# Neutrophil gelatinase associated lipocalin: a new marker for early diagnosis of acute kidney injury in ICU

Hoda M. El-Sayed[a], Hayam H. Mansour[a], Essam Abd El-Aziz Abd El-Mobdy[c], Ragaa R. Mohammed[a], Ahmed N. Ajam[d], Haytham S. Abd El-Hamid[b], Mohammed S. El-Din Zaky[e], Mohamed H. Biomy[c]

***Introduction*** Serum creatinine is a late marker of acute kidney injury (AKI) and its alterations are often not apparent until 48–72 h postinjury. Urine and plasma neutrophil gelatinase associated lipocalin (NGAL) measurements may represent early biomarker of AKI in intensive care, being able to predict this complication ~2 days prior to the rise in serum creatinine.

***Aim*** To evaluate the role of plasma NGAL level as a marker for early diagnosis of AKI in ICU patients and if it is related to the severity of kidney injury and renal outcomes.

***Patients and methods*** Our study including 40 ICU patients, 20 patients admitted for surgical causes and 20 admitted for medical causes. For all participants, clinical examination, laboratory investigations were done in the form of serum creatinine, plasma NGAL, with daily measurement of urine output and estimation of glomerular filtration rate. Patients with AKI were classified according to Risk, Injury, Failure, Loss, End stage renal disease (RIFLE) classification, non-AKI patients served as controls for comparison.

***Results*** Out of 40 patients, 14 (35%) developed AKI, and according to RIFLE classification, seven (17.5%) were class R, four (10%) were class I, three (7.5%) were F. There was statistically significant comparison between operative time and development of AKI in surgical patients. Also patients who did not develop AKI had lowest NGAL level while AKI group showed rising level with RIFLE classes.

***Conclusion*** Plasma NGAL can be used as early biomarker for diagnosis of AKI and its level is increasing with the severity of AKI classes in ICU patients

*Sci J Al-Azhar Med Fac, Girls* 2017 1:1–6



**The Scientific Journal of Al-Azhar Medical Faculty, Girls** 2017 1:1–6

**Keywords:** acute kidney injury, ICU, neutrophil gelatinase associated lipocalin

[a]Internal Medicine Department, Faculty of Medicine for Girls, [b]Internal Medicine Department, Faculty of Medicine for Boys, Al Azhar University, Cairo, [c]Internal Medicine Department, [d]Clinical Pathology Department, Military Medical Academy, [e]Internal Medicine Department, National Institute of Urology and Nephrology,Cairo, Egypt

Correspondence to Hayam H. Mansour, MD, Internal Medicine Department, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.
Tel: 00201004847812;
e-mail: drhayam1971@gmail.com

**Received** 21 May 2017 **Accepted** 25 July 2017

## Introduction

Acute kidney injury (AKI) is seen in as many as 15% of hospitalized individuals and in about 40% of the patients referred to ICUs. Eighty percent of the ICU patients with AKI die, and 13% of the survivors require dialysis. These rates have remained virtually unchanged despite the optimization of care, as a consequence of difficult and late diagnosis of AKI, advanced patient age, presence of multiple comorbidities, and patients undergoing a greater number of invasive procedures [1]. Even the mildest degrees of AKI have been independently associated with significantly increased morbidity and mortality in adults and children, reinforcing the clinical importance of all grades of AKI [2].

The use of serum creatinine as a marker of AKI has significant limitations; it is insensitive to small changes in glomerular filtration rate (GFR), late marker of altered GFR, nonspecific to disease process and altered by clinical characteristics, for example, age, weight, sex, volume status and medication use. Subjects with AKI particularly those with baseline impairment in renal function often have a significant decline in GFR before any observable change in serum creatinine [3]. Furthermore, serum creatinine is a late marker of disease and alterations are often not apparent until 48–72 h postinjury, leading to missed early therapeutic opportunities when treatments may be most effective [4].

It is for these well-recognized limitations of serum creatinine and for the devastating clinical implications surrounding AKI that a search for new noninvasive markers of renal injury has been pushed to the forefront of active research [5].

Urine and plasma neutrophil gelatinase associated lipocalin (NGAL) measurements have been demonstrated to represent early biomarkers of AKI in a heterogeneous



 DOI: 10.4103/sjamf.sjamf_3_17

pediatric intensive care setting, being able to predict this complication ~2 days prior to the rise in serum creatinine, with high sensitivity [6]. In a multicenter study of children with diarrhea-associated hemolytic uremic syndrome, urine NGAL, obtained early predicted the severity of AKI and dialysis requirement with high sensitivity [7]. In adults undergoing cardiopulmonary bypass, those who subsequently required renal replacement therapy were found to have the highest urine NGAL values soon after surgery [8]. Furthermore a number of studies have demonstrated that elevated plasma NGAL level is associated with higher mortality rate and can be accounted for a mortality marker [9].

