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THE ROLE OF NEUTROPHIL TO LYMPHOCYTE RATIO IN PREDICTING CLINICAL OUTCOMES IN PATIENTS WITH END STAGE KIDNEY DISEASE

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ABSTRACT

Neutrophil to lymphocyte ratio (NLR) is a marker that reflects the state of systemic inflammation. A high NLR was reported to be associated with short term mortality. However, little is known about the association between high NLR and short-term mortality in patients with end stage kidney disease (ESKD).To determine the diagnostic accuracy of NLR values in predicting the short-term mortality in ESKD patients keeping actual mortality as gold standard. This cross-sectional validation study was conducted at Department of General Medicine, Fauji Foundation Hospital Rawalpindi from March 2024 to September 2024. A total of 200 male and female patients with age between 20 to 70 years and presented with ESKD were enrolled for this study. Subsequently, a complete blood count (CBC) test was conducted and NLR values were determined. Patients with NLR >8.2 were labelled as high NLR. Short-term mortality was labelled as positive if death of ESKD patient occurs due to any cause with-in 30 days of the enrollment to the study. Collected data was analyzed using SPSS software and diagnostic accuracy was determined. Mortality occurred in 69 patients (34.5%). Among patients who were predicted for 30 days mortality due to high NLR, 75% (n=60) experienced mortality, whereas only 7.5% (n=9) of those with low NLR values experienced mortality. 30.0% of the patients were true positive, 55.5% were true negative, 10.0% of the patients were false positive and only 4.5% were false negative. It was noticed that sensitivity of prediction of 30 days mortality by high NLR value was 86.96% while specificity was 84.73%, positive predictive value was 75%, negative predictive value was 92.5% and overall accuracy was 85.5%.This research identifies the NLR as a reliable predictor of 30-day mortality in patients with ESKD, demonstrating high sensitivity, specificity, and diagnostic accuracy. It also serves as an economical instrument for the early stratification of risk and prompt intervention in the management of ESKD.

Keywords: *neutrophil to lymphocyte ratio, end stage kidney disease, hemodialysis, mortality, accuracy*

INTRODUCTION

End-stage kidney disease (ESKD) is diagnosed when kidney function is no longer adequate for long-term survival without kidney transplantation or dialysis.[i] It is associated with a decreased quality of life and life expectancy of the patient as well as representing a large portion of health care expenditure worldwide.[ii] ESKD affects approximately 745,000 individuals in the United

States only and this number is even high in low- and middle- income countries. Globally five to ten million people die annually due to kidney disease and around 2.3–7.1 million with end stage kidney disease.[iii,iv]

Exaggerated responses of inflammation and inflammatory markers are usually associated with worse outcomes and slower recovery, especially in patients with an established ESKD. Individuals suffering from ESKD commonly exhibit raised levels of inflammatory mediators, likely due to an excessive amount of oxidative stress and an overload of extracellular fluid. Kidney function is inversely associated with traditional inflammatory cytokines, including C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α.[v]

Neutrophils are representative cells of innate immunity, whereas lymphocytes are the core of adaptive immunity. Therefore, NLR, a proportional measure of one type of white blood cells over the other, might serve as a useful marker of systemic inflammation. Also, this measure is readily available through common laboratory tests. NLR is a readily accessible and cost-effective biological parameter that can serve as a reliable prognostic indicator in patients with ESKD.[vi] The neutrophil-to-lymphocyte ratio (NLR) in patients with ESKD not only indicates the presence of inflammation, but also acts as an additional prognostic marker for predicting mortality in ESKD patients.[vii,viii] Few previous studies found a decent accuracy of NLR for predicting mortality among patients with ESKD.[ix,x]

Regrettably, the existing international literature on forecasting short-term mortality in patients with ESKD using NLR is scarce. Despite the fact that ESKD is a common cause of in-hospital mortality in low- and middle-income countries such as Pakistan, there is a lack of local research on this significant matter. The purpose of this study is to record the data from our local population regarding the relationship between NLR and the likelihood of short-term death after admission to the healthcare facility in patients with ESKD. If we discover a satisfactory level of predictive accuracy for high NLR in our patients, it will become a standard practice in our setting to use it as the primary prognostic marker.

