

## Bedside Alarmin: Neutrophil-to-Lymphocyte Ratio in Acute Kidney Injury

Devrim Bozkurt\*, Dilara Kilic, Tugba Kip, Mehmet Berktaş, Kilavuz Asli and Akcicek Fehmi

Internal Medicine, Ege University, Bornova, Izmir, 35100, Turkey

\*Corresponding author: Devrim Bozkurt, Associate Professor, Ege University, Internal Medicine, Bornova, Izmir, 35100, Turkey, Tel: 00902323904287; E-mail: devrim\_bozkurt@yahoo.com

Received date: May 30, 2016; Accepted date: June 9, 2016; Publication date: June 26, 2016

Copyright: © 2016 Bozkurt D, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License; which permits unrestricted use; distribution; and reproduction in any medium; provided the original author and source are credited.

### Abstract

**Introduction:** Acute Kidney injury (AKI) represents a condition reflecting systemic inflammation. Neutrophil-to-lymphocyte ratio (NLR) is novel prognostic marker in various inflammatory conditions. We performed a retrospective study investigating whether NLR has prognostic significance in patients suffered from AKI.

**Materials and Methods:** Two hundred and ninety five AKI patients were evaluated retrospectively. Baseline values on admission, final values at discharge and after discharging during follow-up period in outpatient clinic until six months to one year were recorded.

**Results:** It has been shown that, final NLR and timely changed NLR during hospital course are significant mortality predictors in AKI patients both in univariate and mutually adjusted multivariate logistic regression analysis. To predict mortality, we showed that, level of 9.90 point for final NLR has 73% sensitivity and 87% specificity as compared to value below in ROC analysis (HR: 7.31, CI 3.36-15.91;  $p < 0.001$ ).

**Conclusion:** NLR can be a novel screening tool for AKI patients during their hospital course.

**Keywords:** Acute kidney injury; Neutrophil lymphocyte count; Mortality

### Introduction

Acute renal failure, currently named as acute kidney injury (AKI); is one of the most leading cause of cardiovascular failure, infections, morbidity and mortality in intensive care unit (ICU) patients. AKI, especially requiring hemodialysis represents a condition directly effect patient's survival. AKI represents a systemic inflammatory condition. AKI shows direct cause and effect relationship with inflammation [1-3]. An easily measurable parameter, ratio of neutrophil and lymphocyte counts (NLR), is the novel inflammatory marker in various clinical conditions also which can be used as an indicator of systemic inflammation [4]. Indeed, NLR has been shown to predict outcomes in various clinical conditions including, peripheral vascular disease, end stage renal disease and critically ill patients [5-7]. Therefore, predicting increased mortality and morbidity in AKI is not surprising.

As suggested above AKI is an inflammatory disorder and NLR is a marker of inflammation. Thus it is possible that NLR may have prognostic significance in AKI. Thus this study is performed to investigate whether NLR has a prognostic significance in our pilot case-control study.

### Materials and Method

#### Study population

In this retrospective report, between January 2010 and December 2012, N17 ICD coded patients (considered as acute renal failure,

$n=295$ ) were recruited. The flow chart of the patients was shown in Figure 1.

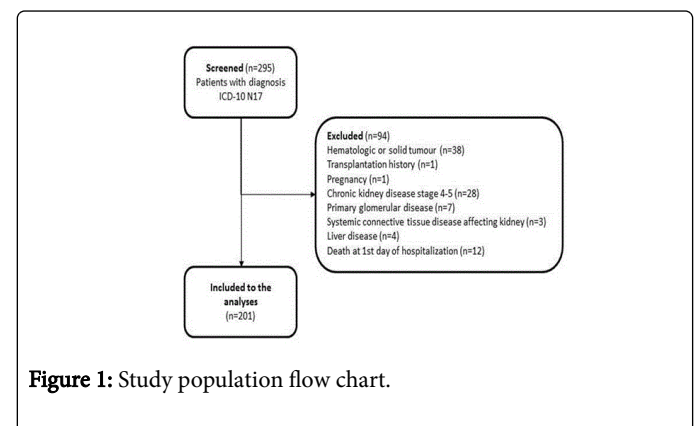


Figure 1: Study population flow chart.

AKI was staged and defined with the guidance of KDIGO-CPGAKI Criteria [8]. Definition was set under the scope of any of the following:

1. Increase in serum creatinine by  $\geq 0.3$  mg/dl within 48 hours or
2. Increase in serum creatinine to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days or
3. Urine volume  $< 0.5$  ml/kg/h for 6 hours.

