

Serum Creatinine Patterns in Neonates Treated with Therapeutic Hypothermia for Neonatal Encephalopathy

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Keywords

Acute kidney injury · Therapeutic hypothermia · Newborn · Perinatal asphyxia · Creatinine · Precision medicine · Reference values

Abstract

Introduction: There is large variability in kidney function and injury in neonates with neonatal encephalopathy (NE) treated with therapeutic hypothermia (TH). Acute kidney injury (AKI) definitions that apply categorical approaches may lose valuable information about kidney function in individual patients. Centile serum creatinine (SCr) over postnatal age

(PNA) may provide more valuable information in TH neonates. **Methods:** Data from seven TH neonates and one non-TH-treated, non-NE control cohorts were pooled in a retrospective study. SCr centiles over PNA, and AKI incidence (definition: SCr $\uparrow \geq 0.3$ mg/dL within 48 h, or $\uparrow \geq 1.5$ fold vs. the lowest prior SCr within 7 days) and mortality were calculated. Repeated measurement linear models were applied to SCr trends, modeling SCr on PNA, birth weight or gestational age (GA), using heterogeneous autoregressive residual covariance structure and maximum likelihood methods. Findings were compared to patterns in the control cohort. **Results:** Among 1,136 TH neonates, representing 4,724 SCr observations, SCr (10th–25th–50th–75th–90th–95th) PNA

centiles (day 1–10) were generated. In TH neonates, the AKI incidence was 132/1,136 (11.6%), mortality 193/1,136 (17%). AKI neonates had a higher mortality (37.2–14.3%, $p < 0.001$). Median SCr patterns over PNA were significantly higher in nonsurvivors ($p < 0.01$) or AKI neonates ($p < 0.001$). In TH-treated neonates, PNA and GA or birth weight explained SCr variability. Patterns over PNA were significantly higher in TH neonates to controls (801 neonates, 2,779 SCr). **Conclusions:** SCr patterns in TH-treated NE neonates are specific. Knowing PNA-related patterns enable clinicians to better assess kidney function and tailor pharmacotherapy, fluids, or kidney supportive therapies.

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Introduction

Perinatal asphyxia is a condition at delivery, caused by oxygen deprivation. When sufficiently long or severe, this can result in neonatal encephalopathy (NE) and subsequent cerebral palsy, neurodevelopmental impairment, or death [1]. When NE is moderate or severe, therapeutic hypothermia (TH) reduces mortality and increases the chance of intact survival at 18–24 months in (near) term neonates [1]. However, perinatal asphyxia is a multiorgan disease. As vasoreactive organs, kidneys are very sensitive to oxygen deprivation. Accordingly, acute kidney injury (AKI, different definitions) is common (up to 40%) in TH-treated NE neonates [2].

Until recently, kidney injury reports in neonates undergoing TH have mainly focused on AKI incidence or mean transient decrease (–40 to –50%) in glomerular filtration rate (GFR) [2, 3]. This is relevant, as AKI is associated with mortality or adverse neurodevelopmental outcome [2, 4]. A recent meta-analysis concluded that TH (whole-body hypothermia [WBH], 9 studies, 504 TH-treated neonates) is renoprotective (AKI incidence reduction), be it with considerable heterogeneity in the AKI definitions [5].

However, there is extensive variability in the magnitude of kidney injury in TH-treated NE neonates. Categorization (AKI, stages 1–3, vs. no AKI) as applied in the modified Kidney Disease Improving Global Outcomes (KDIGO) definition might not fully capture this variability or inpatient trends [2]. Consequently, there is value in considering centile trend patterns as an alternative to a categorical approach. This is similar to the use of growth charts to classify newborns as small, appropriate, or large for gestational age (GA), versus growth patterns based on Z scores or centiles.

We therefore initiated the CreaCool study to pool serum creatinine (SCr) datasets from cohorts of TH-treated (WBH) NE neonates to capture the variability and describe centile values over postnatal age (PNA) and to compare these trends to a dataset in controls (non-TH-treated, non-NE neonates). Our objectives were to describe SCr trends and variability (centiles) over PNA in TH-treated NE neonates and explore potential relevant covariates (AKI, survival, GA, birth weight). As there were no data on urine output, the AKI definition was hereby based on SCr trends, using the KDIGO definition ($\text{SCr}\uparrow \geq 0.3 \text{ mg/dL}$ within 48 h, or $\text{SCr}\uparrow \geq 1.5$ fold vs. the lowest prior SCr within 7 days), as previously applied [2, 4]. As an additional analysis, we also compared SCr trends over PNA in TH-treated NE neonates to non-TH-treated, non-NE controls.

