

To  
Editor-in-Chief  
World Journal of Clinical Pediatrics  
Manuscript NO: 62877  
Date: 15-02-2021

**Subject:** Redressing of the manuscript titled “Indirect Determination of Serum Creatinine Reference Intervals in Pakistani Pediatric Population Using Big Data Analytics”.

Dear Sir,

Thanks for your kind suggestions regarding the redressing of our manuscript. The changes have been incorporated in the attached manuscript. Furthermore, each suggestion has been addressed as per the comments received as follows.

Yours sincerely,

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**Editor:**

**(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.**

**Response:** Original graphs have been included in the revised submission using PowerPoint template.

**(2) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.**

**Response:** Article highlights have been included in the revised manuscript submitted. Please refer to page no 14.

**(3) The reference cited in the text should be superscript.**

**Response:** The references cited have been superscripted in the revised manuscript submitted.

**(4) The authors need to provide the Biostatistics Review Certificate**

**Response:** The Biostatistics Review Certificate has been provided with the revised submission.

**Reviewer:**

**(1) I would like to know about the limitations of your research.**

**Response:** As per the suggestion, limitations have been included in the revised submission, please refer to the section of discussion on page no 13.

Text included:

In addition to the merits of this real-world big-data approach in laboratory medicine, there is notably a limitation of this indirect algorithm, that any potential differences cannot be analyzed between the groups formulated, hence individual results have to be complemented with clinical judgement and correlation. Moreover, the confidence intervals (CI) with the established RIs were not calculated, as the used algorithm doesn't contain a provision for CI generation.

**(2) And secondly, the study used data from healthy children or children with some kind of chronic pathology, was there a distinction between these data?**

**Response:** The method is based on utilizing an input dataset of lab values containing both healthy and pathologic samples, but only one sample per patient. A Power Normal distribution, defined as Gaussian distribution following Box-Cox transformation was performed to model the distribution of non-pathologic samples in the dataset. As per the default settings, the abnormal values are expected outside of the distribution of normal CREA results, with an adjustment of the algorithm for the generation of the upper limits of the RI, by setting the Pathological value to “high”, compared to the physiological test results.

As per the suggestion, limitations have been included in the revised submission, please refer to the section of Materials and Methods on page no 07.