Material and Methods

This cross-sectional validation study was conducted at Department of General Medicine, Fauji Foundation Hospital Rawalpindi from March 2024 to September 2024. Sample size was calculated using sensitivity and specificity sample size calculator with expected sensitivity of 91.3%,[10] specificity of 76%,[10] prevalence of 40.12%[10] and desired precision of 6% for sensitivity and 10% for specificity. A total of 200 male and female patients with age between 20 to 70 years and presented with ESKD were enrolled for this study. Patients with ESKD of < 6 months duration, having any comorbid disease related to bone marrow (disturbing NLR ratio), having compounded infections or sepsis, patients with any oncological diagnosis and those with raised CRP and presented with any kind of major surgery in last 3 months and immunocompromised patients were excluded from the study. A thorough clinical history was taken and physical examination was performed at the time of enrollment for the study. Stringent adherence to exclusion criteria was implemented to effectively manage the effect modifiers, while standardization was employed to eliminate bias. Subsequently, a complete blood count (CBC) test was conducted at the hospital laboratory to diagnose the NLR in all patients. This involved collecting 3 ml of blood in vacuum tubes coated with EDTA. Collected data was analyzed using SPSS software. Diagnostic accuracy was measured using the 2X2 table. Stratification for diagnostic accuracies were be done for all the study confounders such as age, duration of hemodialysis and gender. Post stratification diagnostic accuracies were measured as well. NLR determined by using parameters of the complete blood count (CBC) test and following formula was used:

Neutrophil lymphocyte ratio = Neutrophil% ÷ Lymphocyte% × 100

Patients with NLR >8.2 were labelled as high NLR. Short-term mortality was labelled as positive if death of ESKD patient occurs due to any cause with-in 30 days of the enrollment to the study. Prediction of mortality using NLR was labelled as positive if patient has high-NLR value i.e. >8.2. Diagnostic accuracies were determined in terms of sensitivity, specificity, positive predictive value

(PPV), negative predictive value (NPV), positive likelihood ratio and negative likelihood ratio.

Results

Study population of our study was female dominant as 64% of the study population was female. Cumulative mean age was 49.19±12.75 years (ranging from 21 to 70 years). Mean duration of haemodialysis found to be 13.90±5.67 months, ranging from 6-24 months. While, mean NLR for overall study population was calculated as 6.48±3.02, ranging from 0.23 to 11.20. Patients were categorized in different groups on the basis of age and duration of haemodialysis. Demographic and clinical parameters are illustrated in table 1. Mortality occurred in 69 patients (34.5%). Among patients who were predicted for 30 days mortality due to high NLR, 75% (n=60) experienced mortality, whereas only 7.5% (n=9) of those with low NLR values experienced mortality. 30.0% (n=60/200) of the patients were true positive, 55.5% (n=111/200) were true negative, 10.0% (n=20/200) of the patients were false positive and only 4.5% (n=9/200) were false negative. It was noticed that sensitivity of prediction of 30 days mortality by high NLR value was 86.96% while specificity was 84.73%, positive predictive value was 75%, negative predictive value was 92.5% and overall accuracy was 85.5%, yielding a positive likelihood ratio of 5.69 and a negative likelihood ratio of 0.15 (table 2). Stratification by gender revealed that males had higher sensitivity (89.66%) compared to females (85.00%). Among age groups, patients over 60 years had the highest sensitivity (90%) and specificity (87.50%). The duration of haemodialysis showed significant variation, with the 10–18-month group achieving the highest diagnostic accuracy (sensitivity: 92.59%, specificity: 90.32%). Diagnostic accuracies for study confounders are illuminated in table 3.

Discussion

This study sought to assess the diagnostic effectiveness of the NLR in predicting the mortality among ESKD patients receiving haemodialysis. Inflammation is recognized to play a crucial role in the course of renal disease, and the NLR, as a composite measure of systemic inflammation, provides useful prognostic information. [xi] Our data indicate a significant correlation between high NLR and 30 days mortality among ESKD patients. Research on other chronic illnesses indicates that a higher NLR is associated with worse outcomes resulting from systemic inflammation, which is frequently intensified in ESKD patients. This indicates that NLR may serve as a reliable biomarker for forecasting outcomes in ESKD patients, along with other research that has emphasized the role of NLR in inflammatory and immunological responses. [8,xii]

