

# A New Approach to Recognize Neonatal Impaired Kidney Function



Sofia Perazzo<sup>1</sup>, Mary Revenis<sup>1,2</sup>, An Massaro<sup>1,2</sup>, Billie L. Short<sup>1,2</sup> and Patricio E. Ray<sup>3</sup>

<sup>1</sup>Division of Neonatology, Children's National Hospital, Washington, DC, USA; <sup>2</sup>Department of Pediatrics, The George Washington University, Washington, DC, USA; and <sup>3</sup>Child Health Research Center, Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, Virginia, USA

**Introduction:** Previous studies in term newborns with hypoxic ischemic encephalopathy showed that the rate of serum creatinine (SCr) decline during the first week of life could be used to identify newborns with impaired kidney function (IKF) who are missed by standard definitions of neonatal acute kidney injury (nAKI).

**Methods:** Retrospective review of the medical records of 329 critically ill newborns  $\geq 27$  weeks of gestational age (GA) admitted to a level 4 neonatal intensive care unit (NICU). We tested the hypothesis that the rate of SCr decline combined with SCr thresholds provides a sensitive approach to identify term and preterm newborns with IKF during the first week of life.

**Results:** Excluding neonates with nAKI, an SCr decline  $< 31\%$  by the seventh day of life, combined with an SCr threshold  $\geq 0.7$  mg/dl, recognized newborns of 40 to 31 weeks of GA with IKF. An SCr decline  $< 21\%$  combined with an SCr threshold  $\geq 0.8$  mg/dl identified newborns of 30 to 27 weeks of GA with IKF. Neonates with IKF ( $\sim 17\%$ ), like those with nAKI (7%), showed a more prolonged hospital stay and required more days of mechanical ventilation, vasoactive drugs, and diuretics, when compared with the controls. Changes in urine output did not distinguish newborns with IKF.

**Conclusion:** The rate of SCr decline combined with SCr thresholds identifies newborns with IKF during the first week of life. This distinctive group of newborns that is missed by standard definitions of nAKI, warrants close monitoring in the NICU to prevent further renal complications.

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KEYWORDS: acute kidney injury; first week of life; neonate; renal function; serum creatinine

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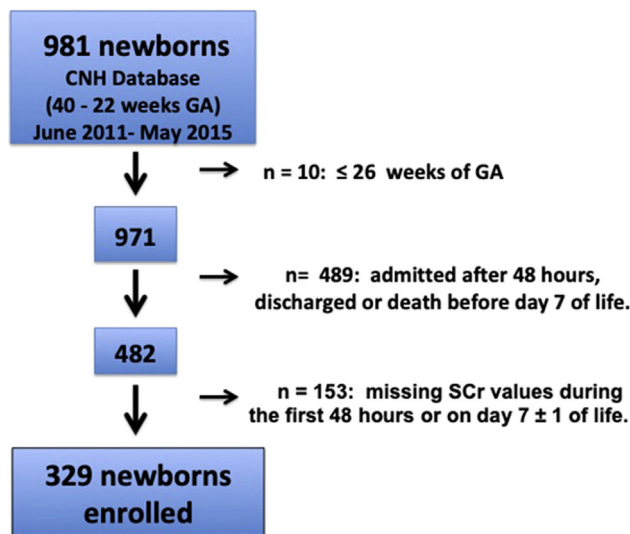
Critically ill newborns are at high risk of developing nAKI due to multiple factors, including intravascular volume depletion, capillary leak, ischemia, low cardiac output, nephrotoxic medications, and multiple organ dysfunction.<sup>1</sup> Under these circumstances, AKI is defined by a sudden decrease in kidney function, and is best diagnosed by measuring changes in the glomerular filtration rate (GFR).<sup>2,3</sup> However, due to the practical challenges involved in measuring the GFR in newborns, the diagnosis of nAKI is made assessing changes in SCr, estimated GFR, and urine output.<sup>4–20</sup> Nonetheless, establishing a diagnosis of AKI on neonates can be problematic, in particular, during the first week of life, when there is no baseline steady-state SCr. In addition, the formulas used to estimate the GFR have

not been validated in newborns.<sup>21–23</sup> Furthermore, given the difficulties involved in measuring the urine output of neonates and their low urinary concentration ability, these records are not always reliable.<sup>12,24</sup> All these limitations highlight the need to develop a more sensitive approach to assess the renal status of newborns during the first week of life.

Despite multiple studies, the development of a standardized definition of nAKI remains a focus of active investigation and controversies.<sup>5,25</sup> In particular, the first days of life create a unique dilemma. Due to the transfer of maternal SCr, a normal decline in the SCr of newborns is expected during the first week of life.<sup>6</sup> Thus, waiting for a rise in the SCr levels may delay the recognition of the early stages of nAKI. In addition, the well-recognized limitations of SCr to assess the renal function in older children and adults, which are based on the observation that at higher GFR the SCr does not change rapidly,<sup>26</sup> do not apply during the first week of life. Given the low GFR values of newborns ( $< 35$  ml/min per  $1.73$  m<sup>2</sup>),<sup>2,3</sup> small changes in GFR could

**Correspondence:** Patricio Ray, Child Health Research Center, MR4 Building, 409 Lane Road, Charlottesville, Virginia 22908, USA. E-mail: [Pray@virginia.edu](mailto:Pray@virginia.edu)

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**Figure 1.** Flow diagram of neonates and reasons for exclusion. CNH, Children's National Hospital; GA, gestational age; SCr, serum creatinine.

be associated with an exponential increase in SCr, as reported in adults with low GFR values.<sup>26</sup>

In a previous study we reviewed the outcome of 106 near-term newborns with hypoxic ischemic encephalopathy treated with hypothermia during the first week of life.<sup>6</sup> We found that a standard nAKI definition derived from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, missed ~20% of newborns who showed a significant delay in the rate of SCr decline. Those neonates with a delayed SCr decline required more days of mechanical ventilation and vasopressor drugs, had higher gentamicin levels, more fluid overload, lower urinary epidermal growth factor levels, and a more prolonged length of hospital stay, when compared with control neonates with hypoxic ischemic encephalopathy. Thus, it appears that the KDIGO-based nAKI definition is not sufficiently sensitive to detect all neonates with IKF.

We carried out this study to validate and expand our previous findings in a large group of term and preterm newborns with different clinical illnesses. More specifically, we tested the hypothesis that the rate of SCr decline during the first week of life, combined with absolute SCr thresholds, can be used to identify a distinctive group of newborns with IKF that are missed by current standard definitions of nAKI, and are at high risk of developing severe clinical complications. In addition, we compared the clinical outcome of newborns with IKF versus those with a KDIGO-based definition of nAKI.

## METHODS

### Study Population

We conducted a retrospective review of 981 medical records of term and preterm neonates treated for a

variety of illnesses in a level 4 NICU at Children's National Hospital, in Washington, DC. De-identified data were collected using the Research Electronic Data Capture (REDCap) database hosted in our institution between July 2011 and March 2015.<sup>27</sup> Entry criteria included all term and preterm newborns ( $\geq 27$  weeks of GA) who were admitted, survived the first week of life, and had at least 1 SCr measured during the first 48 hours of life and another on the  $7 \pm 1$  day of life. The reasons for excluding patients are summarized in Figure 1. A total of 329 patients met the entry criteria, and their medical records were reviewed. The study was approved by the institutional review board from the Children's National Hospital (CNH) and was conducted following the ethical guidelines of our institution with a waiver of consent.