The aim of this study is to evaluate the role of plasma NGAL level as a marker for early diagnosis of AKI in ICU patients and its relation to the severity of kidney injury and renal outcomes in those patients.

## Patients and methods

### Patients

Forty patients who were selected randomly from ICU in Al Maadi Armed Forced Medical Complex. These randomized controled study performed from February 2013 to March 2014. From those 40 patients 24 (60%) were males and 16 (40%) were females. All patients were allocated from ICU, medical or surgical within 12 h of admission. Their age ranged from 26 to 90 years with mean±SD of 57.42±12.02 years.

Patients with evidence of chronic kidney disease, obstructive uropathy or urological malignancy or had urological procedure or surgery immediately before ICU admission, renal transplant, nephrectomy, sepsis, or chronic obstructive pulmonary disease were excluded. Full medical history and thorough medical examination were done for each patient on admission. Written consent was taken from the patient or his family.

### Methods

Serum creatinine was done on ICU admission then daily for 1 week for all patients. At least one serum creatinine level, presurgical or preprocedure were documented from patients prior to presentation to ICU. Also plasma NGAL was measured for each patient on admission using Human Lipocalin-2L NGAL ELISA Kit (Boster Biological Technology Co. Ltd, Pleasanton, California, USA) [10]. Daily measurement of urine output for 1 week with estimated glomerular filtration rate (eGFR) pre-ICU admission then daily for 1 week by using MDRD formula.

Patients with AKI were classified according to Risk, Injury, Failure, Loss, End stage (RIFLE) classification and Acute Kidney Injury Network staging (Tables 1 and 2) [11].

### Statistical analysis

The data were analyzed using statistical program for the social sciences (SPSS), version 21.0.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). A one-way analysis of variance was used to compare between more than two means while $\chi^2$-test was used to compare proportions between qualitative parameters. Pearson's correlation coefficient ($r$) test was used to assess the strength of association between different values and NGAL. Receiver operator

**Table 1 Acute Kidney Injury Network system for acute kidney injury**

| Stage | Serum creatinine criteria | Urine output criteria |
|---|---|---|
| 1 | Serum creatinine increase >26.5 μmol/l (≥0.3 mg/dl) or increase to 1.5–2.0-fold from baseline | <0.5 ml/kg/h for 6 h |
| 2 | Serum creatinine increase >2.0–3.0-fold from baseline | <0.5 ml/kg/h for 12 h |
| 3 | Serum creatinine increase >3.0–fold from baseline or serum creatinine ≥354 μmol/l (≥4.0 mg/dl) with an acute increase of at least 44 μmol/l (0.5 mg/dl) or need for RRT | <0.3 ml/kg/h for 24 h or anuria for 12 h or need for RRT |

RRT, renal replacement therapy.

**Table 2 Risk, Injury, Failure, Loss, End criteria for classifying acute kidney injury**

| Class | Urine output criteria | Estimated glomerular filtration rate criteria |
|---|---|---|
| Risk (R) | <0.5 ml/kg/h×6 h | Serum creatinine×1.5 or decreased eGFR >25% |
| Injury (I) | <0.5 ml/kg/h×12 h | Serum creatinine×2 or decreased eGFR >50% |
| Failure (F) | <0.3 ml/kg/h×24 h, or anuria×12 h | Serum creatinine×3 or serum creatinine ≥4 or decreased eGFR >75% |
| Loss (L) | | Persistent acute renal failure=complete loss of kidney function >4 weeks |
| End stage (E) | | End-stage kidney disease >3 months |

eGFR, estimated glomerular filtration rate.

characteristic analysis was used to explore the ability of NGAL to predict AKI within 1 week when measured on admission. *P*-value less than 0.05 was considered significant and less than 0.01 was considered as highly significant.

