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A novel predictor in acute kidney injury: Neutrophil to lymphocyte count

Akut böbrek hasarlanmasında yeni bir gösterge: Nötrofil-lenfosit oranı

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Abstract

Aim: Acute Kidney injury (AKI) represents a clinical condition reflecting systemic inflammation. Neutrophil-to-lymphocyte ratio (NLR) is novel prognostic marker in various inflammatory conditions. In this retrospective cohort we evaluated two hundred and thirteen AKI patients.

Materials and Methods: The patients' 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. NLR change during follow-up period after hospitalization was also examined.

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% specifity as compared to value below in ROC analysis (HR: 7.31, CI 3.36-15.91; p<0.001).

Conclusion: NLR may be a novel screening tool on patiens' mortality for AKI patients during their hospital course.

Keywords: Acute renal failure, mortality.

Öz

Amaç: *Akut böbrek hasarlanması (ABH), sistemik inflamasyonu yansıtan bir klinik durumdur. Nötrofil-lenfosit oranı (NLO), değişik inflamatuar durumlarda bilinen yeni prognostik göstergedir. Bu retrospektif kohort çalışmasında iki yüz on üç akut böbrek hasarlanmalı hasta incelendi.*

Gereç ve Yöntem: *Hastaların başvuru anı, çıkış anı ve taburculuk sonrası poliklinik takiplerinde var olan altı ay bir yıllık değerleri kaydedildi. Bu takip periyodunda hastaların NLO değişimleri incelendi.*

Bulgular: *Tek değişkenli ve çoklu değişkenli regresyon analizlerinde, hem taburculuk anı NLO değeri hem de zamansal NLO değişimi, akut böbrek hasarlanmalı hastalarda bağımsız mortalite öngörücüsü olarak saptandı. Yapılan ROC analizinde, mortalite ön görücülüğünde, NLO üst sınır için 9.90 değeri, %87 özgüllük ve %73 duyarlılıkta saptandı (HR: 7.31, CI 3.36-15.91; p<0.001).*

Sonuç: *Akut böbrek hasarlanmalı hastalarda, NLO, hastane yatış sürecinde mortalite için yeni bir takip parametresi olabilir.*

Anahtar Sözcükler: *Akut böbrek yetmezliği, mortalite.*

Introduction

Acute kidney injury (AKI) is one of the most leading cause of, cardiovascular failure, infections, increased morbidity and mortality, in hospitalized patients. AKI represents a systemic inflammatory condition and shows a direct "cause and effect" relationship, with inflammation (1-3).

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A simple and "easy to measure" parameter, ratio of neutrophil and lymphocyte counts (NLR) is a novel inflammatory marker in various clinical conditions which can be used as an indicator of systemic inflammation (4). In fact, NLR has been shown to predict outcomes in various clinical conditions including, "peripheral vascular disease", "end stage renal disease" and in "critically ill patients" (5-7). Therefore, usage of NLR to predict the mortality and morbidity in AKI, makes sense.

As suggested above AKI is an inflammatory disorder and NLR is a marker of inflammation which may have

prognostic significance in AKI. Thus this is a case-control study, performed to investigate, whether NLR has a prognostic significance in hospitalised patients who developed AKI.

Materials and Methods

Study population

For this retrospective report, from January 2010 to March 2013, N_{17} ICD coded patients (considered as acute renal failure, n=313) were recruited. After excluding the patients, as seen in figure 1.213 AKI patient were included.

AKI was staged and defined with the guidance of KDIGO-CPGAKI Criteria (8). Definition was set under the 20 scope of any of the following:

- Increase in serum creatinine by ≥0.3 mg/dL within 48 hours or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or
- Urine volume <0.5 mL/kg/h for 6 hours.

