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Original Article

Serum creatinine levels to estimate kidney function in small-for-gestational age and appropriate-for-gestational age newborns

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Abstract

Background The main parameter used to determine renal function in newborns is serum creatinine. Fetal growth restriction during pregnancy can cause the baby to be born small-for-gestational age. Serum creatinine levels in newborns are affected by muscle mass, gestational age, as well as the number of nephrons and kidney development.

Objective To determine the usefulness of serum creatinine levels as an estimate of glomerular filtration rate in small-for-gestational age and appropriate-for-gestational age newborns.

Methods This cross-sectional study was conducted in May-June 2018. The subjects were full term newborn infants consisting of small-for-gestational age and appropriate-for-gestational age groups (16 subjects each), born in Bandung City Regional Public Hospital. Serum creatinine level was tested by the Jaffe method. The estimated glomerular filtration rate was calculated based on serum creatinine, infant height, and a proportionality constant using the original Schwartz method, eGFR = [k * height]/SCr.

Results Of 32 subjects, there were 17 spontaneous deliveries, 14 males, and 18 females. Mean serum creatinine levels in the small-for-gestational age and appropriate-for-gestational age groups were 0.94 (SD 0.36; 95%CI 0.75 to 1.14) mg/dL and 0.69 (SD 0.18; 95%CI 0.60 to 0.79) mg/dL (mean difference 0.25; 95%CI 0.05 to 0.46; P=0.009), respectively. The median estimated glomerular filtration rates (eGFR) in the small-for-gestational age and appropriate-for-gestational age groups were 25.69 mL/min/1.73m^2 and 30.10 mL/min/1.73m^2 (median difference 4.42; 95%CI 2.04 to 15.8; P=0.008), respectively. There was a weak negative correlation between serum creatinine and birth weight (r=–0.344; P=0.027).

Conclusion Serum creatinine levels in small-for-gestational age newborns are significantly higher than in appropriate-for-gestational age newborns. **[Paediatr Indones. 2018;58:305-11; doi: http://dx.doi.org/10.14238/pi58.6.2018.305-11]**.

Keywords: *creatinine; kidney function; small for gestational age*

Acute kidney injury (AKI) in newborns is estimated to be about 0.4–3.5% of hospital admissions and 8% of hospital occurrences, especially for newborns treated in the intensive care unit. In general, newborns with AKI are born prematurely and/or are critically ill.[1] Currently the guidelines used to determine AKI are the RIFLE criteria (risk, injury, failure, loss, and end-stage renal disease).[2] The RIFLE criteria are used to assess the extent to which renal impairment has occurred and monitor the course of the disease, so that renal impairment does not worsen to eventual end-stage renal disease. Serum creatinine level is one of the indicators for assessing renal function both in RIFLE and neonatal-RIFLE (nRIFLE) criteria.[3]

Serum creatinine is an endogenous biological marker used as a parameter to assess renal function through GFR estimates (eGFR). Serum creatinine is thought to be late in detecting a decrease in GFR

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compared to other biological markers such as urinary neutrophil gelatinase associated lipocalin (NGAL) or cystatin-C.[4,5] Serum creatinine levels may increase up to twice as much from normal values, if there has been a 50% decrease in GFR.[6] Serum creatinine levels are strongly influenced by muscle mass, which not only change with age and height, but also with malnutrition due to prolonged hospitalization.[7] Although some limitations exist, serum creatinine is a simple, accurate, and widely used method to estimate kidney function in both the pediatric and newborn populations.[4,8]

Predisposing factors that can increase the incidence of AKI are small-for-gestational age (SGA) as well as prematurity, perinatal asphyxia, congenital heart disease, and sepsis.[9,10] The SGA newborns appear thin because of decreased muscle mass and subcutaneous fat tissue.[11,12] Creatinine is the result of the breakdown of muscle creatine phosphate, and is produced at a fairly constant level by the body depending on muscle mass. The SGA newborns have less muscle mass and higher risk of impaired renal function due to their smaller number of nephrons compared to appropriate-for-gestational age (AGA) newborns.[10]

To our knowledge, there is no normal value of serum creatinine in SGA newborns and normal values of creatinine levels are generally based on gestational age grouping. The relationship between gestational age and renal maturity in newborns may explain why newborns with lower gestational age tend to have higher serum creatinine levels.[13-15] Hence, we aimed to compare serum creatinine levels of SGA and AGA newborns to estimate kidney function.