Materials and Methods

Datasets in TH-Treated NE Neonates and Non-TH-Treated, Non-NE Controls

Data from 7 TH-treated NE cohorts were combined. The first 10 days of PNA were analyzed to assess recovery of kidney function over time. This time window was based on a systematic review suggesting this period sufficiently covers the TH-specific SCr pattern [6]. To facilitate pooling, the covariates collected in the datasets were restricted to birth weight, GA, survival (neonatal death, day 1–28, yes/no), and SCr values (day 1–10). Information on included cohorts of TH-treated NE neonates is provided in Table 1 [7–17].

All included TH-treated cohorts underwent WBH because of moderate-to-severe hypoxic-ischemic encephalopathy. Day 1 was hereby defined as the date of delivery (from birth, until 24 h). AKI detection was based on the KDIGO definition (any AKI): $\text{SCr}\uparrow \geq 0.3 \text{ mg/dL}$ within 48 h or $\text{SCr}\uparrow \geq 1.5$ fold versus the lowest prior SCr within 7 days, irrespective of urine output, as these data were unavailable. Data on fluid management, perinatal pharmacotherapy, comorbidity, or hypoxic-ischemic encephalopathy severity were neither available.

SCr observations in controls were extracted from already published SCr population model as time-dependent covariate in neonates [18]. This dataset has observations in 1,080 neonates admitted in the Leuven neonatal (intensive) care unit (24–42 weeks GA, 2007–2011) for a diversity of clinical indications (including suspected infections, respiratory adaptation, congenital malformations, but excluded NE cases undergoing TH) over the first 6 weeks PNA. To coalign with the cases, this dataset was further restricted to neonates with a GA ≥ 36 weeks and between PNA day 1–10 so that the final control dataset contained 801 controls and 2,779 SCr (all enzymatic) observations, and the covariates (birth weight, GA) of interest. SCr was converted to mg/dL (factor 88.42 to $\mu\text{mol/L}$).