### Definition of the Study Groups and Selection of Control Patients

Newborns were divided in 4 groups according to GAs representative of different stages of kidney maturation (40–37, 36–34, 33–31, and 30–27 weeks of GA, respectively). Subsequently, as reported in previous studies,<sup>6,28</sup> we established the normal SCr values for day 7 of life in term infants within the 97.5th percentile (0.6 mg/dl), which is approximately 2 SDs (0.2 mg/dl) above the mean SCr levels of healthy newborns. To define the cutoff SCr values for all other preterm groups, we calculated the mean SCr levels excluding all patients with AKI based on the KDIGO definition and set the abnormal threshold at 0.2 mg/dl above the mean. This approach took into consideration the standard error of the SCr measurements, as well as an adjustment for the changes in SCr due to the normal fluid losses that occur during the first week of life, as described before.<sup>29</sup> The control neonates included all newborns with normal SCr values at the end of the first week of life. The IKF group included all newborns with abnormal SCr levels at the end of the first week of life, excluding those in the AKI-KDIGO group. The AKI-KDIGO group included newborns who developed nAKI according to a KDIGO definition based on the rise of SCr  $\geq 0.3$  mg/dl within any 48-hour period.<sup>30</sup>

### SCr Decline

The SCr decline was calculated by estimating the % SCr decline from the first 48 hours of life, which represents the transfer of maternal SCr, until day of life 7. We then performed receiver operating characteristic curve analysis and defined optimal cutoff SCr decline values using the Youden index. Approximately 34% of the newborns in the control group (86/255) showed SCr values during the first 48 hours within the normal

**Table 1.** Demographics and clinical characteristic of all the newborns in the study groups

Patient characteristics	Controls	IKF	AKI-KDIGO	All groups
Number of patients, <i>n</i> (%)	255 (78)	53 (16)	21 (6)	329 (100)
GA and birth weight				
40–31 wk GA (mean ± SD, g) (95% CI)	2380 ± 740 (2289–2480)	2292 ± 861 (1991–2592)	2838 ± 808 <sup>d</sup> (2630–2997)	2503 ± 293 (2402–2830)
30–27 wk GA (mean ± SD, g) (95% CI)	1252 ± 344 (1145–1360)	1196 ± 388 (1009–1383)	1296 ± 253 (1187–1398)	1248 ± 50 (1160–1356)
Males/females	143/112	38/15	15/6	196/133 <sup>b</sup>
% Males	56	72	71	60
Weeks of GA (mean ± SD) (95%CI)	33.7 ± 3.1 (32–35)	32 ± 3.5 (31–34)	33.7 ± 3.4 (32–35)	33.1 ± 3.3 (32–34)
Race (total <i>n</i> / %)				
White	73 (29)	12 (23)	8 (38)	93 (28)
Black	101 (39)	25 (47)	7 (33)	133 (41) <sup>c</sup>
Other	81 (32)	16 (30)	6 (29)	103 (32)
Site of delivery (outborn)	255 (100)	53 (100)	21 (100)	329 (100)
Main Reasons for admission (total <i>n</i> / %)	141 (55)	31 (58)	12 (71)	184 (56)
Sepsis evaluation Respiratory symptoms	129 (49)	28 (53)	7 (33)	164 (50)
Malformations requiring surgery or NICU care	74 (29)	12 (23)	4 (19)	90 (27)
HIE—perinatal asphyxia	22 (8)	10 (18) <sup>d</sup>	4 (19)	36 (11)
Congenital heart disease	10 (4)	6 (11) <sup>e</sup>	2 (9.5)	18 (5.4)

AKI-KDIGO, acute kidney injury–Kidney Disease: Improving Global Outcomes; CI, confidence interval; GA, gestational age; HIE, hypoxic ischemic encephalopathy; IKF, impaired kidney function; OR, odds ratio; NICU, neonatal intensive care unit.

Weight: <sup>a</sup>*P* = 0.040 (analysis of variance).

Male/female ratio: <sup>b</sup>*P* = 0.056.

Race: <sup>c</sup>*P* = 0.035  $\chi^2$  test.

<sup>d</sup>*P* = 0.026, OR 2.46; 95% CI 1.09–5.56.

<sup>e</sup>*P* = 0.027, OR 3.12; 95% CI 1.08–9.02 compared with controls by the  $\chi^2$  test.

Main reasons for admission include overlapping diagnosis in addition to prematurity (<35 weeks' GA = 56%).

range for day 7 of life, and were excluded from the receiver operating characteristic analysis because the SCr decline under these circumstances has no clinical value to recognize IKF.

## Data and Sample Collection

Relevant demographic and clinical data were recorded including mortality, days of hospital stay, use and duration of mechanical ventilation, vasoactive drugs, and diuretics. Urine output was measured using urinary catheters or weighing diapers.<sup>6</sup> SCr was measured at Children's National Central laboratory using either the Jaffe's or enzymatic methods.

## Statistical Analysis

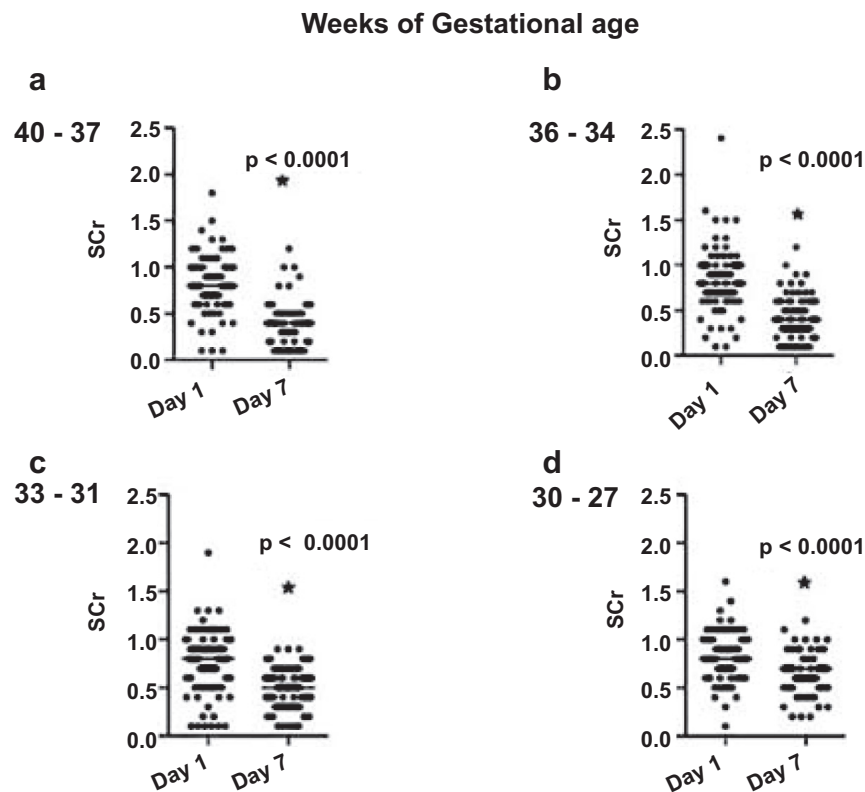
Demographic and clinical data are reported as the mean ± SD or SEM for continuous variables and as proportions for categorical variables. All data sets were tested for normality with the D'Agostino & Pearson and Shapiro-Wilk tests, in addition to residual and Q-Q plots. The median with interquartile range was used for nonnormally distributed variables. Paired *t* tests were done whenever indicated. Differences between 2 groups were analyzed by paired / unpaired *t* tests or the Mann-Whitney test where appropriate. Intergroup comparisons were tested with analysis of variance. Proportional differences were tested with the Fisher exact test or the  $\chi^2$  test with Bonferroni's correction. Odd ratios with 95% confidence intervals (CIs) were