Methods

This cross-sectional study was conducted in SGA and AGA newborns. The subjects had 37–42 weeks gestational age according to New Ballard Score (NBS), 5th minute APGAR score ≥7, were aged 48-72 hours, and chosen by consecutive sampling. Determination of the minimum required sample size was based on the sample size formula to test the difference of two averages, resulting in 16 subjects per group. Our 32 subjects consisted of 16 SGA and 16 AGA newborns. The diagnosis of SGA was in accordance with the Lubchenco criteria, i.e., if the birth weight was less than the 10th percentile for the infant's gestational age.[11] Exclusion criteria were newborns whose mothers had kidney disease or acute renal impairment, absence of diuresis within 48 hours, respiratory distress syndrome, sepsis or infection, major congenital abnormalities, multiple congenital anomalies, syndromes, or congenital heart disease.

This study was conducted in the Neonatology Inpatient Ward of Bandung City General Hospital during May-June 2018 and was approved by the Medical Research Ethics Committee of Universitas Padjadjaran (UNPAD). Subjects' parents provided written informed consent. Blood specimens of 2-3 mL were drawn from peripheral veins of subjects at 2-3 days of age, then sent to Hasan Sadikin General Hospital, Clinical Pathology Laboratory for serum creatinine testing using the Jaffe method (*Siemens Dimension EXL 200*). The eGFR was calculated based on serum creatinine, infant height, and a proportionality constant using the original Schwartz method, eGFR = [k * height]/SCr. Height was measured in centimeters (cm), serum creatinine was measured in mg/dL, and the constant value (k) for full term infants was 0.45 in the equation.

The data obtained was analyzed using *SPSS® version 24* for *Windows*. The independent variables in this study were SGA and AGA, while the dependent variable was serum creatinine level. Data analysis was done by T-test if the data were normally distributed or Mann-Whitney test if data was not normally distributed. The significance of the test result was determined based on P values <0.05.

Results

General characteristics of study subjects were gestational age, birth weight, body length, age, sex, mode of delivery, APGAR scores, and complications of childbirth, as shown in **Table 1**. The mean birth weight of the SGA group was lower than the AGA group.

As shown in **Table 2**, mean serum creatinine level in the SGA group was significantly higher (0.94 mg/dL) than in the AGA group (0.69 mg/dL) (P=0.009). The median eGFR in the SGA group was significantly lower (25.69 mL/min/1.73 m^2) than in the AGA group (30.10 mL/min/1.73 m^2) (P=0.008).

Table 1. Characteristics of subjects

Characteristics	Total N=32	Group	
		SGA newborns (n=160	AGA newborns (n=16)
Median gestational age, weeks (range)	38 (37–40)	38 (37–38)	38,5 (37–40)
Birth weight, grams			
Median (range)	2470 (2000–3570)	2300 (2000–2400)	3180 (2540–3570)
Mean	2689	2216	3162
Median birth length, cm (range)	47 (44–52)	45 (44–47)	50 (45–52)
Age, n			
2 days	24	13	11
3 days	8	3	5
Sex (n)			
Male	14	6	8
Female	18	10	8
Mode of childbirth (n)			
Spontaneous delivery	17	9	8
Caesarean delivery	15	7	8
Median APGAR (range)			
1 minute	7 (3–8)	7 (4–8)	7 (3–8)
5 minute	9 (7–10)	9 (8–9)	9 (7–10)
Complications of childbirth, (n)			
History of caesarean delivery		0	3
Twin pregnancy		6	0
Premature rupture of membrane		0	1
Cephalopelvic disproportion		0	3
Inadequate uterine contraction		1	0
Breech presentation		0	1

SGA=small-for-gestational age, AGA=appropriate-for-gestational age

Table 2. Serum creatinine levels and eGFR in the SGA and AGA groups

Variables	SGA (n=16)	AGA (n=16)	Mean or median difference (95%CI)	P value
Creatinine levels, mg/dL				
Mean (SD)	0.94 (0.36)	0.69 (0.18)	0.25 (0.05 to 0.46)	0.009[a]
Median (range)	0.82 (0.59 - 1.68)	0.75 (0.30 - 0.97)		
eGFR, mL/min/1.73m^2				
Mean (SD)	24.25 (7.40)	35.72 (14.32)	4.42 (2.04 to 15.87)	0.008[b]
Median (range)	25.69 (12.05 - 34.32)	30.10 (20.87 - 75.00)		

[a]independent T-test; [b]Mann-Whitney test; *significant: P<0.05

Data on creatinine levels are normally distributed so we use T-test analysis from the mean value measured. Conversely, the eGFR data is not normally distributed so we use the Mann-Whitney analysis from the median value measured instead of mean.

