Predictive Value of Neutrophil/Lymphocyte Ratio for Developing Acute Renal Failure in Patients with Sepsis Using Colistin in Intensive Care Units

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ABSTRACT

Introduction: Sepsis affects millions of people every year all over the world, and despite increasing knowledge over the years and the use of modern antibiotics and resuscitation treatments, it is the most important cause of morbidity and mortality in intensive care units. Nephrotoxicity is a clinical condition that increases morbidity and mortality in the hospitalized patient population, particularly critically ill patients in intensive care. The neutrophil/lymphocyte ratio (NLR) has emerged as a new biomarker that has begun to be investigated in sepsis and post-surgical acute renal failure (ARF). We determined whether changes in NLR are biomarkers for developing ARF in patients using colistin with a diagnosis of sepsis.

Methods: After obtaining ethics committee permission, the files of patients who were followed up in intensive care with a diagnosis of sepsis and who used colistin in their treatment were retrospectively scanned. In our study, the files of 350 patients followed in intensive care were examined, and it was determined that 70 patients diagnosed with sepsis used colistin. The data of 48 patients included in our study were analyzed.

Results: After colistin use, it was observed that 28 (58%) patients developed ARF, and 20 (41.6%) did not develop ARF. There was no significant difference between the groups in terms of ARF development. In the comparison between the groups, although NLR1 was higher in group 2 than in group 1, and NLR2 was higher in group 1 than in group 2, no significant difference was detected. In the intra-group evaluation, although NLR2 was higher than the baseline value in group 1 and lower in group 2, no statistically significant difference was detected.

Conclusion: The NLR results do not constitute a difference that can be used as a predictive value in showing the development of ARF in patients diagnosed with sepsis and receiving colistin treatment.

Keywords: Sepsis, colistin, acute renal failure, neutrophil lymphocyte ratio

Introduction

Sepsis/septic shock affects millions of people every year all over the world, and despite increasing knowledge over the years and the use of modern antibiotics and resuscitation treatments, it continues to be the most important cause of morbidity and mortality in intensive care units (ICUs). The incidence of sepsis/septic shock; it is increasing due to prolonged intensive care stay, increase in antibiotic resistance, and increase in the number of immunosuppressed patients and the elderly population (1,2). Polymyxins are the preferred drugs for treating multidrug-resistant microorganisms such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which develop multiple antibiotic resistance. Polymyxins were isolated from *Paenibacillus polymyxa* and became available for clinical use in the 1950s (3). Polymyxin B and polymyxin E (also known as colistin) are in clinical use. Its use gradually decreased in the 1970s with the discovery of aminoglycosides, which have fewer side effects than colistin. In the 2000s, it began to be used more frequently for treating microorganisms with multidrug resistance, especially *Pseudomonas* and *Acinetobacter* spp. (4). The most important side effect of intravenous polymyxins is nephrotoxicity (5). Nephrotoxicity is a clinical condition that increases morbidity and mortality in the hospitalized patient population, particularly critically ill patients in intensive care. The neutrophil/lymphocyte ratio (NLR) has emerged as a new biomarker that has begun to be studied in acute renal failure (ARF) that develops after sepsis and surgery.

Table 1. Descriptive and clinical characteristics of the groups

	Group 1	Group 2	p-value
Female/male (number)	10/18	8/12	0.762
Age (years)	73±12	70±13	0.794
Height (cm)	170±10	173±10	0.777
Weight (kg)	80±13	70±13	0.498
SOFA	12±2	11±3	0.612
APACHE II	27±7	29±8	0.924

APACHE: Acute Physiological and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment Score, p<0.005 significant

Table 2. NLR values

NLR	Group 1	Group 2	p-value
NLR1	11±12	14±14	0.446
NLR2	14±12	11±16	0.151

NLR: Neutrophil/lymphocyte ratio, NLR1: NLR calculated just before starting colistin treatment, NLR2: NLR calculated at the 48th hour of colistin treatment, p<0.005 significant

In our study, we compared the NLRs of patients who developed and did not develop ARF after colistin use in patients we followed up with a diagnosis of sepsis. We determined whether changes in NLR are biomarkers for developing ARF in patients using colistin with a diagnosis of sepsis.