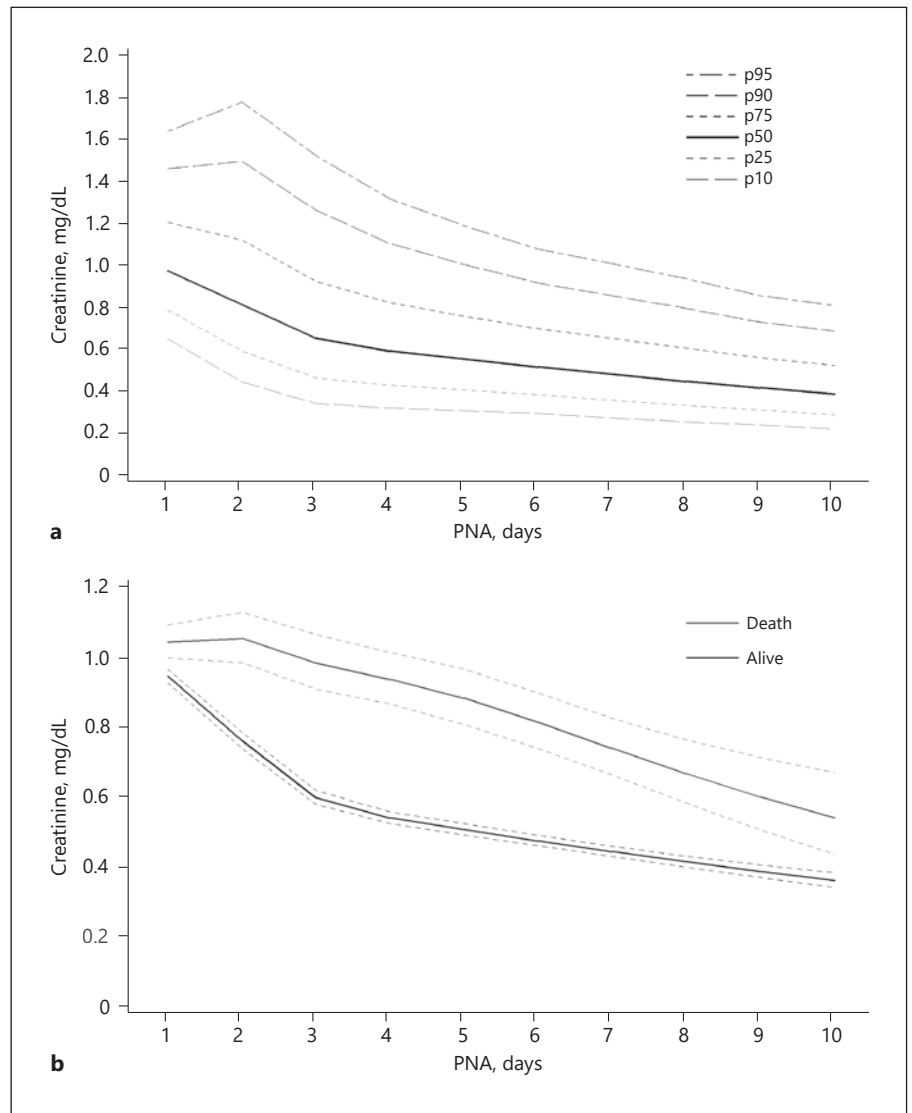
Statistics

Data were reported by median and interquartile range or frequency and percentages for continuous or categorical variables, respectively. Associations were analyzed by χ^2 test. To describe and compare trends, linear models for repeated measurement were used, modeling SCr as function of PNA, birth weight, and/or GA.

Table 1. Description of the cohorts of TH-treated NE neonates included in the pooled study, and the incidence of AKI for each cohort [7–17]

Cohort	Time interval	Characteristics	Observations	TH criteria
Leuven	2010–2020	Neonates undergoing TH in whom amikacin pharmacokinetics (Leuven, Amsterdam) were reported were included [7]. This cohort was further extended to all neonates admitted to the Leuven unit during the time interval	87 neonates 355 SCR assay; Jaffe, to enzymatic AKI: 1.4%	In the first 6 h, and (i) GA ≥ 36 weeks, (ii) at least one asphyxia condition: Apgar _{5min} ≤ 5 , need for resuscitation or respiratory support in the first 10 min, umbilical cord pH < 7.0 with a base deficit ≥ -16 mmol/L, or lactate > 10 mmol/L within the first hour, and (iii) signs of encephalopathy (Thompson ≥ 7 , or aEEG) [8, 9]
CoolCap	1999–2002	A randomized controlled trial to determine whether 72 h of selective head cooling plus mild body cooling (33–34°C) compared to conventional care improved survival without severe disability at 18 months in infants with moderate-to-severe encephalopathy [10]. Only TH-treated neonates were included	111 neonates 430 SCR assay; both, but unknown, center-specific AKI: 20%	(i) GA ≥ 36 weeks, (ii) at least one asphyxia condition: Apgar _{5min} ≤ 5 , or continued need for resuscitation or respiratory support at 10 min after birth, umbilical cord pH < 7.0 or a base deficit > -16 mmol/L, or in an arterial/venous sample within the first hour, (iii) moderate-to-severe encephalopathy consisting of altered state of consciousness (shown by lethargy, stupor, or coma) AND at least one or more of the following: hypotonia, abnormal reflexes, absent or weak suck, clinical seizures, and (iv) abnormal background aEEG (20 min) [10]
Zekai Tahir Burak	2011–2014	Prospective nested case-control study, data in TH-treated neonates provided [11]	40 neonates 80 SCR assay; Jaffe AKI: 1.5%	TH initiation was based on the TOBY criteria [11]
