Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Creatinine filtration kinetics in critically Ill neonates

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BACKGROUND: Creatinine values are unreliable within the first weeks of life; however, creatinine is used most commonly to assess kidney function. Controversy remains surrounding the time required for neonates to clear maternal creatinine.
METHODS: Eligible infants had multiple creatinine lab values and were admitted to the neonatal intensive care unit (NICU). A mathematical model was fit to the lab data to estimate the filtration onset delay, creatinine filtration half-life, and steady-state creatinine concentration for each subject. Infants were grouped by gestational age (GA) [(1) 22–27, (2) >27–32, (3) >32–37, and (4) >37–42 weeks].
RESULTS: A total of 4808 neonates with a mean GA of 34.4 ± 5 weeks and birth weight of 2.34 ± 1.1 kg were enrolled. Median (95% confidence interval) filtration onset delay for Group 1 was 4.3 (3.71, 4.89) days and was significantly different than all other groups ($p < 0.001$). Creatinine filtration half-life of Groups 1, 2, and 3 were significantly different from each other ($p < 0.001$). There was no difference in steady-state creatinine concentration among the groups.
CONCLUSIONS: We quantified the observed kidney behavior in a large NICU population as a function of day of life and GA using creatinine lab results. These results can be used to interpret individual creatinine labs for infants to detect those most at risk for acute kidney injury.

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IMPACT:

- One of the largest cohorts of premature infants to describe the evolution of kidney development and function over their entire hospitalization.
- New concept introduced of the kidney filtration onset delay, the time needed for the kidney to begin clearance of creatinine, and that it can be used as an early indicator of kidney function.
- The smallest premature infants from 22 to 27 weeks gestation took the longest time to begin and complete maternal creatinine clearance.
- Clinicians can easily compare the creatinine level of their patient to the normative curves to improve understanding of kidney function at the bedside

INTRODUCTION

Creatinine is a waste product formed as the body supplies muscles with energy and is eventually cleared by the kidneys. In adults, creatinine clearance is used to approximate the glomerular filtration rate (GFR) to assess kidney function. It is defined as the volume of blood that is cleared of creatinine per unit time. Accurate measurements of creatinine clearance require stable creatinine levels and timed urine and serum sample collections. This process proves difficult in the neonatal intensive care unit (NICU) where it is widely accepted that neonates do not have stable creatinine levels. Additionally, term, developmentally appropriate neonates lack bowel and bladder function, which contributes to difficulties with timed sample collections. In preterm infants, it is further complicated by incomplete nephrogenesis[1] and abnormal glomeruli.[2]

Neonates are born with a relatively high creatinine level for body mass, in part, due to creatinine equilibration in utero. Some studies have shown initial creatinine levels to be equal to or higher than maternal creatinine levels without definitive correlation between the two values.[3–6] Multiple studies have shown increased initial creatinine lab values and variable ranges in the first days to weeks of life.[7–12] Studies have also demonstrated a critical value for creatinine from 1.0 to 1.6 mg/dl depending on gestational age (GA), above which patients have a higher risk for mortality and neurodevelopmental delay.[13] On the other hand, Miall et al.[14] concluded that two- to three-fold increases in creatinine level within the first 48 h of life in premature infants up to 35 weeks gestation can be expected and should not be used to diagnose renal failure. This leaves a critical gap in our assessment of optimal renal function and GFR in the neonatal population.

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During the neonatal period, the inability to monitor creatinine clearance as a surrogate for GFR contributes to a lack of a consensus for the definition of acute kidney injury (AKI).[15] This can be concerning for infants who may experience AKI in that time period, but go undiagnosed.[16] Weintraub et al.[17] showed a 30% incidence of AKI in the NICU population with a median age at onset of 3 days. Kandasamy et al.[18] showed a significant correlation between weight and serum creatinine-based GFR measurement potentially delaying diagnosis of AKI in smaller infants. In another study, Harer et al.[19] found evidence of renal dysfunction in former very low birth weight infants, some of whom had never been diagnosed with AKI. This evidence further supports the theory that renal function in the NICU population warrants closer examination. At this time, in the early clinical course of neonates, we may be missing and not identifying AKI due to a lack of a consistent and easily accessible measurement of GFR. Some have suggested that the use of cystatin C may be superior to creatinine in estimating GFR in neonates;[18,20] however, it is not as readily available and the testing is more expensive than for creatinine. In addition, cystatin C may not be as accurate in the most premature infants.[21]

