Morphological indexes: can they predict lupus nephritis outcomes?

Dear Editor-in-chief,

On behalf of the authors responsible for this manuscript I thank you for the possibility of publishing it. Also, we appreciate the reviewers’ comments, which have contributed to the overall improvement of the paper. We tried to answer to all comments/suggestions (please see below).

Changes to the original manuscript were marked by changing the text color.

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Reviewer A:

Dear Editor in Chief,

The authors have successfully answered all the issues that I have previously

raised.

Please note that I also agree with the authors´ answers to the issues raised by Reviewer B and Reviewer C.

I suggest that the manuscript should be published in AMP.

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Reviewer B:

Penso que o manuscrito deve ser publicado na AMP porque é extremamente relevante a nível científico. É atual e sugere áreas de investigação que podem ter implicação clínica a nível terapêutico e prognóstico dos doentes. É portanto um artigo relevante para a prática clínica dos Nefrologistas mas também alerta os médicos no Geral para a Nefropatia lúpica e sua terapêutica.

Prioridade de publicação: primeiros 10% dos artigos a publicar.

We thank the reviewers A and B, and we’re satisfied that their feedback helped improve the manuscript.

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Reviewer C:

1. Although this paper has been reviewed in accordance to many of the previous suggestions made by the several reviewers, mine included, I still have some issues, being the most important related to the nature of the Austin and Hill’s indexes. Although in the analyses they have been treated as being quantitative I’m afraid that they are qualitative in nature, isn’t that right? The values they can take refer to levels, isn’t that right? If this is the case the statistical procedures that assume a quantitative index, such as the ANOVA or the Spearman correlation, no longer apply.

The indexes are not classified as levels, they are quantitative in nature. We’ve included them in table 2, for easier understanding.

1. Additionally, I believe that when a multivariate analysis is referred it should be more detailed as to what it is meant, as explained in the author’s reply.

We accept your suggestion. We added those details to the methods section: "After this first analysis, we fitted a model of multivariate analysis using all subjects and defining the chronicity indexes as our main predictors and eGFR at the end of follow-up as our main outcome. Age, gender and proteinuria were the variables used as potential confounders (older patients may have less renal function, women tend to have lower GFR and proteinuria is associated with rapid decline of renal function). All tests were performed using STATA software version 13, and a p-value <0.05 was considered statistically significant."

1. Also, in the Materials and Methods’ section:

- Where it reads “Associations between the different LN classes and clinical and laboratory variables were performed using Fisher’s exact test and Wilcoxon.” It should read “Associations between the different LN classes and clinical and laboratory variables were investigated using Fisher’s exact test and Wilcoxon.”

- Where it reads “Associations between Austin and Hill indexes and laboratory variables were performed using Spearman test.” It should read “Associations between Austin and Hill indexes and laboratory variables were investigated using Spearman test.”

- Where it reads “After this first analysis, we performed a model of multivariate analysis using all subjects and defining the chronicity indexes as our main predictors and eGFR as our main outcome. All tests were performed using STATA software version 13, and a p-value <0.05 was considered statistically significant.” It should read “After this first analysis, we fitted a model of multivariate analysis using all subjects and defining the chronicity indexes as our main predictors and eGFR as our main outcome. All tests were performed using STATA software version 13, and a p-value <0.05 was considered statistically significant.”.

We have corrected the text as per your suggestions.

1. Finally, in table 1, NS stands for “non-statistical”, but I’m not sure what does this mean.

We meant to write “non-significant”. This had been corrected.

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Reviewer D:

1. I think the idea of the manuscript is interesting, though I have some problems with the execution of the paper. I think that it is important to understand if the morphological pattern of the kidney biopsies correlate with the prognosis, however this isn’t well understood through the paper

We are unsure what the reviewer understands by morphological pattern in lupus nephritis. In fact, the ISN/RPS classification represents the different possible morphological patterns. In that sense, our manuscript answers the reviewer question, since it does not correlate with prognosis. We’ve included the abbreviated ISN/RPS classification in table 1.

1. The abstract I don’t think it is relevant the information the authors add about class IV of ISN/RPS, and they should specify the system score they use.

As per the above point, the authors consider that it is relevant to include the fact that patients with a typically aggressive lupus nephritis morphological pattern was not a reliable predictor of outcome. Therefore, in our view, the most commonly used classification (ISN/RPS) can be insufficient when managing such patients and additional morphological indexes should be applied.

1. In the introduction the authors should further enlighten the reader about the different scores they talk. Perhaps they could put a table specifying the criteria used in each score, and their pontuation. As the readers are not familiarized with the scores perhaps this would facilitate the understanding of the scores and the indication for biopsy.

We agree with the reviewer that readers might not be familiarized with the scores. We have added a description of the indexes (table 2).

1. In the Methods section I think that they should state the remission criteria as in the LUNAR study (if cr was normal at the beginning and if it was not). You should state the minimum time of follow up. And the chronological evolution of remission.

We accept your suggestion, and the full LUNAR study remission criteria were specified: ”The LUNAR trial

The overall follow-up in stated within the manuscript: “The 46 patients were evaluated during a median follow-up of 31.9 months (13.2-45.6) months.“ The patients with the lowest follow-up time were the ones with ongoing induction therapy, which were excluded from outcome analysis, as answered in the next point.

1. In table 2 I would like to see the ISN/RPS classification. I think that the 4 patients that are still doing induction immunossupression should be excluded, as we still cannot figure out their evolution.

We’ve included the abbreviated ISN/RPS classification in table 1.

As for the 4 patients with ongoing induction, they have been excluded from the outcome analysis: “Excluding patients with ongoing induction immunosuppression, clinical remission was obtained in 93.8% (30/32) of patients – we observed 15 complete,15 partial remissions and 4 patients suffered LN recurrence.”

1. I like your discussion, I think it has some interesting ideas, I think that you have to state that the ISN/RPS was older than Austin and Hill criteria, but it as evolved, and still in your paper it did not correlate with the follow up.

We agree with the reviewers suggestion, and think it is already implied in this segment of the discussion: “It is therefore not surprising that, despite being extensively used, the ISN/RPS classification could not predict clinical outcomes. This has led to the development of the indexes described by Austin and later by Hill, which have proven capable of estimating renal outcomes from the renal biopsy findings. Their integration in the most recent ISN/RPS classification reflects its importance.”

1. I believe that though morphological scores are important your paper does not demonstrate that with the most used score, the ISN/RPS. Perhaps you should encourage the use of the other scores you applied in your paper.

We agree. We’ve added a sentence to the manuscript’s summary to further emphasize that point: “In summary, the most recent ISN/RPS consensus recognizes the efficacy of histomorphological indexes in the evaluation of LN, and our data supports that. We observed a significant correlation between the renal outcomes and the indexes described by Austin and Hill. We encourage other units to include morphological indexes in their evaluation of such patients, as they are easily applicable scores and may provide a useful and individualized quantitative measure of clinical outcomes.”

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Once again, we acknowledge and kindly thank the reviewers for their observations and hope the manuscript has been improved by these changes.

Best regards,