

Article

Creatinine trends and patterns in neonates undergoing whole body hypothermia: a systematic review

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Abstract: Many neonates undergoing whole body hypothermia (WBH) following moderate to severe perinatal asphyxia suffer from renal impairment. While recent data suggest a WBH-related reno-protection, the differences in serum creatinine (Scr) patterns to reference patterns were not yet reported. We therefore aimed to document Scr trends and patterns in asphyxiated neonates undergoing WBH, and compared these to centiles reference Scr dataset of non-asphyxia neonates. Using a systematic review strategy, reports on Scr trends (mean \pm SD, or median and range) were collected (day 1-7) in WBH cohorts, and compared to centiles of an earlier reported reference cohort of non-asphyxia cases. Based on 13 papers on asphyxia+WBH cases, a pattern on postnatal Scr trends in asphyxia+WBH cases was constructed. Compared to the reference cohort, mean or median Scr values at birth (>90th centile) and the first two days of WBH (>75th centile) remained clinical relevantly higher in asphyxia+WBH cases, with a subsequent decline to reach at best high or high normal creatinine values (all >50th centile, but mainly >75th centile) from day 4 onwards. Such patterns are valuable to anticipate average changes in renal clearance capacity relevant for pharmacotherapy, but do not yet cover the relevant inter-patient variability observed in WBH cases.

Keywords: creatinine; cystatin C; asphyxia; whole body hypothermia; acute kidney injury; renal clearance; kidney function.

1. Introduction: perinatal asphyxia, whole body hypothermia and renal impairment

Perinatal asphyxia is a condition at delivery, driven by deprivation of oxygen sufficiently long enough to potentially result in several sequelae like hypoxic-ischemic encephalopathy (HIE) and cerebral palsy [1,2]. Perinatal asphyxia can result from variable events, like placental blood flow disruption, prolonged labour, or compression of the umbilical cord, all resulting in reduced circulating blood oxygen, while it is the most common cause of encephalopathy in neonates. HIE is hereby characterized by clinical and biomarker-based (laboratory, electro-encephalography (EEG)) evidence of acute or subacute brain injury (encephalopathy) due to intrapartum or late antepartum brain hypoxia and ischemia [2,3]. It still accounts for a relevant proportion of neonatal deaths,

especially when we focus on mortality in (near)term neonates [4]. Whole body hypothermia (WBH) is an effective intervention to reduce this mortality, even more pronounced in low-income countries [5,6]. About 0.5 % of live born neonates are affected with perinatal asphyxia, while 0.18 % are diagnosed with hypoxic-ischemic encephalopathy (HIE), either mild, moderate or severe [2,7]. Both the hypoxic-ischemic phase as well as the reoxygenation-reperfusion event of perinatal asphyxia contribute to the presence and extent of brain injury [8,9]. The inflammatory response is another relevant contributor to neurodevelopmental outcome in newborns following WBH [10].

Asphyxia is a multi-organ disease, so that asphyxia also affects multiple other organs besides the brain. This is because the initial cardiovascular response to oxygen depletion is organ-specific vasoconstriction. This results in redistribution of oxygen from non-vital organs to the heart and brain, while other organs like the intestines, liver or kidneys are underperfused [11-13]. As vasoreactive organs, the kidneys are very sensitive for oxygen deprivation and this commonly (39-42 %) results in oliguric or non-oliguric acute kidney injury (AKI) in this setting [14].

AKI was observed in about 1.5 % of admissions in a single neonatal intensive care unit. When the authors focussed on the subgroup of term neonates, perinatal asphyxia was the most common cause (72 % of 72 term cases) of AKI, followed by congenital kidney and urinary tract malformations (CAKUT, 8.3 %), congenital heart disease (6.9 %) or sepsis (2.8 %) [15]. This confirms to a large extent the patterns on incidence and risk factors of early onset neonatal AKI as described in the AWAKEN (Assessment of Worldwide Acute Kidney Epidemiology in Neonates) study [14,16]. To further illustrate the interrelatedness of this multi-organ disease, Cavallin et al recently reported on the prognostic role of AKI on long-term outcome in HIE infants. The presence of AKI has hereby been suggested to be a reliable indicator of death or long-term disability in HIE neonates undergoing WBH, while its absence was not a guarantee for a favorable long-term outcome [17]. Along the same concept, a higher positive fluid balance (oliguria, as another indicator of AKI, (besides serum creatinine (Scr) and Scr trends) was associated with death or moderate-to-severe brain injury in cases following WBH because of HIE [18].

WBH became the standard neuroprotective treatment for moderate to severe perinatal asphyxia since 2010, driven by meta-analytical evidence that WBH significantly reduces both mortality and morbidity (relative risk (RR) reduction of 25 % for survival with normal neurocognitive outcome, equal to a number needed to treat (NNT) for an additional beneficial outcome of 7) in moderate to severe HIE cases [19,20]. Interestingly and besides improved neurodevelopmental outcome following WBH, there is very recent meta-analytical evidence that WBH also reduces the incidence of AKI ((RR) 0.81, 95 % Confidence Interval (CI) 0.67-0.98, NNT = 7). Consequently, besides improving mortality and neurocognitive outcome, WBH turns out to be also a reno-protective intervention, at least if we focus on the short term outcome (i.e. AKI), while data on long term renal outcome are not yet available [21]. Consequently, there is clinical relevance to describe the overall Scr trends as reported in cohorts undergoing WBH to better understand the postnatal Scr trends and to compare these patterns with the centiles of a reference dataset in non-asphyxiatic (near)term neonates, as this reflects renal (drug) clearance capacity.

This should also enable clinicians to plot or compare observations in individual patients to the average trends.