The objective of this study was to quantify the behavior of kidney function in a large NICU population using readily available creatinine measurements over the length of the hospitalization. The interpretation of the absolute value of the creatinine level of a neonate in early life is confounded due to the presence of maternal creatinine. While the maternal creatinine is removed over time by the kidney, the rate at which this happens can be different for each patient depending on GA as well as day of life. Our study sought to quantify this trend and apply a mathematical model to describe the observed behavior in order to better understand how far from average a given creatinine value is based on day of life and GA at birth.

METHODS

We performed a retrospective cohort study to delineate renal dynamics using serum creatinine measurements in patients admitted to the NICU at Texas Children's Hospital. The study was approved by the Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals. A waiver of consent was obtained. Patient demographics, medication use, and lab values were extracted from the electronic medical records (EPIC, Hyperspace EPIC 2014, Madison, WI). Infants were initially included if they had at least one serum creatinine measurement obtained between 1 January 2013 and 31 December 2018. Creatinine measurements were obtained via enzymatic spectrophotometry. Patients were separated into four groups for statistical analysis based on GA at birth in weeks [Group 1 ($22 < GA \le 27$), Group 2 ($27 < GA \le 32$), Group 3 ($32 < GA \le 37$), Group 4 ($37 < GA \le 42$)].

Exclusion criteria for advanced analysis

In order to characterize and quantify the creatinine trend and kidney function after birth, additional exclusion criteria were needed for advanced time-dynamics analysis. Patients were excluded if they had <5 available creatinine labs in the first year of life or did not have a lab within the first 3 days or after 10 days of life. These criteria ensured that a creatinine trend over time could be robustly quantified. With the criteria, the cohort reduced to 1782 patients (37.1% of original cohort) with a total of 55,193 available labs (70.2% of the original set).

Evaluation for selection bias

The possible bias introduced by requiring additional criteria for the advanced analysis is tested by comparing the corresponding moving-in-time distributions of creatinine lab values. For all time, from day 1 to day 200, the Kolmogorov–Smirnov metric is consistently below 0.04. Hence, the error in estimating the percentile ranks from the entire cohort, when using the reduced cohort, is below 4%. In all of our results, each Xth percentile curve should be understood as having a margin of error in its rank and appropriately interpreted as the $(X \pm 4)$th percentile curve. We conclude that the subset of labs chosen for the advanced analysis has a moving distribution that does not differ substantially from the entire set.

Filtration dynamics of creatinine

A mathematical model was derived from basic filtration kinetics to describe the expected time course of creatinine filtration in NICU patients. The concentration of creatinine in the blood stream is governed by the law of conservation of mass. This law allows us to describe the change in concentration of creatinine at any time as the difference between the amount of creatinine added to the blood stream (i.e., creatinine that is generated by the body) and the amount of creatinine removed from the blood stream (i.e., creatinine that is filtered out by the kidney). This can be written as a simple differential equation of the form:

$$\frac{\mathrm{dC(t)}}{\mathrm{dt}} = G(t) - F(t),$$

where $C(t)$ is the concentration of creatinine over time, $G(t)$ is the generation rate of creatinine, and $F(t)$ is the filtration rate of creatinine. Since there is expected to be only a small amount (if any) of creatinine generated by a neonate, and that this small generation rate will likely be constant in time, we assume that the creatinine generation rate is a constant, but unknown parameter with small magnitude:

$$G(t) = G_0.$$

We also assume that creatinine filtration from the kidney follows first-order filtration kinetics once the kidneys are fully functioning. This is a reasonable starting assumption given that it is the simplest type of kinetic model that accurately describes filtration. This can be mathematically expressed as:

$$F(t) = K(t) \times C,$$

where $K(t)$ is the first-order filtration coefficient of creatinine. From clinical experience, we know that the filtration rate is not constant, but can change over time in early life.

