ORIGINAL ARTICLE

C-reactive protein and haemoglobin level in acute kidney injury among preterm newborns

Fiva Aprilia Kadi, Tetty Yuniati, Yunia Sribudiani, Dedi Rachmadi

Department of Child Health, Universitas Padjadjaran Medical School/Dr Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.

ABSTRACT

Aim To explore the possibility of C-reactive protein (CRP) and haemoglobin (Hb) in prediction and risk assessment of acute kidney injury (AKI) among preterm newborns. This is believed to be closely related to the incidences of AKI, and could be the most affordable in early detection of AKI.

Methods A case control study was carried out at Dr Hasan Sadikin Hospital in Bandung with a total of 112 preterms divided into two groups: with and without AKI based on the neonatal KDIGO (Kidney Disease: Improving Global Outcomes). CRP and creatinine serum were measured within 6 hours and at 72-96 hours after birth. The routine blood count included haemoglobin, haematocrit, leucocyte, and thrombocyte in the first 24 hours of life.

Results CRP increase was the most influential factor for AKI with sensitivity of 80.6% and specificity of 60.2%. An increase in CRP >0.04 had an aOR (95% CI) of 5.64 (1.89–16.84). Haemoglobin <14.5 g/dL had slightly increased aOR (95% CI) of 1.65 (1.05-8.63)

Conclusion CRP increases >0.04 and level Hb <14.5 g/dL showed acceptable as an early warning for AKI in preterm newborns.

Key words: AKI, anaemia, CRP, neonates, renal injury

Corresponding author:
Fiva Aprilia Kadi
Department of Child Health, Universitas Padjadjaran Medical School/ Dr Hasan Sadikin General Hospital.
Jalan Pasteur no. 38 Bandung 40161, West Java, Indonesia.
Phone +62 8112222908
E-mail: fiva.kadi@unpad.ac.id
ORCID ID: https://orcid.org/0000-0001-5789-6010

Original submission:
05 March 2021;
Revised submission:
23 April 2021;
Accepted:
05 May 2021
doi: 10.17392/1371-21

Med Glas (Zenica) 2021; 18(2):410-414

INTRODUCTION

Acute kidney injury (AKI) among neonates is a common problem in Neonatal Intensive Care Unit (NICU) (1,2). Two studies reported its incidence between 2.4% up to a staggering figure of 56% (3,4). Mortality rate reached 50% or more (1–6). The reported short-term findings were proteinuria and glomerulosclerosis, whereas with delayed or inadequate management its long-term effect could be hypertension and chronic renal failure (3,5,7,8).

Early detection of AKI among neonates is important to prevent these short and or long-term effects as well as mortality. Unfortunately no agreement has been reached on its best screening method, especially as some of the suggested markers were less accurate or impractical or not 24/7 readily unavailable in less developed centres (1–5). The use of elevated/raised serum creatinine (sCr) within 48-72 hours among neonates had been reported to be affected by maternal creatinine level (1–9). The latest diagnostic criteria for AKI as proposed by the Acute Kidney Injury Working Group of KDIGO (Kidney Disease: Improving Global Outcomes) are based on absolute increase of sCr, at least 0.3 mg/dL (26.5 μmol/L) within 48 hours or by a 50% increase in sCr from a baseline within 7 days, or a urine volume of less than 0.5 mL/kg/h for at least 6 hours (7–10).

Acute kidney injury is a complex disorder with a wide variety of etiologies and corresponding risk factors, the main risk factors are prematurity, sepsis, asphyxia and respiratory distress (11,12). It is known that preterm delivery (PTD) is preceded by inflammation and or an infection (13). In addition to systemic inflammation which promotes tubular injury in a newborn, it also increases the risk of renal ischemia/reperfusion injury (11,12).