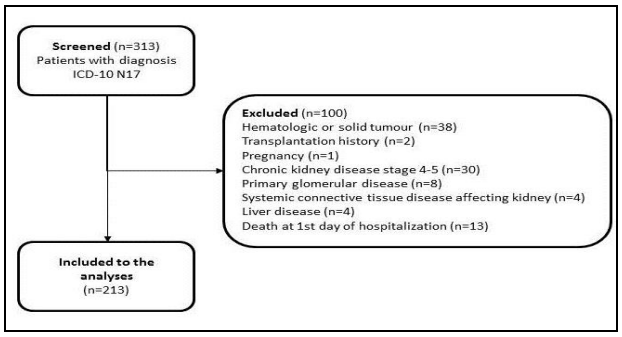

Figure-1. Study population flow chart.

Reasons for entering dialysis on admission and during the hospital course were recorded. All patients requiring 26 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. Data was including demographical properties such as age, sex, reason for admission and comorbid clinical illnesses with previous medical history. Nontraditional inflammation marker, NLR, routine serum biochemical analysis and complete blood count were recorded. For the statistical analysis, data were consisted of the records taken at baseline, at discharge and at the latest follow up taken, during 6 to 12 months period from discharge. Timely NLR change between admission and final, calculated as follows: [(Final NLR-Baseline NLR)/days of hospital course)]. To estimate kidney function, the most recently advocated formula of Modification of Diet in Renal Disease Study Group (MDRD-eGFR) was used (9). The predictors of all cause of mortality were examined.

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 313 eligible acute renal failures, N_{17} ICD coded patients admitted to internal medicine intensive care unit, 213 patients were recruited into retrospective cohort study. Eighty one patients had diabetes mellitus and 33 of them required insulin. Baseline characteristics of study population were summarized in Table-1.

Table-1. Study Cohort Baseline Characteristics. Continuous Variables are Summarized Mean±Standard Deviation.

Patients (Alive/Deceased)		213 (157/56)
Age		72.48±14.7
Gender(M/F)		112/101
AKI	Stage1	55
	Stage 2	48
	Stage 3	110
Infection related AKI		118 (55%)
Hemodialysis		77 (36%)
Inotrope usage		55 (26%)
Previous CKD		48 (22%)
Previous CVD		60 (28%)
Hospital duration (in days)		12.1±9.2
BP		115.8±32.1/66.2±17.3
BUN		85.5±40.2
Creatinine		4.2±2.7
eGFR MDRD		19.5±15.8
CRP		13.4±12.3
Albumin		3.4±0.7
NLR		14.4±13.2
MPV		11.7±1.3
Uric Acid		9.9±2.9

AKI: acute kidney injury; BP: blood pressure presented as systolic blood pressure/diastolic blood pressure; BUN: blood urea nitrogen; CKD: chronic kidney disease stage 1-3; CRP: C reactive protein; CVD: cardiovascular disease; MDRD eGFR: Modification of Diet in Renal Disease Study Group estimated glomerular filtration rate formula; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio.

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-2).