To model the inability of the kidneys to fully function during the first few days after birth, we assume the form of $K(t)$ to be a step function of the form:

$$K(t) = \begin{cases} 0, 0 < t < T_\mathrm{d}, \\ k, T_\mathrm{d} < t < \infty. \end{cases}$$

This definition means that the kidneys do not provide any filtration of creatinine until the time T_d is reached, after which time the kidneys achieve a constant filtration rate quantified by the constant $k > 0$. The advantage of this definition is that it allows the model to be generalized, describing both the creatinine profiles of patients with kidneys that are always filtering from birth (i.e., $T_\mathrm{d} = 0$) as well as creatinine profiles of patients whose kidneys have delayed onset of filtering (i.e., $T_\mathrm{d} > 0$).

Combining these governing equations and integrating over time (assuming an initial concentration of creatinine to be C_0) leads to a solution given by:

$$C(t) = \begin{cases} C_0 + Gt, 0 < t < T_\mathrm{d}, \\ G/k + e^{-k(t-T_\mathrm{d})}(C_0 + GT_\mathrm{d} - G/k), T_\mathrm{d} < t < \infty. \end{cases}$$

Overall, this model allows a creatinine concentration profile to be described with only three parameters: the kidney filtration

onset delay (T_d), the creatinine half-life (ln(2)/k), and the steady-state creatinine concentration (G/k).

This mathematical model can be fit to the measured values of creatinine on a patient-by-patient basis using simplex optimization (Matlab, Mathworks Inc., Natick, MA), resulting in an estimate of the three model parameters for each patient in the data set. An R^2 value was calculated to measure goodness of fit between the model fit and the measured values of creatinine. In addition, subjects were excluded if model fit was $R^2 < 0.5$ (10% loss).

RESULTS

A total of 4808 patients (55.7% male) met the inclusion criteria providing 78,634 creatinine measurements for this study. Patient demographics are listed in Table 1. Using all the available labs, percentile curves as functions of age were developed for each of the GA groups as shown in Fig. 1. The curves represent the moving 10th percentiles from 10 to 90. The 10th (blue line), 50th (black dashed line), and 90th (red line) percentiles are highlighted for easier reference. The 95% confidence region for the moving medians of the GA groups is displayed in Fig. 2. These values are computed as functions of age in order to visualize the difference between these four GA groups in creatinine trend after birth.

Results from advanced analysis

Quality of model fit. After implementing exclusion criteria, a total of 1782 patients (57.2% male) were included in the advanced analysis. An example of the fitting result of the mathematical model is shown in Fig. 3. The differential equation model fit the creatinine concentration data extremely well. The R^2 value for goodness of fit was found to be >0.80 for more than 80% of the creatinine concentration profiles measured on study subjects. This indicates that 80% of the observed changes in creatinine in neonates in their early life can be explained by our model for over 80% of study subjects.

Analysis of variance. After the mathematical model was fit to the creatinine measurements, analysis of variance (ANOVA) was performed to test the effect of GA group, 5-min APGAR score, receipt of antenatal steroids, and gentamicin or indomethacin administration on the filtration onset delay, filtration half-life, and

Table 1. Patient Characteristics.