Different studies have quantified the impact of asphyxia and WBH on the elimination of drugs who are dependent on glomerular filtration rate (GFR). Renal elimination is reduced (-25 % up to -40 %), as reflected by a reduction in gentamicin clearance by 25 to 35.3 %, with a progressive trend to normalisation after termination of WBH (>72 hours after initiation of WBH). As similar pattern of decreased clearance (-40 %) has been described for amikacin during WBH, or even up to -60 % when estimated based on mannitol clearance estimates [22-26].

Although there are different and perhaps more performant biomarkers to quantify renal function like cystatin C, Scr is still the most frequently used and accessible biomarker to evaluate renal (dys)function or GFR, including in the neonatal intensive care setting [27-30]. Assuming stable creatinine synthesis (reflecting muscular mass), an increase in Scr reflects poorer GFR. Despite its common use, this biomarker has some disadvantages. At birth, creatinine still somewhat reflects maternal Scr levels. Furthermore, there is no active renal tubular secretion in neonates yet, but rather passive renal tubular back leak, so that creatinine clearance does not yet entirely reflect GFR. This is in contrast to older children or adults, where active tubular creatinine secretion results in a minor overestimation of the 'true' GFR, when based on creatinine clearance [27-30]. Another specific issue are the variability in Scr assays, as the Jaffé - and to a certain extent - the enzymatic assays can be affected by the plasma matrix in neonates, with a lower albumin concentration, and a commonly higher bilirubin in this specific population [27-30].

Despite these limitations, Scr values to estimate GFR are at present worldwide routinely used in neonatal clinical care, so that we decided to focus in our systematic review on the Scr trends in WBH cohorts, but also searched for Cystatin C values. As recent data suggest a WBH-related reno-protective effect, we aimed to document Scr trends in asphyxiated neonates undergoing WBH based on a systematic search strategy on published cohorts, and compare these values to the centiles of a reference Scr dataset restricted to (near)term neonates (≥ 36 weeks gestational age) of a similar gestational age [21,27].

2. Materials and Methods

This systematic review has been performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [31]. The literature search was performed on the first of May 2020 using Embase, Pubmed, Cochrane Libraries and Web of Science as information sources. The search was limited to the English language and papers had to report on values or trends in Scr or Cystatin C in human newborns with asphyxia and undergoing WBH. An overview of the manual performed search strategies is provided in Figure 1. When the full text was not found, we tried to contact the corresponding author to request a full text version.

Pubmed	<ul style="list-style-type: none">• ("Infant, Newborn"[Mesh] OR "Asphyxia Neonatorum"[Mesh] OR "newborn hypoxia"[tiab] OR "perinatal asphyxia"[tiab]) AND ("Hypothermia, Induced"[Mesh] OR "cooling"[tiab] OR "whole body hypothermia"[tiab] OR "therapeutic cooling"[tiab] OR "selective head hypothermia" OR "hypothermia"[tiab]) AND ("Cystatin C"[Mesh] OR "Creatinine"[Mesh] OR "Glomerular Filtration Rate"[Mesh] OR "kidney function"[tiab] OR "renal outcome"[tiab] OR "renal biomarkers"[tiab] OR "kidney function tests"[Mesh] OR "Acute Kidney Injury"[Mesh])
Embase	<ul style="list-style-type: none">• Newborn OR 'newborn hypoxia' OR infant OR 'perinatal asphyxia' OR 'newborn disease') AND ('induced hypothermia' OR cooling OR 'whole body hypothermia' OR 'selective head cooling') AND (creatinine OR 'cystatin c' OR 'glomerulus filtration rate' OR 'kidney failure' OR 'kidney function' OR 'kidney function test' OR 'acute kidney injury'
Cochrane library	<ul style="list-style-type: none">• "Newborn" OR "Asphyxia" OR "Asphyxia neonatorum" OR "newborn hypoxia" OR "perinatal asphyxia") AND ("Hypothermia" OR "Induced hypothermia" OR "cooling" OR "therapeutic cooling" OR "whole body hypothermia" OR "therapeutic hypothermia" OR "selective head hypothermia") AND ("Cystatin C" OR "Creatinine" OR "Glomerular Filtration Rate" OR "kidney function" OR "renal outcome" OR "renal biomarkers" OR "kidney function tests" OR "acute kidney injury" OR "acute kidney failure"
Web of Science	<ul style="list-style-type: none">• "Newborn" OR "Asphyxia" OR "Asphyxia neonatorum" OR "newborn hypoxia" OR "perinatal asphyxia") AND ("Hypothermia" OR "Induced hypothermia" OR "cooling" OR "therapeutic cooling" OR "whole body hypothermia" OR "therapeutic hypothermia" OR "selective head hypothermia") AND ("Cystatin C" OR "Creatinine" OR "Glomerular Filtration Rate" OR "kidney function" OR "renal outcome" OR "renal biomarkers" OR "kidney function tests"

Figure 1. Search strategy as conducted on PubMed, Embase, Cochrane library and Web of Science respectively.

Screening, eligibility and inclusion assessment were performed independent by two reviewers (NB, KA), with subsequent discussion in the event of disagreement until consensus was reached. Inclusion was based on the PICO criteria. (1) **Population:** asphyxiated newborns; (2) **Intervention:** therapeutic hypothermia; (3) **Control:** normothermia; (4) **Outcome:** Scr or Cystatin C values reported. Only articles, written in English and with access to the full text were included. Postmortem and animal studies, congress abstracts without full-text availability and neonates with a history of cardiac problems or surgery were not included, in line with the other reported risk groups for AKI in (near)term neonates [15,16].

Data items extracted were journal, type of study (observational, interventional), year of publication, duration of hypothermia, population (demographic data, number), intervention (hypothermia, either WBH or selective head cooling (SHC)), control and outcome (Scr, Cystatin C), equipment used to induce hypothermia or for the Scr or Cystatin C measurements (assays involved). Demographic data extracted were gestational age, birth weight, male or female, APGAR score at 5 and 10 minutes of age. The individual papers were also screened for data on the Thompson score and lactate measurements.