Rank Spearman test revealed a significant negative correlation between serum creatinine level and birth weight (r=–0.344; P=0.027), although the relationship was weak based on the correlation coefficient.

Figure 1 describes the data value of creatinine levels in the study subjects. The normality test shows the data are normally distributed so that the mean value of creatinine levels is used. It can be seen here that the mean creatinine levels of SGA infants were higher compared to AGA infants.

Figure 2 describes the data value of eGFR in the research subject. There are values for outliers in the AGA group with high eGFR. The normality test shows that the data is not normally distributed so that

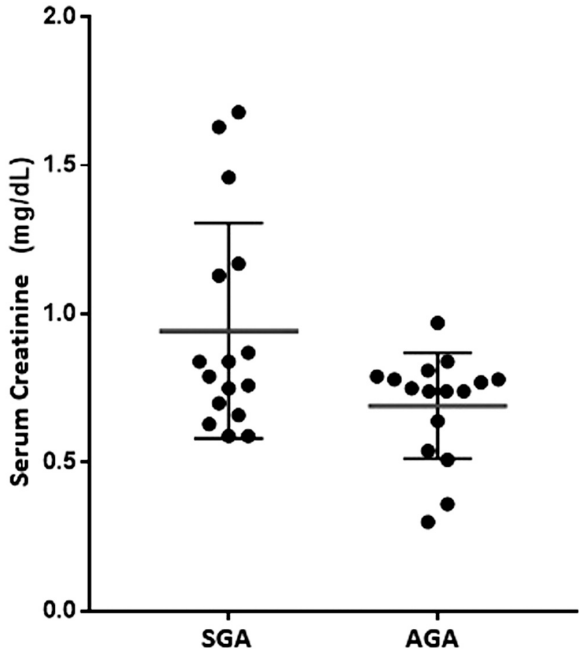

Figure 1. Scatterplot diagram for serum creatinine levels in SGA and AGA infants

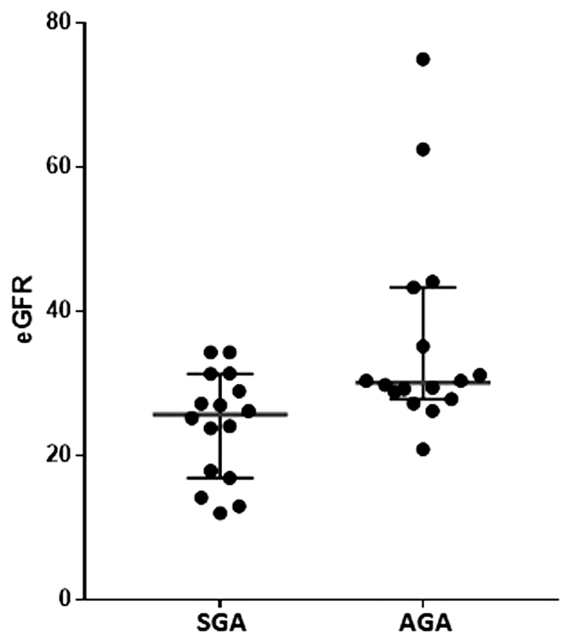

Figure 2. Scatterplot diagram for eGFR value in SGA and AGA infants

the median value of eGFR is used. It can be seen here that the median eGFR value of SGA infants was lower than for AGA infants.

Discussion

Serum creatinine is an endogenous biological marker that is often used to assess renal function via GFR estimation. Creatinine is the product of creatine breakdown. Creatine is synthesized in the liver and present in almost all skeletal muscles in the form of creatine phosphate (CP), an energy storage compound. In the synthesis of ATP (adenosine triphosphate) from ADP (adenosine diphosphate), creatine phosphate is converted into creatine by the catalysis of creatine kinase (CK) enzyme. Along with energy use, a small amount is irreversibly converted to creatinine, which is further filtered by the glomerulus and excreted in the urine.[16,17] Serum creatinine levels in newborns are affected by muscle mass, gestational age, maternal conditions, the number of nephrons, and kidney development. Serum creatinine is thought to be late in detecting a decrease in GFR, and its levels may increase to twice as much as normal if there is a 50% decrease in GFR.[6] Creatinine, in addition to being excreted, is secreted in the renal tubules. Levels increase when capacity of these alternative tubular secretion pathways has been reached. As such, there is a creatinine blind range that limits sensitivity; creatinine levels remain in the normal range during mild GFR decline.[18] Despite some disadvantages, serum creatinine is still an easy and accurate parameter to estimate renal function. Serum creatinine level has been used extensively as an indicator for assessing renal function, including in newborns.[4,19]

