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Reply

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Rescaling Creatinine Centiles in Neonates Treated with Therapeutic Hypothermia for Neonatal Encephalopathy

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Dear Editor,

We thank Manzar for the questions raised on the applicability of centile approaches for serum creatinine (SCr) in neonates treated with therapeutic hypothermia (TH) for neonatal encephalopathy, as this enables us to further explain the potential relevance and use of centile approaches [1, 2].

We obviously confirm the neonatal SCr pattern suggested by Manzar, albeit with the additional point that the highest SCr at birth is observed in term neonates, with a subsequent initial increase to peak SCr followed by a decrease over time [3]. In fact, it is because of this complex SCr pattern in early neonatal life (first week of life) that the Kidney Disease Improving Global Outcome (KDIGO) definition has some limitations and does not fully capture the inter- and intra-patient variability over postnatal age (PNA) [2, 4]. In contrast, the centile concept is similar to Z-score growth curves to assess individual weight trends (initial weight loss, subsequent increase). Therefore, a given SCr can be at the 10th, 50th, or 90th centile, while the same SCr concentration may be at a different centile when collected at different time points, and the absence of an expected SCr decrease may reflect impaired GFR compared to the reference postnatal trend.

Using the published TH (1,136 cases, 4,724 SCr observations) and control (801 cases, 2,779 SCr observations) datasets, we tried to further illustrate the different patterns over PNA between both cohorts, applying the "res-

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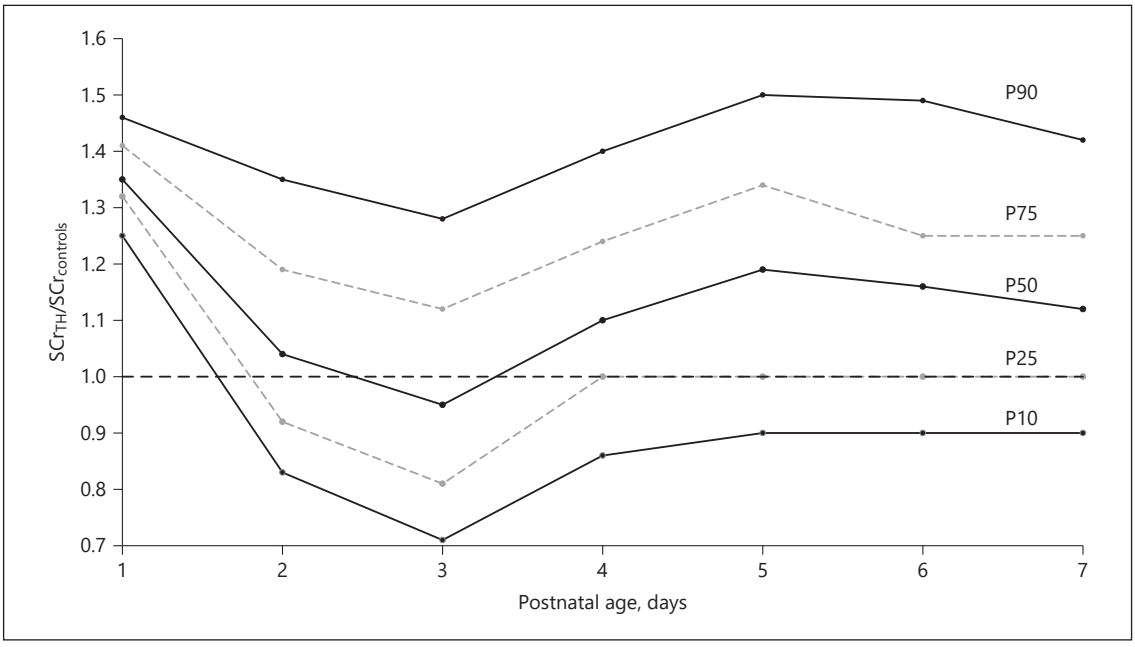


Fig. 1. Based on the centiles (10th, 25th, 50th, 75th, and 90th) SCr values over PNA (day 1–day 7) previously reported in the TH (1,136 cases, 4,724 SCr values) and the control (801 cases, 2,779 SCr values) group, the $SCr_{TH}/SCr_{controls}$ ratio has been calculated [2, 5]. Black continuous lines: P10, P50, and P90; grey discontinuous lines: P25 and P75; black discontinuous line: line of "equal" ratio.

caling SCr biomarker approach," described by Pottel et al. [5]. In essence, we calculated the $SCr_{TH}/Scr_{controls}$ ratio (TH to controls) for 10th-25th-50th-75th-90th centiles as published in the Neonatology paper and its supplement [2]. In the event of "similar SCr values," the centiles for this ratio should be straight lines around 1. In the paper of Pottel et al. [5], it was suggested that a ratio threshold >1.33 reflects clinically relevant impairment (GFR <60 mL/min/1.73 m^2, equal to chronic kidney disease, stage 3a onward). However, this approach was validated based on the measured GFR or estimated GFR equations, validated in young children (from 2 years onward) but not yet in neonates. Although this absolute threshold value is not useful in the absence of validation for GFR equations, the $SCr_{TH}/Scr_{controls}$ ratio can still be applied to compare SCr observations between the cohorts.

Applying this approach, Figure 1 clearly illustrates that TH cases compared to controls have ratios >1 (for all centiles) at birth, reflecting uniform renal impairment in the first day of life in TH cases, with a subsequent trend toward 1 from day 3 onward, reflecting a tendency to "normalization." However, the 75th and 90th centiles remain far >1, at the end of the first week of life, so that an important minority of TH cases still display clinically relevant impaired GFR. In comparison, other subjects have normalized, reflecting extensive variability in SCr and GFR. In this way, we suggest that a SCr centile approach may support clinical management, as it provides a tool for renal precision medicine, tailored fluid and pharmacotherapy, and individualized follow-up [2].

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Conflict of Interest Statement

None of the authors has a conflict of interest directly relevant to the content of this article.

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Author Contributions

Karel Allegaert, Anne Smits, and Djalila Mekahli drafted the initial manuscript. Karel Allegaert was responsible for data pooling, assisted by Pieter Annaert, Annouschka Laenen, and Anne Smits. Elif Keles, Pia Wintermark, Floris Groenendaal, Noor Borloo, Anne Smits, Suzan Sahin, Mehmet Yekta Oncel, Valerie Chock, Didem Armangil, Esin Koc, Malcolm R. Battin, and Adam Frymoyer provided data on the different cohorts. All the authors contributed to the interpretations of the data, provided input on the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Data Availability Statement

The pooled datasets were obtained for this analysis and remain the property of these groups, so that publicly sharing these data is not possible. Researchers interested in using the data can contact the corresponding author (karel.allegaert@uzleuven.be) as a contact point.

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