The aim was to extract Scr data as reported, per individual day in either mean ± SD, or median and range in the first week of postnatal life (day 1-7) in asphyxia + WBH cases. When data were not reported in the source paper, corresponding authors were contacted and asked if they were willing to provide the needed information. In the absence

of a reply by the corresponding author, we used WebPlotDigitizer (by Ankit Rohatgi), to extract data from the charts as provided [32]. Alternatively, when the population of interest (asphyxia + WBH) was reported in subgroups with number of cases, and mean or median (like AKI versus non-AKI cases), we calculated a proportional mean/median and standard deviation for the full population of interest based on the observations reported in the subgroups. Scr values per day are reported uniformly in mg/dL, following conversion from $\mu\text{mol/L}$, by dividing by 88.4, when appropriate. Furthermore, we used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist to assess the quality of the included studies [33].

We subsequently compared our obtained results with the centiles and Scr trends from an earlier reported dataset [27]. To ensure similarity in clinical characteristics besides the asphyxia + WBH, we hereby have restricted this dataset to 1 456 Scr observations in a reference cohort of (near)term neonates (≥ 36 weeks gestational age) without asphyxia (UZ Leuven) in the first week of postnatal life [27].

Table 1. Centile serum creatinine values (Scr, mg/dL, 90th, 75th, 50th, 25th and 10th) at birth, and during the consecutive days in early neonatal life (until day 7), based on 1 456 Scr observations in 495 (near)term cases (gestational age ≥ 36 weeks), extracted from a previously reported dataset of neonates [27].

	< 6 h	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
P90	0.86	1.01	0.95	0.82	0.66	0.58	0.62	0.61
P75	0.76	0.86	0.73	0.6	0.53	0.5	0.51	0.48
P50	0.65	0.72	0.63	0.5	0.46	0.41	0.41	0,4
P25	0.58	0.65	0.53	0.43	0.37	0.34	0.33	0.33
P10	0.51	0.57	0.47	0.39	0.31	0.29	0.29	0.29
<i>Number</i>	293	239	215	213	160	129	106	101

3. Results

Our search strategy identified 213 articles: 41 articles with the Pubmed search, 126 hits as result of the Embase search, 9 reviews and 18 trials by the Cochrane search and 18 results via Web of Science. Among these, 35 articles were duplicates. After application of inclusion and exclusion criteria 43 articles were eligible by title and abstract, of which we subsequently included 13 articles after screening the full text version, based on the approach ealier described. The search strategy and its outcome in the consecutive steps of the process are provided in Figure 2, as PRISMA flow diagram.

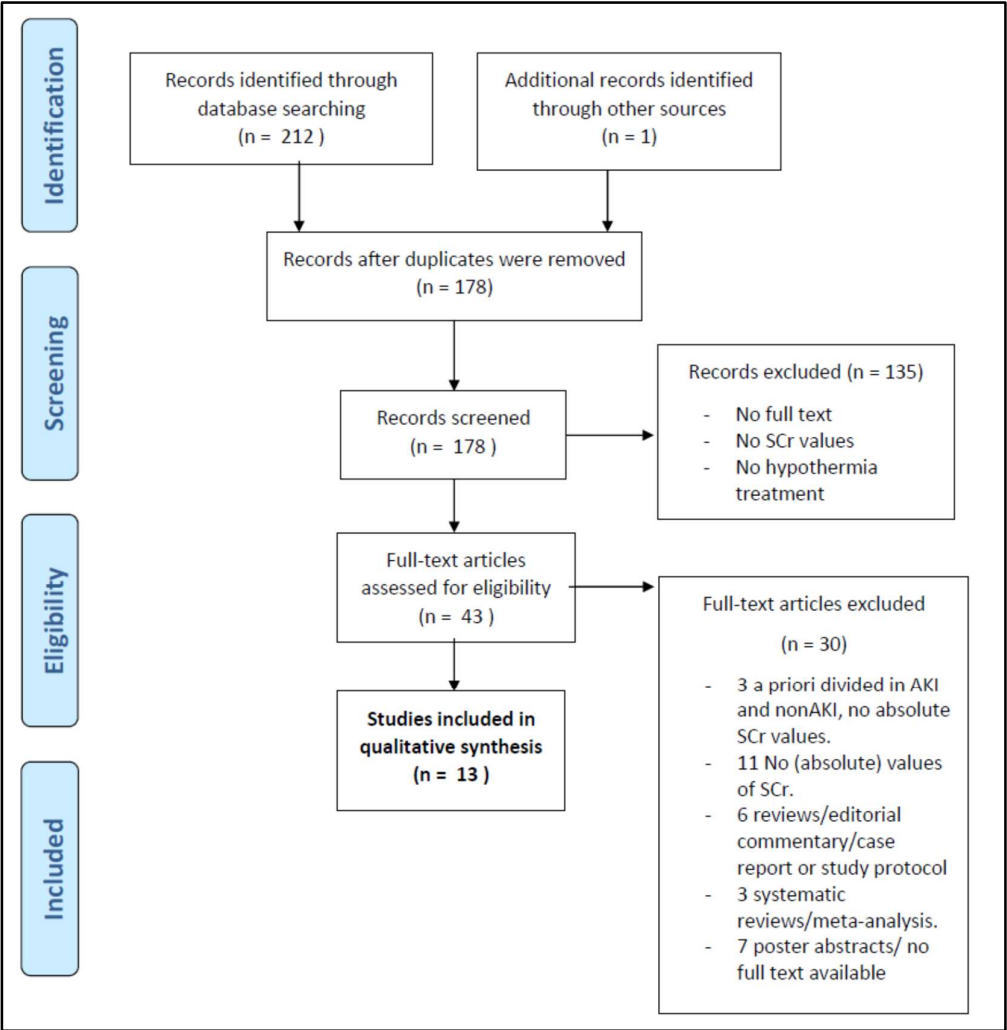


Figure 2. PRISMA flow diagram of the systematic search strategy.