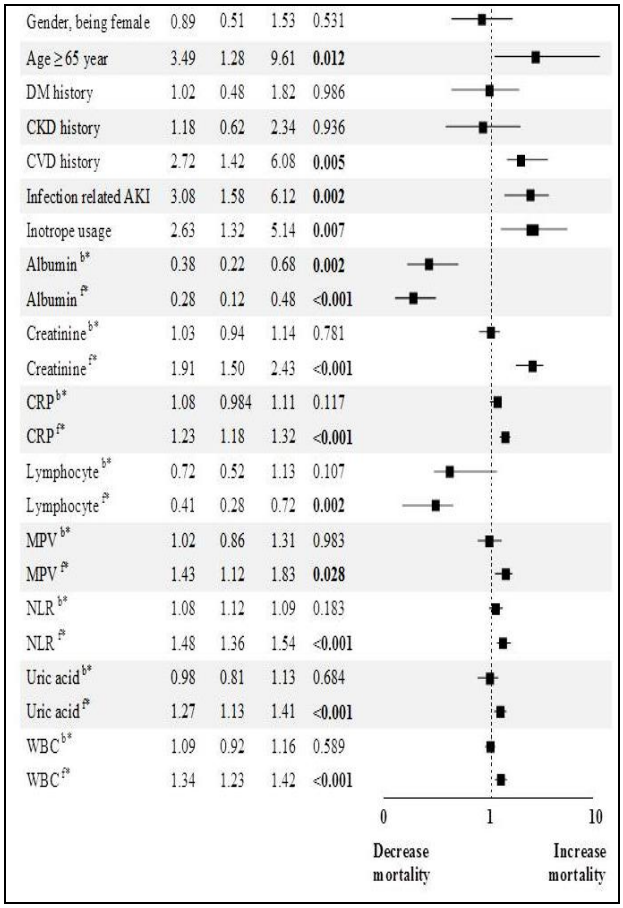

Figure-2. Univariate analysis of mortality predictors.

AKI: acute kidney injury, CI= lower and upper boundaries of 95% confidence interval, CKD: chronic kidney disease; CRP: C- reactive protein, mg/dL; CVD: cardiovascular disease; DM: diabetes mellitus; MPV: mean platelet volume, fL; NLR: neutrophil lymphocyte ratio, OR= odds ratio, WBC: white blood cell, 103/μL; Albumin, g/dL; creatinine, mg/dL; Lymphocyte, 103/μL; Uric acid, mg/dL; *b: measurement on hospital admission, f: last measurement before death or hospital discharge.

"Mutually adjusted multiple logistic regression analysis" was also performed with "significant mortality predictors of univariate analysis" as shown in figure 3. Increment in timely changed NLR and serum creatinine levels were independent mortality predictors in our AKI cohort (Figure-3).

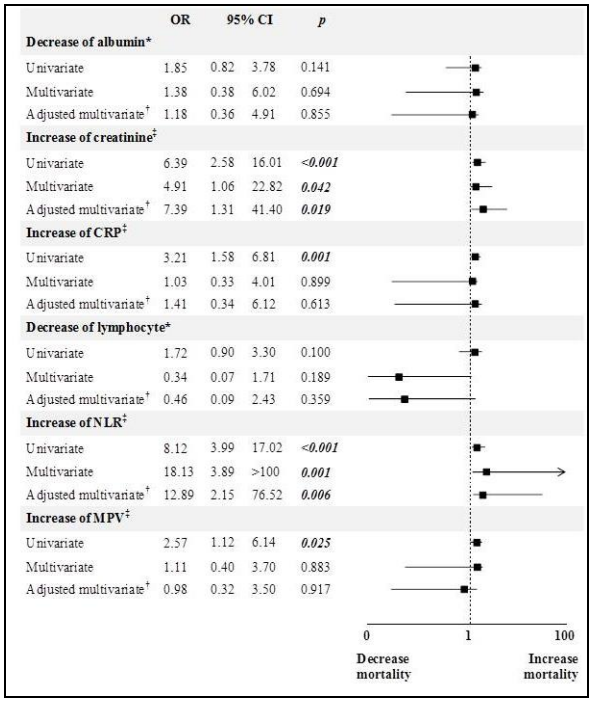

Figure-3. Mutually adjusted multiple logistic regression analysis of mortality predictors.

*CI= lower and upper boundaries of 95% confidence interval, CKD: chronic kidney disease, CRP: C- reactive protein, MPV: mean platelet volume, NLR: neutrophil lymphocyte ratio, OR= odds ratio, Albumin, g/dL; Creatinine, mg/dL; CRP, mg/d L; Lymphocyte, .103/mm^3, MPV, fL. * reference to no change or increased †model was adjusted for age (< 65 years vs. ≥65 years), having cardiovascular disease and having infection related acute kidney injury; these variable were found to be significant estimator of mortality in univariate logistic regression models (see figure 2) ‡reference to no change or decreased.*

Nontraditional predictor of systemic inflammation, NLR, at the end of ICU course was independent predictor of mortality (HR: 1.48, CI 1.36-1.54; 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 a 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:7.39, CI 3.58-12.88; 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=118), timely changed NLR was also a significant mortality predictor (HR: 30.99, CI 1.13-4.16; p=0.019) (Figure-4).