Characteristic	Entire cohort ($N = 4808$)	Reduced cohort ($N = 1782$)
Birth weight (g), mean ± SD	2340 ± 1070	2180 ± 1150
Gestational age (weeks), mean ± SD	34.41 ± 5	33.54 ± 5.7
Male sex, *n* (%)	2678 (55.7)	1020 (57.2)
Race, *n* (%)		
White	3391 (70.5)	1274 (71.5)
Black	1019 (21.2)	377 (21.2)
Other	398 (8.3)	131 (7.3)
Hispanic, *n* (%)	1610 (33.5)	599 (33.6)
Antenatal steroids, *n* (%)	1915 (39.8)	776 (43.6)
5-min APGAR, median [IQR]	8 [7, 9]	8 [7, 9]
Indomethacin, *n* (%)	327 (6.8)	252 (14.1)
Gentamicin, *n* (%)	2219 (46.2)	1094 (61.4)
Length of hospital stay (days), median [IQR]	32 [12, 67]	60 [28, 113]

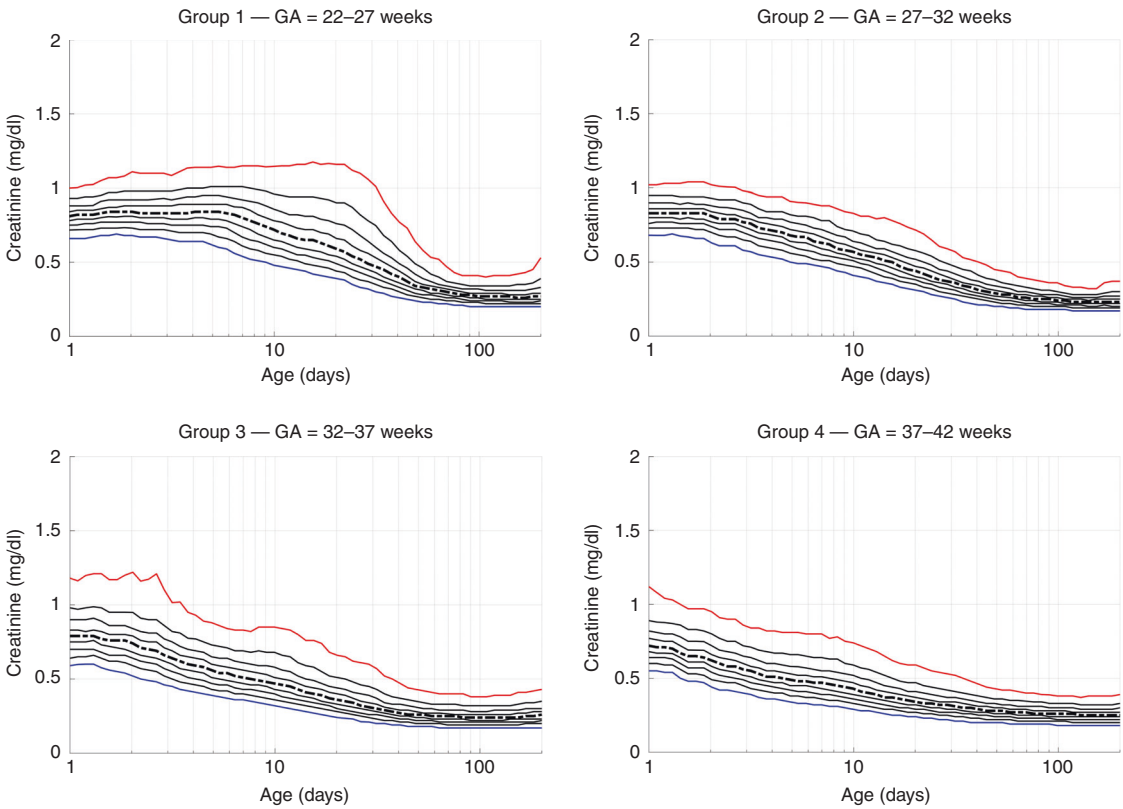

Fig. 1 Nomograms for Creatinine Filtration Kinetics by GA. 10th to 90th Percentile curves by group number with highlighted 10th percentile (blue), 50th percentile (dashed black line), and 90th percentile (red line).