We hereby included one paper that was not part of the results of the initial search strategy, but has been suggested by one of the corresponding authors of the eligible studies, when we contacted her for a full text version (*Dr. P. S. Wintermark*) of her paper.

Characteristics of all included articles are listed in Table 2 [34-46]. These articles included data of WBH neonates diagnosed with HIE, admitted to the neonatal intensive care unit within 6 hours after birth. WBH for 72 hours was used in almost all studies but one, where selective head cooling was applied, in addition to mild systemic hypothermia [46]. Patient inclusion criteria for all studies were infants of ≥ 36 weeks of gestation (except for Gupta et al. > 35 weeks + birth weight ≥ 1800 g) [40], with diagnosis of significant (moderate to severe) perinatal asphyxia within 6 hours after birth. HIE diagnostic criteria are also listed per study in Table 2, they combine both clinical and EEG criteria.

Table 2. Study characteristics of the 13 studies retained in the systematic review [HIE: hypoxic ischemic event; WBH: whole body hypothermia; Scr: serum creatinine; NICHD: National Institute of Child Health and Human Development; SHC: selective head cooling; TOBY: Total Body Hypothermia trial]. The group of interest in the apshyxia + hypothermia group, when based on WBH [34-46].

<i>Author</i>	<i>n</i>	<i>Study design</i>	<i>HIE diagnosis</i>	<i>Hypothermia</i>	<i>Control</i>	<i>Time of SCr sampling</i>	<i>Additional information</i>
Lee et al. 2017 [34]	72	Observational, prospective study	(1) blood gas pH <7.15 or base deficit >10 mmol/L + Moderate-to-severe encephalopathy OR (2) acute perinatal event, and 10 min APGAR <5, OR assisted ventilation for 10 min after birth, and Moderate-to-severe encephalopathy	WBH for 72h (NICHD)	/	Max creatinine measurement between 24h and 96h of age	Scr assay: not mentioned Cooling blanket (Mul-T Blanket)
Sarkar et al. 2009 [35]	28	Observational study	Cool Cap trial	WBH for 72h (NICHD) (n=28)	SHC for 72h (Cool Cap) (n=31)	24h, 48h, 72h	Scr assay: not mentioned
Sarkar et al. 2014 [36]	88	Retrospective, observational review	Cool Cap and NICHD protocol	WBH for 72h (NICHD)	/	Baseline, 24h, 48h, 72h, d 5/7	Scr assay: not mentioned
Róka, et al. 2007 [37]	12	Randomized controlled trial	TOBY study	WBH for 72h (n=12)	Normothermia (n=9)	6h, 24h, 48h, 72h	Scr assay: not mentioned Cooling mattress – Core temp 33-34°C.
Chalak et al. 2014 [38]	20	Prospective cohort pilot study	(1) pH 7.00 or base deficit 16 mEq/L in umbilical arterial cord plasma OR (2) history of an acute perinatal event and either no blood gs available or a	WBH for 72h (NICHD)	/	Within the first 24h	Scr assay: not mentioned cooling blanket (Blanketrol II)

			pH from cord arterial serum ranging from 7.01 to 7.15 or a base deficit from 10 to 15.9 mEq/L; AND (3) 10 min Apgar score < 5 OR assisted ventilation at birth, AND moderate or severe encephalopathy				
<i>La Haye-Caty et al.</i> 2020 [39]	202	Retrospective review	(1) History of an acute perinatal event, cord pH ≤ 7.0 or base deficit ≤ -16 mEq/L; OR (2) evidence of neonatal distress, such as an Apgar score ≤ 5 at 10 min, postnatal blood gas pH obtained within the first hour of life ≤ 7.0 or base deficit ≤ -16 mEq/L; OR (3) a continued need for ventilation initiated at birth and for at least 10 min; AND (4) moderate to severe neonatal encephalopathy	WBH for 72h (NICHD)	/	Scr on admission; Highest Scr during hospitalization; difference between both	Scr assay: not mentioned

<i>Gupta et al. 2016</i> [40]	106	Retrospective review	(1) Metabolic acidosis; OR (2) Need for prolonged resuscitation, AND moderate to severe encephalopathy	WBH for 72h (NICHD)	/		Scr assay: Jaffe, Siemens Dimension RXL Chemistry Analyzer
<i>Tanigasalam et al. 2016</i> [41]	60	Randomized controlled trial	(1) pH ≤ 7 or base deficit ≥ 12 mEq in cord blood (2) AND 2 of the following: Apgar 10 min ≤ 5 ; fetal distress; assisted ventilation for at least 10 min after birth; evidence of any organ dysfunction AND encephalopathy.	WBH for 72h (n=60)	Standard treatment (n=60)	6h, 36h, 72h	Scr assay: not mentioned. Pre-cooled gel packs (± 4) to keep core temperature between 33-34°C (chest, abdomen, back, head, axilla). Continuous rectal and skin temperature monitoring. Every 15 min for the first four h, every 2 h for the next 68 h. After cooling, gel packs were removed and radiant warmer was set at 0.5°C/h to reach the target temperature of 36.5°C in the next 6 hours.
<i>Selewski et al. 2013</i> [42]	53	Retrospective review	Cool Cap trial	WBH (n=53) (NICHD)	SHC (n=43)	6h, 24h, 48h, 72h, d5, d7, d10 (as clinically indicated)	Scr assay: not mentioned
<i>Frymoyer et al. 2013</i> [43]	61	Retrospective chart review	One or more of the following: APGAR score < 5 (at 10 min of life); history of prolonged resuscitation at birth; presence of severe acidosis defined as a cord pH or	WBH for 72h with gentamicin at Q36 (n=27) OR WBH for 72h with gentamicin at Q24 (n=34)	/	d2	Scr assay: not mentioned. Blanket cooling device (Cincinnati Subzero Blanketrol III). Rectal monitoring keeping core temperature at 33.5°C.

