VOLUME-7, ISSUE-11, NOVEMBER-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

General Medicine

EFFICACY OF NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN AS AN EARLY MARKER OF AKI IN ADULT ICU PATIENTS

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ABSTRACT

Early diagnosis of AKI currently depends on detection of reduced kidney function by the rise in serum creatinine concentration, which is a delayed and unreliable measure in the acute setting. The lack of specific biomarkers for early recognition of AKI has meant a delayed onset of treatment. NGAL fulfils many of the characteristics important for a useful AKI biomarker. NGAL represents a significant component in the pathophysiology of the disease. The concentration of NGAL in urine or plasma rises rapidly in a dose-dependent manner that is proportional to the degree of damage. **Aims and objectives** Assessing efficacy of NGAL as a marker of early development of acute kidney injury in adult ICU patients and compare among AKI and NON-AKI patients. **Method** It is a hospital based prospective study of 53 patients, which is conducted at SREE BALAJI MEDICAL COLLEGE CHENNAI. The material for study is formed by adult patients admitted to adult ICU. Between DECEMBER 2016 – AUGUST 2018 fulfilling the inclusion and exclusion criteria. **Conclusion** Our study demonstrated that admission blood NGAL measurements are useful in early diagnosis of AKI.

KEYWORDS : AKI, NGAL

INTRODUCTION

Acute kidney injury (AKI) is one of the major healthcare issues in medicine today. Reportedly occurring in 1–32% of all hospital admissions and 10–90% of intensive care unit admissions. The wide variation is due to different criteria used to define AKI.

However, a diagnosis of AKI is consistently associated with an increase in both short- and long-term morbidity and mortality. Even the mildest forms of AKI are independently associated with an increase in early & long-term mortality, the risk increasing as severity of renal injury increases.

Furthermore, there is an increase in incidence of AKI. Based on a large administrative database study of hospital admissions from 1992 to 2001, Xue et al. estimated an increase of 11% per year in the incidence of AKI. However, of even greater concern is the failure to develop effective interventions to prevent occurrence or treat AKI, meaning that the current line of management remains directed toward supportive therapy while awaiting recovery of renal function.

A major setback to developing effective therapeutic interventions to combat AKI has been the limited ability to accurately detect significant renal injury in a timely manner. Serum creatinine has been the predominant marker of renal function in clinical practice for more than half a century and its limitations are well documented. As a marker of renal function rather than injury, the nonlinear relationship between glomerular filtration rate and serum creatinine means glomerular filtration rate may decrease by more than 50% from normal before the rise in serum creatinine is significant. This makes serum creatinine insensitive to small but significant reductions in glomerular filtration rate. Furthermore, serum concentration is influenced by numerous non-renal factors including age, race, gender, and muscle mass as well as factors such as drug metabolism, protein intake, per operative fluid administration and hydration status. However, another limitation in the use of creatinine to diagnose AKI is the inevitable delay between injury and the subsequent rise in serum creatinine. Although serum creatinine may begin to increase during sepsis/hypotension/injury to kidney/post operatively, majority of patients who develop AKI do not meet diagnostic criteria until day 2 of presentation or post operative status. As a result, by the time serum creatinine can identify AKI, the inciting injury may be days old.

Acknowledging the inherent deficiencies of serum creatinine to diagnose AKI, the American Society of Nephrology in 2005 designated identification, characterization, and development of new AKI biomarkers as a key research area. An ideal biomarker would enable us to identify patients at highest risk for AKI in a timely manner, thus allowing early and potentially effective intervention. Characteristics of the ideal AKI biomarker have been described and include early identification of injury, stratification according to injury severity, etiologic specificity for the injury, and providing valuable prognostic information.

Many new promising biomarkers of AKI have been identified, both in urine and plasma, and are currently the subject of ongoing studies defining their clinical utility.

AIMS AND OBJECTIVES:

AIMS

To evaluate Neutrophil Gelatinase Associated Lipocalin (NGAL) as a marker of early development of acute kidney injury in adult ICU patients.

Objective:

Assessing efficacy of NGAL as a marker of early development of acute kidney injury in adult ICU patients and compare among AKI and NON-AKI patients.