Methods

After obtaining permission from the Balıkesir University Faculty of Medicine Ethics Committee (approval number: 2022/02, date: 26.01.2022), the files of patients who were followed up in the ICU with a diagnosis of sepsis and used colistin in their treatment between January 2019 and December 2021 were retrospectively scanned. Patients who stayed in intensive care for more than 48 h were included in our study. Patients were diagnosed with sepsis and septic shock according to the "Sepsis Survival Campaign Severe Sepsis and Septic Shock Management 2021 guideline". Patients had to be over 18 years of age and use colistin for at least 48 h. Patients who used colistin before ICU admission, patients who were diagnosed with AKI and/or chronic renal failure before colistin treatment, and patients who used colistin for less than 48 h were not included in the study.

Risk-injury-failure-loss of renal function-End-stage kidney disease (RIFLE) criteria were used to eliminate patients diagnosed with renal failure in patients in whom colistin treatment was initiated at a standard dose of 2.5-5 mg/kg/day (maximum: 300 mg). The creatine value calculated just before colistin treatment was recorded as the baseline value and re-evaluated for ARF at the 48th hour of colistin treatment. Patients were divided into two groups: those who developed ARF (group 1) and those who did not (group 2). NLR values of the patients were calculated immediately before and 48 h after starting colistin treatment. NLR was obtained by dividing the absolute neutrophil count by the lymphocyte count. It was defined as NLR1 calculated immediately before starting colistin treatment and NLR2 calculated at the 48th hour. NLR1 and NLR2 were examined in patients in both groups to determine whether the change in NLR was a predictive value in terms of ARF.

Statistical Analysis

The SPSS 22.0 (SPSS, Inc., Chicago, IL) package program was used for the analysis of data. The descriptive statistics of the quantitative variables included in the study are as follows: arithmetic mean, standard deviation, median, minimum, and maximum values. Qualitative variables are shown as frequency and percentage (%). The suitability of quantitative variables to normal distribution was examined using the Shapiro-Wilk test. Chi-square tests were used in intergroup comparisons of qualitative variables. The Independent sample t-test was used for comparisons of variables with normal distribution between two independent groups. Those not normally distributed were compared using the Mann-Whitney U test to compare the two groups. The statistical significance level was determined as 0.05.

Results

In our study, the files of 350 patients followed up in the ICU were examined, and it was determined that 70 patients diagnosed with sepsis used colistin. Twenty patients were excluded from the study because of the diagnosis of chronic renal failure, and 2 patients were excluded because they were under 18 years of age. Data of 48 patients included in our study were analyzed. Of the patients, 18 were women and 30 were men. While the average age of all patients included in the study was 71±9, the average age of only female patients was 73±5 and only male patients was 71±3. The demographic characteristics of group 1 and group 2 patients were similar. Sequential Organ Failure Assessment Score and Acute Physiological and Chronic Health Evaluation II score distributions were similar between the groups (Table 1).

After colistin use, it was observed that 28 (58%) of the patients developed ARF, and 20 (41.6%) did not develop ARF. There was no significant difference between the groups in terms of AKI development. In the comparison between the groups, although NLR1 was higher in group 2 than in group 1, and NLR2 was higher in group 1 than in group 2, no significant difference was detected. In the intra-group evaluation, although NLR2 was higher than the baseline value in group 1 and lower in group 2, no statistically significant difference was detected (Table 2).

Discussion

The NLR results do not constitute a difference that can be used as a predictive value in showing the development of ARF in patients diagnosed with sepsis and receiving colistin treatment.

In their study, Yilmaz et al. (6) examined the data of 118 patients hospitalized in intensive care with a diagnosis of sepsis. Suggested that the

ARF development rate was 61% and that there was a statistical correlation between ARF and NLR. Bu et al. (7) suggested that ARF develops in 59% of patients hospitalized in intensive care and diagnosed with sepsis, the average NLR is 17±4, and there is a significant correlation between ARF and NLR. Various studies have reported a relationship between ARF and NLR (8-10). We believe that the different results obtained from our study are due to the difference in the number of patients, the fact that the studies were not specific to patients using colistin, and the lack of etiology discrimination. In addition, in these studies, criteria different from the RIFLE criteria were used in the diagnosis of ARF. It has been observed that more patients can be diagnosed with the Acute Kidney Injury Network criteria than with the RIFLE criteria (11-14).

