SPECIAL REPORT

Neutrophil:Lymphocyte Ratio as a Predictive Factor for Success of Nephron-Sparing Procedures in Patients with Emphysematous Pyelonephritis

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ABSTRACT

Introduction: We studied the value of neutrophil:lymphocyte ratio (NLR) in predicting the success of nephron-sparing procedures in management of emphysematous pyelonephritis.

Methods: In this single-center retrospective study, patients underwent nephron-sparing procedures between 2007 and 2014. Severity was graded by Huang-Tseng classification. Thrombocytopenia, acute renal failure (ARF), shock, altered sensorium, and admission NLR were evaluated for predictive value for successful outcomes. Receiver operating characteristic curves were plotted to determine optimal cutoff of NLR for differentiating successful and unsuccessful outcomes. Two-sided p values were calculated with the χ^2 test. Factors that were significant on univariate analysis were combined in a model with NLR.

Results: Sixteen patients, 14 (87.5%) of whom were female and 14 (87.5%) of whom had diabetes, were included. Ten (63%) had severe emphysematous pyelonephritis. The optimal cutoff of NLR was 5. Four (44%) of 9 patients with NLR above 5 had unfavorable outcomes compared with none of 7 with NLR of 5 or less, giving a risk ratio of 1.8 (95% confidence interval [CI]= 1.01-3.22, p = 0.0417). Area under the curve for NLR alone was 0.77 (95% CI = 0.55-0.99, p = 0.014). High NLR and ARF were the only factors predicting unsuccessful outcome (p = 0.0417 each). When these were combined in a model (NLR as continuous variable), the area under the curve increased to 0.92.

Conclusion: NLR is a useful predictive marker in emphysematous pyelonephritis. Its predictive value increases when combined with presence or absence of ARF. In patients with high NLR and ARF, the threshold for considering nephrectomy should be low.

INTRODUCTION

Emphysematous pyelonephritis (EPN) is a severe necrotizing infection of the renal parenchyma; it is characterized by gas formation in the collecting system, renal parenchyma, and/or perirenal tissues.[1] Diabetes is the most common predisposing factor; more than 95% of the cases are reported in patients with diabetes.[2] Obstruction is the most common precipitating factor.[2] Renal failure and immunosuppression generally add to the insult. *Escherichia coli* is the most common infecting organism and in some studies has been reported to be responsible for more than two-thirds of the cases.[2]

Conventionally, nephrectomy was considered as the treatment of choice. However, several recent studies have challenged this view and have reported successful outcomes with conservative measures (stenting, percutaneous drainage or open drainage, and medical management).[2-10] One study even suggested that an urgent nephrectomy without a trial of conservative management may even be detrimental and may be associated with increased mortality.[8] Some other studies have contradicted this.[2] Globally, there is an increasing trend to manage EPN conservatively.

With an increasing trend toward conservative management, it has become important to identify factors predicting the success of medical management and, hence, to identify patients for whom the threshold for consideration for nephrectomy should be low. Few factors—such as acute renal failure (ARF), altered mentation, and thrombocytopenia—have been found to predict an unsuccessful outcome in some studies.[2,8] On the other hand, evaluation of factors such as radiologic class and shock have yielded conflicting results.[2,8] Additionally, there is no good model combining more than one factor to predict the outcomes.

In the past few years, several studies have studied the neutrophil:lymphocyte ratio (NLR) in acute illness and have found this to be a useful marker of acute stress.[11-14] One of these studies has also reported that NLR can better predict bacteremia compared with other conventional markers of infection like C-reactive protein and total leukocyte count.[11] Because EPN is an acute bacterial infection, we hypothesized that NLR might correlate with the severity of EPN and might have a predictive role in patients receiving conservative management of EPN. To test this hypothesis, we analyzed the predictive value of NLR at hospital admission in our cohort of patients whose EPN was managed with conservative measures. We also evaluated whether adding NLR improves the predictive accuracy of the other factors and tried to develop a model combining factors found to be significant in our study.

