

The value of serum NGAL in determination of dialysis indication

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Abstract

Objective: To investigate if Neutrophil Gelatinase-associated Lipocalin can be used or not as a biochemical marker to determine the indications for emergency dialysis treatment.

Methods: The study was conducted at the Emergency Department of Numune Taraining and Research Hospital, Ankara, Turkey, in 2012, and comprised 60 patients who had uraemic symptoms and abnormal laboratory tests, including elevated potassium, blood urea nitrogen, and creatinine level or lowered pH and bicarbonate. They were divided in to 2 equal groups as those having indication for dialysis (Group 1) and those not having such indications (Group 2). Relevant values, including that of Neutrophil Gelatinase-associated Lipocalin, were compared between the two groups. To assess the utility of Neutrophil Gelatinase-associated Lipocalin measurements at varying cut-off values to predict indications for dialysis, a conventional receiver operating characteristic curve was generated and the area under the curve was calculated. $P < 0.05$ was considered statistically significant.

Results: The mean age of the 30 patients in Group 1 was 68.29 ± 16.9 years, while in Group 2 it was 66.47 ± 14.2 years ($p < 0.65$). The mean Neutrophil Gelatinase-associated Lipocalin level was 817.65 ± 334.76 ng/mL in Group 1 and 398.97 ± 202.42 ng/mL in Group 2 ($p < 0.001$). The best cut-off level for Neutrophil Gelatinase-associated Lipocalin to predict emergency haemodialysis indication was 615 ng/mL with a sensitivity of 82% and a specificity of 80%, and the areas under curve was 0.84.

Conclusion: Serum Neutrophil Gelatinase-associated Lipocalin level may be a determining parameter for indication of emergency haemodialysis.

Keywords: Emergency, Dialysis, NGAL. (JPMA 64: 739; 2014)

Introduction

Acute kidney injury (AKI) refers to a condition in which a reduction occurs in glomerular filtration rate (GFR) leading to accumulation of blood urea nitrogen (BUN), creatinine and other uraemic toxins in the body. Reduction in GFR in AKI is relatively faster and develops within days to weeks in contrast to chronic renal failure in which GFR reduces within months to years.¹

Chronic Kidney Disease (CKD) is defined as chronic and progressive impairment of the renal functions as a result of reduced GFR, including fluid-solute homeostasis and metabolic-endocrine functions. End-stage renal disease (ESRD) is considered when GFR decreases to 5-10 mL/min; these patients need renal replacement therapies like dialysis and renal transplantation.²

The incidence of acute renal failure is 1-5% for all hospital admissions.^{3,4} AKI may complicate the existing disease in 5% of the hospitalised patients; among these, dialysis may be needed in 0.05%.⁵⁻⁷ This rate may be as high as 20% in

patients with severe disease.^{6,8} Mortality rate varies between 7-80% depending on the severity of renal failure.^{9,10}

Dialysis can normalise fluid balance in patients with deteriorated renal functions, restore electrolyte and solute abnormalities, and eliminate uraemic toxins and drugs.¹¹ Indications of dialysis are severe metabolic acidosis ($\text{pH} < 7.1$), elevated potassium (K) level ($\text{K} > 7$ mEq/L), $\text{BUN} > 100$ mg/dL, serum creatinine > 8 mg/dL, bicarbonate (HCO_3) < 11 mEq/L, and signs and symptoms of severe volume loading.^{12,13}

Neutrophil Gelatinase-associated Lipocalin (NGAL) is a glycoprotein with a molecular weight of 25-kDA found in neutrophil granules and expressed at low concentrations in normal kidney, trachea, lungs, stomach, and colon.^{14,15} NGAL is expressed and secreted from renal tubular cells, hepatocytes, and immune cells in several pathological conditions.¹⁶ Its expression is also induced in injured epithelia, including lung, colon, and, in particular, kidney.¹⁵ NGAL, a new member of lipocalin, is excreted in urine and it can readily be detected as it has low molecular weight and it is resistant against fragmentation. NGAL accumulates in human renal cortical tubules, blood, and urine after nephrotoxic and ischaemic injuries.¹⁷ Thus, NGAL protein was easily detected in blood

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and urine soon after acute renal injury. NGAL has the advantages of being an early, sensitive and non-invasive biomarker for acute renal injury.¹⁸

In this study, we aimed to investigate if we can use NGAL as a biochemical marker to determine the indications for emergency dialysis treatment or not.