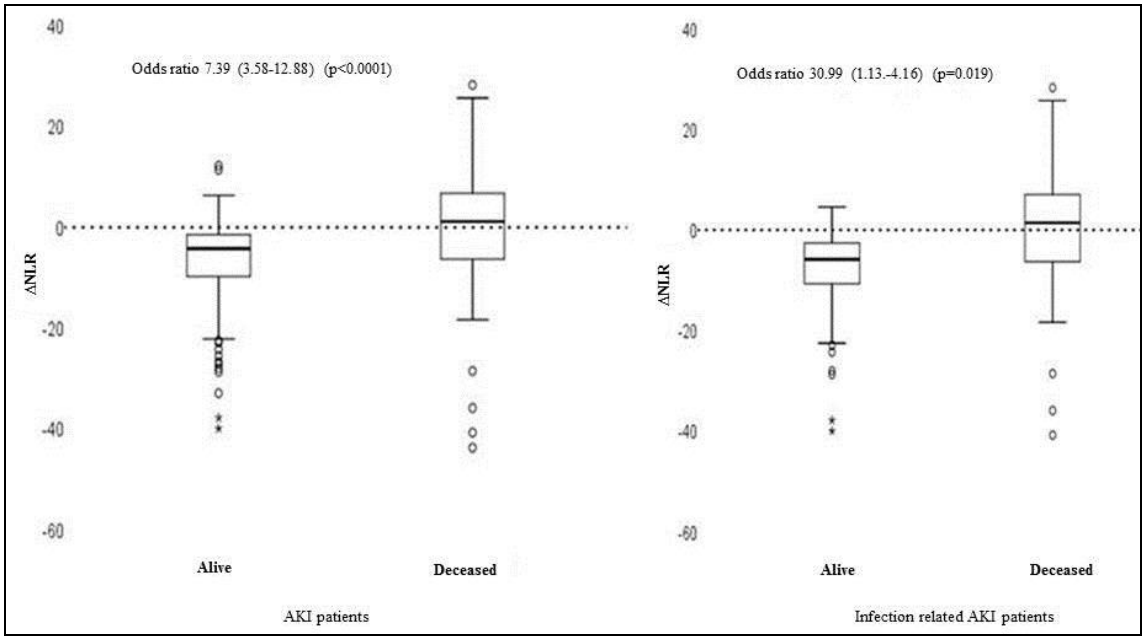

Figure-4. Timely changed NLR (ΔNLR) in study population.

Discussion

We conducted a retrospective analysis included 213 ICU admission due to acute kidney injury. This is the first study in literature evaluating the effects of NLR "predicting the outcome", mainly evaluating 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' increased rate of mortality and development or progression of preexistent kidney disease (9). Therefore, AKI has great socioeconomic and public health burden. Ischeamia-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 are not surprising. 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 increment in NLR values compared to the ones pointed at baseline, final and last follow-up particularly in mortal patients. Indeed we observed that, there were lowest NLR value recordings in alive patients, as compared to value of deceased patients on admission. This seems to be important, NLR change during hospital course may be a 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 had 73% sensitivity and 87% specifity. Change in NLR timely and change in percentage NLR as compared to baseline were also significant predictors 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 a 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 may reflect patients' outcome.

There are several limitations. This is the pilot study which is performed on retrospective cohort evaluating the impact of NLR on predicting the mortality rate in AKI. Single center 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 the analysis of whole ICU population retrospectively and intend to prepare a prospective design in the future.

Conclusion

This is the first study evaluating NLR on patients' outcome in AKI population. 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. NLR is the easily acceptable and cheap reliable marker for screening generalized systemic inflammation. 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 alarm and a screening tool, for patients suffered from AKI.

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