METHODS

In this single-center retrospective study, we included all patients with EPN admitted between January 2007 and June 2014 at our hospital, PD Hinduja National Hospital and Medical Research Centre in Mumbai, India. The study was approved by the hospital's institutional review board and ethical committee. The diagnosis of EPN was suspected on the basis of sonography

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done in the Emergency Department, the result of which showed gas in the renal parenchyma. This was further confirmed by computed tomography (CT). Only those patients who were confirmed to have gas in the renal parenchyma and/or perirenal tissues on CT scan were included in the study.

All patients were treated by medical management, stenting, and percutaneous or surgical drainage; no patient received an upfront (urgent initial) nephrectomy. All patients received intravenous antibiotics, on the basis of any previous culture report available, if any, within the first hour after presentation. For those for whom no previous culture report was available, cefoperazone and sulbactam was given empirically in appropriate doses, considering the creatinine values. The first dose of antibiotic was given after blood and urine samples were collected for culture.

Data regarding the clinical presentation, laboratory parameters, radiologic findings, treatment outcomes, and follow-up were retrieved from patients' medical records. Blood, urine, and drained pus were sent for cultures in all patients according to institutional protocols. The glomerular filtration rate was estimated using the modification of diet in renal disease formula (or using the diethylene triamine pentaacetic acid scan results wherever available). Particular attention was paid to the presence at admission of known risk factors: Thrombocytopenia (platelet count < 100×10^9/L), ARF (defined as either urine output of < 0.5mL/kg/h × 6 hours *or* an increase in creatinine level by ≥ 0.3mg/dL over 48 hours *or* an increase in creatinine level by 1.5 times over 7 days), altered sensorium, and presence of shock (according to the standard definition of septic shock[15]). The NLR was calculated from the automated complete blood cell counts obtained at admission. Radiologic classification of EPN was done using the Huang-Tseng classification[2] (based on the CT findings at admission). The presence of obstruction was determined on the CT scan (in all cases done preoperatively). The diethylene triamine pentaacetic acid scan (wherever available) was also useful in determining the presence or absence of obstruction. A retrograde pyelogram was obtained at the time of intervention to further look for any obstruction.

Treatment outcomes were categorized as successful or unsuccessful. A successful outcome was defined as meeting all the following criteria without the need for nephrectomy: Resolution of fever and other clinical symptoms, resolution of leukocytosis, conversion of positive urine culture to negative, and improvement/stable calculated glomerular filtration rate at 3-month follow-up (calculated with the modification of diet in renal disease formula). Patients who required nephrectomy, who died without resolution of the acute condition, or those not fulfilling the aforementioned criteria were considered to have unsuccessful outcomes.

We correlated the NLR at admission to the outcomes and plotted a receiver operating characteristic (ROC) curve to determine the optimal cutoff value of NLR for differentiating between successful and unsuccessful outcomes. We also evaluated the presence of ARF, shock, altered sensorium, thrombocytopenia, and advanced Huang-Tseng radiologic class (Classes 3 and 4) as predictive factors for unfavorable outcome of the treatment. For the purpose of analysis, we dichotomized variables. We combined the risk factors found to be significant on univariate analysis in our cohort with NLR and evaluated whether this combination increased the predictive accuracy. Fisher exact test and χ^2 test were used as appropriate. All p values were 2-sided. Statistical analysis was done using GraphPad software (GraphPad Software, La Jolla, CA).

RESULTS

Sixteen patients with EPN were treated with nephron-sparing procedures between January 2007 and June 2014. The

Table 1. Baseline characteristics (N = 16)

Characteristic	Patient population
Median age, years (range)	54 (27-79)
Women, no. (%)	14 (87.5)
Diabetes, no. (%)	14 (87.5)
Duration of diabetes, median (range) (n = 14)	9 y (7 d-15 y)
Side affected, no. (%) (n = 15)[a]	
Left	13 (86.6)
Right	2 (13.4)
Symptoms, no. (%)	
Prodromal symptoms	6 (37.5)
Flank pain	11 (68.8)
Fever	15 (93.8)
Urinary symptoms	10 (62.5)
Duration of symptoms, days, median (range)	6 (2-180)
Adverse factors at presentation, no. (%)	
Acute renal failure	9 (56.3)
Shock	2 (12.5)
Altered sensorium	2 (12.5)
Thrombocytopenia	4 (25.0)

[a] One patient had involvement of a transplanted kidney.