Patients and Methods

The study was conducted at the Emergency Department of Numune Taraining and Research Hospital, Ankara, Turkey, in 2012 after approval by the institutional ethics committee. Written informed consent was also obtained from the patients or the attendants in case patients were unconscious. Patients over 18 years of age with uraemic symptoms, including nausea, vomiting, altered consciousness, and willing to participate in the study were included, while those who did not meet the criteria were excluded.

A total of 60 patients represented the final study sample. Blood samples were drawn for the measurement of pH, HCO₃, BUN, creatinine, potassium, and NGAL at presentation. Thirty patients having indications for emergency dialysis were determined as Group 1, and 30 patients not having indications for emergency dialysis as Group 2. Serum NGAL levels were studied with a bedside kit (Triage NGAL test, Biosite, USA).

Serum pH, BUN, creatinine, K, HCO₃ and NGAL values were compared between the two groups.

Descriptive statistics were expressed as frequency and percentage, and mean \pm standard deviation (SD). Normality of data distribution was tested with Kolmogorov-Smirnov test. X² test was used to compare categorical variables. Student's t test was used for the comparison of continuous variables between the groups because distribution of data was normal. To assess the utility of NGAL measurements at varying cut-off values to predict dialysis indication, a conventional receiver operating characteristic (ROC) curve was generated and the area under curve (AUC) was calculated. The statistical analysis was performed using SPSS version 18.00 and $p < 0.05$ was considered statistically significant.

Results

The characteristics of the 60 patients in the study were noted at the outset and there was no significant difference between the groups with respect to gender ($p > 0.05$) and age ($p > 0.05$).

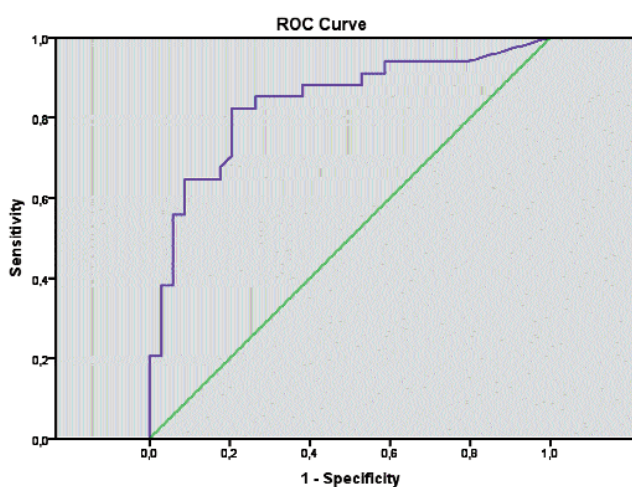
In terms of laboratory findings, there was a significant difference between the groups for BUN, creatinine, K, and blood pH, HCO₃ levels ($p < 0.05$) (Table).

Table-1: Demographic, clinical and laboratory characteristics.

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)	p
Ngal (ng/mL)	817.65 \pm 334.7	429.30 \pm 287.5	t=4,944, p<0.001
pH	7.20 \pm 0.1	7.30 \pm 0.1	t=-3,672, p<0.001
Urea (mg/dL)	228.11 \pm 132.4	74.06 \pm 23.8	t=6,275, p<0.001
Creatinine (mg/dL)	7.37 \pm 5.6	4.04 \pm 2.6	t=2,937, p<0.005
Potassium (mEq/L)	6.15 \pm 2.4	4.56 \pm 1.2	t=3,236, p<0.05
HCO ₃ (mEq/L)	15.23 \pm 5.4	21.04 \pm 7.4	t=-3.578, p<0.01
Age (year)	68,29 \pm 16,9	66.47 \pm 14.2	t=0.46, p=0.65
Gender (M/F)	16/14	12/18	X ² =2.55, p=0.133

NGAL: Neutrophil Gelatinase-associated Lipocalin.

HCO₃: Bicarbonate.



The area under curve (AUC) of 0.84 (95% CI 0.74-0.94). The best cut-off level for NGAL to predict haemodialysis indication was 615 ng/mL with a sensitivity of 82% and a specificity of 80%.

Figure: ROC analysis for endication of dialysis.