METHODS

It is a hospital based prospective study of 53 patients, which is conducted at Sree Balaji Medical College and hospital, Chennai. The material for study is formed by adult patients admitted in adult ICU. Between DECEMBER 2016 – AUGUST 2018 fulfilling the inclusion and exclusion criteria.

RESULTS

1. Total 53 patients were included in study, out of which 34 (64.2%) patients developed Acute Kidney Injury as per RIFLE criteria with Male patients being more than female patients.

2. In this study, we found that S. NGAL measured at the time of admission was good predictors of AKI. S. NGAL levels were significantly elevated among AKI patients when compared to non-AKI patients. Mean levels for AKI patients at 0, 4 and 8 hours are 870.53, 1074.9 and 1090 respectively when compared to mean levels for NON-AKI patients at 0, 4 and 8 hours are 337, 307 and 292.

3. S. NGAL levels at 4 hours statistically more significant than 0 and 8

hours. Serum NGAL at 4 hours is 0.97 with sensitivity and specificity of 93% and 83% respectively.

4. AKI developed with greater severity and required RRT in 16 out of 34 (47%) patients included in this study. Patients who developed AKI and required dialysis showed higher level of NGAL compared to patients who developed AKI without requirement of dialysis and patients who did not develop AKI.

5. NGAL levels were slightly elevated among sepsis patients when compared to that of other etiology at 0, 4 and 8 hours.

CONCLUSION

1. In summary, our study demonstrated that admission blood NGAL measurements are useful in the early diagnosis of AKI. Baseline NGAL measurement allows detection of AKI earlier than S. Creatinine.

2. S NGAL levels detected development of acute renal injury at 4 hours, nearly 2 days earlier than S. Creatinine increases at 48 hours.

3. S NGAL assessment at the moment of hospital admission predicted the combined outcome of RRT and in-hospital mortality.

4. In our study, length of hospital stay is significantly different in both AKI and Non AKI group. NGAL levels were more among AKI patients and they required longer length of stay.

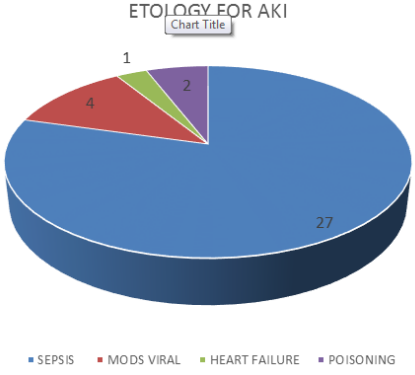
5. The use of this kidney injury biomarker in the early detection of renal involvement and risk stratification of patients at the time of presentation may permit earlier interventions and more appropriate patient management strategies.

DEMOGRAPHICS

Table 2

Variables	AKI group	Non AKI group
Total patients	34	19
Mean age	55.6±15.8	50.3±15.6
GENDER		
Male	21	10
Female	13	9
ETIOLOGY FOR AKI		
Sepsis	27	7
Other Etiology	7	12
S. creatinine mean (Baseline)	1.15±.18	0.97±0.22
Mortality	13 (38.2%)	0

Graph 1: ETIOLOGY FOR AKI



Graph 3: DISTRIBUTION OF AGE AMONG AKI PATIENTS

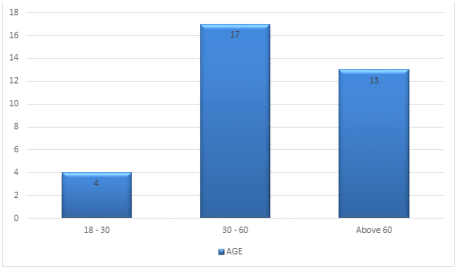


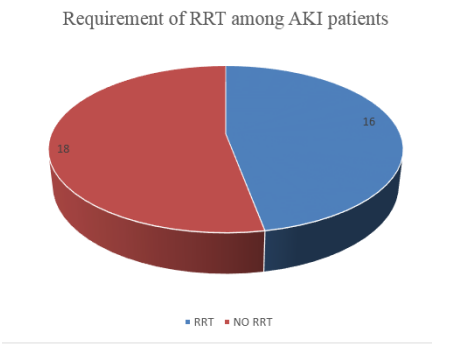
Table 6 - Depicting Requirement of RRT among AKI patients

TABLE – 6

		AKI	
		n	%
RRT	No	18	52.9
	Yes	16	47.1

Table 6 showing number of patients requiring RRT among AKI patients.