reported whenever indicated. The Kaplan-Meier method was used to estimate the survival curves, and the curves were compared with the log-rank test. The Youden index was used to define optimal SCr decline cutoff points to identify newborns with IKF. The statistical analysis was done using the Prism 7 and MedCal software programs from GraphPad Software, Inc. (La Jolla, CA, and Oostend, Belgium, respectively).

## RESULTS

### Demographics and Clinical Characteristics

We examined 981 medical records of newborns who were admitted to the NICU with a variety of clinical diagnoses (Table 1). From this group, 329 newborns met the study entry criteria (Figure 1), and their medical records were reviewed in depth. The demographic characteristics of the patients excluded were similar to those enrolled, with 2 exceptions. There were a higher proportion of female (56%) and term neonates (52% vs. 21%) in those excluded. The baseline birth weight, gender, and race of the patients recruited are shown in Table 1. The birth weights (mean ± SD) were 3089 ± 666 g (37–40 weeks of GA); 2514 ± 547 g (34–36 weeks of GA); 1714 ± 424 g (31–33 weeks of GA); and 1239 ± 348 g (27–30 weeks of GA). The most common reasons for admission are reported in Table 1.



**Figure 2.** Serum creatinine (SCr) levels during the first week of life in neonates of different gestational ages. (a–d) Shown are mean SCr values for the first and seventh days of life, excluding all patients who developed neonatal acute kidney injury according to the Kidney Disease: Improving Global Outcomes definition. The mean differences in SCr between the first and seventh days of life in each gestational age (GA) group were as follows: 0.436 (95% confidence interval [CI] 0.357–0.514); 0.427 (95% CI 0.357–0.498); 0.288 (95% CI 0.0220–0.355); and 0.1746 (95% CI 0.018–0.250) for newborns of 40 to 37, 36 to 34; 33 to 31, and 30 to 27 weeks of GA, respectively. \**P* values < 0.05 were considered statistically significantly by paired *t* test.

### Renal Status, Creatinine Levels, and Rate of SCr Decline

Approximately 7% of the neonates developed AKI based on the neonatal KDIGO definition, and these patients showed the highest SCr levels by the end of the first week of life ( $2.6 \pm 1.9$  mg/dl; mean  $\pm$  SD). The SCr values for all patients in the control and IKF groups are shown in [Figure 2](#) and [Table 2](#), and [Supplementary Table S1](#). Briefly, the SCr was elevated in the first 48 hours of life, reflecting the transfer of maternal SCr; however, no significant differences were noted between groups ( $P = 0.746$ , analysis of variance). On day 7 of life, term (40–37 weeks of GA) and late preterm neonates (36–34 weeks of GA) showed similar SCr levels ([Figure 3](#)). Moderate preterm newborns (33–31 weeks of GA) showed a modest but significant increase in SCr, when compared with term and late preterm groups ([Figure 3](#)). Very preterm infants (30–27 weeks of GA) showed the highest SCr values when compared with all other groups ([Figure 3](#), [Table 2](#); [Supplementary Table S1](#)). Based on these data, as described in the methods section, we established the absolute SCr abnormal cutoff values for the seventh day of life, which were  $\geq 0.7$  and  $\geq 0.8$  mg/dl for the 40 to 31 and

30 to 27 weeks of GA groups, respectively. Because high plasma bilirubin levels may have negative interference in the estimation of SCr by the Jaffe's method, we recorded the bilirubin levels on day  $7 \pm 1$  of life. No significant differences in bilirubin levels were detected between newborns in the control and IKF groups (40–31 weeks of GA =  $7.9 \pm 4.2$  vs.  $7.6 \pm 4.8$ ; and 30–27 weeks of GA =  $4.8 \pm 1.8$  vs.  $5.2 \pm 2.8$  mg/dl, mean  $\pm$  SD, respectively). Then, we determined the differences in SCr levels during the first and seventh days of life in newborns with and without IKF ([Figure 4a](#) and [b](#)). No significant differences in SCr were noted on day 1 of life. In contrast, on day 7, the differences in SCr between the control and IKF groups were both statistically and clinically significant ([Figure 4a](#) and [b](#)).

Next, we determined the changes in SCr decline in all newborns excluding those with KDIGO-based nAKI ([Table 2](#) and [Supplementary Table S1](#)). No significant differences in SCr decline were detected between term and late preterm infants during the first week of life ([Table 2](#)). Moderate preterm infants showed lower SCr decline values when compared with term or late preterm newborns ([Table 2](#)). As expected, the very

**Table 2.** SCr and SCr decline values of critically ill newborns on day 7 of life, excluding all patients with KDIGO-based nAKI

Group number and gestational age, week	Number (%) Total = 308	SCr (7th day of life)		% SCr decline (Days of life: 1–7 ± 1)	
		Median (IQR) (95% CI)	Mean ± SD (95% CI) (mg/dl)	Median (IQR) (95% CI)	Mean ± SD (95% CI)
1. 40–37	64 (21)	<b>0.40</b> (0.2–0.5) (0.30–0.40)	<b>0.38</b> ± 0.23 (0.32–0.44)	<b>50</b> (43–67) (50–62)	<b>53.0</b> ± 17 (44–55)
2. 36–34	98 (32)	<b>0.40</b> (0.3–0.6) (0.31–0.42)	<b>0.41</b> ± 0.22 (0.36–0.46)	<b>55</b> (33–67) (44–60)	<b>45.4</b> ± 21 (42–52)
3. 33–31	85 (27)	<b>0.50</b> (0.3–0.6) (0.42–0.51)	<b>0.48</b> ± 0.20 <sup>b</sup> (0.43–0.52)	<b>43</b> (22–57) <sup>b</sup> (31–50)	<b>41.0</b> ± 21 (34–43)
4. 30–27	61 (20)	<b>0.65</b> (0.50–0.80) (0.63–0.71)	<b>0.65</b> ± 0.22 <sup>c</sup> (0.59–0.70)	<b>25</b> (6–44) <sup>d</sup> (14–33)	<b>26.6</b> ± 22 (20–33)

CI, confidence interval; IQR, interquartile range (25<sup>th</sup>–75<sup>th</sup> percentiles); SCr, serum creatinine in mg/dl.

