Author’s response to reviews

Title: The Impact of IgM Deposits on the Outcome of Nephrotic Syndrome in Children

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Author’s response to reviews:

Editor's comments:

i. Clearly stating how patients were identified. Inclusion of clinical information about children with nephrotic syndrome who did not receive a renal biopsy would help strengthen some of the findings and conclusions.

The primary goal of our study was to compare the clinical outcomes between IgM positive and IgM negative nephrotic syndrome patients therefore our study model was set to identify and include all pediatric patients with kidney biopsies performed during the 2000-2015 year period. To achieve this, we accessed the National Center of Pathology database identifying all pediatric patients who had kidney biopsies performed between 2000-2015 year period. We have identified 58 patients: 5 patients were lost to follow-up, 4 were excluded due to incomplete medical documentation, 4 were excluded due to secondary condition that could have influenced the course of nephrotic syndrome. For final analysis we included 45 patients that were further divided into IgM positive and IgM negative groups.

We agree that it would be useful to have the number of all patients, diagnosed with nephrotic syndrome. Total number of patients diagnosed with nephritic syndrome during the study period is 111 patients. However, some of the patients were diagnosed earlier, but the biopsy was performed during the mentioned study period. Therefore this number cannot be used to estimate the disease prevalence in this population.

ii. An overview of the patient population with nephrotic syndrome seen at the authors unit and criteria that decide patients that have renal biopsies and those that do not.

We indeed agree that defining indications for biopsy are essential to avoid any bias, currently these are listed in the methods section but could be emphasized more if further requested.
Reviewer reports:

Reviewer 1:

Please introduce every abbreviation in the abstract and in the text first before using the abbreviation.

Corrected.

It is unclear how the patients were identified.

The primary goal of our study was to compare the clinical outcomes between IgM positive and IgM negative nephrotic syndrome patients therefore our study model was set to identify and include all pediatric patients with kidney biopsies performed during the 2000-2015 year period. To achieve this, we accessed the National Center of Pathology database identifying all pediatric patients who had kidney biopsies performed between 2000-2015 year period. We have identified 58 patients: 5 patients were lost to follow-up, 4 were excluded due to incomplete medical documentation, 4 were excluded due to secondary condition that could have influenced the course of nephrotic syndrome. For final analysis we included 45 patients that were further divided into IgM positive and IgM negative groups.

A control group would be good, namely all of the patients who presented with childhood nephrotic syndrome during the same study period but did not receive a renal biopsy.

Since the aim of the study was to identify the significance of IgM deposits for the clinical course and outcomes of the nephrotic syndrome, for the control group we used IgM negative patients.

As this is a retrospective cohort study, consider reporting the findings as per the STROBE criteria.

We are grateful for the suggestion, but we believe that data in the article is being reported according to the STROBE criteria: we have stated that this is a retrospective study in the abstract, we have explained the background of the investigation in the introduction section, we have described patient selection system, all the variables, and diagnostic definitions in the method section, we have reported all descriptive data and study results. Also in the discussion section we have stated the main results and weaknesses of the study.

Page 3, line 69: Be specific. Define nephrotic range proteinuria, hypoalbuminaemia (e.g. < 25 g/L), and consider omitting oedema and hyperlipidaemia, as these are not mandatory for the definition of nephrotic syndrome. Hyperlipidaemia can be defined, oedema is challenging to define.
Thank you for clarifying this issue. In this article we used the KDIGO definition of nephrotic syndrome, defined as edema or nephrotic range proteinuria (≥ 3+ in urine dipstick test) and hypoalbuminemia ≤ 25 g/l. According to this definition, edema is not a mandatory criterion.

Page 4, line 77: Do you have a better definition for IgM positivity?

We agree that the definition is not unified. Other authors consider IgM positive biopsy if ≥ 2+ on immunostaining, but we have chosen ≥ 1+ to include as many patients, as possible.

Page 4, line 80: Provide the reference for the Fourth Report. It is presumed that you used those reference intervals.

The diagnosis of arterial hypertension was made according to The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. We have also provided the reference, as requested.

Page 4, line 84: It is important to note if serum creatinine was IDMS traceable. If so, you must use the latest improved Schwartz formula: Schwartz GJ, Schneider MF, Maier PS, et al. improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. Aug 2012; 82(4):445-453.


Page 5, line 96: How was "persistent proteinuria" assessed? Please provide a clear definition.

We indeed agree that the term “persistent proteinuria” can be misleading; therefore we define it as positive urine dipstick test (≥ 1+) at the last follow-up.