GRAPH – 7



Graph – 5 showing pie chart where 16 (47.1%) patients required RRT - blue color, 18 (52.9%) patients did not require RRT – red color out of total 34 patients who had AKI.

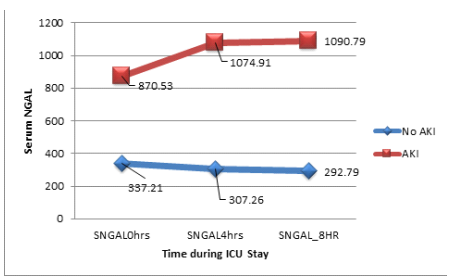
Table 7: Comparison of Serum NGAL levels at different point of time during ICU Stay among AKI and NO AKI patients

TABLE - 7

	NO AKI		AKI		
	Mean	SD	Mean	SD	p
SNGAL0hrs	337.21	195.02	870.53	309.68	<0.0001
SNGAL4hrs	307.26	166.31	1074.91	277.13	<0.0001
SNGAL_8HR	292.79	167.48	1090.79	292.77	<0.0001

Table 7 showing Serum NGAL levels at different point of time for AKI and NON-AKI patients. S. NGAL levels were significantly raised among AKI patients compared to NON-AKI patients.

GRAPH – 8



Graph 8 showing mean levels for AKI patients at 0,4 and 8 hours are 870.53, 1074.9 and 1090 respectively. Mean levels for NON-AKI patients at 0,4 and 8 hours are 337, 307 and 292.

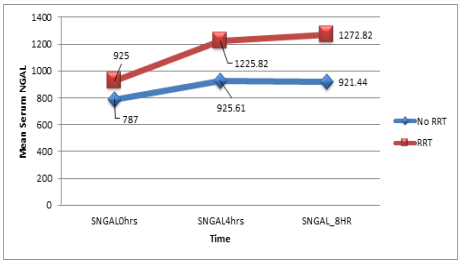
Table 8: Comparison of S. NGAL levels in those requiring RRT Vs those not requiring RRT

TABLE – 8

	No RRT		RRT		
	Mean	SD	Mean	SD	p
SNGAL0hrs	787.00	324.15	925.00	276.56	<0.0001
SNGAL4hrs	925.61	290.55	1225.82	152.22	<0.0001
SNGAL_8HR	921.44	311.34	1272.82	90.15	<0.0001

Table 8 showing S. NGAL mean levels of patients requiring RRT vs NO RRT. On comparing both groups by T test, S. NGAL values for patients with RRT has statistical significance.

GRAPH – 9



Graph 9 showing mean levels of patients not requiring RRT at 0,4 and 8 hours are 787,925 and 921.Values remain elevated in both the groups showing Serum NGAL in RRT group was higher at 0,4 and 8 hours as compared to AKI group.

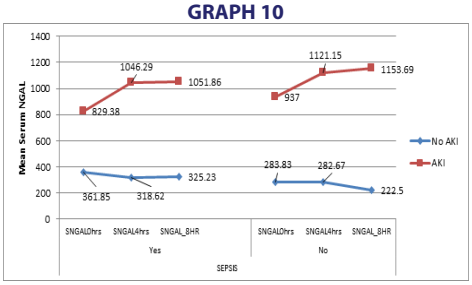
Table 9: S. NGAL levels in septic AKI Vs AKI of other etiology

TABLE 9

		NO AKI		AKI		P
		Mean	SD	Mean	SD	
Sepsis	SNGAL0hrs	361.85	197.19	829.38	271.39	<0.0001
	SNGAL4hrs	318.62	178.30	1046.29	251.95	<0.0001
	SNGAL_8HR	325.23	180.72	1051.86	285.25	<0.0001
Other etiology	SNGAL0hrs	283.83	196.48	937.00	365.00	<0.0001
	SNGAL4hrs	282.67	149.03	1121.15	318.83	<0.0001
	SNGAL_8HR	222.50	118.03	1153.69	305.24	<0.0001

Table 9 showing mean values of S. NGAL levels in patients of sepsis and other etiology.