Table 2. Microbiology and radiologic findings (N = 16)

Parameter	No. (%) of patients
Causative microorganism	
Gas-forming organism identified	
Escherichia coli	6 (37.5)
Klebsiella pneumoniae	2 (12.5)
No gas-forming organism identified	
Pseudomonas aeruginosa	8 (50.0)
Blood culture positive	9 (56.3)
Hydronephrosis	6 (37.5)
Renal obstruction	5 (31.3)
Huang-Tseng classification	
2	6 (37.5)
3A	6 (37.5)
3B	3 (18.8)
4	1 (6.2)
Glomerular filtration rate (GFR)	
Calculated GFR, mL/min, median (range)	34 (3-100)

median age of patients was 54 years (range = 27-79 years), and 14 (87.5%) were women. Fourteen patients (87.5%) had diabetes, with the median duration of diabetes being 9 years. In 5 (55%) of 9 patients for whom glycated hemoglobin value was available, the value was above 7%, indicating poor control of diabetes. Of the 2 patients without diabetes, 1 was immunosuppressed after a previous renal transplant, and the other patient had ureteric obstruction caused by calculus. Left-sided renal involvement was seen in 13 (87%) of 15 patients (in 1 patient a transplanted kidney was involved). Fever was the most common presenting symptom, followed by flank pain. These details are summarized in Table 1.

Through a combination of cultures of the drained pus, blood, and urine, the causative microorganism was identified in all cases; all were bacterial. Polymicrobial and fungal infections were not seen. Radiologic features of obstruction were seen in 5 (31.3%) of the 16 patients. Of these, 3 cases were caused by papillary necrosis, and 2 were caused by calculus disease. The details of the microbiological and radiologic findings are summarized in Table 2.

The interventions consisted of surgical drainage alone in 6 patients (37.5%), stenting alone in 2 patients (12.5%), and a combination of both in the remaining 50% of patients (n = 8). Fifteen (93.7%) of the patients received the required intervention either on the day of admission or on the next day. In surviving patients, the median follow-up time was 6 months. Overall, 4 patients had unfavorable outcomes. Therapy details, complications, and long-term outcomes are summarized in Table 3.

Table 3. Treatment and outcomes (N = 16)

Parameter	No. (%) of patients
Intervention	
Surgical drainage alone	6 (37.5)
Stenting alone	2 (12.5)
Surgical drainage and stenting	8 (50.0)
Delay in intervention, median days (range)	0.5 (0-2)
Complications	
Wound infection	1 (6.2)
Residual collection	1 (6.2)
Pleural effusion	1 (6.2)
Reexploration	1 (6.2)
Nephrectomy	1 (6.2)
Mortality	2 (12.5)
Renal scan/calculated GFR, mL/min,at follow-up, median (range) (n = 14)	75 (7-139)
Final treatment outcome	
Successful	12 (75.0)
Unsuccessful	4 (25.0)
Reason for unsuccessful outcome (n = 4)	
Persistent urine culture positive	1 (25.0)
Nephrectomy	1 (25.0)
Death	2 (50.0)

GFR = glomerular filtration rate.

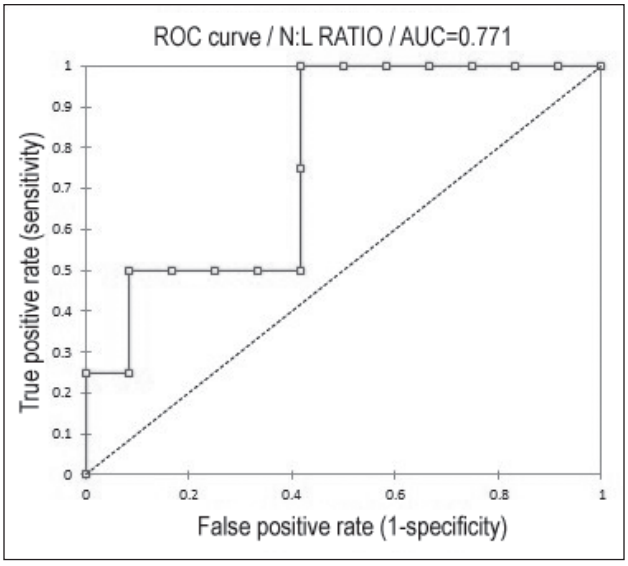

Figure 1. Receiver operating characteristic (ROC) curves for predictive value of neutrophil:lymphocyte (N:L) ratio alone.
AUC = area under the curve.