<sup>a</sup> $P = 0.021$  vs. group 2.

<sup>b</sup> $P = 0.001$  vs. group 2.

<sup>c</sup> $P < 0.0001$  vs. all other groups.

<sup>d</sup> $P < 0.0001$  vs. all other groups.

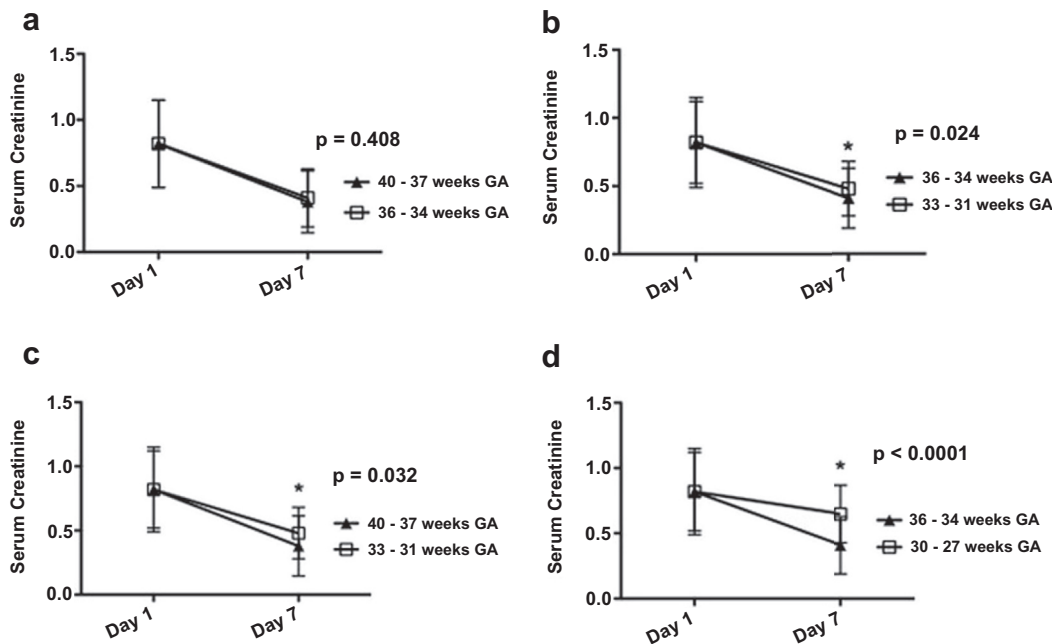
$P = 0.397$  SCr group 1 vs. 2;  $P = 0.808$  SCr decline group 1 vs. 2.

Comparisons were made using an unpaired  $t$  test, Mann-Whitney test, or analysis of variance Kruskal Wallis test whenever appropriate.

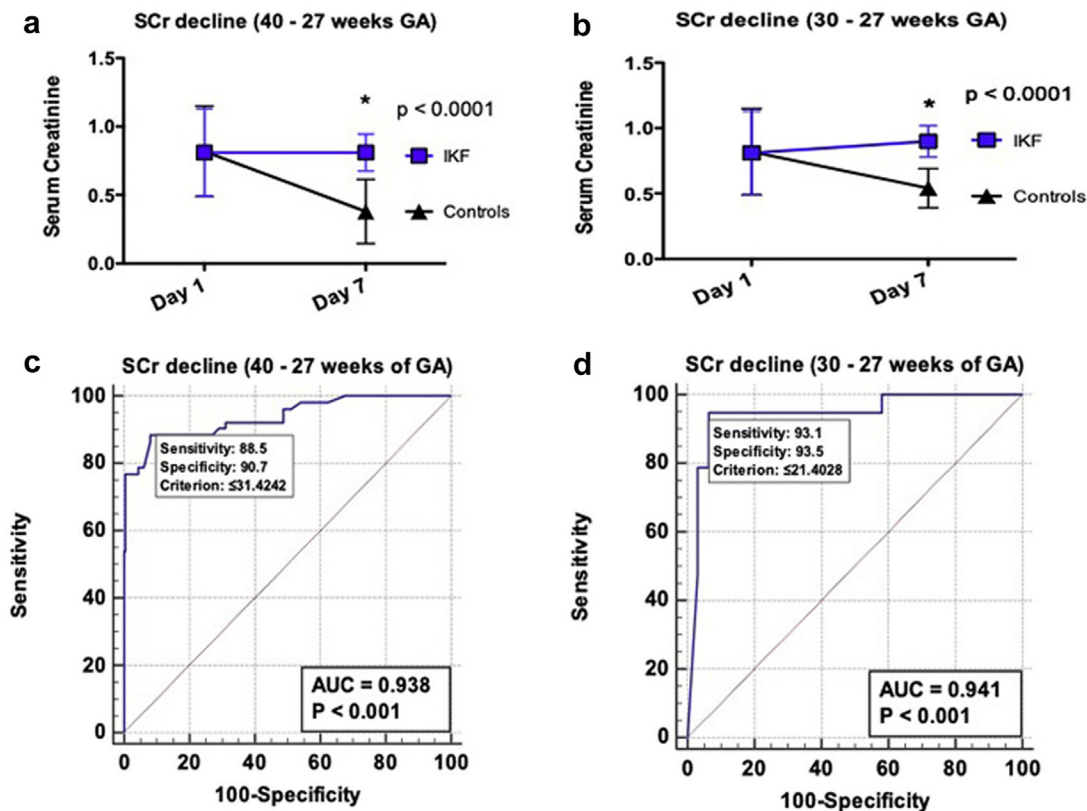
All median and mean values are in bold.

preterm infants (30–27 weeks of GA) had the lowest SCr decline values (Table 2). The median difference in SCr decline between very preterm infants and all other groups pooled together was 20% (95% CI 12–26). Therefore, we performed receiver operating characteristic analysis and established the optimal SCr decline

cutoff points using the Youden index (Figure 4c and d). An SCr decline criterion of <31%, yielded 81% sensitivity (95% CI 76.6–95.6), and 86% specificity (95% CI 87.2–95.3) to identify newborns of 40 to 27 weeks of GA with IKF (area under the curve 0.92;  $P < 0.001$ ) (Figure. 4c). An SCr decline criterion <30%



**Figure 3.** Comparison of serum creatinine (SCr) levels between groups on days 1 and 7 of life. All newborns with Kidney Disease: Improving Global Outcomes–based neonatal acute kidney injury were excluded from this analysis. No significant differences in SCr levels were noted between all groups at birth (a–d). The mean differences in SCr levels between groups on day 7 of life were: 0.029 (95% confidence interval [CI] –0.043 to 0.102); 0.061 (95% CI –0.001 to 0.12); 0.091 (95% CI 0.021 to 0.161), and 0.238 (95% CI 0.166 to 0.310) for (a–d), respectively.  $P$  values < 0.05 were considered statistically significant by unpaired  $t$  test.