			any arterial or venous pH of <7 within 60 min of birth, or a base deficit of >-12 from cord blood or any arterial blood gas within 60min of life, AND moderate-severe encephalopathy.				
<i>Chock et al.</i> 2018 [44]	38	Retrospective review	NICHD criteria	WBH for 72h (NICHD)	/	d1, d2, d3, d4	Scr assay: enzymatic (isotope dilution mass spectrometry traceable) Cincinnati Sub-Zero Hyper- Hypothermia Blanketrol system (Cincinnati Sub-Zero, Cincinnati, Ohio).
<i>Oncel et al.</i> 2016 [45]	41	Prospective nested case-control study	TOBY study criteria AND Sarnat stage II or III	WBH (n=41)	Healthy controls (n=20)	24h, 48 h, 72h results: d1, d4	Scr assay: not mentioned Cooling at rectal temperature of 33–34°C with Tecotherm TS med 200 N (Inspiration Healthcare Ltd, Leicester, UK). After cooling, rewarming with 0.5°C, reaching normal body temperature within 8 hours.
<i>Battin et al.</i> 2003 [46]	13	Randomized controlled trial	(1) Gestational age >37w; OR (2) 5 min APGAR <6 OR cord/first pH <7.1 AND (3) Encephalopathy consisting of lethargy/stupor, hypotonia and	SHC (rectal T 34,5°- 35°C) (n=13)	SHC + Normothermic (n=13)		Scr assay: not mentioned Cooling cap: Silclear tubing (Degania Silicone Ltd, Degania Bet, Israel) and a commercially made device (Olympic Medical, Seattle, WA). Initial water temperature: 10°C.

			abnormal reflexes, including an absent or weak suck.				Continuous monitoring of rectal, fontanelle and nasopharyngeal temperature and keeping rectal temperature at 34,5°C±0.5°C – 35°C ±0.5°C or normothermic. After cooling, rewarming at 0.5°C/ hour until temperature reached the normal range.
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Patient characteristics per study are listed in Table 3. Thompson score and lactate measurements reflecting disease severity were not available, so were not retained in the reporting. Two out of 13 included studies [37,45] used the HIE inclusion criteria from the Total Body Hypothermia (TOBY) trial and 3 out of 13 studies [35,36,42] used the inclusion criteria of the Cool Cap trial [47-49]. The clinical inclusion criteria of the Cool Cap protocol were similar to the TOBY protocol, be it with minor differences for the EEG inclusion criteria. The TOBY trial included neonates with signs of at least 30 minutes of amplitude integrated EEG recording that shows abnormal background (amplitudo) aEEG activity or seizures, while the Cool Cap trial included neonates with signs of at least 20 minutes duration of amplitude integrated EEG with cerebral function monitoring (aEEG/CFM) recording that shows abnormal background aEEG/CFM activity or seizures [47-49].

Twelve out of the 13 included studies used WBH as cooling strategy, while the other paper related to the Cool Cap trial. WBH was initiated within 6 hours after birth and core temperature was kept at 33-34°C for 72 hours in all studies. After cooling, rewarming was set at 0.5°C per hour to reach normal body temperature within 6-8 hours. Seven articles followed the National Institute of Child Health and Human Development (NICHD) criteria for WBH [39]. The other 5 studies followed a similar protocol (Table 2 provides additional details for these studies) [34-46]. Battin et al. used selective head cooling as cooling mechanism, combined with mild systemic hypothermia [46]. This was reached by using different cooling caps, precooled to 10°C. Rectal, fontanelle and nasopharyngeal temperatures were continuously monitored, keeping rectal temperatures for 72 hours at 34,5°C to 35,5°C or normothermia, dependent of the study group allocation. Like in the NICHD protocol, rewarming was performed with 0.5°C per hour, eventually reaching normal body temperature.

Finally, related to the STROBE quality assessment, all included studies performed well on this checklist. Potential bias was mentioned in two cohorts [34,38]. Limitations were explicitly discussed in 10 out of the 13 studies.

Table 3. Patient characteristics (gestational age, birth weight, Apgar score at 5 and 10 minutes, % female) as reported in the retained studies of this meta-analysis [IQR: interquartile range][34-46].

	<i>Lee et al.</i> [34]	<i>Sarkar. et al</i> 2009 [35]	<i>Sarkar el al.</i> 2014 [36]	<i>Roka et al.</i> [37]	<i>Chalak et al.</i> [38]	<i>La Haye-Cathy et al.</i> [39]	<i>Gupta et al.</i> [40]	<i>Tangi-salam et al.</i> [41]	<i>Selewski et al.</i> [42]	<i>Frymoyer et al.</i> [43]	<i>Chock et al.</i> [44]	<i>Oncel et al.</i> [45]	<i>Battin et al.</i> [46]
<i>mean gestational age (wk)</i>	38 6/7 ± 1 5/7	38.5 ± 1.7	/	/	39±2	39.15 ±1.6	38.7	39.5 ±1.3	39 ± 1.6	39.7 ± 1.6	38.6 ±2	38.7 ±1.6	40.1 ±1.6
<i>mean birth weight (g)</i>	3161 ± 869	3112 ± 755	/	/	3156 ±624	3375 ±626	3305	2690 ±340	3313 ±618	3340 ±600	3258 ±653	3264 ±509	3634 ±598
<i>median Apgar 5 min (IQR)</i>	4 (2-5)	68 %: 0-3, 20 %: 4-5, 12 %: ≥ 6	/	/	6(5-7)	/	/	/	(Median, SD) 3 ±2	3.4 ±2	4(0-9)	30 % <5	4.5 (0-7)
<i>median Apgar 10 min (IQR)</i>	5 (3-7)	33 %: 0-3, 45 %: 4-5, 22 %: ≥ 6	/	/	/	/	/	5 (3-6)	/	5±2	/	/	/
<i>female (%)</i>	41 %	36 %	/	/	30 %	44 %	41 %	/	43 %	/	44 %	77 %	/