With use of an ROC curve, the optimal cutoff of NLR for differentiating between successful and unsuccessful outcome was found to be 5. Four (44%) of 9 patients with NLR above 5 had an unfavorable outcome compared with none of 7 patients with NLR of 5 or less. The risk ratio for an unfavorable outcome in patients with high NLR was 1.8 (95% CI = 1.01-3.22, p = 0.0417). The area under the ROC curve was 0.77 (95% CI = 0.55-0.99, p = 0.014), indicating a moderately good clinical usefulness of NLR for predicting outcomes (Figure 1).

The details of univariate analysis of NLR and other risk factors are shown in Table 4. The presence of ARF at admission and high NLR (> 5) were the only factors associated with increased risk of unfavorable outcomes (p = 0.0417 for both). Unfavorable outcomes occurred in 4 (67%) of the 6 patients who had both risk factors (high NLR *and* presence of ARF) but in none of the 6 patients with only 1 risk factor (high NLR *or* presence of ARF), and in 0 patients with neither risk factor (p = 0.011). When these 2 factors were combined in a model (with NLR taken as a continuous variable), the area under the ROC curve increased to 0.92, thereby indicating an excellent predictive accuracy of this model (Figure 2).

DISCUSSION

EPN is a potentially life-threatening infection of the kidney, occurring predominantly in diabetic patients or in patients with obstruction of the upper urinary tract. The condition most commonly affects women in the sixth decade of life and more commonly involves the left side.[2,9] In our study, the median age was 54 years, and nearly 90% of patients were women. Also, the left side was much more commonly affected than the right. These findings from our study concur with those reported from other studies.[2,8-10]

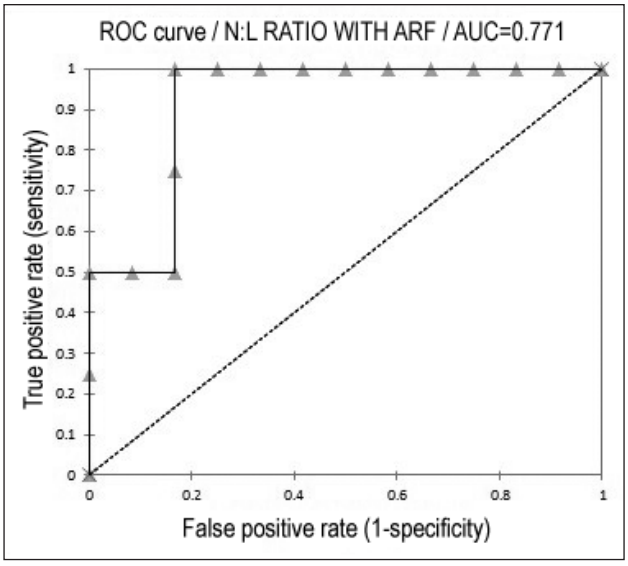

Figure 2. Receiver operating characteristic (ROC) curves for predictive value of a model combing neutrophil:lymphocyte (N:L) ratio (continuous variable) and acute renal failure (ARF).
AUC = area under the curve.