Page 5, line 109: How many patients were diagnosed with childhood nephrotic syndrome during the study period? What were the criteria for renal biopsy? How many were not biopsied. This is important as the reader wants to assess the selection bias due to the inclusion of biopsied cases only. The time from diagnosis to biopsy should also be noted.

The primary goal of our study was to compare the clinical outcomes between IgM positive and IgM negative nephrotic syndrome patients therefore our study model was set to identify and include all pediatric patients with kidney biopsies performed during the 2000-2015 year period. To achieve this, we accessed the National Center of Pathology database identifying all pediatric patients who had kidney biopsies performed between 2000-2015 year period. We have identified 58 patients: 5 patients were lost to follow-up, 4 were excluded due to incomplete medical documentation, 4 were excluded due to secondary condition that could have influenced the course of nephrotic syndrome. For final analysis we included 45 patients that were further divided into IgM positive and IgM negative groups.
We agree that it would be useful to have the number of all patients, diagnosed with nephrotic syndrome. Total number of patients diagnosed with nephritic syndrome during the study period is 111 patients. However, some of the patients were diagnosed earlier, but the biopsy was performed during the mentioned study period. Therefore this number cannot be used to estimate the disease prevalence in this population.

Page 7, table 2: Please provide the cumulative steroid dose at the time of assessment. Also, your cyclophosphamide spelling is unusual. Were the cyclosporine or MPA levels different?

Thank you for a very good comment. The mean cumulative steroid dose at the time of the biopsy in IgM positive group 523.3 mg/kg compared with 492.6 mg/kg in IgM negative group. The difference between groups is not statistically significant (p= 0.8). We maintained the serum levels of cyclosporine at 80-100 ng/ml for all patients treated for nephrotic syndrome, MPA levels were not significantly different between the groups.

Reviewer 2: In this paper the authors analyze the outcome of children with IgM deposits and without deposits in the mesangium of glomeruli in renal biopsies and conclude that there is no difference in the outcome among the two groups. This is an interesting study and adds to the growing literature on this topic, which is still controversial at best. The results are potentially important for pediatric nephrologists and nephropathologists. However, the study cannot be published in the present form. There are many concerns as under:

1. English language needs careful review and correction throughout the manuscript. It is very important. Preferably this should be done by a native English speaking colleague.

2. There is no need to give dates of commencement and end of study. Only months and year of study are enough.

Corrected as proposed.

3. Please also provide reference or definitions of SDNS, SRNS, FRNS, etc. in Methods.

We fully agree that the definitions are especially important; therefore we have provided them in the method section.

4. In results, outcome, time to progression to ESRD average value is not given. Only range is given.

We are grateful for the comment. Indeed, we did not provide the time to progression to the ESRD. However, since the distribution of the data is not normal, we can only provide the median value. The median of time to progression to ESRD was 5.53 years, range 0.94 - 12.37 years.

5. In discussion, it is stated that IgM deposits were seen in 66.6% of cases, while in the beginning of results it is shown as 40%. Please explain the discrepancy or rectify it.
We are grateful for the comment. The number of IgM positive biopsies is indeed 40%, we apologize for any misleading data and we have corrected the number in the article.

Corrected.

7. A figure of IgM positivity will be very helpful for the readers.
A figure of IgM positive glomerulus has been added.

Reviewer 3: This is a retrospective study analyzing the impact of IgM deposits on renal biopsy on clinical course and outcome of nephrotic syndrome (NS) in children.

The authors defined IgM nephropathy as presence of IgM mesangial deposition on immunofluorescence (IF) and divided patients into IgM+ and IgM- groups for further analysis.

- In Methods (Patient selection), on page 3, line 58, the authors introduced abbreviation "MH" without explanation. Does MH stand for mesangial hypercellularity?
We apologize for any misinterpretation and we’ve already corrected this issue.

- The conclusions of the study are somewhat confusing: the conclusion of the abstract says that there is no difference in clinical course and disease outcome between with IgM-positive and IgM-negative patients. However, the conclusion at the end of the article (page 11, lines 199-200) suggests that IgM induced glomerular injury leads to challenging disease due to tendency for steroid resistance and the need for more immunosuppressive agents - this statement would indicate that patients with IgM positivity have a more severe clinical course. Please clarify and unify the conclusion in the abstract with the conclusion at the end of the manuscript.
Corrected.

- The tables are embedded into the text of the article. Usually, all the tables and figures are placed at the end of the manuscript.

The tables are now moved at the end of the paper.