GRAPH 10



Graph 10 showing Mean S. NGAL values of sepsis patients who met AKI definition by RIFLE criteria and mean S. NGAL values of other etiology patients at 0,4 and 8 hours. Among sepsis patients mean NGAL levels were slightly elevated compared to AKI of other etiology at 0,4 and 8 hours.

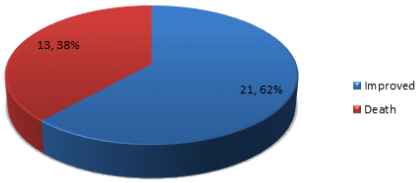
Table 10 - Outcome among AKI patients

TABLE - 10

		AKI	
		n	%
Out come	Improved	21	61.8
	Death	13	38.2

Table 10 showing Out of 34 patients who fulfilled RIFLE criteria for AKI, 13(38%) patients died and 21 (62%) patients improved either by RRT or medical management.

GRAPH - 11



Serum creatinine is not an adequate marker for AKI. First, substantial losses of glomerular filtration rate (GFR) may occur before there is an increase in serum creatinine. Second, Serum creatinine does not accurately depict kidney function until a steady state has been reached, which may require several days.

NGAL fulfills a central role in regulating epithelial neo- genesis, and in iron chelation and delivery after ischemic or toxic insults to the renal tubular epithelium. After kidney injury, NGAL is rapidly expressed on the apical epithelial membranes of the distal nephron1,2. NGAL is excreted in the urine through exocytosis and has local bacteriostatic and proapoptotic effects. S. NGAL is easily filtered by the glomerulus and reabsorbed in the apical membranes of the proximal tubules. Reabsorbtion is mediated by megalin-cubulin dependent endo- cytosis with a very high affinity1. The delivered iron is needed in processes activating and repressing iron-responsive genes that are vital to the regeneration processes that occur after damage is inflicted to these cells. Under normal circumstances the estimated half life of pNGAL is approximately 10 minutes, with urinary loss less than 0.2%. S. NGAL and uNGAL concentrations increase by 10- to 100-fold during the 2 hours that follow tubular injury, whereas SCr does not start to rise until 24 to 72 hours after the initial renal insult.

Total 53 patients were included in study, out of which 34 (64.2%) patients developed Acute Kidney Injury as per RIFLE criteria with Male patients being more than female patients. Etiology among AKI patients were predominantly septic, fulfilling SOFA criteria as compared with patients of other etiologies. Number of patients with AKI in age group of 30-60 years were more in comparison with other age groups in our study. S. Creatinine levels which were normal at the time of admission were followed up to 72hours. Among AKI patients average S. Creatinine at baseline was 1.16 mg/dl which increased during follow up till 72 hours meeting RIFLE criteria of AKI. In this study, we found that S. NGAL measured at the time of admission were good predictors of AKI. S. NGAL levels were significantly elevated among patients with AKI when compared to non-AKI patients. Mean s.NGAL for AKI patients at 0,4 and 8 hours were 870.53, 1074.9 and 1090 respectively when compared to mean s.NGAL levels for NON-AKI patients at 0,4 and 8 hours are 337, 307 and 292. Our study results indicate that monitoring of S. NGAL levels can provide a very early warning to development of AKI when compared to serum creatinine. This goes hand in hand with Mishra et al. (2005) and Wheeler et al. (2008)3 who demonstrated that serum NGAL concentrations within 24 hours of PICU admission were significantly increased in these children who developed AKI compared to children who did not develop AKI. In our study S. NGAL levels at 4 hours statistically more significant than 0 and 8 hours. Serum NGAL at 4 hours is 0.97 with sensitivity and specificity of 93% and 83% respectively. AUC at 8 hours is 0.92 with sensitivity and specificity of 78% and 80% respectively. In adults, Makris et al. found uNGAL measured within 24 h from injury to be a useful early AKI marker in critically ill trauma patients, with AuROC of 0.974,5. Previous studies in pediatric patients in the ICU with sepsis and septic shock and in a group of adult critically ill patients have studied

the predictive accuracy of pNGAL and uNGAL reporting AUCs of 0.68 and 0.64 for sustained AKI. Both Zappitelli and coworkers8 (pediatric population) and Cruz and coworkers9 (adult population) observed AUC's for prediction of RIFLE R or worse AKI by NGAL that were comparable with those observed in the present study. Constantin and coworkers and Nickolas and coworkers reported very high AUCs for the ability of pNGAL and uNGAL to predict AKI in critically ill adult and emergency department patients (0.92 and 0.95, respectively).