The causative microorganisms are usually gram-negative bacilli. *E coli* has been the most common pathogen reported from several previous studies.[2,8-10] In our study, however, *Pseudomonas* was the most common isolated pathogen. This possibly reflects a change in the prevalence and virulence amongst the gram-negative bacilli over time. In our hospital, *Pseudomonas* has already overtaken *E coli* in intensive care units as a causative pathogen for various serious infections.[16]

During the past several years, the trend is shifting from an upfront nephrectomy to kidney-sparing management. With this trend, it has become imperative to identify factors that will help predict the outcome of conservative management. Several studies[2,8] have tried to address these with some similar and some conflicting results. In their seminal article, Huang and Tseng[2] proposed a radiologic classification of the severity of EPN and found that all patients with Class 1 or 2 EPN had a favorable outcome with conservative management alone. For those with Classes 3 and 4 EPN, the success of conservative management depended on the presence or absence of additional risk factors.[2] This study identified shock, altered sensorium, ARF, and thrombocytopenia as additional risk factors.[2] Thrombocytopenia, renal failure, and altered mentation were also found to be associated with poor outcomes in another study.[8] However, contrary to the findings of Huang and Tseng, Kapoor et al[8] did not find radiologic findings to be predictive of the final outcome. Additionally, the study by Kapoor et al did not find hypotension to be associated with poor outcome, in contrast to the study by Huang and Tseng. These differences are likely caused by small sample sizes in these studies and differences in the definitions used for defining these risk factors. Our study found that ARF and high NLR at admission predicted an unsuccessful outcome. However, thrombocytopenia, shock, and altered sensorium were not significant predictors in our study.

Using a combination of NLR (as a continuous variable) and the presence or absence of ARF, we devised a model with a higher predictive accuracy compared with NLR alone. When both these factors were combined in a model, the area under the ROC curve increased from 0.77 for NLR alone to 0.92 for the model. This indicates that when these 2 factors are

Table 4. Univariate analysis of predictive factors for outcome (N = 16)

Factor	No. of patients	Successful outcome	Unsuccessful outcome	Risk ratio (95% CI)	p value
Acute renal failure					
Present	9	5	4	1.8 (1.01-3.22)	0.0417
Absent	7	7	0		
Shock					
Present	2	1	1	1.57 (0.38-6.45)	0.3827
Absent	14	11	3		
Altered sensorium					
Present	2	1	1	1.57 (0.38-6.45)	0.3827
Absent	14	11	3		
Thrombocytopenia					
Present	4	3	1	1.00 (0.52-1.92)	> 0.999
Absent	12	9	3		
Huang-Tseng grading					
Mild (1 and 2)	6	5	1	0.84 (0.49-1.44)	> 0.999
Severe (3 and 4)	10	7	3		
Neutrophil:lymphocyte ratio					
> 5	9	5	4	1.8 (1.01-3.22)	0.0417
≤ 5	7	7	0		

CI = confidence interval.

combined, the resulting model has an excellent ability to identify patients in whom conservative management is likely to fail.

Our study has some limitations. First, it is a retrospective study and hence is likely to have the drawbacks of a retrospective study. However, in our study, we had the required baseline data for all patients, and follow-up data for all surviving patients. Second, the number of patients in our study is small and this could have affected the statistical significance of some of the risk factors. Two of the 5 factors tested (NLR and ARF) turned out to be statistically significant in our study, probably indicating that these 2 are the most important factors among others. However, considering the small number of patients, these results could be underpowered or biased, and would need larger studies for better statistical evaluation.

Furthermore, the intrinsic limitations of NLR also must be kept in mind. Overwhelming infections can at times suppress the bone marrow and result in severe neutropenia, for which this ratio will not help. Also, immunosuppressed and elderly patients may not mount an adequate response to infection, and one needs to be cautious in interpreting the results in these patients.

CONCLUSION

Our study shows that NLR is a useful predictive marker in patients with EPN. Its predictive value increases when combined with the presence or absence of ARF. However, these findings must be confirmed in larger prospective studies. We do not intend to suggest an upfront nephrectomy for all patieints with EPN. However, in patients with high NLR and ARF at presentation, the threshold for consideration for nephrectomy should be low. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Author Contributions

Chirag Punatar, MS, DNB, was responsible for conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; Vikash Kumar, MS, DNB, for acquisition of data; Kunal Jadhav, MS, DNB, for acquisition of data; Vinod Joshi, MS, MCh, for conception and design of the study and drafting the manuscript; and Sharad Sagade, MS, MCh, for conception and design of the study and critical revision of the manuscript.

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