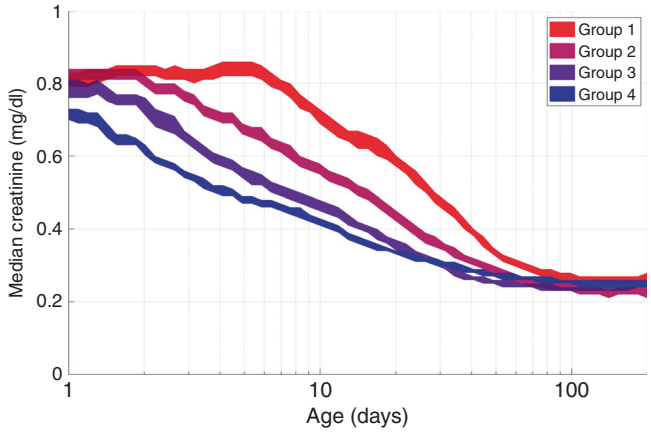

Fig. 2 Median Creatinine levels by Group number. 95% Confidence region for moving median for each group.

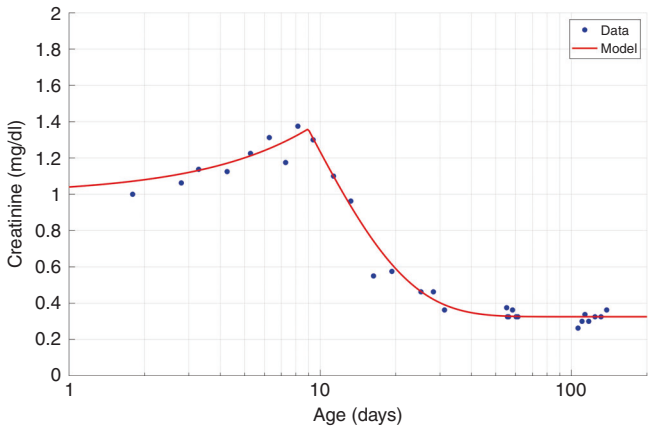

Fig. 3 Depiction of Model Fitting Result for One Patient. Mathematical model fit to creatinine lab for one patient from Group 1.

steady-state creatinine concentration. Each of the parameters were log transformed for this analysis.

Kidney filtration onset delay. Figure 4 displays the filtration onset delay versus GA, and the boxplots (median, 25th, and 75th percentiles, and robust extrema) for the kidney filtration onset delay from each of the four GA groups. Table 2 displays the median filtration onset delay and 95% confidence intervals. The median filtration onset delay for Group 1 is statistically greater than the medians for Groups 2, 3, and 4 ($p < 0.001$). There is an overall decreasing trend in filtration onset delay with increasing GA (Kruskal–Wallis Test, $p < 0.001$). The ANOVA result for the filtration onset delay is shown in Table 3. The most significant factor is GA ($p < 0.0001$); however, indomethacin administration also showed a significant effect ($p < 0.01$).

Filtration half-life. Figure 5 displays the half-life for creatinine filtration versus GA superimposed with the boxplots as previously described for each of the four GA groups. Table 2 displays the median filtration half-life and its 95% confidence interval for each group. The median creatinine clearance half-life for Groups 1, 2, and 3 are statistically different from each other ($p < 0.001$), while there is no difference between Groups 3 and 4 ($p = 0.17$). There is an overall decreasing trend in filtration half-life with increasing GA (Kruskal–Wallis Test, $p < 0.001$). The ANOVA result for the filtration half-life is shown in Table 3. It shows that the only significant factor is GA.

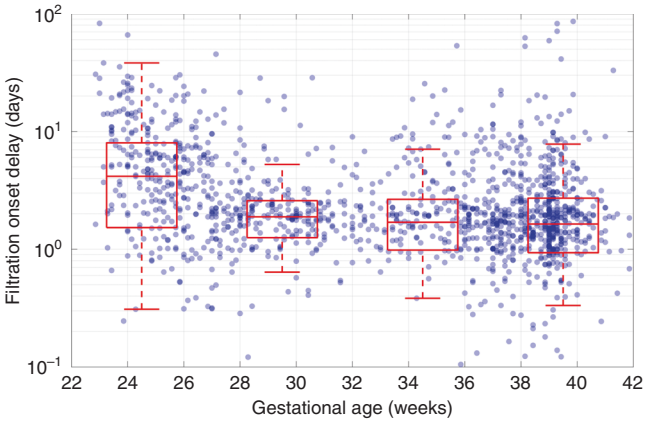

Fig. 4 Kidney Filtration Onset Delay. Filtration onset delay in days versus gestational age in weeks by group.