Reasons for entering dialysis on admission and during the hospital course were recorded. All patients requiring dialysis were evaluated and managed by the same team of nephrologists and ICU practitioner. Prescribed dialysis modes were daily conventional dialysis with or without ultrafiltration. Demographical properties such as age, sex, reason for admission and comorbid clinical illnesses with previous

medical history was recorded. Non traditional inflammation marker, NLR, routine serum biochemical analysis and complete blood count were recorded. Records at baseline (baseline), at discharge (final) and after discharging during outpatient clinic follow-up (last follow-up, 6 months to one year after discharging) were included in statistical analysis). Timely NLR change between admission and final, calculated as follow: [(Final NLR-Baseline NLR)/hospital stay in days)]. To estimate kidney function, the most recently advocated formula of Modification of Diet in Renal Disease Study Group (MDRD-eGFR) [9] was used. The predictors of all cause mortality were examined.

The need for informed consent was waived by the institutional review board.

### Statistical Analysis

Categorical variables are summarized count, percentage whereas continuous ones are summarized mean, standard deviation, median, interquartile range, minimum and maximum as appropriate. Cox proportional-hazards regression model and mutually adjusted multivariate regression analysis were used to determine the effects of independent parameters on mortality. ROC analysis was performed to determine cut-off values for final NLR level and timely changed NLR ratios during hospital course. Overall significance level is 5%. IBM SPSS ver 21.0 is used for analyses.

### Results

Of 295 eligible acute renal failures, N17 ICD coded patients admitted to internal medicine intensive care unit, 201 patients, was recruited into retrospective cohort study. Sixteen patients have previous renal disease, other than stage 3 or more. Eighty one patients have diabetes mellitus with 33 of them had been required insulin treatment. Baseline characteristics of study population were summarized in Figure 2.

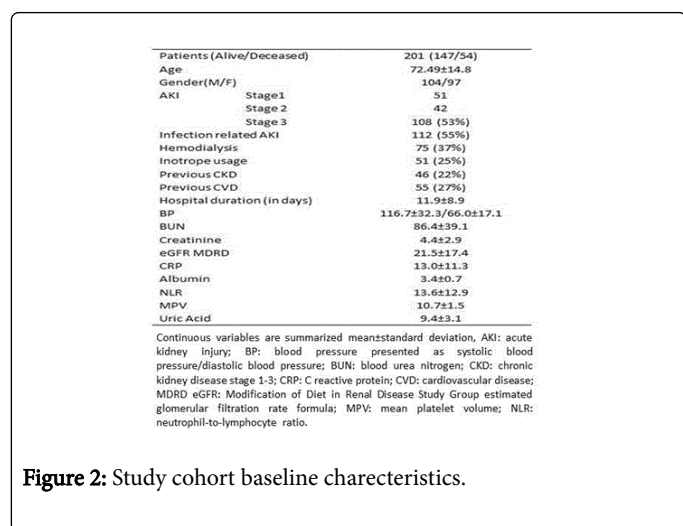


Figure 2: Study cohort baseline characteristics.

According to univariate analysis, being older than 65 years old, having CVD history and infection related AKI, decreased level of serum albumin on admission and inotrope usage were independent mortality predictors. At discharge, increased level of WBC, uric acid level, NLR, MPV, lymphocyte count, CRP and serum creatinine levels as compared to baseline were independent mortality predictors Figure 3.

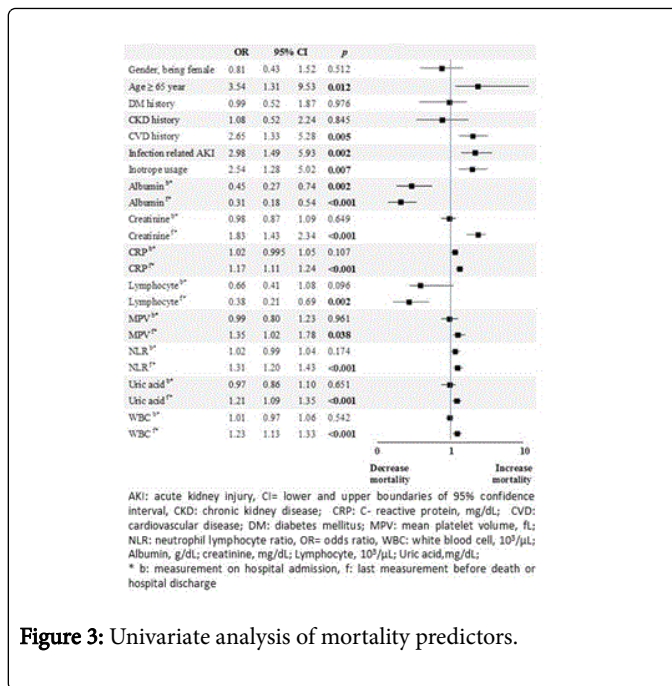


Figure 3: Univariate analysis of mortality predictors.