In our current study, AKI developed in 16 out of 34 (47%) patients included in this study had a greater severity of illness and required RRT. Patients who developed AKI and requirement dialysis showed higher level of NGAL compared to patients who developed AKI without requirement of dialysis and patients who did not develop AKI. Values remain elevated in both the groups showing Serum NGAL in RRT group was higher as compared to AKI group. These findings are in agreement with Hoste et al. (2003)9 who found that AKI developed in 32 out of 69 (46.3%) critically ill children—all but 8 of these critically ill children (11.5%) had a greater severity of illness and need to dialysis. Shapiro et al.10 investigated the use of a blood NGAL assessment in the ED, they considered only patients with suspected sepsis. Our study included patients with sepsis, MODS, pneumonia, severe dehydration and several other critical conditions. Consequently, our data are applicable to undifferentiated patients requiring hospitalization. Our results are more generalizable to the undifferentiated ED population because the recently published data on the role of blood NGAL in detecting AKI in the ED have been showed in restricted populations such as patients with sepsis. In this current study, NGAL levels comparison was done among septic patients and of other etiology. NGAL levels were slightly elevated among sepsis patients when compared to that of other etiology at 0,4 and 8 hours. Wheeler and colleagues demonstrated in a cohort study that, serum NGAL was significantly increased in critically ill children with sepsis compared with critically ill children without sepsis.

In our study NGAL levels were significantly raised among mortality patients compared to patients who improved indicating NGAL can be a predictor of mortality also. Though there is no representable data of length of stay in ICU, patients having raised NGAL levels among AKI had longer stay when compared to patients with NON-AKI patients.

There are only few studies available for S. NGAL among adult ICU patients as an early marker of AKI, majority of the studies being in pediatric set up. Our study adds to the current literature because it showed that NGAL significantly improves the diagnostic accuracy for severe AKI adding it to MDRD eGFR calculated at ICU admission, even in patients having an apparently normal eGFR at admission. Especially in these patients this could be of value because their AKI is not yet reflected in an increase in SCr. Patients in the ICU are typically diagnosed with AKI several days after the onset of their illness or injury, resulting in a delay in the discontinuation or dose adjustment of nephrotoxic medications or continued use of procedures that could cause further renal damage. These studies may include applying more intensive resuscitation, avoiding nephrotoxic drugs, or implementation of a timelier initiation of RRT in patients with elevated NGAL levels. In addition, recent animal studies examining interventions to reverse AKI have been promising, implying that it may be possible to reverse AKI in humans if it is treated early6-7. Second, this study adds to current knowledge because we defined a most efficient clinical model in the prediction of AKI using available data at the time of ICU admission, improving the predictive accuracy for RIFLE significantly with NGAL above eGFR and clinical predictors. The predictive accuracy of eGFR on its own was roughly comparable with that of pNGAL or uNGAL. However, we should take into account that SCr is used to define the end point RIFLE F and is likewise used to calculate eGFR, which is incorporation bias. Therefore, it is somewhat biased to compare NGAL's performance with the ability of SCr to predict itself.

Whether NGAL levels have the potential to influence clinical decision making in the ICU should be the topic for further randomized studies that should be performed before using NGAL measurements in clinical practice. Our results of early predictive, sensitive, nonspecific serum NGAL, although of clear statistical significance, will certainly need to be validated in a larger trial, including patients with preexisting chronic kidney disease and co morbid conditions that normally accumulate with impaired renal function. The ability of biomarkers, such as NGAL, to discern both the onset and resolution of AKI will further validate their use in the clinical setting and greatly enhance our understanding of AKI.

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