Steady-state creatinine concentration. Figure 6 displays the steady-state creatinine concentration versus GA superimposed with the boxplots as previously described for each of the four GA groups. Table 2 displays the median steady-state creatinine concentration and its 95% confidence interval for each group. The median steady-state creatinine for the four GA groups are not statistically different from each other. The ANOVA result for the steady-state creatinine concentration is shown in Table 3. It shows that only GA has a statistically significant effect on the steady-state creatinine concentration.

DISCUSSION

Historically, the evaluation of GFR and creatinine clearance in neonates has been difficult. Assessments of kidney function in the neonatal population have been inconsistent or difficult to apply clinically at the bedside. Few studies include patients at the lower limits of viability and those who do are limited by low numbers of subjects. The current study examines kidney function in a novel way by using multiple creatinine measurements and mathematical modeling in neonates from 22 to 42 weeks gestation to describe the natural course of kidney function postnatally. We used the data to construct percentile curves based on GA that are representative of the expected renal function in neonates. Then, we examined three key aspects of kidney function in this analysis: the filtration onset delay, the creatinine filtration rate, and the steady-state creatinine concentration.

To our knowledge, this is the largest cohort of neonates studied to evaluate creatinine clearance across advancing GA that provides new perspective on the evolution of postnatal kidney development. In addition, by using multiple measurements of creatinine across the entire hospitalization for each subject, we could investigate the time it took for the kidney to begin clearance of creatinine, or the filtration onset delay. We then determined the creatinine filtration rate to evaluate the time it took for the subjects to reach steady-state creatinine concentration. Using all these metrics combined, it was possible to get a more holistic understanding of the natural course of kidney development across the whole cohort.

Bateman et al.[7] describes a phenomenon of serum creatinine going through phases in 218 appropriate for GA very low birth weight infants born between 25 and 33 weeks gestation with no history of congenital malformations or diagnosis of AKI. They showed that creatinine will initially rise for 3–4 days, peak, and then decline over 7 weeks. Although informative, this study included a small number of subjects, followed for only 60 days with none at the lower limit of viability (<25 weeks). They reported the mean and 95th percentile for the three GA groups evaluated.

Table 2. Median kidney filtration onset delay, filtration half-life, and steady-state creatinine level with CI by gestational age group.

GA groups in weeks	Median (95% CI) filtration onset delay in days	Median (95% CI) filtration half-life in days	Median (95% CI) steady-state creatinine in mg/dl
1 (22 < GA ≤ 27)	4.26 (3.71, 4.89)*	8.69 (7.99, 9.46)**	0.28 (0.27, 0.29)
2 (27 < GA ≤ 32)	1.89 (1.76, 2.02)	6.26 (5.69, 6.89)**	0.29 (0.27, 0.31)
3 (32 < GA ≤ 37)	1.71 (1.57, 1.86)	4.38 (3.91, 4.91)**	0.26 (0.25, 0.27)
4 (37 < GA ≤ 42)	1.64 (1.53, 1.75)	4.05 (3.74, 4.40)†	0.27 (0.26, 0.28)

*Group 1 statistically different than Groups 2, 3, and 4 ($p < 0.001$).
**Groups 1, 2, and 3 are significantly different from each other ($p < 0.001$).
†Group 4 is not significantly different from Group 3, but is from Groups 1 and 2 ($p < 0.001$).

Table 3. Analysis of variance.

