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ORIGINAL ARTICLE

Cystatin C compared to serum creatinine as a marker of acute kidney injury in critically ill neonates

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Abstract

Background Acute kidney injury (AKI) is one of the most common causes of neonatal morbidity and mortality. Diagnosing AKI in neonates is challenging as it lacks specific signs, symptoms, and biomarkers. However, detecting AKI in critically ill neonates is crucial to determine appropriate management and prevent complications. Cystatin C (CysC) has been recognized as a superior kidney biomarker reflecting kidney function in neonates. The objective of this study is to evaluate the diagnostic value of CysC as an AKI biomarker in critically ill neonates.

Methods We performed a diagnostic test between cystatin C-based estimated glomerular filtration rate (eGFR-CysC) and serum creatinine-based estimated glomerular filtration rate (eGFR-SCr) as the gold standard to diagnose AKI in 135 critically ill neonates treated in Cipto Mangunkusumo National Hospital from July 2017 to January 2018.

Results Prevalence of AKI was 23.7% predominantly in neonates with a very preterm gestational age, low birthweight, probable sepsis, and those receiving invasive oxygen therapy or nephrotoxic drugs. The proportion of AKI based on neonate RIFLE criteria was 72.7% risk, 18.9% injury, and 9% failure. eGFR-CysC had the following parameters: sensitivity, 84.8%; specificity, 61.8%; PPV, 41.8%; NPV, 89.7%; LR(+), 2.2; LR(−), 0.24; and accuracy, 67.4%. The AUROC for CysC was 84.9%. The optimal cut-off value for CysC was 1.605 mg/l.

Conclusions CysC may be used as a screening biomarker of AKI in critically ill neonates; yet, it was not superior to serum creatinine.

Keywords Acute kidney injury · Cystatin C · Serum creatinine · Critically ill neonates

Introduction

Acute kidney injury (AKI) is one of the most common causes of neonatal morbidity and mortality. An estimated 8–24% of critically ill neonates develop AKI, with a mortality rate of 50% and a higher risk of developing chronic kidney disease in the surviving group [1–3]. Several factors associated with neonatal AKI have been identified, including prematurity, neonatal asphyxia, sepsis, congenital kidney and urinary tract abnormalities, congenital heart disease, use of nephrotoxic drugs, and oxygen therapy [4–8].

AKI is defined as the sudden derangement of kidney function [9]. Currently, there is no consensus on the definition of neonatal AKI, making its identification and management difficult [1–7, 10–12]. Several criteria for the diagnosis of AKI have been proposed, such as the RIFLE criteria for pediatric patients (pRIFLE) and neonates (nRIFLE) who are categorized as risk, injury, failure, loss, and end stage; RIFLE uses serum creatinine (SCr), glomerular filtration rate (GFR), and urine output as the basis for classification. However, using SCr to diagnose AKI in neonates has its drawbacks: (i) neonatal SCr is highly affected by maternal SCr; (ii) it measures kidney function rather than injury; (iii) it is a late marker of injury since > 50% of nephrons may be compromised before a significant increase in SCr is detected, which occurs 48–72 h from the injury onset; (iv) it is affected by age and gestational age; and (v) the higher level of SCr commonly found in

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premature neonates reflects tubular abnormalities due to immaturity (not injury) [2, 6, 13–18]. Schwartz et al. [17] proposed that estimated glomerular filtration rate (eGFR) is more accurate and superior in reflecting kidney function in neonates than SCr alone. Due to the limitations of SCr, recent studies have focused on evaluating other possible AKI biomarkers including neutrophil gelatinase-associated lipocalin, urine interleukin-18, kidney injury molecule-1 (KIM-1), and cystatin C (CysC) [19].

CysC is a cysteine proteinase inhibitor with a molecular mass of 13 kDa. Produced in all nucleated cells at a constant rate, its small size allows 99% filtration through the glomerulus before being completely reabsorbed and catabolized in the proximal tubule [20]. CysC does not cross the placental barrier, which allows a more accurate reflection of neonatal kidney function. However, data on the value of CysC as an AKI biomarker have been inconsistent. Armangil et al. [21] concluded that although CysC may be an alternative, it is not superior to SCr for evaluating kidney function in premature neonates. Treiber et al. [22] demonstrated similar results in a newborn population. Conversely, two studies have shown that CysC plays a superior role in identifying AKI in premature neonates with respiratory distress syndrome [23, 24]. Two systematic reviews concluded that CysC is superior to SCr for the detection of kidney dysfunction in children and adults [25]. Coll et al. [26] demonstrated a high sensitivity (93.4%) and specificity (100%) of CysC when it was used to assess kidney impairment in an adult population. CysC also has potential value as an early biomarker of kidney injury because it increases as soon as GFR decreases [26, 27].