Prematurity comes with immature organs, including tubular immaturity. In such condition less production to insufficient level of erythropoietin (EPO) may result in a lower haemoglobin level. A previous study had shown that tubular immaturity caused insufficient EPO production, which further explained the presence of anaemia (14,15). As the diagnosis of AKI in preterm infants is very difficult, especially during the 1st until 3rd postnatal days of life, they are the most vulnerable to develop AKI. In order to reduce AKI-related morbidity and mortality of prematurity we need to be able to detect it as early as possible, preferably with the simplest, easiest and most affordable examination (1–5). In this study an increased CRP and low haemoglobin were expected to be early acceptable predictors of AKI. The risk of AKI will affect the choice of antibiotics, because until now the macrolide group with nephrotoxic effects is still empiric therapy.

The aim of this study was to find a new predictor marker for neonatal preterm AKI that is affordable in a country with low health resources such as CRP and haemoglobin.

PATIENTS AND METHODS

Patients and study design

This case control study was conducted at the Hasan Sadikin Hospital Bandung, Indonesia between the March and November 2020. All preterm infants with 30-36 weeks gestational age were enrolled. Neonates born to prolonged premature rupture of membrane (PPROM) more than 18 hours, having 5-minute Apgar score <7 and/or showed respiratory distress (defined by Downe's score >4 within the first 24 hours) were excluded. The sample size formula was used to test the hypothesis of two proportions difference, with a minimum of 52 subjects required per group.

Written informed consents were obtained from all parents of the preterm newborns who were enrolled in this study.

The Ethics Committee of Padjadjaran University approved the study.

Methods

Apart from the routine examination of haemoglobin, haematocrit, leucocyte and thrombocyte count in 24 hours and examinations of CRP and sCr were added during an admission (within 6 hours of life) and in 72-96 hours. Routine haematology examination was done (Sysmex America). CRP and sCr were performed by Siemens USA dimension EXL 200 Integrated Chemistry System. Acute kidney injury diagnostic criteria in this study followed the consensus by the Working Group of KDIGO, which is an absolute increase in sCr, at least 0.3 mg/dL (26.5 μmol/L) within 48 hours, which were recorded between hospital admission and the first 72 hours, or a urine volume of less than 0.5 mL/kg/h for at least 6 hours (7,10,11).

Statistical analysis

The initial set of potential variables associated with AKI was found during univariate analysis, which was significantly different between the two groups ($p<0.05$). A cut-off value for increased CRP level was set based on receiver operating curve (ROC), sensitivity and specificity, while the cut-off value of haemoglobin <14.5 g/dL was based on a previous study (15). The identification of independent predictors of AKI in the whole population was assessed by a logistic regression analysis, which included all variables with $p<0.25$ during bivariate analysis. Results are presented as odds ratio (OR) with 95% confidence intervals (CI).

RESULTS

A total of 112 preterm neonates were enrolled in this study, 56 with AKI and 56 without AKI (no AKI). The baseline clinical characteristics of the patients with and without AKI are shown in Table 1, which shows no significant differences in birth weight, gestational age and sex.

Table 1. Characteristics of 112 premature newborns with and without acute kidney injury (AKI)

Variable	Acute kidney injury		p
	YES (n = 56)	**NO** (n = 56)	
Gender (No; %)			0.85
Male	27 (48.2)	26 (44.8)	
Female	29 (51.8)	27 (47.4)	
Gestational age (weeks)			0.82
Mean (SD)	32.3 (1.4)	32.3 (1.4)	
Median	32	32	
Range	30 – 36	30 – 36	
Birth weight (g)			0.97
Mean (SD)	1665.8 (309.4)	1639 (324.7)	
Median	1630	1645	
Range	1000 – 2210	1100 – 2320	

Leucocytes, haematocrit and thrombocyte counts between the groups were also comparable (Table 2), leaving that preterms with AKI had lower median haemoglobin value (14.37 vs. 18.2; $p<0,05$). The two median values of CRP in preterm neonates with AKI were higher than those without AKI (consecutive comparison results 0.3 vs. 0.15 ($p=0.013$) measured within 6 hours and 0.4 vs. 0.2 ($p=0.016$) measured within 72-96 hours of life. Setting for the largest area under the curve, which was 67.2%, the cut-off point for CRP increase was >0.04. The sensitivity and specificity of CRP increase of >0.04 were 80.6% and 60.2%, respectively (Figure 1).