Consistent with the literature, the most common growth in microbiological samples is *Acinetobacter baumannii*, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* a, respectively. For this reason, colistin is used for treating sepsis (15-17).

It has been reported that before 1975, colistimethate sodium was mostly used intramuscularly and in higher doses than today, and the nephrotoxicity rate was approximately 30% (20-50%) (4). The rates of nephrotoxicity caused by colistin vary in various studies. This is because different criteria are used in the diagnosis of renal failure and different patient groups are evaluated (18,19).

Study Limitations

The limiting factors of our study are the small number of patients included in the study, the fact that many factors may be associated with renal failure during the hospitalization period, and the fact that it was conducted as a retrospective file scan.

Conclusion

Because of our study, we concluded that it is not appropriate to use NLR as a predictive value in ARF in patients diagnosed with sepsis and starting colistin treatment in intensive care.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801-10.

2. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013; 41: 1167-74.

3. Kumazawa J, Yagisawa M. The history of antibiotics: the Japanese story. J Infect Chemother 2002; 8: 125-33.

4. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005; 40: 1333-41.

5. Mirjalili M, Mirzaei E, Vazin A. Pharmacological agents for the prevention of colistin-induced nephrotoxicity. Eur J Med Res 2022; 27: 64.

6. Yilmaz H, Cakmak M, Inan O, Darcin T, Akcay A. Can neutrophil-lymphocyte ratio be independent risk factor for predicting acute kidney injury in patients with severe sepsis? Ren Fail 2015; 37: 225-9.

7. Bu X, Zhang L, Chen P, Wu X. Relation of neutrophil-to-lymphocyte ratio to acute kidney injury in patients with sepsis and septic shock: A retrospective study. Int Immunopharmacol 2019; 70: 372-7.

8. Jiang F, Lei J, Xiang J, Chen Y, Feng J, Xu W, Ou J, Yang B, Zhang L. Monocyte-to-lymphocyte ratio: a potential novel predictor for acute kidney injury in the intensive care unit. Ren Fail 2022; 44: 1004-11.

9. Xie T, Xin Q, Chen R, Zhang X, Zhang F, Ren H, et al. Clinical Value of Prognostic Nutritional Index and Neutrophil-to-Lymphocyte Ratio in Prediction of the Development of Sepsis-Induced Kidney Injury. Dis Markers 2022; 2022: 1449758.

10. Bu X, Zhang L, Chen P, Wu X. Relation of neutrophil-to-lymphocyte ratio to acute kidney injury in patients with sepsis and septic shock: A retrospective study. Int Immunopharmacol 2019; 70: 372-7.

11. Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2020; 395: 1506-15.

12. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Crit Care Med 2008; 36: 1129-37.

13. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 2009; 35: 1692-702.

14. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, et al. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011; 15: R16.

15. Giamarellou H. Multidrug-resistant Gram-negative bacteria: how to treat and for how long. Int J Antimicrob Agents 2010; 36 Suppl 2: S50-4.

16. Kaya M, Tunçel Yİ, Kuru RN, Menteş S, Ünver S, Çeken S, et al. Retrospective Evaluation of Colistin-Associated Nephrotoxicity in the Intensive Care Unit of the Oncology Hospital. Journal of the Turkish Society of Intensive Care 2014; 12.

17. Inci A, Toker MK, Bicer IG, Derbent A, Salihoglu Z. Determination of colistin-related nephrotoxicity and risk factors in intensive care unit. North Clin Istanb 2018; 5: 120-4.

18. Lim LM, Ly N, Anderson D, Yang JC, Macander L, Jarkowski A, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. Pharmacotherapy 2010; 30: 1279-91.

19. Ordooei Javan A, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol 2015; 71: 801-10.