## Results

Twenty (50%) patients with surgical causes and 20 (50%) with medical causes, were admitted to the study. Patients on admission diagnosed as; 11 (27%) with ischemic heart disease for coronary artery bypass graft, eight (20%) patients with cerebral infarction, seven (17.5%) patients with cerebral hemorrhage, five (12.5%) patients with hepatic precoma, four (10%) with liver cell failure for liver transplantation. Ten (5%) patients mitral regurge for mitral valve replacement, another two (5%) with mitral stenosis for mitral valvotomy and one (2.5%) had aortic stenosis for aortic valve replacement (Table 3). Fourteen (35%) patients developed AKI of whom seven (17.5%) were class R, four (10%) class I, three (7.5%) F according to RIFLE classification while 10 (25%) of patients died in ICU (Table 4).

There was a highly significant increase in the mean±SD of operative duration (304.00±78.63) when compared to that of the non AKI group (219.00±60.08) (*P*? 0.014), while there was no significant relationship between presence of complications during surgery or receiving contrast media and developed AKI (Table 5). Interestingly, we did not find significant relationship

**Table 3 Clinical diagnosis of 40 patients admitted to ICU included in the study**

| ICU [*n* (%)] | |
|---|---|
| Medical | 20 (50) |
| Surgical | 20 (50) |
| Diagnosis at admission [*n* (%)] | |
| IHD for CABG | 11 (27.5) |
| Cerebral infarction | 8 (20) |
| Cerebral hemorrhage | 7 (17.5) |
| Hepatic precoma | 5 (12.5) |
| Liver cell failure for liver transplantation | 4 (10) |
| Mitral regurge for mitral valve replacement | 2 (5) |
| Mitral stenosis for valvotomy | 2 (5) |
| Aortic stenosis for aortic valve replacement | 1 (2.5) |

CABG, coronary artery bypass graft; IHD, ischemic heart disease.

**Table 4 Patients characteristics at discharge from ICU**

| Outcomes [*n* (%)] | |
|---|---|
| Discharge | 30 (75) |
| Death | 10 (25) |
| AKI by RIFLE [*n* (%)] | |
| Yes | 14 (35) |
| No | 26 (65) |
| RIFLE [*n* (%)] | |
| R | 7 (17.5) |
| I | 4 (10) |
| F | 3 (7.5) |
| Staging of AKI [*n* (%)] | |
| 1 | 7 (17.5) |
| 2 | 5 (12.5) |
| 3 | 5 (12.5) |
| RRT [*n* (%)] | |
| HD | 2 (5) |
| CRRT | 1 (2.5) |

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; F, failure; HD, hemodialysis; I, injury; R, risk; RIFLE, Risk, Injury, Failure, Loss, End.

**Table 5 Comparison between acute kidney injury and nonacute kidney injury patients and some risk factors**

| Surgical patients | Non-AKI (*N*=10) [*n* (%)] | AKI (*N*=10) [*n* (%)] | *t* | *P* |
|---|---|---|---|---|
| Operative duration (for surgical patients) (min) | 219.00±60.08 | 304.00±78.63 | –2.716 | 0.014* |
| Complication during surgery | | | | |
| No | 6 (60) | 2 (20) | 3.333 | 0.068 |
| Yes | 4 (40) | 8 (80) | | |
| Contrast exposure | | | | |
| No | 3 (30) | 6 (60) | 1.818 | 0.178 |
| Yes | 7 (70) | 4 (40) | | |

AKI, acute kidney injury. *$P<0.01$, highly significant.

**Table 6 Comparison between different classes of Risk, Injury, Failure, Loss, End classification as regard neutrophil gelatinase associated lipocalin level**

| | | AKI (*N*=14) | | | | |
|---|---|---|---|---|---|---|
| Variable | No-AKI (*N*=26) | RIFLE R (*N*=7) | RIFLE I (*N*=4) | RIFLE F (*N*=3) | Total (*N*=14) | *P* |
| NGAL (ng/ml) | 124.42±38.31 | 264.29±91.58 | 365.00±173.11 | 843.33±225.02 | 417.14±211.86 | <0.01** |

Receiver operating characteristics study was used for evaluating the best cutoff value of NGAL for early diagnosis of AKI in in ICU patients showed that, cutoff value of 143 ng/ml with sensitivity 92.9% and the specificity was 80.8% (Fig. 1). AKI, acute kidney injury; NGAL, neutrophil gelatinase associated lipocalin; RIFLE, Risk, Injury, Failure, Loss, End. **$P<0.01$, highly significant.