Ankara units	2015–2021 2013–2021	Koru Hospital Gazi University Hospital	82 neonates 483 SCR assay; Jaffe AKI: 6% 54 neonates 355 SCR assay; Jaffe AKI: 1.9%	Asphyxia was defined by (i) Apgar _{5/10min} ≤ 5 ; (ii) cord blood pH < 7.00 or BE ≥ -16 mmol/L, further confirmed by; (iii) imaging evidence of NE-compatible brain injury or multiorgan failure [15]. Neonates (GA ≥ 36 weeks) with perinatal asphyxia were eligible within 6 h if they had encephalopathy (Thompson > 5 , Sarnat stage 2 or 3, discontinuous normal voltage pattern or worse on aEEG, or convulsions). Neonates with known congenital deformities or disorders were excluded. Patients who did not meet all diagnostic criteria (neonates 34–35 weeks GA, patients, a cord blood gas pH > 7 , and a BE between -12 and -16), TH initiation was discussed with the consultant [12]
Montreal	2008–2021	SCR observations reported ($n = 202$, 2009–2015) were further extended [13]	439 neonates 1,776 SCR assay; enzymatic AKI: 10%	TH criteria were (i) GA ≥ 36 weeks and birth weight $\geq 1,800$ g; (ii) evidence of fetal distress, i.e., history of an acute perinatal event, cord pH < 7.0 , or base deficit > -16 mEq/L; (iii) evidence of neonatal distress, such as an Apgar _{10min} ≤ 5 , postnatal blood gas pH obtained within the first hour ≤ 7.0 , base deficit > -16 mEq/L, or continued need for ventilation initiated at birth and continued for at least 10 min; and (iv) evidence of moderate-to-severe NE indicated by abnormal neurological exam and/or aEEG [13]
Stanford	Various (study specific)	Pooling of 3 previously reported studies [14–16]	63 neonates 385 SCR assay; both (study specific) AKI: 1.2%	≥ 36 weeks GA diagnosed with moderate or severe NE underwent TH. TH criteria were as outlined in the National Institute of Child Health and Human Development (NICHD) TH study [17]
Utrecht	2008–2021	Data extraction from the medical files in all TH neonates	260 neonates 860 SCR assay; enzymatic AKI: 1.1%	TH inclusion criteria in the first 6 h were (i) GA ≥ 36 weeks; (ii) at least one asphyxia condition: Apgar _{5min} ≤ 5 , need for resuscitation or respiratory support in the first 10 min, cord blood pH < 7.0 with a base deficit > -16 mmol/L, or lactate > 10 mmol/L within the first hour; and (iii) clinical signs of encephalopathy (Thompson ≥ 7) or aEEG background abnormalities (discontinuous normal voltage with a baseline below 5 μ V) or seizures [9]
TOBY, Total Body Hypothermia for Perinatal Asphyxia; aEEG, amplitude-integrated electroencephalography.				