**Figure 4.** Comparisons of serum creatinine (SCr) levels and SCr decline between newborns with and without impaired kidney function (IKF). (a,b) Mean SCr levels on days 1 and 7 of life. No significant differences were noted between the control and IKF groups on day 1 of life (a,b). The mean differences in SCr levels on day 7 of life were: 0.457 (95% confidence interval [CI] 0.401–0.541) for newborns 40 to 31 weeks of gestational age (GA), and 0.323 (95% CI 0.239–0.406) for newborns 30 to 27 weeks of GA. (c,d) The SCr decline receiver operating characteristic curve analysis corresponding to all newborns (40–27 weeks of GA), and for newborns of 30 to 27 weeks of GA only. The dashed reference line represents a receiver operating characteristic curve for a test with no discriminatory ability. The sensitivity, specificity, and criterion values are shown on (c) and (d).  $P$  values  $< 0.05$  were considered statistically significant.

yielded a sensitivity of 84% (95% CI 68.9–95.0) and specificity of 96% (95% CI 91.7–98.3) to identify newborns of 40 to 31 weeks of GA with IKF (area under the curve 0.925;  $P < 0.001$ ). An SCr criterion  $< 21\%$  showed 93% sensitivity (95% CI 74.0–99.9) and 93% specificity (95% CI 78.6–99.2) to identify neonates of 30 to 27 weeks of GA with IKF (area under the curve 0.941;  $P < 0.001$ ) (Figure 4d).

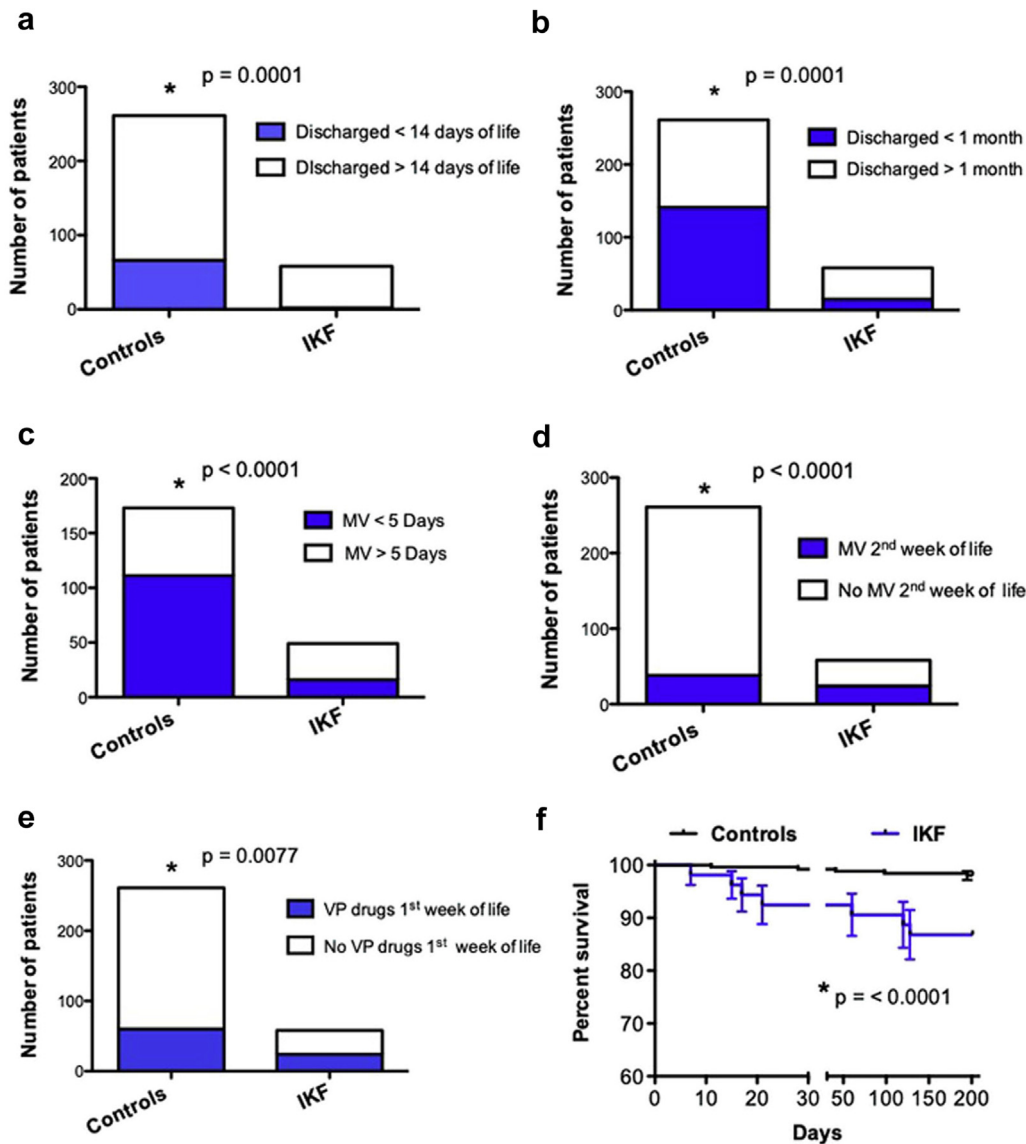
### Clinical Outcome

Initially, we compared the clinical outcome of control neonates with those with IKF. Newborns with IKF had a more prolonged hospital stay, greater requirement for mechanical ventilation, vasoactive drugs, and higher mortality rates (Figure 5a–f). No significant differences in urine output were detected between the control and IKF groups, but the latter group required more diuretics and had higher blood urea nitrogen levels (Figure 6). In addition, more neonates with IKF developed nAKI later in the NICU stay, when compared with controls (odds ratio 3.38; CI 0.92–12.46;  $P = 0.052$ ;  $\chi^2$  test). Alternatively, newborns with nAKI showed more

significant oliguria and need of diuretics, and had higher blood urea nitrogen levels and mortality rates, when compared with all other groups (Figures 6 and 7); however, no statistically significant differences in the length of stay, requirement of mechanical ventilation, and use of vasopressor drugs were noted between the AKI-KDIGO and IKF groups (Figure 7a–e).

### DISCUSSION

The major finding of this study is that the rate of SCr decline combined with absolute threshold SCr levels, as shown in Figure 8, provide a new approach to identify term and preterm infants (40 to 27 weeks of GA) with impaired kidney function during the first week of life. Moreover, our data show that the standard neonatal AKI-KDIGO definition is not sufficiently sensitive to identify all newborns with IKF during the first week of life. We used the new term IKF because changes in SCr decline and absolute SCr levels during the first week of life reflect changes in kidney function that may not necessarily be considered in the KDIGO diagnosis nAKI. We propose that neonates showing abnormal SCr