Table 2. Laboratory parameters characteristics of 112 premature newborns with and without acute kidney injury (AKI)

Parameter	AKI		p
	YES (n = 56)	**NO** (n = 56)	
Haemoglobin (g/dL)			0.03
Mean (SD)	13.57 (2.86)	17.60 (2.19)	
Median	14,37	18,2	
Range	8,00 – 18,97	12,00 – 22,7	
Leucocytes (mm^3)			0.78
Mean (SD)	11.70 (1.93 – 27.6)	11.99 (3,83 – 31.15)	
Median	10.77	11.26	
Range	3.00 – 27,60	3.83 – 31.15	
Haematocrit (%)			0.81
Mean (SD)	51.3 (8.19)	51.9 (6.10)	
Median	50.50	51.95	
Range	23.2 – 71.3	33.4 – 64.9	
Thrombocyte (mm^3)			0.09
Range (SD)	125.78 (70.90)	259.38 (135.86)	
Median	150	244,50	
Range	69 – 390	151 – 460	
CRP 1 (mg/dL)			0.01
Median (SD)	0.36 (2.81)	0.20 (0.59)	
Median	0.3	0.15	
Range	0.09 – 5.00	0.04 – 4.02	
CRP 2 (mg/dL)			0.02
Mean (SD)	1.98 (4.79)	0.58(0.95)	
Median	0.4	0.2	
Range	0.07 – 30.71	0.03 – 5.03	

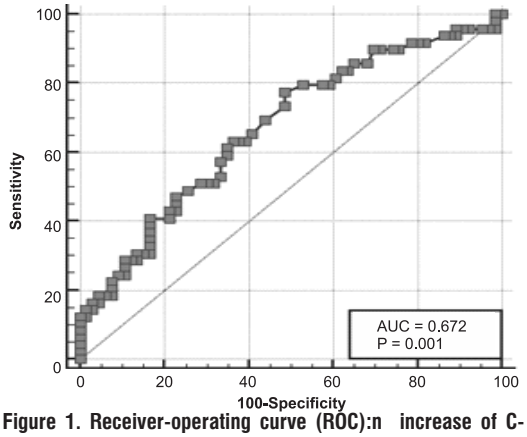

Figure 1. Receiver-operating curve (ROC):n increase of C-reactive protein (CRP) in preterm newborns with acute kidney injury (AKI)

The cut-off points of CRP increase >0.04, haemoglobin <14.5 g/dL and platelet count <150,000/mm^3 were included in the logistic regression calculation (16).

The logistic regression analysis showed that the increase of CRP (>0.04) and Hb level of <14.5 g/dL were the factors associated with preterm AKI (Table 3).

Table 3. Factors associated with acute kidney injury*

Variable	Coeff-B	SE (B)	p	OR_{adj} (CI 95%)
Increasing CRP (>0.04)	1.729	0.558	0.002	5.64 (1.89 – 16.84)
Hb (<14.5 g/dL)	1.437	0.823	0.041	1.65 (1.05 – 8.63)
Thrombocyte (<150.000/mm^3)	0.542	1.450	0.728	0.78 (0.20 – 3.09)

*Based on Multiple Logistic Regression Analysis R2 (Nagelkerke) = 39%; ORadj (CI 95%), Odds ratio adjusted and confident interval 95%, accuracy = 75.0%;

DISCUSSION

Recent studies already showed a few potential biomarkers in AKI are urinary such as neutrophil gelatinase- associated lipocalin (uNGAL), interleukin-18 (uIL-18), netrin-1 (uNTN-1), and sodium hydrogen exchanger isoform 3 (uNHE3) (17,18), but all the biomarkers are expensive and not always available in limited hospitals. Our study intends to identify a usual and simple predictor to prevent AKI in preterm newborns. Prematurity by itself is an independent risk factor for AKI as the result of an incomplete nephrogenesis, immature vasoregulation with high renal vascular resistance, high plasma renin activity, low GFR and decreased inter-cortical perfusion (1).