Methods

Study design and population

A diagnostic test study was conducted in 135 critically ill neonates to evaluate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (LR+ and LR−, respectively), and the accuracy of eGFR-CysC compared to eGFR-SCr. The investigation was performed in the Cipto Mangunkusumo National Hospital over a 7-month period (July 2017 to January 2018). Critically ill neonates were included in the study and were defined as newborns < 28 days old or with a correction age < 40 weeks, who were at risk or had experienced organ failure and thus required intensive monitoring, mechanical respiratory support, and/or drugs. The exclusion criteria included conditions such as clinical improvement (no longer at risk of organ failure; thus, continuing intensive monitoring, therapy, and mechanical respiratory support were not required) or death before 48 h of age.

In all neonates, demographic and perinatal characteristics including age, estimated gestational age according to Ballard score, sex, birth weight and length, AKI risk factors, and survival outcome (patients died or survived) were recorded. Risk factors of AKI included (a) sepsis, (b) Apgar score, (c) need for intubation at birth or receiving supportive oxygen therapy (invasive or noninvasive), and (d) receiving nephrotoxic drugs. Neonatal AKI was defined according to the nRIFLE criteria as a 25% or more reduction of eGFR from baseline and was classified as follows: risk (eGFR decrease > 25%), injury (eGFR decrease > 50%), and failure (eGFR decrease > 75%).

Sampling measurements

The patients' venous blood for measuring CysC and SCr was obtained at the same time, from routine blood work. The samples for the CysC measurements were centrifuged at 1300–2000×*g* for 15 min, followed by separation of the sera. CysC was measured by an immunonephelometry method using Behring Nephelometer (BN ProSpec®) and N Latex Cystatin C reagent whereas SCr concentrations were evaluated using the Jaffe method. We calculated eGFR-Cr using the Schwartz formula and expressed it in ml/min/1.73 m^2, whereas eGFR-CysC was evaluated using the formula according to KDIGO guidelines: $70.69 \times (\mathrm{SCysC})^{0.931}$ [10, 17].

Statistical analysis

The statistical analysis was performed using SPSS 23.0 (SPSS, Chicago, IL, USA). Depending on the presence of normality (Kolmogorv-Smirnov test), numerical data are presented as mean and standard deviation or median and range. The diagnostic accuracy of CysC to identify neonatal AKI was evaluated using a receiver operating characteristics (ROC) curve. Sensitivity, specificity, PPV, NPV, LR+, LR−, and accuracy were also calculated. A P value < 0.05 was considered statistically significant.

Results

Study population

During the study period, 153 of the total 316 critically ill neonates fulfilled the inclusion criteria. However, only 135 were enrolled in this study because 13 patients' samples failed to be collected due to technical reasons and five patients' parents refused to provide consent. The subjects comprised 52% boys. The patients' ages at sample collection time ranged from 0 to 28 days. Most of the subjects had 5-min Apgar scores > 5. However, Apgar score data were missing for 19 subjects. The baseline characteristics of the newborns

Table 1 Baseline characteristics ($n = 135$)

Variable	*n*	%
Sex		
Male	71	52.6
Female	64	47.4
Gestational age (weeks)	33 (26–40)	
Term (≥ 37)	47	34.8
Late preterm (34 to < 37)	20	14.8
Moderate preterm (32 to < 34)	29	21.5
Very preterm (28 to < 32)	34	25.2
Extremely preterm (< 28)	5	3.7
Age at sample collecting time (days)	5 (0–28)	
0–7	96	71.1
≥ 8	39	28.9
Birthweight (g)	1750 (720–3950)	
Normal (2500–4000)	40	29.6
Low (1500–2499)	49	36.3
Very low (1000–1499)	37	27.4
Extremely low (< 1000)	9	6.7
5-min Apgar score		
≥ 4	111	82.2
0–3	4	2.9
Intubation at birth		
No	96	71.1
Yes	39	28.9
Oxygen therapy		
Without oxygen therapy	14	10.4
Noninvasive (NIV, CPAP, HFN)	68	50.4
Invasive (ventilator, HFO)	53	39.2
Neonatal sepsis		
No sepsis	66	48.9
Probable sepsis	58	42.9
Sepsis	11	8.2
Received nephrotoxic drug		
No	12	8.9
Yes	123	91.1
Outcome		
Survived	97	71.9
Died	38	28.1

Numerical data are expressed as the mean ± SD or median (range)

CPAP continuous positive airway pressure, *HFN* high flow nasal, *HFO* high frequency oscillatory, *NIV* noninvasive ventilation

included in this study are presented in Table 1, and the measurement results are presented in Table 2.