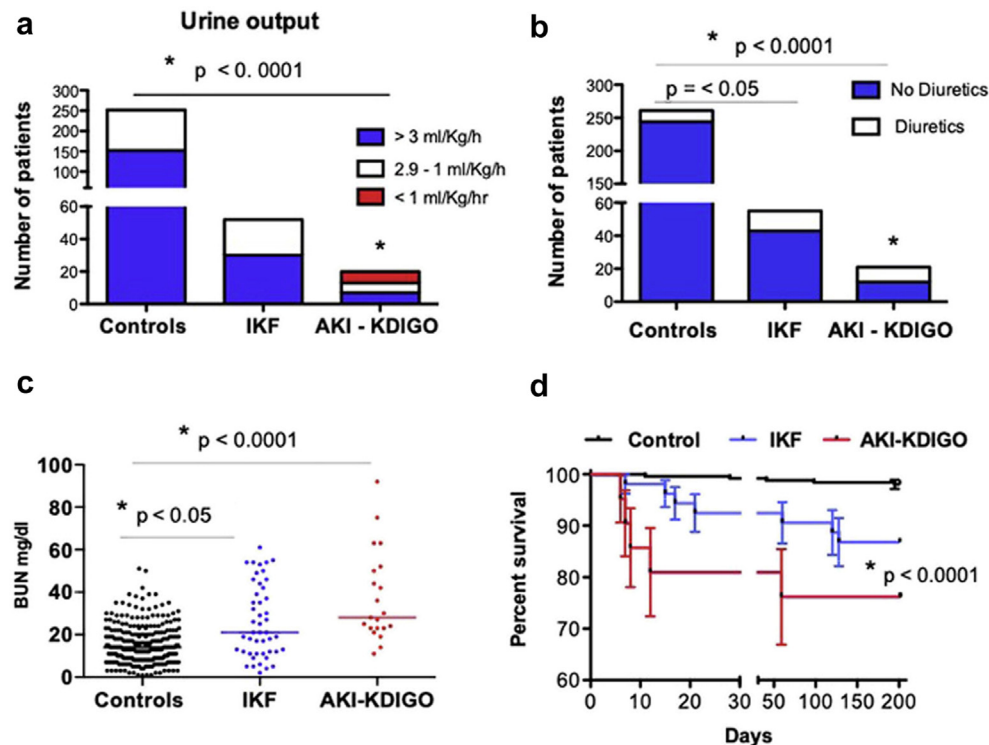


**Figure 5.** Clinical outcome of newborns with impaired kidney function (IKF) compared with controls. (a,b) Newborns with IKF required more days of hospitalization (discharge at 14 days, odds ratio [OR] 8.8; 95% confidence interval [CI] 2.3–37.6); discharge at 30 days, OR 3.9; 95% CI 2.0–7.5). (c,d) Newborns in the IKF group required more days of mechanical ventilation (MV) (> 5 days, OR 3.3; 95% CI 1.6–6.6; ≥ 2 weeks, OR 4.2; 95% CI 2.1–8.6). (e) Newborns with IKF required more vasopressor (VP) drugs during the first week of life (OR 2.6; 95% CI 1.4–4.7). (f) Newborns with IKF had higher mortality when compared with the control group (hazard ratio 21.5; 95% CI 4.5–99.3). Comparisons between group proportions were made using either the Fisher's exact or  $\chi^2$  tests. The survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. The error bars in the survival graph represent the 95% CI.  $P$  values < 0.05 were considered statistically significant.

threshold and decline values by the end of first week of life constitute a distinctive clinical group of newborns with IKF that warrants close monitoring in the NICU to prevent acute and chronic renal complications.

To the best of our knowledge, this is the first study to use SCr decline values combined with absolute SCr cutoff points to assess the renal status of preterm infants during the first week of life. We were able to identify a group of newborns with IKF, who were missed by the nAKI-KDIGO definition, and required more days of mechanical ventilation, more continuous use of vasopressor drugs, diuretics, and had an increased length of hospital

stay when compared with the controls. Newborns with nAKI based on the KDIGO definition showed similar clinical complications, although more severe oliguria, increased need of diuretics, and higher mortality rates. Although diuretics can mask the detection of oliguria as an early sign of nAKI, our findings are in agreement with previous studies showing that oliguria may not be a sensitive clinical sign of neonatal AKI<sup>11,12,24</sup>; however, it is worth mentioning that some methods used to collect the urine output of newborns are less reliable than others (e.g., weighing diapers) and may affect the sensitivity of these measurements. Taken



**Figure 6.** Comparisons between (a) urine output, (b) use of diuretics, (c) blood urea nitrogen (BUN) levels, and (d) survival between all groups. Newborns with Kidney Disease: Improving Global Outcomes–defined neonatal acute kidney injury (AKI-KDIGO) showed more significant oliguria, required more diuretics, and had higher BUN levels and mortality rates when compared with all other groups. In addition, newborns with impaired kidney function (IKF) required more diuretics (b) when compared with controls (odds ratio 3.75; 95% confidence interval [CI] 1.6–8.7) and had higher BUN levels (c). Comparisons between group proportions were done using the Fisher’s exact test or  $\chi^2$  test. Changes in BUN levels were analyzed with analysis of variance Kruskal Wallis test. The survival curves were estimated using the Kaplan Meier method, and compared with the log-rank test. The error bars in the survival graph represent the 95% CI. *P* values < 0.05 were considered statistically significant.

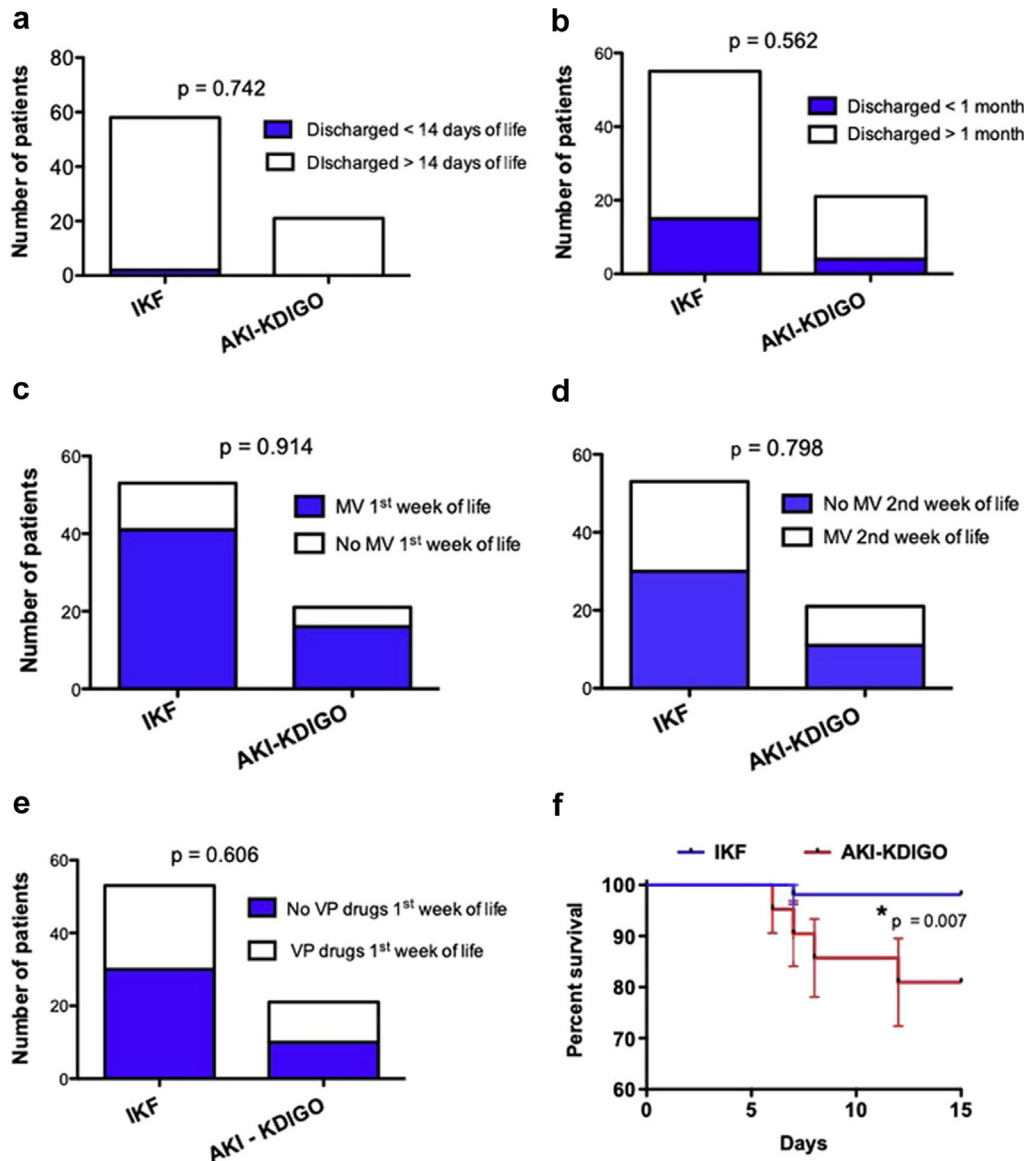
together, our findings suggest that the rate of SCr decline combined with SCr thresholds provide a sensitive approach to assess the renal function of newborns during the first week of life.