In our study, serum creatinine level of SGA newborns was significantly higher (0.94 mg/dL) than the AGA newborns (0.69 mg/dL). Small-for-gestational age infants have birth weight less than the 10th percentile for gestational age, as well as decreased muscle mass and subcutaneous fat tissue caused by intrauterine growth restriction (IUGR).[11] In addition, SGA newborns are at greater risk of impaired renal function due to fewer nephrons compared to AGA newborns.[10]

A previous study reported mean serum creatinine levels in very low birth weight (VLBW), low birth weight (LBW), and normal birth weight infants at 3 days of age to be 0.97 mg/dL, 0.58 mg/dL, and 0.48

mg/dL, respectively. This study also noted mean serum creatinine levels of 3-day-old infants at various gestational ages of 28-32 weeks, 33-37 weeks, and 38-42 weeks with successive results of 1.08 mg/dL, 0.6 mg/dL, and 0.51 mg/dL, respectively.[20] The changes in serum creatinine levels showed relationships between creatinine levels with birth weight and gestational age.[13,17]

An autopsy study reported a lower number of nephrons in SGA infants.[21] Also, another study found significantly lower number of nephrons in SGA infants than in AGA newborns.[22] In addition, Holland *et al.* obtained a linear relationship between the number of glomeruli and birth weight in full term infants, while infants below the 10th percentile for birth weight had 30% fewer glomeruli than infants with birth weight above the 10th percentile.[23] In SGA infants, small kidney weights showed lower number of nephrons, causing the filtration of various proteins including creatinine to be reduced, so that creatinine levels in the circulation increased.[24]

In our study, median eGFR of the SGA group was significantly lower (25.69 mL/min/1.73m^2) compared to the AGA group (30.10 mL/min/1.73m^2) (P=0.008). Heilbron *et al.* reported median GFR in infants at 2-8 days of age to be 39 mL/min/1.73m^2, with a range of 17-60 mL/min/1.73m^2.[25] Marsoosi *et al.* studied the differences of GFR in SGA and AGA infants based on cystatin-C level, and obtained GFRs of 24 (SD 4.4) mL/min in the SGA group and 35.6 (SD 3.2) mL/min in the AGA group.[26] We also noted a similar trend.

The GFR increases as newborns get older; this maturation process of renal function depends on the nephrons already formed. The formation of nephrons stops before the fetus reaches maturation, i.e., at 34-36 weeks gestation.[27] The pattern of kidney growth is centrifugal, with the first nephron formed in the deepest part, i.e., in the juxtamedullary region, and active at birth. The last nephrons formed are in the superficial cortex and undergo further maturation when the juxtamedullary nephron is completed. By the end of pregnancy, the kidneys have approximately 850,000 to 1,000,000 nephrons per kidney. Postnatal maturation continues, with more superficial nephrons attaining proper function. This nephron maturation continues until the age of 18-24 months.[24]

Rank-Spearman test revealed a significant negative correlation between serum creatinine level and birth weight (r=-0.334; P=0.027), with a correlation coefficient indicating a weak relationship. This finding indicates that if the birth weight is low, the serum creatinine level will be higher. Moreover, previous studies support this finding; SGA newborns had fewer nephrons and smaller kidney size based on ultrasound examination.[23,26]

A limitation of our study was potential selection bias when the birth attendant performed the NBS. Newborns who met the inclusion criteria are term newborns based on NBS assessment. According to Ballard *et al.*[28] and Limawal *et al.*,[29] NBS is accurate because it approaches the calculation of the last menstruation period (LMP). In full term infants, the infant's age at the examination does not affect the validity of NBS up to 96 hours of age.[28] However, according to Singhal *et al.*, NBS in SGA newborns overestimated gestational age by 0.7 weeks, especially in the physical maturity aspect.[30]

High serum creatinine in full term newborns even with decreased muscle mass indicates immature kidney function.[31] Given the difference in creatinine levels in SGA and AGA newborns, it is necessary to consider larger-scale studies to determine the creatinine levels that ideally take into account the weight in the SGA and AGA groups. This study provides basic information, so further prospective cohort studies to observe the health outcomes of SGA newborns may also be considered. Considering the kidney immaturity of SGA newborns, this study strengthens the importance of drug dosage adjustment, especially for potentially nephrotoxic drugs.

Conflict of Interest

None declared.

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