

Agreed and thanks.

Action: The new figure 1 reflects this recommendation.

5. Under discretionary revisions, the reviewer refers to Hoe et al study wherein 43% of their subjects are SIC sero-positive.

However, Hoe et al did not undertake assessment of CKD or ESRD in their population as the reviewer states.

Action: Nil.

Jonathan Chemouny’s comments:

1. Under major comments, the reviewer seeks clarifications of GAS seropositivity and comparison to study 15.

GAS infection is very common in children and adolescents. Given the Indian population is endemic for streptococcal infections and diseases, almost all would have been exposed to this pathogen sometime. In the study 15 (now ref 16 in the new version), the control subjects are those with no recorded history of PSGN, and NOT “unexposed” population. Some times PSGN is subclinical and hence not often diagnosed. Indeed, our current approach is similar to what we used in that study.

Action: Nil.

2. As the reviewer pointed out, the effects of age, sex and diabetes status were studied in CKD and ESRD patients, and not in the healthy controls.

For a strong antigen (such as SIC) with persistent immune response, it is possible that the proportion of SIC-positivity may increase with age. We did not observe this (please see response to comment 3), suggesting that infections with SIC- and DRS- positive strains may have happened at an early age. Because our healthy cohort is non-diabetic, we cannot make comparison between healthy and patient cohorts for this parameter (also see our response to comment 3 below)

Action: As below.

3. The reviewer comments on differences in mean age of patients and controls and their effects.

In order to take into account any potential confounding effects of the relationship between renal disease and antibody positivity we re-calculated odds ratios adjusted for age and sex. Furthermore, we did not observe age related
acquisition of SIC or DRS seropositivity in either the patients or the controls. Our response to this and for the comment number 2 is the same.

Action: We have modified the Statistical Analysis section to describe the adjusted analysis and have added a corresponding sentence to the results section: “After adjustment for age and sex the ORs showed a similar although somewhat reduced effect: 2.33 (95% CI 0.75, 7.22) and 3.95 (95% CI 2.16, 21.24).” at the end of 1st paragraph of the section “SIC and DRS seroprevalence among the CKD and ESRD patients”.


We thank the reviewer for commending the manuscript.

Action: We have corrected misspellings and errors in the manuscript.

5. Comment on retrospective study and causal relationship.

We agree with the reviewer. However, the statement “that past streptococcal infection is an independent risk factor for CKD” does not portray causal relationship (but only shows it is a risk factor).

Action: Nil, unless the editors wish to recommend differently.

6. Under discretionary revisions, the reviewer suggests presenting a table for demographic data.

The data 240 subjects (patients + controls) can be provided. This would be a large table. Instead, a table summarizing age, sex ratio, proportion of diabetics, and proportion of SIC and DRS seropositivity can be provided.

Action: Table 1 summarizing the above has been added.

We sincerely hope this vastly revised version meets your approval for publication of the manuscript.

Regards

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