Fig. 1. a Median trend lines and centiles (10th–25th–50th–75th–90th–95th) of SCr (mg/dL) observations in TH-treated NE neonates over PNA (days). **b** Trends in median SCr values (and 95% confidence intervals) (mg/dL) in TH-treated NE neonates, survivors (alive) versus nonsurvivors (death) over PNA (days). **c** Trends in median SCr values (and 95% confidence intervals) (mg/dL) in TH-treated NE neonates, AKI cases (AKI+) cases versus non-AKI cases (AKI–) over PNA (days). **d** Trends in median SCr values (and 95% confidence intervals) (mg/dL) in TH-treated NE neonates (TH) or controls (reference) over PNA (days).



(Figure continued on next page.)

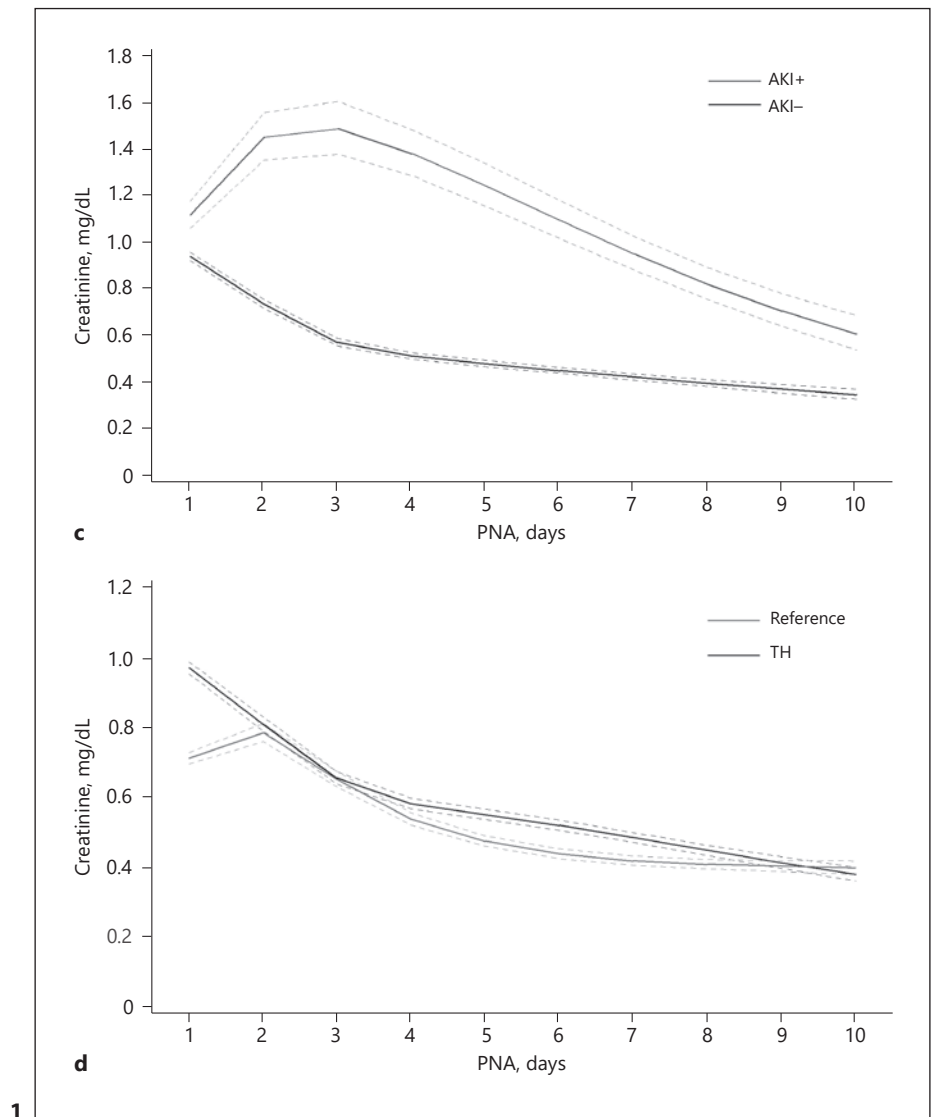
A heterogeneous autoregressive residual covariance structure was modeled to account for the repeated measures data structure. Maximum likelihood methods were used for parameter estimation. This approach can flexibly deal with drop-out, inherent to these data. Log transformation was applied to SCr (outcome variable) to account for skewness, while results are presented after back-transformation. Restricted cubic splines were used to model nonlinear trends. Analyses were performed using SAS software (Windows version 9.4).

Results

The pooled TH dataset contained 1136 TH-treated NE neonates and 4,724 SCr observations (median [interquartile range] weight 3,350 [2,930–3,740] g, GA 39 [38–40]

weeks). The median number of SCr observations per patient was 4 (range 1–10). SCr centiles (10th–25th–50th–75th–90th–95th centiles) and the number of observations over PNA is provided in Figure 1a ($p < 0.001$ for PNA trend) and Table 2.

AKI incidence was 132/1,136 (11.6%, range between the 7 cohorts 6–20%, Table 1). Mortality was 193/1,136 (17%). AKI neonates had a higher mortality (37.2 vs. 14.3%, $p < 0.001$). When focusing on SCr patterns in TH-treated NE neonates, patterns in median and 95% CI over PNA were significantly higher when comparing nonsurvivors to survivors (723 vs. 4,001 SCr in nonsurvivors and survivors) (Fig. 1b) ($p < 0.01$) and AKI to non-AKI neonates (Fig. 1c) ($p < 0.001$). The number of SCr observa-



tions over PNA decreased, with a proportional increase of observations in survivors (Table 2).

Furthermore, a slightly higher median SCr over PNA range was observed with increasing birth weight (50th centile for a birth weight of 2, 3, and 4 kg, SCr were 0.92, 0.95, and 0.99 mg/dL, respectively, on PNA day 1) (online suppl. Fig. 1, $p < 0.01$; for all online suppl. material, see www.karger.com/doi/10.1159/000525574). A similar pattern was observed for GA (50th centile for a GA of 36, 38, and 40 weeks, SCr were 0.89, 0.94, and 0.99 mg/dL, respectively, on day 1) (online suppl. Fig. 2, $p < 0.001$). Models were constructed with PNA, birth weight, and GA as explanatory covariates. Birth weight subsequently became insignificant in the presence of GA (online suppl.

Table 1). Online supplementary Figure 3 and online supplementary Table 2 provide the same information on SCr centiles in controls, while Figure 1d plots the estimated SCr (+95% confidence interval) trends for both cohorts (TH-treated NE neonates and controls) ($p < 0.001$).