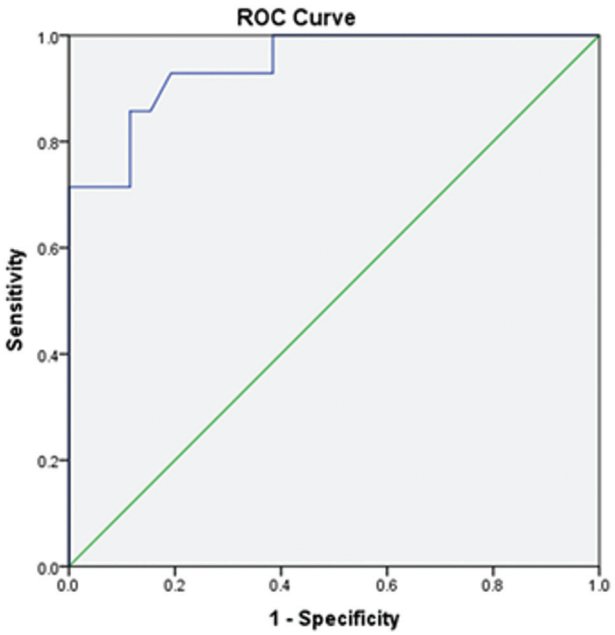
between presence of diabetes and hypertension and development of AKI in postoperative period.

There was a significant increase in plasma NGAL levels in AKI patients with different RIFLE classes compared with those who did not developed AKI ($P \leq 0.01$) (Table 6 and Fig. 1).

The majority of patients with NGAL level of at least 143 ng/ml, 13 (72.2%) patients developed AKI while 21 (95.5%) of the patients who had NGAL level less than 143 ng/ml did not developed AKI ($P<0.01$) (Table 7). In the study there was insignificant correlation between plasma NGAL level and patient's outcome and renal replacement therapy.

Also there was a highly significant positive correlation between plasma NGAL and serum creatinine ($P \leq 0.01$) and highly significant negative correlation with urine output (UOP) from day 1 ($P \leq 0.01$) and with eGFR from day 2 ($P \leq 0.01$) (Table 8).

**Figure 1**




Receiver operator characteristic curve for detection of NEGAL cut off.

## Discussion

Patients admitted to ICU have higher levels of comorbidities than other patient categories. Also, the exact onset of a renal insult in intensive care patients is often less clear, and this further hampers the interpretation of elevated NGAL in these patients. NGAL fulfils many characteristics for an ideal biomarker for AKI. It is rapidly induced and released from the injured distal nephron in experimental models and human disease; its urine and plasma concentrations increase proportionally to severity and duration of renal injury; its concentration rapidly decreases with attenuation of renal injury and it is readily and easily measured in plasma and urine [12].

Our aim in the present study is to assess the plasma level of NGAL for early detection of AKI in the ICU admitted patients and if it has a role in predicting renal outcomes in those populations. Forty randomly selected patients from surgical and medical ICUs with different diagnosis including medical 20 (50%) and surgical 20 (50%) were studied.

**Table 7 Comparisons between patients with neutrophil gelatinase associated lipocalin less than 143 ng/ml and patients with neutrophil gelatinase associated lipocalin of at least 143 ng/ml and Risk, Injury, Failure, Loss, End classes and patients outcomes**

| | NGAL <143 ng/ml (*N*=22) [*n* (%)] | NGAL ≥143 ng/ml (*N*=18) [*n* (%)] | *P* |
|---|---|---|---|
| Outcomes | | | |
| Discharge | 17 (77.3) | 13 (72.2) | 0.714 |
| Death | 5 (22.7) | 5 (27.8) | |
| AKI | | | |
| Yes | 1 (4.5) | 13 (72.2) | ≤0.01** |
| No | 21 (95.5) | 5 (27.8) | |
| RIFLE | | | |
| No | 21 (95.5) | 5 (27.8) | ≤0.01** |
| R | 0 (0) | 7(38.9) | |
| I | 1 (4.5) | 3 (16.7) | |
| F | 0 (0) | 3 (16.7) | |
| RRT | | | |
| No | 22 (100) | 15(83.3) | 0.138 |
| HD | 0 (0) | 2 (11.1) | |
| CRRT | 0 (0) | 1 (5.6) | |

AKI, acute kidney injury; NGAL, neutrophil gelatinase associated lipocalin; RIFLE, Risk, Injury, Failure, Loss, End stage; RRT, renal replacement therapy. **$P<0.01$ highly significant.