Mutually adjusted multiple logistic regression analysis was also performed with significant mortality predictors of univariate analysis as shown in Figure 4. Increment in timely changed NLR and serum creatinine levels were independent mortality predictors in our AKI cohort (Figure 4).

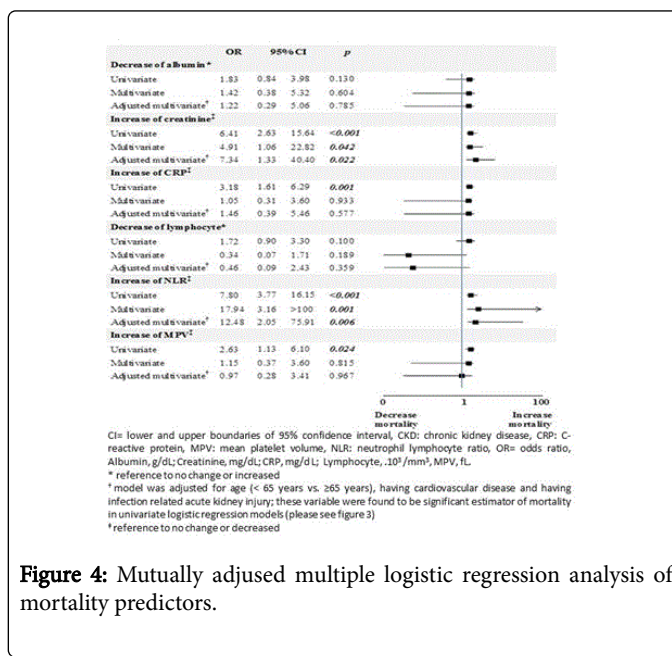


Figure 4: Mutually adjusted multiple logistic regression analysis of mortality predictors.

Non traditional predictor of systemic inflammation, NLR, at the end of ICU course was independent predictor of mortality (HR: 7.80, CI 3.77-16.15; p<0.001). To determine cut-off value for final NLR, ROC analysis was performed. Level of 9.90 point for final NLR has 73% sensitivity and 87% specificity. The value for final NLR level above the median (=10) was significant mortality predictor as compared to value below (HR: 7.31, CI 3.36-15.91; p<0.001). Timely changed NLR(ΔNLR) was significant (HR:7.41, CI 3.60-13.26; p<0.001)

mortality predictor. Timely change in absolute NLR, even considered last to follow-up values were significantly associated with mortality. In infection related AKI group (n =112), timely changed NLR was also significant mortality predictor (HR: 31.77, CI 1.14-4.05; p = 0.018) (Figure 5).

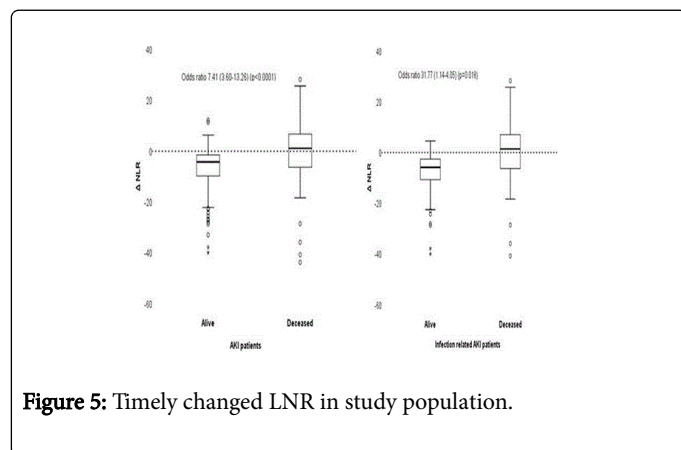


Figure 5: Timely changed LNR in study population.

## Conclusion

We conducted a retrospective analysis included 201 ICU admission due to acute kidney injury. This is the first study in literature evaluating the effects of NLR on outcome mainly mortality in AKI population. As a result we have demonstrated that insulin required diabetes mellitus (2.18, 1.08-4.4, p = 0.030, data not shown), infection related AKI, decreased albumin levels, CVD history, inotrope usage and aging were mortality predictors. We also showed that, increment in serum creatinine level and timely changed NLR were also independent mortality predictors in mutually adjusted multivariate logistic regression analysis.