Prevalence and risk factors of AKI

The prevalence of AKI in this study was 23.7%, and it was further classified according to the nRIFLE criteria as follows:

Table 2 Measurement results

Variable	Result ($n = 135$)
Body length (cm)	42 (30–55)
Serum creatinine (mg/dl)	0.7 (0.13–5.92)
Cystatin C (mg/dl)	1.59 (0.65–4.32)
eGFR-SCr (ml/min/1.73 m^2)	22 (3.62–152.31)
eGFR-CysC (ml/min/1.73 m^2)	46 (18–105)

Numerical data are expressed as the mean ± SD or median (range)

eGFR-SCr estimated glomerular filtration rate based on serum creatinine value, *eGFR-CysC* estimated glomerular filtration rated based on cystatin C value

72.7% risk, 18.9% injury, and 9% failure. The median SCr and serum CysC values in the AKI group were 1 (range, 0.4 to 5.92) and 2 mg/dl (range, 1.03 to 4.32), respectively. The median eGFR-SCr and eGFR-CysC values were 14.03 (range, 3.62 to 30.43) and 37 ml/min/1.73 m^2 (range, 18 to 69), respectively.

Among the newborns in the AKI group, 60.6% were born preterm and 72.7% had a birthweight < 2500 g, with the distribution as follows: 45.5% LBW, 24.2% VLBW, and 3% ELBW. A total of 48.5% of neonates in the AKI group received invasive oxygen therapy, and only 9% did not receive any respiratory support. Additionally, most newborns with AKI received nephrotoxic drugs (87.9%), and at least 66.7% of newborns with AKI were categorized as having probable sepsis. The mortality rate in critically ill neonates with AKI was 33.4%.

Diagnostic performance of CysC

The sensitivity of eGFR-CysC was 84.8% (95% CI 0.75–0.987), the specificity was 61.8% (95% CI 0.52–0.72), the PPV was 41.8% (95% CI 0.30–0.55), the NPV was 89.7% (95% CI 0.88–0.99), and the positive and negative likelihood ratios (LR+ and LR−) were low: 2.2 (95% CI 1.89–3.30) and 0.24 (95% CI 0.03–0.44), respectively. Furthermore, the accuracy of eGFR-CysC was low in our study (only 67.4%).

The ROC curve analyzing the neonatal AKI group versus the non-AKI group showed that the area under the curve (AUC) of CysC was 84.9% (95% CI 0.76–0.94, $P < 0.0001$). The most optimal cut-off for serum CysC was established at 1.605 mg/l (sensitivity 84.8%, specificity 62.7%) (Fig. 1).

Discussion

This diagnostic study compared AKI biomarkers in critically ill neonates. eGFR-CysC as the index test was compared to

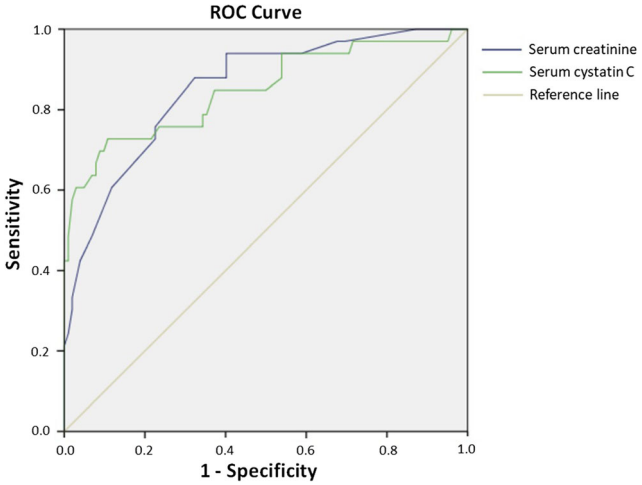

Fig. 1 Receiver operating characteristic (ROC) curves of serum cystatin C and creatinine to identify AKI in neonates

eGFR-SCr for its ability to detect AKI among critically ill neonates. We found that the prevalence of AKI within this study was 23.7%. Most newborns in the AKI group were born preterm, had a birthweight < 2500 g, or received respiratory support or nephrotoxic drugs. The high rate of exposure to nephrotoxic drugs was a result of the policy in our neonatology unit to give empirical antibiotics to all neonates with clinical symptoms of sepsis. Hence, more than 90% of neonates with AKI in this study received aminoglycosides such as gentamicin and/or amikacin.