**Table 8 Correlation of serum neutrophil gelatinase associated lipocalin levels and serum creatinine, estimated glomerular filtration rate and urine output**

| | Neutrophil gelatinase associated lipocalin | |
|---|---|---|
| | *r* | *P* |
| Serum creatinine | | |
| Day 0 | 0.190 | 0.240 |
| Day 1 | 0.893 | <0.01** |
| Day 2 | 0.910 | <0.01** |
| Day 3 | 0.859 | <0.01** |
| Day 4 | 0.549 | <0.01** |
| Day 5 | 0.910 | <0.01** |
| Day 6 | 0.928 | <0.01** |
| Day 7 | 0.937 | <0.01** |
| Estimated glomerular filtration rate | | |
| Day 0 | −0.019 | 0.909 |
| Day 1 | −0.282 | 0.078 |
| Day 2 | −0.972 | <0.01** |
| Day 3 | −0.651 | <0.01** |
| Day 4 | −0.622 | <0.01** |
| Day 5 | −0.755 | <0.01** |
| Day 6 | −0.712 | <0.01** |
| Day 7 | 0.759 | <0.01** |
| Urine output | | |
| Day 0 | −0.270 | 0.092 |
| Day 1 | −0.735 | <0.01** |
| Day 2 | −0.720 | <0.01** |
| Day 3 | −0.727 | <0.01** |
| Day 4 | −0.703 | <0.01** |
| Day 5 | −0.713 | <0.01** |
| Day 6 | −0.739 | <0.01** |
| Day 7 | −0.720 | <0.01** |

**$P<0.01$, highly significant.

In our study, there was statistical positive significant relation between operative duration and the subsequent development of AKI in postoperative period. There was an increase in the operative time among the AKI group. This was in parallel with Li *et al.* [13], and Teixeira *et al.* [14], who present a linear relationship between time on cardiopulmonary bypass machine and the development of postoperative AKI. Moreover, they were identical with ours regarding the insignificance of diabetes and hypertension as a risk factor for development of AKI in postoperative period.

While in our study we did not find statistical significant relationship with intraoperative complications and the later development of AKI. Karkouti *et al.* [15], and Teixeira *et al.* [14], did find a linear relationship between surgical complications and the later development of AKI.

Patients without AKI show lesser NGAL level compared to AKI patients with increasing its level in parallel to RIFLE classes; class R then class I and class F showed the highest NGAL level. Haase-Fielitz *et al.* [16] found that, the discriminatory ability of NGAL for AKI increased with increasing severity as classified by risk of renal dysfunction; injury to the kidney; failure of kidney function; loss of kidney function; and end-stage kidney disease criteria.

Receiver operator characteristic analysis for detection of best cutoff value for early diagnosis of AKI in our study, showed that the sensitivity of serum NGAL for diagnosis of AKI within the first week of admission at ICU was 92.9% and specificity was 80.8% at cut off value of 143 ng/ml.

Various authors have reported different NGAL cut off values, Mishra *et al.* [17] reported cut off value of 50 ng/ml, Krawczeski *et al.* [18], of 45 ng/ml, while Haase-Fielitz *et al.* [16], reported cut off value of 150 ng/ml and Perry *et al.* [19], and Tuladhar *et al.* [20], reported 350 and 430 ng/ml, respectively, these difference may be due to difference in patients age included in their studies, or due to ethnic backgrounds, or the big numbers of patients included in these studies, as well as the different inclusion and exclusion criteria in these studies.

In our studied patients, those admitted with surgical causes (72.2%) had higher levels than those with medical causes (27.8%), many mechanisms may explain these results include ischemia-reperfusion injury caused by low mean arterial pressures and loss of pulsatile renal blood flow, exogenous toxins caused by contrast media, NSAIDs, endogenous toxins caused by iron released from hemolysis, and inflammation and oxidative stress from contact with bypass circuit, surgical trauma and intra-renal inflammatory responses. These mechanisms of injury are likely to be active at different times with different intensities and may act synergistically [21].

Our study showed that, NGAL was successful in predicting AKI, and failed to predict outcomes and the need for dialysis, while a number of studies have demonstrated the utility of early NGAL measurements for predicting the severity and clinical outcomes of AKI. In children undergoing cardiac surgery, early postoperative plasma NGAL levels strongly correlated with duration and severity of AKI, length of hospital stay and mortality [22]. We also noted an early rise of serum NGAL levels on day 0 prior to rise of serum creatinine and 1 day prior to decrease in urine output, and 2 days prior to decrease in eGFR, in one study performed in children undergoing cardiac surgery evaluating urinary NGAL, The diagnosis using serum creatinine was delayed by 2–3 days after

cardiopulmonary bypass while urine NGAL levels increased 15-fold within 2 h and by 25-fold at 4 and 6 h after cardiopulmonary bypass [23].