Source	*F*	Prob > *F*
Filtration onset delay		
Indomethacin	4.7221	**0.0091**
Antenatal steroid	2.1813	0.1399
APGAR 5 min	0.3627	0.5471
Gentamicin	0.0302	0.8620
Gestational age	15.1544	**<0.0001**
Filtration half-life		
Indomethacin	1.7518	0.1642
Antenatal steroid	2.0016	0.1144
APGAR 5 min	0.2412	0.7446
Gentamicin	1.0178	0.3132
Gestational age	14.7475	**<0.0001**
Steady-state creatinine concentration		
Indomethacin	1.8278	0.1220
Antenatal steroid	0.0355	0.8505
APGAR 5 min	1.8887	0.1696
Gentamicin	1.9829	0.1593
Gestational age	5.9230	**<0.001**

Statistically significant factors signified in bold type.

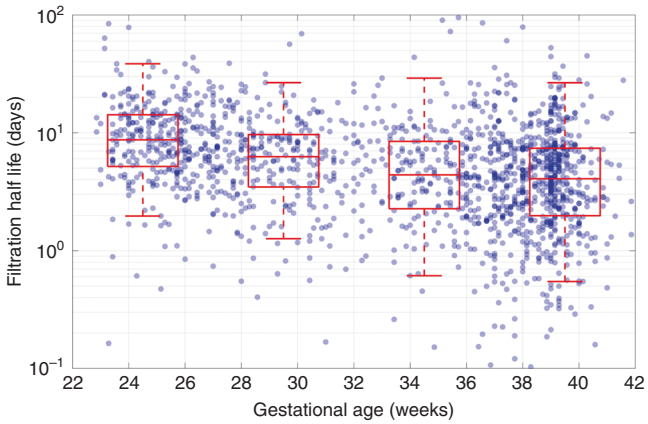

Fig. 5 Creatinine Filtration Half-life. Half-life for creatinine filtration in days versus gestational age in weeks by group.

In our study, we expanded on the evolution of kidney development. First, we were able to mathematically model the time at which the kidney began to function after birth and clear creatinine, known as the filtration onset delay. The filtration onset delay was

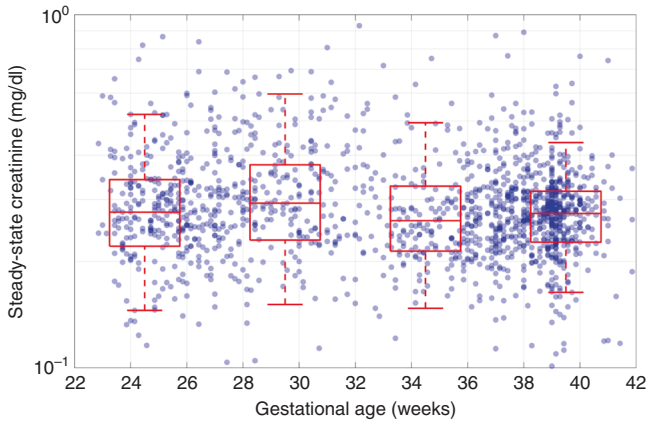

Fig. 6 Steady-state Creatinine Concentration by Group Number. Steady-state creatinine concentration versus gestational age in weeks by group.

inversely proportional to GA as the smallest infants had the longest filtration onset delays over the first 5 days of life. In addition, when examining factors associated with this delay, exposure to indomethacin and GA were found to be significant. Indomethacin is known to result in decreased GFR, and a relative contraindication to its use is renal dysfunction and it is therefore not surprising that early in life this impacted the filtration onset delay. Second, we were able to show that following this onset delay, the kidneys then started to clear the creatinine. This was demonstrated by showing the decay of creatinine using the filtration half-life as a metric for evaluating this function. It is notable that again, creatinine filtration half-life was also inversely proportional to GA. Finally, it appears that eventually, the kidneys reach a steady-state creatinine concentration regardless of GA. In this cohort, we showed that the median steady-state creatinine concentration was <0.3 mg/dl for all GA groups.