The mean NGAL level was 817.65 \pm 334.7ng/mL in Group 1 and 398.97 \pm 202.4ng/mL in Group 2 (t=4.944; $p < 0.001$).

To assess the utility of NGAL measurements at varying cut-off values to predict dialysis indication, a conventional receiver operating characteristic curve was generated and the AUC was calculated. The best cut-off level for NGAL to predict emergency haemodialysis indication was 615ng/mL with a sensitivity of 82% and a specificity of 80%, and an AUC of 0.84 (95% CI: 0.74-0.94) which was statistically significant ($p < 0.001$) (Figure).

Discussion

The definitive therapy for CKD is renal transplantation.

Dialysis therapy, on the other hand, is only a temporary solution until a definitive therapy has been constituted. Emergency dialysis is life-saving under some circumstances.¹⁹

BUN or serum creatinine levels are elevated in renal failure. However, further tests are needed to distinguish between acute and chronic renal failure. A previously increased BUN, a previously increased and long-term stable serum creatinine level, and an abnormal urinalysis are supportive for CKD.¹⁴ Among them, creatinine is the most commonly used laboratory parameter in clinical practice. Although it is widely used in clinical practice, it has some potential disadvantages: it is affected by several factors such as age and gender, and it is unable to reflect acute renal injury as early as desired.²⁰ First of all, renal functions are needed to be impaired more than 50% for an elevation in serum creatinine level to occur. Moreover, serum creatinine does not reflect renal function accurately until a stable renal condition has been reached, which requires several days.²¹ Serum creatinine value is a poor indicator for acute renal injury.²² In our study, serum BUN and creatinine levels were higher in both groups (Table). There was a significant difference between two groups in terms of serum BUN or creatinine levels ($p < 0.05$). A serum pH level below 7.1 is another emergency dialysis indication.^{12,13} Subjects in both groups in our study had acidic blood pHs (Table). There was a significant difference between the two groups ($p < 0.05$). A serum K level greater than 7mEq/dL constitutes another indication for emergency dialysis.¹² Subjects in Group 1 had a higher potassium level (Table). There was a significant difference between the two groups ($p < 0.05$). A serum HCO₃ level below 11mEq/dL is another emergency dialysis indication.^{12,13} There was a significant difference between the two groups ($p < 0.05$) in our study.

NGAL is a marker of active tubular pathology.^{23,24} Serum NGAL level is arguably the most promising novel biomarker for detection of AKI.²⁴ The reasons for NGAL increase in AKI are acute tubular injury and NGAL secretion from neutrophils, macrophages, and other immune cells as an acute phase reactant.¹⁵ There is growing literature suggesting that NGAL is also a marker of kidney disease and severity in CKD.²³ It has been shown that tubulo-interstitial injury occurs in almost all forms of CKD and serum NGAL increases as a result of this insult.²⁴ A study found that NGAL is a potential early marker for impaired kidney function/kidney injury.²⁵

A study in patients with AKI in ICUs detected that NGAL levels were elevated 10-fold in plasma and 100-fold in

urine secondary to sepsis, ischaemia and nephrotoxins. Both urine and plasma levels were found to be correlated with serum creatinine levels.¹⁶ A prospective study reported that acute renal injury developed in 28% of the children who underwent cardiopulmonary bypass where serum creatinine levels were elevated 1-3 days after the surgery. However, NGAL levels were elevated 10-fold and it was detected in urine and plasma within 2-6 hours after the surgery. It was concluded that both urine and plasma levels of NGAL are strong, independent markers for acute renal injury.²⁶

One study suggested that serum NGAL levels can be used as a marker for initiation of renal replacement therapy (RRT) in critical care patients.²⁷ Others reported that serum NGAL level is a potential early, sensitive marker of kidney impairment/injury,²⁸ and that serum NGAL levels were higher in haemodialysis patients compared to the control subjects.²⁹ In the current study, NGAL values were elevated in both groups. However, when NGAL values were considered, a statistically significant difference was detected between the two groups ($p < 0.05$). An ROC analysis was performed to ascertain the effectiveness of serum NGAL in determination of emergency dialysis indication. The sensitivity and specificity of a cut-off level of 615ng/mL were 82% and 80%, respectively.

Conclusion

Serum NGAL level may determine the indication of emergency dialysis which can be life-saving.

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