This study reveals notable gender disparities in death rates among individuals with elevated NLR. The cause of this disparity remains unclear; however, it may be associated with gender-specific variations in immunological responses, inflammatory pathways, or comorbidities. Prior research indicates that males often exhibit more pronounced inflammation in reaction to diverse health problems, thereby explaining their elevated mortality risk associated with increased NLR. Conversely, females, despite exhibiting a comparable inflammatory response, may have advantages from superior immune system modulation or other protective variables, such as hormonal variations, which might mitigate mortality risk. [xiii]

The correlation between NLR and mortality was also analysed across age demographics. The greatest death rate was noted in the >60 years cohort among patients with elevated NLR, while the ≤40 years group had a decreased mortality rate despite high NLR levels. These findings align with the prevailing knowledge that older persons with ESKD have an elevated risk of adverse outcomes, including death, attributable to the accumulation of comorbidities and age-related immune system deterioration. Age has long been acknowledged as an independent risk factor for death in ESKD. With advancing age, the body's capacity to regulate inflammation declines, and elevated levels of inflammatory markers such as NLR may signify a diminished ability to resist illness, resulting in worse outcomes. The elevated death rates in older demographics correspond with prior research and underscore the importance of age as a vital determinant in mortality forecasting within this patient cohort. [xiv]

The examination of haemodialysis duration indicated a notable correlation, wherein patients

with elevated NLR and haemodialysis durations exceeding 18 months exhibited the greatest death rates, whereas those receiving haemodialysis for less than 10 months demonstrated a considerably reduced mortality rate despite high NLR levels. This data may indicate that prolonged haemodialysis correlates with increased cumulative exposure to the adverse consequences of inflammation, oxidative stress, and other comorbidities. [xv] Consequently, NLR may function not only as a prognostic indicator of death but also as a manifestation of the sustained inflammatory load endured by patients undergoing long-term haemodialysis.[xvi]

Our study offers significant insights; nonetheless, numerous limitations must be acknowledged. The sample size, while adequately substantial, was confined to a specific cohort of ESKD patients receiving haemodialysis, perhaps restricting the generalizability of the results to wider groups. Furthermore, we did not consider all potential confounding variables, including drug usage (e.g., immunosuppressants), preexisting comorbidities (e.g., diabetes, cardiovascular disease), or laboratory findings other from NLR, which may also affect mortality. A further issue is the lack of longitudinal follow-up data. Long-term changes in NLR and their connection with survival might give a more thorough grasp of its prognostic usefulness. Ultimately, given that NLR serves as an inflammatory marker, it is crucial to incorporate additional indicators of inflammation and immune function to construct a more comprehensive model for predicting mortality.

The diagnostic performance indicators further confirm the reliability of NLR as a prediction instrument. The sensitivity (86.96%) and specificity (84.73%) of elevated NLR for predicting mortality demonstrate its efficacy in properly distinguishing individuals at risk and those unlikely to encounter poor outcomes. The positive predictive value (PPV) of 75% and negative predictive value (NPV) of 92.5% demonstrate its practical efficacy in validating high-risk instances and offering comfort in low-risk situations. The computed positive likelihood ratio (5.69) and negative likelihood ratio (0.15) reinforce the dependability of elevated NLR, with the former signifying a robust correlation between high NLR and mortality risk, while the latter illustrates a minimal probability of mortality in patients with low NLR values. The total accuracy of 85.5% underscores the clinical utility of NLR as a screening instrument. The findings of this study correspond with previous studies highlighting the prognostic importance of NLR in critical care and chronic illness contexts. This study specifically examines the relationship between NLR and mortality in patients with ESKD, contributing new insights to a hitherto underexplored area, since prior research mostly concentrated on general intensive care unit populations. The elevated diagnosis accuracy among stratified subgroups highlights the dependability of NLR across various demographic and clinical features.

Recently, Muresan AV and others, analyzed the predictive value of NLR in the outcome of ESKD patients and they reported nearly similar results as our findings. They found that frequency of high NLR in their study was 34.6% and mortality rate within a month of presentation to the hospital was 40.12% in the patients with high-NLR value. They further analyzed the predicting value of NLR for short term mortality in ESKD patients and found that sensitivity and specificity of NLR for predicting 30 days mortality was 91.3% and 76% respectively.[xvii] In a population-based, multi-institutional study, Chen JJ et al,[9] endorsed our study findings and they advocated that high NLR is a reliable predictor for in-hospital or early mortality among kidney patients. Wei W et al in a recent cohort study evaluated the prognostic value of NLR in kidney patients and contrary to our findings, they found relatively lesser sensitivity, specificity and overall accuracy parameters of NLR value for 30 days mortality that were 57%, 69%, and 58.6% respectively.[xviii]