Contrary to the findings of Bateman et al.,[7] we show that in a majority of neonates, the creatinine does not rise a significant amount. Only in the lowest GA group (Group 1) was there a noticeable increase in creatinine level after birth. Our overall findings are also consistent with those of Bruel et al.,[13] who showed that creatinine values >1.6, 1.1, and 1.0 mg/dl for 24–27, 28–29, and 30–32 weeks GA groups, respectively, are critically elevated values and are associated with mortality or poor outcomes. We showed that especially in the lowest GAs, the creatinine level at which there should be cause for concern is much <1.6 mg/dl. In fact, the 50th percentile curve for those infants at 22–27 weeks gestation is well below 1 mg/dl. These percentile curves may assist bedside clinicians in the NICU with interpretation of creatinine measurements for their patients and may lead to earlier recognition of poor renal function by allowing them to more easily recognize creatinine values that are >90th percentile for GA and postnatal age and/or crossing percentiles.

After determining the kidney filtration onset delay, the creatinine filtration rate, and the steady-state creatinine concentration, we examined differences across GA. Specifically, we demonstrate that the functions related to the onset of creatinine filtration and overall clearance vary substantially between those infants at the lowest and highest ends of the GA spectrum. In fact, lowest GA infants (22–27 weeks) have both the longest filtration onset delay and filtration half-life compared to all other infants >27 weeks' gestation. The longer length of time for filtration onset and clearance is likely due to and representative of the on-going nephrogenesis in the smallest infants.

Importantly, the relative difference between creatinine measurements of the smallest and largest infants (GA groups 1 and 4) grows steadily over for the first 20 days of life, reaching more than 60% difference at its peak. At that point, the difference begins to reduce, and it returns to baseline at ~80 days of age (data not shown). This demonstrates the natural evolution of creatinine in the extremes of this cohort, but also shows that over time even the smallest infants eventually achieve similar kidney behavior compared to their term equivalent GA peers.

Limitations

There are several limitations to this study. It is a single center cohort study and a retrospective analysis of prospectively collected data. Despite these facts, we were still able to analyze a large number of patients in the population of interest. In addition, for advanced analysis, the smaller number of patients analyzed is still one of the largest cohorts evaluating creatinine clearance in neonates found in the literature. Since we were only able to include patients who had at least one creatinine measurement in this cohort, we are not able to analyze data from those patients with no creatinine measurements. In addition, standard practice at our institution is to check creatinine routinely; infants without measurements often represent short-stay or transitional nursery admissions and not the population of interest for this study. Finally, creatinine measurements were obtained at the discretion of the clinical team during this time period, making uniformity of timing when these were made not possible. It would be ideal to have a regimented timing for this evaluation, but was not possible in this retrospective study.

CONCLUSION

This study represents one of the largest cohorts of premature infants to monitor the evolution of kidney development and function over their entire hospitalization. We introduce the idea of the time it takes for the kidney to begin clearance of creatinine, or filtration onset delay, as an early indicator of kidney function. We also found that GA played a significant role in the filtration onset and creatinine clearance as the smallest cohort of infants 22–27 weeks gestation took the longest time to begin and complete maternal creatinine clearance. However, despite these developmental changes, all infants in this cohort eventually achieved a steady-state creatinine level of <0.3 mg/dl around 80 days of age regardless of GA.

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AUTHOR CONTRIBUTIONS

D.R.R. had substantial contributions to the conception and design of the study, interpretation of the data, drafting of the article, and approved the final version. C.J.R. had substantial contributions to the conception and design of the study, interpretation of the data, revised the article critically, and approved the final version. L.E. had substantial contributions to interpretation of the data, revised the article critically for important intellectual content, and approved the final version. K. M.B. had substantial contributions to the conception and design of the study, interpretation of the data, revision of the article critically, and approval of the final version. C.G.R. had substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of the data, and revising the article critically and approving the final version. S.A. had substantial contributions to acquisition of data, analysis and interpretation of the data, drafting of the article, revising the article critically, and approving the final version.

ADDITIONAL INFORMATION

Competing interests: C.G.R. has an SFI in Medical Informatics Corp (MIC). MIC has no financial interests in this work.

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