Mechanisms of CRP in acute AKI were shown by Tang et. Al. (19). CRP through its receptors promotes AKI by activating its downstream pathways including nuclear factor (NF)-κB and transforming growth factor (TGF)-β to cause renal inflammation and macrophage activation. A previous study by Nickavar (20) showed that CRP could be used as a predictive factor for AKI in neonate septicaemia with 83% sensitivity and 60% specificity. In this study we have excluded the risk of infection in preterm infants such as preterm premature rupture of membranes (PPROM), maternal leukocytosis and maternal fever, to determine preterm itself on inflammation. This study has shown that the increase of CRP >0.04 with the AUC of-CRP 0.67 could be used as a biomarker for early detection of preterm AKI with sensitivity 80.6% and specificity 60.2%. This result is strengthened with the data from logistic regression analysis which show that the increase of CRP>0.04 in preterm newborns has 5.64 times higher risk to develop AKI with 95% confident interval and accuracy of 75%. A previous study by Cosentino (21) in patients with acute myocardial infarction showed that the AUC of-CRP could be a prediction of AKI (0.69; p<0.0001). There has been no study of preterm infants with AKI yet (21).

Growing attention has been focused on CRP, a simply detectable inflammation biomarker, as a possible predictor of AKI and it has been recently recognized that CRP actively contributes in the pathogenesis and progression of AKI, by exacerbating local inflammation, impairing the proliferation of damaged tubular epithelial cells (11,19,22).

The tubular maturation is required for initiation EPO production. A human study showed the level of Hb and Haematocrit (Ht) correlated with tubular function (15). The previous study showed anaemia in preterm newborns if Hb less than 14.5 g/dL (15). Our study showed that the median Hb in preterm AKI was less than in preterms with no AKI (14,37 vs 18,2), with statistical logistic regression showing that the level Hb <14.5 g/dL is one of the risk factors of AKI in preterm newborns with OR= 1.65 with 95% confident interval and accuracy of 75%. This study showed that PTD causing tubular immaturity could be a risk factor of AKI in preterm newborns and further important for anaemia due to EPO dysfunction.

This study showed that birth weight, gestational age and sex were not statistically different between preterm newborns with AKI and without AKI. This is the different result from a previous study by Nickavar and Ghobrial (20) that showed that neonatal AKI was influenced by gestational age and birth weight - the lower gestational age and birth weight, the higher the risk of AKI (12,20). In our study this difference is caused by done homogeneity of subjects before enrolment.

Difficulties in serum creatinine interpretation make it more difficult to achieve a consensus regarding AKI definition in newborns. Because of all these difficulties in diagnosing AKI in newborns, new biomarkers are expected to be of greater importance in AKI approach in high-risk neonatal populations such as preterm newborns, but we need a biomarker that is easier to obtain in limited hospitals (20,21).

In conclusion, CRP and Hb estimation do have a role in the diagnosis of AKI in preterm newborns, but the test is not specific enough to be relied upon as the only indicator. The sensitivity is good enough, specificity not high enough, positive and negative predictive values were not calculated in this study. Considering high morbidity and mortality associated with neonatal AKI, CRP and haemoglobin should be considered to be one of the predictors for neonatal AKI.

ACKNOWLEDGEMENT

The authors thank to Abdurachman Sukadi, Sjarief Hidajat and Aris Primadi of Paediatric Neonatology Division for their support and contribution to this research, as well as to the staff of medical records for their assistance with this study.