In humans, the process of nephrogenesis is completed between 35 and 32 weeks of GA.<sup>5,31</sup> In agreement with this notion, the SCr levels and SCr decline of newborns of ~32 weeks of GA, reflected the maturational GFR changes characteristic of preterm infants during the first week of life. As expected, very preterm infants of 30 to 27 weeks of GA, showed the highest SCr levels during the first week of life and the lowest rate of SCr decline. Therefore, the rate of SCr decline appears to be determined by the renal physiological and maturational changes characteristic of each gestational stage, and can be used in a reliable manner during the first week of life to assess the renal function of newborns of at least 30 weeks of GA.

In addition to the KDIGO definition, nAKI has been defined by other methods,<sup>32</sup> including an SCr greater than 1.5 mg/dl or an increase of at least 0.2 to 0.3 mg/dl per day from a previous lower value. Several SCr AKI cutoff points have been recommended for preterm infants (>1.6, >1.1, and > 1.0 SCr mg/dl, for infants of

24 to 27, 28 to 29, and 30 to 32 weeks of GA, respectively).<sup>1</sup> These cutoff points, however, have not been validated during the first week of life, and if they are applied to our cohort, they will miss a significant number of newborns with IKF. A recent retrospective multicenter study identified multiple SCr rise cutoff points in neonates of different GA during the first week of life (ranging from  $\geq 0.1$  to 0.3 mg/dl) that predict mortality.<sup>30</sup> However, we focused our approach on the SCr decline, taking into consideration the transfer of maternal SCr that occurs after birth, and the changes associated with the maturation of renal function. During the first few hours of life, the GFR reflects the functional renal status in utero, when the placenta plays a key role in this process. Subsequently, during the first 3 days of life, there is a rapid increase in renal function,<sup>11,28,31,33,34</sup> and given the low GFR values of newborns,<sup>20</sup> the SCr can change in an exponential fashion in response to a small change in GFR, as reported in adults with GFRs <40 ml/min per 1.73 m<sup>2</sup>.<sup>26</sup> Nonetheless, due to the transfer of maternal SCr, a significant renal injury event may not necessarily increase the SCr levels by 0.2 or 0.3 mg/dl. Our previous study in term newborns with hypoxic ischemic



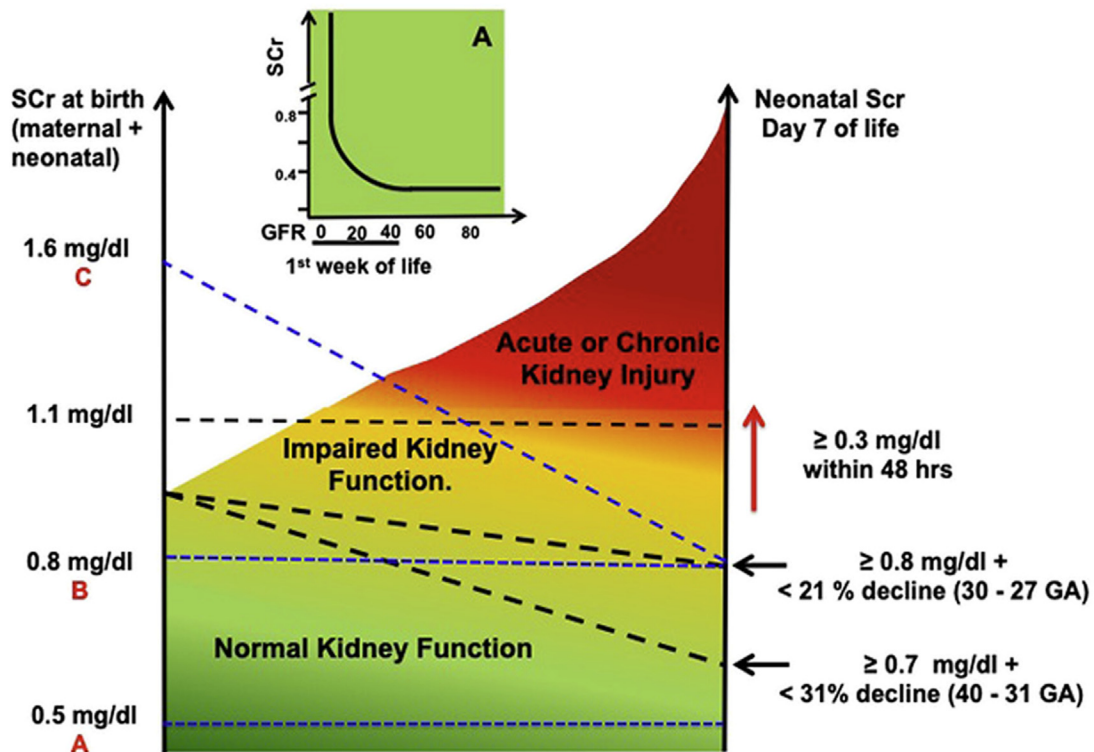


**Figure 7.** Clinical outcome of newborns with impaired kidney function (IKF) compared with those with Kidney Disease: Improving Global Outcomes (KDIGO)-defined neonatal acute kidney injury (nAKI). No significant differences were noted in the length of stay, days of mechanical ventilation requirements, and use of vasopressor drugs, between newborns with IKF and those with AKI-KIDGO (a–e). However, newborns with KDIGO-defined nAKI showed higher mortality rates during the first 2 weeks of life (hazard ratio: 14.7; 95% confidence interval [CI] 2.0–106.5) (f). Comparisons between group proportions were made using the Fisher’s exact or  $\chi^2$  tests. The survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. The error bars represent the 95% CIs.  $P$  values < 0.05 were considered statistically significant.

encephalopathy shows that the neonatal AKI-KDIGO definition misses many newborns undergoing the early stages of nAKI. The current study validated and expanded our previous findings. In addition, combining SCr thresholds and SCr decline cutoff values provides a simple approach that can be easily translated to bedside care. It requires performing measurements of SCr within the first and seventh days of life and assessing the SCr decline as shown in Figure 8. Then, newborns with IKF can be recognized and treated earlier to prevent further renal injury. Finally, we found that neonates with IKF during the first week of life may be more likely to die or develop nAKI at later

stages, further supporting the need to recognize these patients as soon as possible.