Discussion

Based on the largest pooled dataset on 4,724 SCr observations in 1,136 TH-treated (WBH) NE neonates, we described postnatal SCr trends and variability by centile values. When comparing patterns to controls, higher SCr values were observed beyond the first 3 days of PNA in

Table 2. Estimated centiles (10–95th) of SCr (mg/dL) observations over PNA in 1,136 neonates who underwent TH, based on 4,724 observations

Centile	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
p10	0.64	0.44	0.33	0.31	0.30	0.28	0.26	0.25	0.23	0.21
p25	0.78	0.58	0.45	0.42	0.40	0.37	0.35	0.32	0.30	0.28
p50	0.96	0.80	0.64	0.58	0.55	0.51	0.47	0.44	0.41	0.38
p75	1.20	1.11	0.91	0.81	0.75	0.69	0.64	0.60	0.55	0.51
p90	1.45	1.49	1.25	1.09	0.99	0.91	0.85	0.79	0.72	0.68
p95	1.63	1.77	1.51	1.31	1.18	1.07	1.00	0.93	0.85	0.80
SCr (number)	1,066	921	801	668	385	270	231	180	106	96
SCr, survivors/nonsurvivors	825/241	519/173	692/109	583/85	349/36	244/26	208/23	164/16	100/6	88/8

TH-treated NE neonates, reflecting prolonged kidney injury. Besides PNA, the SCr values further depended on GA.

When focusing on the 75th or 90th centiles, these trend lines were significantly higher in TH-treated NE neonates (Fig. 1; online suppl. Fig. 3). These 75th and 90th centiles remained higher even after the first 3 days of PNA (so during normothermia), likely reflecting a TH-treated NE subpopulation with more pronounced and prolonged kidney injury. In TH neonates with any AKI, there was a delayed SCr peak (day 3), with subsequent blunted decrease with PNA compared to non-AKI cases (Fig. 1c). AKI was also associated with a higher mortality risk, confirming previous reports [4, 19–21]. Finally, PNA and GA were explanatory maturational covariates for SCr. These findings warrant that PNA and GA should also be carefully considered with interpreting SCr values in TH-treated NE neonates.

First, and despite the common claim that SCr values at birth merely reflect maternal SCr values, SCr values in TH-treated NE neonates were already elevated on day 1 when compared to SCr values in controls (Fig. 1d). This is consistent with a recent meta-analysis and has more recently also been reported by Robertsson Grossmann et al. [3, 5]. This matters as the KDIGO AKI criteria are based on an absolute (≥ 0.3 mg/dL) or proportional (>1.5 -fold) SCr increase. Consequently, in newborns who already start with an elevated SCr, the criteria to qualify for AKI will be more difficult to attain. In these neonates, SCr centiles might be more useful to assess AKI severity and inpatient trends.

In addition to the absence of data on urine output, the elevated SCr values on day 1 may in part also explain the low AKI incidence (11.6%, between cohort range 6–20%) in the pooled dataset compared to literature (up to 40% in TH-treated NE neonates) but closer to a single center

report [2, 3, 20]. The between cohort variability hereby confirms the AWAKEN findings on extensive AKI incidence variability [4].

The AKI incidence in a given cohort or case may in part be determined by the availability of SCr observations in the first hours after birth. At least, this suggests that SCr at day 1 already (partially) reflects neonatal GFR and is not only determined by maternal SCr. Mechanistically, this further extends the imbalance on prenatal placental-fetal to maternal SCr elimination to this specific TH subpopulation [22]. The findings on the impact of GA or weight on SCr observations in TH-treated NE neonates confirm previous observations, as SCr at delivery correlated with GA in different cohorts (24–42 weeks GA, highest values in term neonates), despite stable or even slightly decreasing maternal SCr values from 28 weeks GA onwards [22–24]. Moreover, these findings were reassuring for the validity of the centiles approach, as the maturational variables are similar to observations in other cohorts [22, 23].

Second, the disappearance of median SCr value differences between TH-treated NE neonates and controls does not fully reflect the interindividual variability (75th or 90th centiles), either during or shortly after TH ($>$ day 3). Individual SCr trends converted to centiles may therefore be a more consistent approach to enable integration of precision medicine approaches. In particular, these data may inform us on pharmacotherapy, fluid administration, or may potentially be useful in combination with other factors in determining outcome in TH-treated NE neonates [8, 13, 20, 25].