FUNDING

An Academic Leadership Grant (ALG) from Padjadjaran University (Grant number 855/UN6.3.1/PL/2017) supported the work.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Viswanathan S, Mhanna MJ. Acute Kidney Injury in Premature Infants. J Clin Pediatr 2013; 1.
2. Luyckx VA. Preterm birth and its impact on renal health. Semin Nephrol 2017; 37:311–9.
3. Bruel A, Rozé J-C, Quere M-P, Flamant C, Boivin M, Roussey-Kesler G, Allain-Launay E. Renal outcome in children born preterm with neonatal acute renal failure: IRENEO—a prospective controlled study. Pediatr Nephrol 2016; 31:2365–73.
4. Stojanovic V, Barisie N, Milanovic B, Doronjski A. Acute kidney injury in preterm infants admitted to a neonatal intensive care unit. Pediatr Nephrol 2014; 29:2213–20.
5. Black MJ, Sutherland MR, Gubhaju L. Effects of Preterm Birth on the Kidney. In: Sahay M. Editor. Basic Nephrology and Acute Kidney Injury. 1st ed. IntechOpen, London, UK: IAD Press 2011; 61–88.
6. Momtaz H. Sabzehei M, Rasuli B, Torabian S, The main etiologies of acute Kidney injury in the newborns hospitalized in the neonatal intensive care unit. J Clin Neonatol 2014; 3: 99.
7. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev 2016; 37:85-97.
8. Ottonello G, Dessì A, Neroni P, Trudu ME, Manus D, Fanos V. Acute kidney injury in neonatal age. J Pediatr Neonatal Individ Med 2014; 3:2–5.
9. Durkan AM, Alexander RT. Acute kidney injury post neonatal asphyxia. J Pediatr 2011; 158(Suppl 2):29–33.
10. KDIGO. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. J Int Soc Nephrol 2012; 21.
11. Marenzy G, Consentino N, Bartorelli A. Acute kidney injury in patients with acute coronary syndromes. Heart 2015; 101:1778–85.
12. Ghobrial EE, Elhouchi SZ, Eltatawy SS, Beshara LO. Risk factors associated with acute kidney injury in newborn. Saudi J Kidney Dis Transpl 2018; 29:81–7.
13. Bullen B, Jones NM, Holzman CB, Tian Y, Senagore PK, Thorsen P, Skogtrands K, Hougaard DM, Sikorskii A. C-reactive protein and preterm delivery. Reprod Sci 2013; 20:715–22.
14. Asada N. Tubular immaturity causes erythropoietin-deficiency anemia of prematurity in preterm neonates. Sci Rep 2018; 8:4448.
15. Kates EH, Kate J. Anemia and polycythemia in the newborn. Pediatr Rev 2007; 28:33-4.
16. Siller L, Slambrouck CV, Lapping-carr G. Neonatal thrombocytopenia: etiology and diagnosis. Pediatr Ann 2015; 44:175–80.
17. Oncel MY, Canpolat FE, Arayici S, Dizdar EA, Uras N, Oguz SS. Urinary markers of acute kidney injury in newborns with perinatal asphyxia. Renal Failure 2016; 38:882–8.
18. Libório AB, Branco KMPC, Torres De Melo Bezerra C. Acute kidney injury in neonates: From urine output to new biomarkers. Biomed Res Int 2014; 2014:601568.
19. Tang Y, Kwong-Mak S, Xu AP, Yao Lan -H. Role of C□reactive protein in the pathogenesis of acute kidney injury. Nephrology (Carlton) 2018); 23(Suppl 4):50-52.
20. Nickavar A, Khosravi N, Mazouri A. Predictive Factors for Acute Renal Failure in Neonates with Septicemia. Arch Pediatr Infect Dis 2017; 5:e61627.
21. Cosentino N, Genovese S, Campodonico J, Bonomi A, Lucci C, Milazzo V, Moltrasio M, Biondi ML, Riggio D, Veglia F, Ceriani R, Celentano K, Metrio MD, Rubino M, Bartorelli AL, Marenzi G. High-sensitivity c-reactive protein and acute kidney injury in patients with acute myocardial infarction: a prospective observational study. J Clin Med 2019; 8:2192.
22. Pageus M, McCrory M, Zarjou A, Szalai A. C-reactive protein exacerbates renal ischemia reperfusion injury (P4021). J Immunol 2013: 190 (Suppl):131–11.
23. Stritzke A, Thomas S, Amin H, Fusch C, Abhay L. Renal consequences of preterm birth. Mol Cel Pediatr 2017; 4:1–9.