## Conclusion

According to our study, plasma NGAL can be used as early biomarker for diagnosis of AKI in ICU patients preceding the rising of serum creatinine and drop of GFR. Further studies on a large number of ICU patients are needed to assess the relation between plasma NGAL and AKI outcomes.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1 Peres LA, Wandeur V, Matsuo T. Predictors of acute kidney injury and mortality in an intensive care unit. *J Bras Nefrol* 2015; **37**:38–46.

2 Symons JM, Chua AN, Somers MJ, Baum MA, Bunchman TE, Benfield MR, *et al.* Demographic characteristics of pediatric continuous renal replacement therapy. *Clin J Am Soc Nephrol* 2007; **2**:732–738.

3 Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol* 2009; **20**:672–679.

4 Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, *et al.* Liver fatty acid binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2008; **73**:465–472.

5 Slocum JL, Heung M, Pennathur S. Marking renal injury: can we move beyond serum creatinine?. *Transl Res* 2012; **159**:277–289.

6 Devarajan P. Neutrophil gelatinase-associated lipocalin: apromising biomarker for human acute kidney injury. *Biomark Med* 2010; **4**: 265–280.

7 Trachtman H, Christen E, Cnaan A, Patrick J, Mai V, Mishra J, *et al.* Urinary neutrophil gelatinase-associated lipocalcin in D+HUS: a novel marker of renal injury. *Pediatr Nephrol* 2006; **21**:989–994.

8 Bagshaw SM, George C, Bellomo R. ANZICS Database Management Committee. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; **23**: 1569–1574.

9 Cruz D, de Cal M, Garzotto F, Mark A, Paolo P, Valentina P, *et al.* Plasma neutrophil gelatinase associated liipiocalin is an early biomarker for acute kidney injury in an adult ICU population. *Intensive Care Med* 2010; **36**:444–451.

10 Kjeldsen L, Johnsen AH, Sengelov H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. *J Biol Chem* 1993; **268**:10425–10432.

11 Kidney diseaseImproving Global Outcomes (KDIGO). Acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**:1–138.

12 Howell E, Sen S, Palmieri T, Godwin Z, Bockhold J, Greenhalgh D, *et al.* Point-of-care B-type natriuretic peptide and neutrophil gelatinase-associated lipocalin measurements for acute resuscitation: a pilot study. *J Burn Care Res* 2015; **36**:26–33.

13 Li S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, Coca SG, *et al.* Incidence, risk factor, and outcome of acute kidney injury after pediatric cardiac surgery – a prospective multicenter study. *Crit Care Med* 2011; **39**:1493–1499.

14 Teixeira C, Rosa R, Rodrigues N, Mendes I, Peixoto L, Dias S, *et al.* Acute kidney injury after major abdominal surgery: a retrospective cohort analysis. *Crit Care Res Pract* 2014; **2014**:132175.

15 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, *et al.* Advance targeted transfusion in advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. *Anesthesiology* 2012; **116**:613–621.

16 Haase-Fielitz A, Bellomo R, Devarajan P, Bennett M, Story D, Matalanis G, *et al.* The predictive performance of plasma neutrophilgelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. *Nephrol Dial Transplant* 2009; **24**:3349–3354.

17 Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury following cardiac surgery. *Lancet* 2005; **365**:1231–1238.

18 Krawczeski CD, Woo JG, Wang Y, Bennett MR, Ma Q, Devarajan P. Neutrophil gelatinase associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. *J Pediatr* 2011; **158**:1009–1015.

19 Perry TE, Muehlschlegel JD, Liu KY, Fox AA, Collard CD, Shernan SK, *et al.* Plasma neutrophil gelatinase associated lipocalin and acute postoperative kidney injury in adult cardiac surgical patients. *Anesth Analg* 2010; **110**:1541–1547.

20 Tuladhar SM, Püntmann VO, Soni M, Punjabi PP, Bogle RG. Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase associated lipocalin after cardiopulmonary bypass. *J Cardiovasc Pharmacol* 2009; **53**:261–266.

21 Bellomo R, Auriemma S, Fabbri A, D'Onofrio A, Katz N, McCullough PA, *et al.* The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). *Int J Artif Organs* 2008; **31**:166–178.

22 Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, *et al.* Plasma NGAL predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. *Crit Care* 2007; **11**:R127.

23 Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, *et al.* Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol* 2008; **3**:665–673.