We listed the available Scr data per day (Table 4, data listed in mean ± SD or median + interquartile, or range). We hereby also would like to mention that data on cystatin C values or trends in perinatal asphyxia + WBH were not retrieved in this meta-analysis, so cannot be provided.

Table 4: serum creatinine (Scr) values as reported in the retained studies of this meta-analysis [HT: hypothermia; RW: rewarming; NT: normothermia; SD= standard deviation, IQR= interquartile range] [34-46].

Study	outcome measure	Median Scr (range) 0-72h	Maximal Scr	Scr, 6h	Scr, 24h	Scr, 36h	Scr, 48h	Scr, 72h	Scr, 96h	Scr, 5d	Scr, 7d
Lee et al. 2017 [34]	Scr during HT-NT-RW, (mean, SD)		0.9 (0.6)								
Sarkar et al. 2009 [35]	Scr, during HT (median, IQR)		1 (0.8, 1.4)	1 (0.8, 1.3)							
Sarkar et al. 2014 [36]	Scr, during HT+RW (mean, SEM)			0.9 ± 0.1	0.9 ± 0.2		0.9 ± 0.3	0.8 ± 0.4		0.8 ± 0.4	
Róka et al. 2007 [37]	Scr during HT (median, IQR)			1.04 (0.87-1.15)	0.8 (0.73-0.99)		0.65 (0.5-0.74)	0.57 (0.47-0.69)			
Chalak et al. 2014 [38]	Scr (median, IQR)				1 (0.8 – 1.5)						
La Haye-Caty, et al. 2019 [39]	Scr (mean, SD, or median, IQR)		1.02±0.3	0.95 ± 0.29	highest 0.95 (0.79-1.13)		highest 0.66 (0.5-0.92)	highest 0.48 (0.35-0.66)	highest 0.45 (0.36-0.66)		
Gupta et al. 2016 [40]	Scr (median)				1.09			0.66		0.65	0.51
Tanigasalam et al. 2016 [41]	Scr (mean, SD)			1.15 ± 0.31		1.13 ± 0.33		1.195 ± 0.55			
Selewski et al. 2013 [42]	Scr (mean, SD)			0.97 ± 0.26	1 ± 0.42		0.91 ± 0.57	0.85 ± 0.65		0.79 ± 0.75	0.74 ± 0.88 discharge: 0.49 ± 0.49

<i>Frymoyer et al.</i> 2013 [43]	Scr, range or mean, SD	range (d2): 0.5-1.5					1 ± 0.2				
<i>Chock et al.</i> 2018 [44]	Scr (mean, SD)				1.2 (0.23)		0.9 (0.34)	0.7 (0.37)	0.6 (0.40)		
<i>Oncel et al.</i> 2016 [45]	Scr (mean, SD)				1.02 ± 0.37			0.83 ± 0.5			
<i>Battin et al.</i> 2003 [46]	Scr (mean, SD)	1.6 ± 0.76									

In both datasets, we noticed a similar pattern with an initial increase from birth onwards over the first day of postnatal life, and a subsequent decline after the first day of postnatal life, confirming the patterns earlier described in other cohorts of (near)term neonates [50-52].

When comparing both datasets by visual inspection, we noticed that the Scr values at birth and the first two days during WBH, were clinically relevant higher in the asphyxia + WBH cases than in non-asphyxia cases. Already before initiation of WBH, the Scr values were significantly higher (between 0.8 and 1.2 mg/dL), with a further rising trend to the first day of postnatal life, with Scr values equivalent to the 90th centile and beyond, when compared to the reference dataset (Figure 3, Table 4).

We subsequently notice a decline in both datasets, be it with a different slope in the decline (more blunted in the asphyxia + WBH cases), to eventually reach high normal (50th-90th) creatinine values in WBH cases when compared to the reference centiles of the dataset (Figure 3). However, in some WBH cohorts, the mean or median values remain above the 90th centile in the second part of the first week of postnatal life, so extended beyond WBH finalisation, with Scr values between 0.4 and 0.8 mg/dL (for some cohorts, crossing the centiles to the 50th-90th centile range).