Obviously, there are study limitations related to the pragmatic retrospective approach. Data on asphyxia severity (sentinel event, elevated erythroblasts, or moderate vs. severe based on clinical assessment) or urine output were not collected, while the source data were generated

between 1999 and 2021. SCr sampling is likely also driven by clinical indication, so more likely to occur in cases with a previously raised Scr, while nonsurvival obviously also terminates sampling (Table 2). Clinical management was neither standardized, potentially resulting in diversity in actual clinical practices or shifts in practices.

Among others, this includes pharmacotherapy (like nephrotoxic drugs or methylxanthines), fluid management, pragmatism on TH inclusion, or SCr assay variability. The diversity in management may affect SCr values, as La Haye-Caty et al. [13] documented that a more restricted fluid management was associated with higher SCr in TH-treated NE neonates. Along the same line, there is an increased tendency to start TH in mild NE neonates [26]. Future changes in the case-mix will likely affect the median SCr values and AKI incidence. However, using centiles, the severity of kidney injury over time can still be assessed, plotted, and compared. Finally, the SCr assay remains an issue in neonates (enzymatic vs. colorimetric, Jaffe) as the magnitude of between-assay differences in SCr measurements was significantly reduced – but not been fully eliminated – following introduction of isotope dilution mass spectrometry (IDMS) traceability in laboratory medicine to calibrate any assay to IDMS reference measurement [27, 28]. At present, IDMS traceability is implemented in all units who contributed to the pooling initiative, except for the units that contributed to the CoolCAP trial (unknown) [10]. Because of the diversity in time intervals and units included in the pooling, we were not able to retrieve the date of introduction of IDMS (Table 1) [7–17]. Furthermore, IDMS traceability does not eliminate assay interaction related to drugs (like dopamine for the enzymatic, or cephalosporins for the Jaffe assay) [27, 28].

Taking these limitations into account, we are confident that an SCr centile approach holds the promise to better capture individual patterns. These descriptive data should be further validated and should be considered for future improvement in neonatal AKI definition. A centile-based approach could provide guidance on management (i.e., pharmacotherapy, fluid management, kidney supportive therapies). This matters, since the Baby NINJA study recently illustrated that medication-associated AKI risk can be mitigated or negated using systematic surveillance [29]. A centile approach hereby holds the potential of secondary or personalized prevention.

Furthermore, we anticipate that this approach holds the potential to select a subgroup in need of secondary preventive renal follow-up because of increased risk to develop subnormal GFR during childhood. This matters as a relevant portion (21%) of former TH-treated NE ne-

onates has subnormal GFR (estimated GFR <90 mL/min/1.73 m² at 10–12 years) [3]. Unfortunately, subnormal GFR during follow-up was not predicted by neonatal AKI presence [3]. This suggests that neonatal SCr trends should be part of a broader panel of covariates to explore links between perinatal events and long-term outcome in former TH-treated NE neonates.

Conclusions

SCr patterns and centiles in TH-treated NE neonates were highly variable and different compared to controls. SCr values in TH-treated NE neonates were correlated with PNA, and GA or birth weight. Knowledge of these trends and their variability should enable clinicians to better assess SCr trends in individual TH-treated NE cases and to facilitate the integration of precision medicine for pharmacotherapy, fluid management, or kidney supportive therapies.

Acknowledgment

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of UZ Leuven (S-63365). Informed written consent was hereby not required (waived).

Conflict of Interest Statement

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

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Author Contributions

Elif Keles, Anne Smits, Pieter Annaert, and Karel Allegaert conceptualized and designed the study. Karel Allegaert was responsible for data pooling. Elif Keles, Pia Wintermark, Floris Groenendaal, Noor Borloo, Anne Smits, Suzan Sahin, Mehmet Yekta Oncel, Valerie Y. Chock, Didem Armangil, Esin Koc, Malcolm R. Battin, and Adam Frymoyer provided data on the different cohorts and provided input on the final version of the study design. Karel Allegaert conducted the initial analysis, supported by Annouschka Laenen for the statistical analysis. Elif Keles and Karel Allegaert drafted the initial manuscript. All authors contributed to the interpretations

of the data and analyses, 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 remain the property of the individual groups, so that public sharing is impossible. Researchers interested in using the data can contact the corresponding author (karel.allegaert@uzleuven.be).

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