Previous studies have used creatinine kinetic models to review the definitions of AKI in adults.<sup>35</sup> These models are based on the mass balance principles, which assuming a constant creatinine generation rate and volume of distribution, predict that GFR changes in people with high baseline SCr can be estimated more accurately by measuring absolute SCr levels, rather than a % rise.<sup>35</sup> For this reason, we established absolute SCr cutoff points to interpret the changes in SCr decline. It could be argued that the mass balance principles cannot be applied to the first



**Figure 8.** Approach to identify newborns with impaired kidney function (IKF) during the first week of life. (a) At high levels of kidney function, large changes in glomerular filtration rate (GFR) result in small or no changes in serum creatinine (SCr). In contrast, at lower levels of kidney function, as seen in neonates during the first week of life, small changes in the SCr decline are associated with clinically relevant changes in GFR. The graph shows the SCr decline and threshold cutoff values for newborns of 40 to 31 and 30 to 27 weeks of gestational age (GA), respectively. Patient A shows SCr levels on day 1 (0.5 mg/dl) that are normal for the 7 day of life as well. In this case, the SCr decline cannot be used to detect IKF, because a further decline or lack of decline, within the normal SCr range, has no clinical value for this purpose. Patient B shows normal SCr levels for the first day of life (0.8 mg/dl). However, on day 7, both the SCr decline and absolute SCr values are abnormal. Patient C shows high SCr levels for the first day of life (1.6 mg/dl) and a normal SCr decline for the first week of life. Both patients B and C show similar abnormal SCr values on day 7 of life (blue dotted lines representing both patients merge at 0.8 mg/dl). However, assuming they have similar GA and risk factors, patient B is more likely to have a worse renal outcome in subsequent days. Finally, patients who show a rise in SCr from baseline  $\geq 0.3$  mg/dl within 48 hours are considered to have neonatal acute kidney injury according to the Kidney Disease: Improving Global Outcomes definition.

week of life, because the SCr is not in a steady-state balance and its volume of distribution is changing. However, as discussed in the methods section, to establish the SCr thresholds, we took into consideration the changes in SCr associated with the normal fluid losses expected during the first week of life, as well as the standard error of the SCr measurements. In addition, the low GFR and high SCr levels seen in newborns during the first days of life, mimic the clinical situation of people with chronic kidney failure who receive a kidney transplant. In these cases too, the SCr decline is predictive of the renal outcome. In support of this notion, we noted that the rate of SCr decline has additional value to assess the renal status of neonates born with abnormal SCr levels ( $\geq 1.2$  mg/dl). In fact,  $\sim 60\%$  of the neonates who showed normal SCr decline values associated with abnormal SCr levels by the end of the first week of life, had favorable clinical outcomes. Therefore, both the SCr decline and threshold values

should be taken into consideration to assess the renal status of newborns during this time.

We recognize that the ideal definition of nAKI should rely on the discovery of specific biomarkers of kidney injury. Unfortunately, currently we lack specific biomarkers of renal injury for the first week of life,<sup>5,36</sup> and the nAKI definitions are based on assessing % or absolute changes in SCr,<sup>5,6,19,30,36</sup> which reflect changes in kidney function rather than injury. For this reason, we propose to use the term impaired kidney function (IKF) to group all neonates with a slow SCr decline during the first week of life. This term includes neonates undergoing hemodynamic changes leading to poor renal perfusion, extracellular volume depletion, congenital kidney abnormalities, drug-induced nephrotoxicity, and/or AKI. All these factors contribute to precipitate or exacerbate AKI events, and newborns undergoing the early stages of AKI usually meet the IKF criteria. Thus, the early recognition of newborns with IKF provides a great opportunity to discover and

validate new biomarkers of nAKI during the first week of life. We should mention that definitions of nAKI that place too much emphasis on predicting the worst outcomes (e.g., mortality) could miss the early stages of nAKI and delay its recognition. In summary, we need a standardized definition of nAKI that predicts clinical outcomes, but that also recognizes the early stages of nAKI, to initiate early treatments and discover new biomarkers of renal injury.

Our study has several limitations, including its retrospective nature, single center, lack of GFR measurements as the golden standard to define IKF, and more accurate calculations of urine output and fluid overload. In addition, the clinical parameters selected to assess the outcome of newborns with IKF are not specific indicators of renal dysfunction. For example, the length of hospital stay, need of mechanical ventilation, and mortality, are all affected by the GA as well as the presence of nonkidney diseases and complications. However, the newborns in the control and IKF groups were of similar GA, and previous studies have used the same criteria to assess the outcome of newborns with AKI.<sup>5,6,3</sup> In addition, because the Children's Hospital laboratory used 2 different methods to measure the SCr during the study period, we took into consideration the standard error of both methods to define the normal SCr cutoff points. Furthermore, although high bilirubin levels may have a negative interference in the estimation of SCr with Jaffe's method, no significant differences in the total bilirubin levels were noted between neonates in the control and IKF groups. Overall, the SCr values reported in this study are consistent with the values reported in large multicenter studies that have used similar methods to measure SCr.<sup>30</sup> Nonetheless, a more in-depth comparison of the demographics and clinical illnesses of our patients with other newborn populations needs to be done to determine whether similar cutoff points could be used in other populations. Finally, the relative small number of newborns with IKF and nAKI in each group of patients with different GA prevented us from doing a powerful statistical comparison between these groups. Nevertheless, when data derived from more than 300 newborns are taken together, they provide strong statistical evidence to support our conclusions.

In summary, we propose that an SCr decline  $\leq 31\%$  in combination with a threshold for SCr  $\geq 0.7$  mg/dl by the end of the first week of life, provides a sensitive method to assess the renal function of term and preterm newborns  $>30$  weeks of GA. In a similar manner, an SCr decline  $\leq 21\%$  combined with a threshold for SCr  $\geq 0.8$  mg/dl by the end of the first week of life, recognizes very preterm infants (30–27 weeks of GA)

with IKF. However, a larger group of very preterm infants needs to be studied to validate the latter cutoff points. Hopefully, this approach will facilitate the early detection and treatment of neonates with IKF during the first week of life, provide an opportunity to discover new and more specific biomarkers of nAKI, and identify neonates at higher risk of developing acute or chronic kidney complications in the NICU.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** SCr and SCr decline values of all critically ill newborns of different gestational ages on day  $7 \pm 1$  of life, excluding all patients with KDIGO-based nAKI.

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