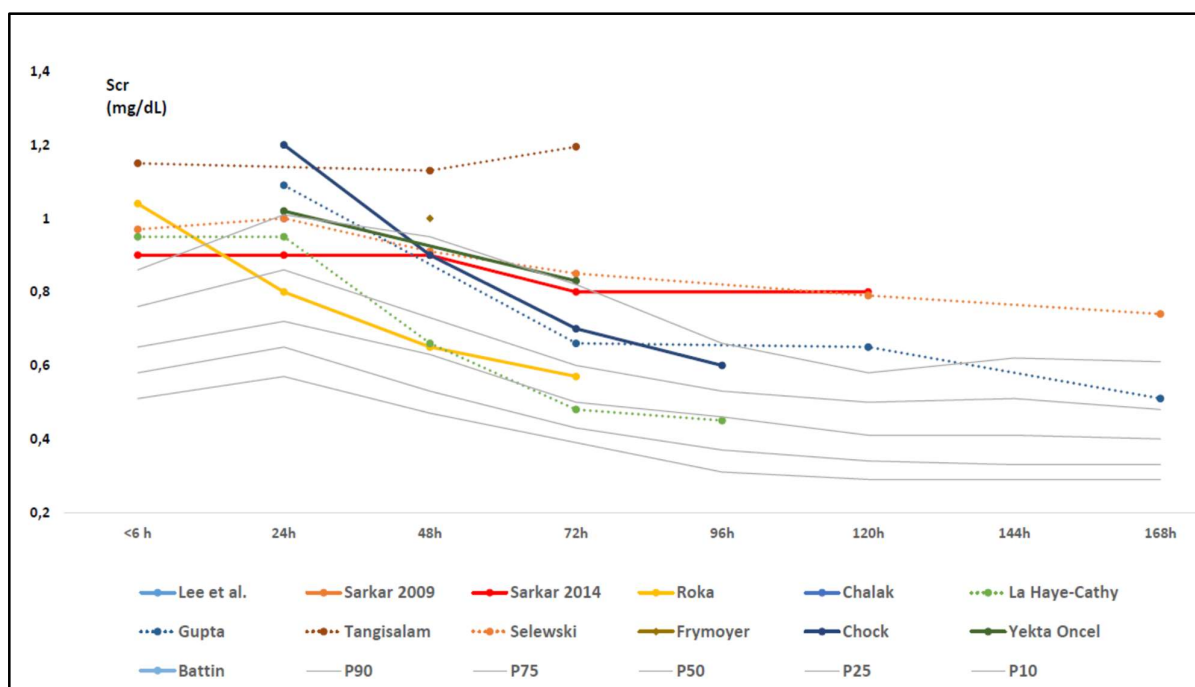


Figure 3. Serum creatinine (Scr) data as reported in the individual retained studies (colored trends) compared to centile (10th, 25th, 50th, 75th, 90th centiles) trend values in the reference cohort (Table 1, grey trends) in the first week of postnatal life [27,34-46].

4. Discussion

Besides the fact that kidney function is a prognostic factor for the general and neurocognitive outcome in neonates born with asphyxia, Scr trends are also relevant to adjust pharmacotherapy and fluid management to the individual neonatal kidney function [17,18]. So far, there was no information on the Scr trends for neonates with perinatal asphyxia + WBH, while a recent meta-analysis provided evidence for a specific reno-protective effect of WBH (NNT 7 to prevent AKI in this specific setting) [21].

The current systematic review intended to provide a comprehensive overview of the dynamic Scr trends for (near)term neonates born with asphyxia, treated with WBH within the first 6 hours after birth. We hereby focused on the Scr results documented from birth (so before initiation of WBH) until day 7 after birth. This time interval is generally classified as 'early neonatal life', and covers both the full duration of WBH (72 hours), followed by rewarming to reach normothermia. We subsequently compared these results in WBH cases to the daily creatinine values and patterns from non-asphyxia cases, obtained from an earlier published dataset [42].

Based on this approach, we noticed that the initial Scr values are already increased before WBH. This is relevant, as the most currently used definitions for AKI and their staging in neonates - like the Kidney Disease Improving Global Outcome (KDIGO) definition - are also based on proportional Scr increase (stage 1: + 0.3 mg/dL, or 1.5 to 1.9-fold increase in Scr; stage 2: 2 to 2.9-fold increase in Scr) from a baseline observation [53]. Based on the current analysis, the first Scr (<6 h, reflecting the baseline value) is already significantly higher when compared to the reference centiles (Table 1). This implies that

technically, a proportional increase needs a higher absolute increase in Scr value in this population to classify for stage 1 or stage 2 AKI [53]. This reflects somewhat a limitation of the AKI definition, and perhaps the development of centile values for Scr should be further considered to better capture the maturational versus non-maturational trends in Scr in neonates [52].

Biomarkers like cystatin C are perceived to be better markers of kidney damage, but these are not yet commonly implemented in this specific clinical neonatal setting [27,52,54]. This results in the absence of papers in this systematic review reporting on cystatin C trends in asphyxia + WBH cases, so we only could include studies that reported on Scr values and trends during, and in the days following WBH. This is another take home message of this analysis, and a call to clinical researchers to assess the potential add on value of cystatin C to Scr in this population. However, Cystatin C also comes with some analytical limitations in neonates [55,56].

Our approach and analysis obviously has its limitations, as well as some strengths. Based on the current systematic search strategy, 13 papers met our inclusion criteria and were retained to extract longitudinal mean or median Scr values. Unfortunately, we were not able to further explore Scr variability within and between these cohorts, as this necessitates access to individual data, similar to meta-analysis of individual patient data to facilitate data aggregation or explore trends, as recently illustrated by Hage et al to study the shifts in clinical characteristics of HIE cases in England, Wales and Scotland [57].

In general, the pattern of postnatal Scr trends with an initial increase up to 24 h, and a subsequent decrease over the first week of postnatal life is similar in asphyxia + WBH cases when compared to (near)term non-apshyxia cases. However, the Scr values in asphyxia cases before cooling are already clinical relevantly higher than those of the reference cohort, with a higher Scr peak on day 1 and a subsequent blunted decrease (Figure 3). Based on the available data, it's difficult to draw conclusions on the variability, because of limitations in our analysis.

