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

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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.

Materias 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.

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 \( \geq 0.3 \text{ mg/dl} \) within 48 hours or
2. Increase in serum creatinine to \( \geq 1.5 \times \text{baseline} \), 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 adjused 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 3.56-15.91; p<0.001). Timely changed NLR(∆NLR) 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. Therefore,
AKI has great socioeconomic and public health burden. Ischemia-
reperfusion injury, sepsis and nephotoxicity 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
anomalities. 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,
have 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 institution 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 desent 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 suffering from AKI.

**References**

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