This study's strength is in its capacity to stratify the association between NLR and mortality based on significant demographic and clinical variables, such as gender, age, and HD duration. This method improves the therapeutic significance of the results, enabling customized therapies according to patient attributes. Furthermore, the focus on ESKD patients receiving haemodialysis contributes to the expanding body of research on the use of NLR as a prognostic marker in kidney disease, offering fresh insights into its potential value in this patient group. The results highlight the feasibility of including NLR as a standard, economical

biomarker in the treatment of ESKD. Its elevated sensitivity and specificity, together with strong performance across stratified cohorts, endorse its application for early risk stratification and customized management measures. The considerable difference in diagnostic accuracy related to hemodialysis duration indicates the necessity for longitudinal monitoring of inflammatory markers to enhance prognostic evaluations.

Conclusion

This study emphasizes the diagnostic importance of the NLR in forecasting 30-day mortality among patients with ESKD. A high NLR correlates with a significantly elevated risk of mortality, exhibiting strong sensitivity, specificity, and overall diagnostic accuracy. Stratification analyses indicated improved predictive performance in older patients, males, and individuals undergoing prolonged haemodialysis, highlighting the utility of NLR as a prognostic biomarker across various patient subgroups. The findings highlight the clinical value of integrating NLR as a standard, economical method for early risk assessment and personalized management in ESKD patients. NLR enables the prompt identification of high-risk individuals, thereby facilitating proactive interventions to enhance clinical outcomes. Further multicentre studies are necessary to validate these findings and investigate the integration of NLR with additional biomarkers for the development of comprehensive risk assessment models.

Table 1: Analysis of Demographic and Clinical Parameters of the study Population

Variable	Frequency	Percentage
Gender		
Males	72	36.0
Females	128	64.0
Total	200	100.0
Age Groups		
Up to 40 Years	55	27.5
41 – 60 Years	93	46.5
> 60 Years	52	26.0
Total	200	100.0
Duration of Hemodialysis		
< 10 months	58	29.0
10-18 months	89	44.5
> 18 months	53	26.5
Total	200	100.0

Table 2: Cross-tabulation of prediction of mortality on High NLR and actual mortality

Prediction of Mortality on High NLR	Actual Mortality		Total
	Positive	Negative	
Positive	60 (True Positives)	20 (False Positives)	80
Negative	09 (False Negatives)	111 (True Negatives)	120
Total	69	131	200

- Sensitivity: 87.0%,
- Specificity: 84.7%
- Positive Predictive Value: 75.0%
- Negative Predictive Value: 92.5%
- Diagnostic Accuracy: 85.5%
- Positive Likelihood Ratio: 5.69
- Negative Likelihood Ratio: 0.15

Table 3: Diagnostic accuracy parameters for study confounders

Study Confounder	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall Accuracy (%)	PLR (%)	NLR (%)
Gender							
Male	**89.7**	**88.4**	**83.9**	**92.7**	**88.89**	**7.69**	**0.12**
Female	**85.0**	**83.0**	**69.4**	**92.4**	**83.59**	**4.72**	**0.18**
Age Groups							
Up to 40 Years	**86.7**	**82.5**	**65.0**	**94.3**	**83.64**	**4.95**	**0.16**
41 – 60 Years	**85.3**	**84.7**	**76.3**	**90.9**	**84.95**	**5.60**	**0.17**
> 60 Years	**90.0**	**87.5**	**81.8**	**93.3**	**88.46**	**7.20**	**0.11**
Duration of Hemodialysis							
< 10 months	**83.3**	**72.5**	**57.7**	**90.6**	**75.86**	**3.03**	**0.23**
10-18 months	**92.6**	**90.3**	**80.6**	**96.6**	**91.01**	**9.55**	**0.08**
> 18 months	**83.3**	**89.7**	**87.0**	**86.7**	**86.79**	**8.05**	**0.19**

PPV: Positive Predictive Value, NPV: Negative Predictive Value, NLR: Negative Likelihood Ratio, PLR: Positive Likelihood Ratio

Conflict of Interest

There is no conflict of interest among authors.

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