First, the pattern can differ because of methodological limitations or variability related to the meta-analysis. Individual Scr values were never available, while assays for obtaining those data were not always reported (Table 4). For pragmatic reasons, the extracted data were based on median or mean values as reported in the individual cohorts. As described in the methods, if these data were not reported in the individual paper, we contacted the corresponding author (only one author replied and provided this information). Alternatively, the data were extracted from the plots or recalculated, if data were only reported in different subgroups of asphyxia + WBH cases. Consequently, the data obtained in the asphyxia + WBH cohorts were limited to mean or median Scr observations for consecutive days, in contrast to the centile Scr data reference cohort, as we were unable to calculate centiles in the asphyxia + WBH cohorts. Along the same line, we neither were able to explore potential covariates of further raised Scr, like covariates of disease-severity (like lactate or Thompson score), as such data could neither be retrieved. Furthermore, 8 out of the 13 included papers were observational studies. Although this potentially enhances the risk of selection bias, asphyxia + WBH is a very operational and rather reliable inclusion criterium. Besides these limitations, there are also some strengths in this analysis.

A strength of this literature review is the extensive search conducted in four databases, using hand-search to include a maximum number of relevant results, and the independent analysis by two authors. As an additional support for the pattern as described, we noticed that after our search strategy was conducted, Mok et al. (2020) published another retrospective observational cohort and - being it post hoc - also meeting all inclusion criteria of our literature review [58]. As an ‘external validation’, we plotted these Scr observations (day 1-7) in Figure 4 on top of the data initially summarized in Figure 3. This more recently published dataset to a large extent confirms the pattern described, including the blunted decrease of Scr in the second part of the first week of postnatal life. Finally, this paper further supports other recent efforts to also assess non-neurodevelopmental aspects of the outcome (renal, cardiac) in asphyxia + WBH cases, and as well suggests to incorporate these aspects in the ongoing efforts to develop a core outcome set specific on neonatal encephalopathy trials [21,59].

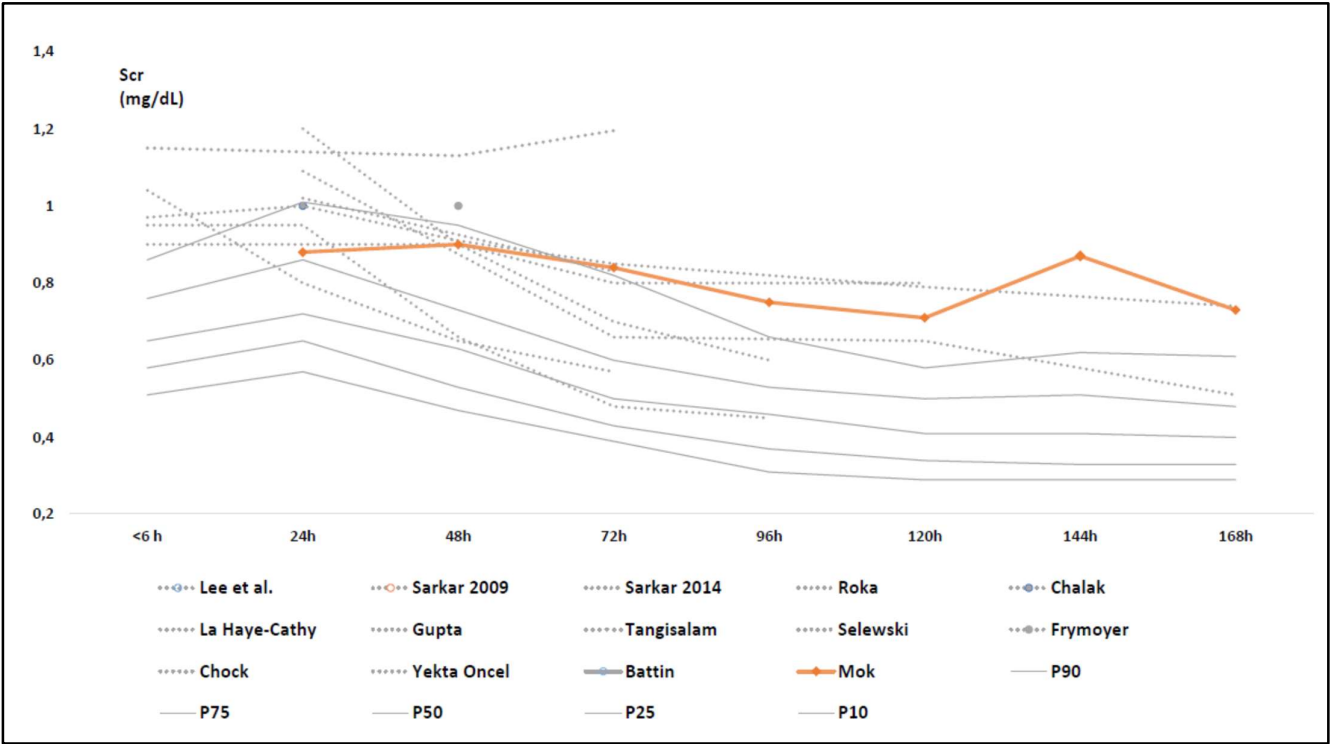


Figure 4. Serum creatinine (Scr) data as reported in the individual retained studies (dashed grey trends) compared to centile (10th, 25th, 50th, 75th, 90th centiles) trend values (full grey) in the reference cohort (Table 1) in the first week of postnatal life, with the trends in Scr median values as reported in the Mok cohort (orange) [27,34-46,58].

5. Conclusions

Based on a systematic search strategy, 13 papers reporting data on neonates with asphyxia + WBH were retained to construct a pattern on postnatal Scr trends in asphyxia + WBH cases. Compared to a reference cohort of (near) term non-asphyxia cases, mean or median Scr values at birth (>90th centile) and the first two days during WBH (>75th centile) remained significantly higher in asphyxia + WBH cases, with a subsequent decline to reach at best high or high normal creatinine values (all >50th centile, but mainly >75th centile) from

day 4 onwards. Such patterns are valuable to anticipate average changes in renal clearance capacity relevant for pharmacotherapy, but do not yet cover the relevant inter-patient variability observed in WBH cases. Finally, it also illustrates the limitations of the Scr thresholds used in the even most recently developed AKI stage definition.

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