Our study reports that the sensitivity of eGFR-CysC was higher than its specificity; thus, it may have a potential modality to be used as an early screening test for AKI in critically ill neonates rather than as a diagnostic tool. Similarly, Yuliya et al. [28] reported that the sensitivity of eGFR-CysC was higher than the specificity in identifying AKI in 67 critically ill mature neonates. This study also suggested a low value of eGFR-CysC accuracy (67.4%), supporting the possible use of the biomarker as a screening test. Compared to previous studies, the low accuracy as one of our findings might be influenced by the subjects' characteristics (preterm and term neonates) and/or the baseline criteria to determine AKI (eGFR-SCr).

Interestingly, a high sensitivity and specificity of CysC are obtained when the absolute value of CysC is 1.605 mg/dl. Therefore, a CysC level ≥ 1.605 mg/dl may be considered a tool to perform AKI screening in critically ill neonates. In agreement with our findings, a previous study involving critically ill full-term neonates reported a good sensitivity of CysC with a cut-off value of 1.59 mg/l [28]. Furthermore, this study suggests that the absolute value of serum CysC may be used to identify neonatal AKI (AUC ROC 84.9%, 95% CI 0.762–0.937). However, the AUC of SCr is 85.3% (95% CI 0.78–0.93); thus, CysC is not superior to SCr ($P < 0.0001$). Lagos-Arevalo et al. [29] supported that CysC cannot replace SCr to define AKI, but they found that CysC measurement early on in ICU admission is beneficial to predict AKI development. Maruniak-Chudek et al. [30] reported that CysC concentration is influenced by severe inflammatory processes; therefore, its level in blood does not reflect the current kidney condition. However, Abdelaal et al. [24] reported that CysC measured on the third day of life was superior to SCr in detecting AKI in critically ill neonates.

Studies on neonatal AKI are still lacking; therefore, this study may contribute in terms of identifying AKI in neonates using a novel kidney injury biomarker. Furthermore, this study included a large sample size compared to previous studies [28, 31]. However, some limitations are present. This study was performed in a single tertiary center; thus, the AKI prevalence may be higher in this study and less reflective of the condition in the community. Secondly, this study did not include urinary output measurements due to the lack of validation of neonatal urine measurement methods in our institution. Thirdly, this diagnostic study collected data consecutively over 7 months. A cohort study with serial sampling may provide better data, as provided by Ahmed et al. [32], who recommended using CysC to diagnose AKI from the first day of life. We only performed sampling once due to limited funding. For diagnostic accuracy, it would be better to compare with a gold standard measured GFR, which is renal inulin clearance. However, it has many limitations, especially in pediatric clinical practice. It is not readily available, difficult to measure, and not representable if there is vesicoureteral reflux due to the underlying disease. Other studies use plasma iohexol disappearance to measure renal clearance [33]. However, both markers are not readily available in many countries.

We calculated eGFR-CysC using the formula derived by the Chronic Kidney Disease in Children (CKiD) 2012 cohort study. They recruited subjects 1–16 years of age, and the formula has not been well validated in neonatal population. However, CKiD 2012 is the most commonly used formula to estimate GFR based on serum CysC values in pediatric populations and it is superior compared to other eGFR-CysC equations [33]. Only limited studies with small numbers of patients have evaluated CysC as a marker of GFR in neonates. Among them, only one study has derived an eGFR-CysC equation [34]. However, in that equation, one of the components is kidney 3D volumetry, which is not commonly measured in daily practice. Finally, the broad definition of "critically ill" infant may result in a heterogenous population. Further studies with more specific populations of neonates are needed to validate novel kidney injury biomarkers.

In summary, we discovered that a higher prevalence of AKI occurs not only in premature or low birthweight neonates but also in those who experience sepsis or received nephrotoxic drugs. Serum CysC may be beneficial as a screening tool

for AKI in critically ill neonates. However, we found that CysC was not superior to serum creatinine in detecting neonatal AKI. We suggest that more prospective cohort studies with a serial CysC test will be helpful in determining the onset of AKI in critically ill neonates and in evaluating the progression of AKI.

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Data availability Data are available from corresponding author upon reasonable request.

Compliance with ethical standards This study was approved by the Ethical Committee of Cipto Mangunkusumo Hospital–Faculty of Medicine Universitas Indonesia (No. 633/UN2.F1/ETIJ/2017). This study complied with the 1964 Declaration of Helsinki. Written informed consent was obtained from all the patients' parents.

Conflict of interest The authors declare that they have no conflict of interest.

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