Incidence of AKI in worldwide is steadily increasing. AKI associates directly with longevity of hospital duration, patients' mortality and development or progression of preexistent kidney disease<sup>9</sup>. Therefore, AKI has great socioeconomic and public health burden. Ischemia-reperfusion injury, sepsis and nephrotoxicity are the leading cause of this entity. Especially in elderly population, as in our cohort population, sepsis is the leading cause of all AKI cases [10-16].

After polytrauma, major surgical procedures or sepsis, marked neutrophilia and a lymphocytopenia are well known laboratory abnormalities. Correlation between the severity of clinical course and the grade of neutrophilia and lymphocytopenia is well established in clinical settings [17]. Sepsis is the leading cause of AKI and carries high mortality rates. Increased generalized inflammation and inflammation in kidney during sepsis is not surprised. From that point of view it has been reported that the kidney endothelial cells and tubular cells play an active role in inflammatory process [18]. Recent studies have demonstrated that inflammation-based prognostic scores are useful in predicting cardiovascular risk. An easy measurable laboratory test, NLR, was also reported in various cardiovascular diseases. The association between NLR and mortality has been showed previously in coronary artery diseases, coronary calcification scores, arterial stiffness, myocardial infarction, cerebrovascular accidents and cardiac syndrome X [19-26]. NLR was also examined in patients with renal failure. More recently increased NLR, above the median value, has been shown as a cardiovascular and overall mortality predictor in maintenance peritoneal dialysis patients [27]. In hemodialysis patients

NLR was also correlated patients' mortality. Median value >5/1 was associated mortality significantly as compared to value < 5/1 [28].

Final NLR and increment in timely changed NLR during hospital stay were significantly correlated with mortality. There was a steadily decrease NLR values pointed at baseline, final and last follow-up especially in mortal patients. Indeed we observed that there was lowest NLR value recordings as compared to value of admission in alive patients. This seems to be important, NLR change during hospital course may be screening tool for patients' outcome. Above the median value, 10/1, as compared to value < 10/1 was significantly better mortality predictor. ROC analysis revealed cut-off value for final NLR is 9.90 which has 73% sensitivity and 87% specificity. Change in NLR timely and change in percent NLR as compared to baseline were also significant predictor of mortality. These were the first detected NLR values predicting mortality in AKI.

MPV and Lymphocyte count change during ICU course are the novel tools for predicting mortality [29,30]. Our study has also showed that final MPV and Lymphocyte counts were mortality predictors. Although this relationship has not reached statistical significance in multivariate regression analysis, this might be clear in larger retrospective populations or prospective designs. Besides NLR, MPV and lymphocyte counts are also cheaper and easily measurable laboratory values which reflect patients' prognosis.

There are several limitations. This is the pilot study which is performed on retrospective cohort evaluating the impact of NLR on mortality in AKI. Single centre experience which can result in selection bias is another point of view. Our institute has seven ICU affiliations such as Anesthesiology and Reanimation, Chest Disease, Cardiology, Cardiovascular Surgery, General Surgery and Emergency Department ICUs. Highly selected population, representing only internal medicine ICU admissions, were evaluated. Therefore, it is important to realize that our findings may not be applicable to all ICU patients suffering from AKI due to the other types of causes. We only considered the development of AKI on admission rather than the development of AKI later in the hospital course. Patients were examined during ICU stay and until six months after hospital discharge. This scenario may represent the limited patients and time interval for analyzing outcome predictors of AKI. Under the scope of this point of view, we started to analysis of whole ICU population retrospectively and then will prepare a prospective design.

In conclusion, using NLR as a screening tool in AKI management may possess some advantages for clinicians. During the course of AKI, an alarming increase or lack of descent in NLR as compared to baseline, clinician should be focused on taking preventive modalities otherwise mortality is inevitable. Although it is necessary to evaluate NLR on more patients coming from other ICU departments in randomised controlled trials, we speculate that NLR can be a bedside alarmin, a screening tool, for patients suffered from AKI.

## References

1. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC (2006) RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 10: R73.
2. Vallés PG, Lorenzo AG, Bocanegra V, Vallés R (2014) Acute kidney injury: what part do toll-like receptors play. *Int J Nephrol Renovasc Dis* 7: 241-251.
3. Powell TC, Powell SL, Allen BK, Griffin RL, Warnock DG, et al. (2014) Association of inflammatory and endothelial cell activation biomarkers with acute kidney injury after sepsis. *Springerplus* 28: 207.

4. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, et al. (2014) Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. *Atherosclerosis* 234: 206-213.
5. Ouellet G, Malhotra R, Penne EL, Usuya L, Levin NW, et al. (2016) Neutrophil-lymphocyte ratio as a novel predictor of survival in chronic hemodialysis patients. *Clin Nephrol* 85: 191-198
6. Bhat TM, Afari ME, Garcia LA (2016) Neutrophil lymphocyte ratio in peripheral vascular disease: a review. *Expert Rev Cardiovasc Ther* 14: 871-875.
7. Dilektasli E, Inaba K, Haltmeier T, Wong MD, Clark D, et al. (2016) The prognostic value of neutrophil to lymphocyte ratio on mortality in critically ill trauma patients. *J Trauma Acute Care Surg*.
8. Aki K (2012) Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney IntSuppl* 2: 1-138.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, et al. (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine* 130 : 461-470.
10. Gammelager H, Christiansen CF, Johansen MB, Tannesen E, Jespersen B, et al. (2013) Fiveyear risk of endstage renal disease among intensive care patients surviving dialysis-requiring acute kidneyinjury: a nationwide cohort study. *Crit Care* 22: 17-145.
11. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, et al. (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31: 1250-1256.
12. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, et al. (2013) Acute kidney injury: an increasing global concern. *Lancet* 382: 170-179.
13. Cruz DN, Ronco C (2007) Acute kidney injury in the intensive care unit: current trends in incidence and outcome. *Crit Care* 11: 149.
14. Chronopoulos A, Rosner MH, Cruz DN, Ronco C (2010) Acute kidney injury in elderly intensive care patients: a review. *Intensive Care Med* 36: 1454-1464.
15. Bellomo R, Wan L, Langenberg C, May C (2008) Septic acute kidney injury: new concepts. *Nephron Exp Nephrol* 109: e95-100.
16. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, et al. (2007) Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin J Am Soc Nephrol* 2: 431-439.
17. Zahorec R (2001) Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* 102: 5-14.
18. Kinsey GR, Li L, Okusa MD (2008) Inflammation in acute kidney injury. *Nephron Exp Nephrol* 109: e102-107.
19. Celikbilek A, Ismailogullari S, Zararsiz G (2014) Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *J Clin Lab Anal* 28: 27-31.
20. Sawant AC, Adhikari P, Narra SR, Srivatsa SS, Mills PK, et al. (2014) Neutrophil to lymphocyte ratio predicts short and long term mortality following revascularization therapy for STElevation myocardial infarction. *Cardiol J* 10: 5603.
21. Demirkol S, Balta S, Unlu M, Arslan Z, Cakar M, et al. (2012) Neutrophils/lymphocytes ratio in patients with cardiac syndrome X and its association with carotid intima-media thickness. *Clin Appl Thromb Hemost* 20: 250-255.
22. Park BJ, Shim JY, Lee HR, Lee JH, Jung DH, et al. (2011) Relationship of neutrophil-lymphocyte ratio with arterial stiffness and coronary calcium score. *Clin Chim Acta* 412: 925-929.
23. Arbel Y, Finkelstein A, Halkin A (2012) Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patient undergoing angiography. *Atherosclerosis* 225: 456-460.
24. Park JJ, Jang HJ, Oh IY (2013) Prognostic value of neutrophil to lymphocyte ratio in patients presenting with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 111: 636-642.
25. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, et al. (2008) Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. *Clin Chim Acta* 395: 27-31.
26. Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, et al. (2011) Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. *J Cardiol* 107: 433-438.
27. An X, Mao HP, Wei X, Chen JH, Yang X, et al. (2012) Elevated neutrophil to lymphocyte ratio predicts overall and cardiovascular mortality in maintenance peritoneal dialysis patients. *Int Urol Nephrol* 44: 1521-1528.
28. Kato A, Tsuji T, Sakao Y, Ohashi N, Yasuda H, Fujimoto T, et al. (2013) A Comparison of Systemic Inflammation-Based Prognostic Scores in Patients on Regular Hemodialysis. *Nephron Extra* 3: 91-100.
29. Hudzik B, Szkodziński J, Lekston A, Gierlotka M, Poloński L, et al. (2016) Mean platelet volume-to-lymphocyte ratio: a novel marker of poor short- and long-term prognosis in patients with diabetes mellitus and acute myocardial infarction. *J Diabetes Complications* S: 1056-8727.
30. Liu X, Shen Y, Wang H, Ge Q, Fei A (2016) Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Patients with Sepsis: A Prospective Observational Study. *Mediators Inflamm*. 2016: 8191254.