



Neutrophil-to-lymphocyte ratio for early renal failure under extracorporeal membrane oxygenation support for postcardiotomy shock

Postkardiyotomi şok nedeniyle ekstrakorporeal membran oksijenasyon desteği altında erken böbrek hasarında nötrofil-lenfosit oranı

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ABSTRACT

Background: This study aims to investigate the relationship between the neutrophil-to-lymphocyte ratio and renal injury in patients under extracorporeal membrane oxygenation support for postcardiotomy shock.

Methods: Between January 2007 and July 2018, a total of 119 patients (38 males, 81 females; mean age 54.4±13.0 years; range, 24 to 74 years) who received extracorporeal membrane oxygenation support for postcardiotomy shock and survived at least 48 hours in our center were retrospectively analyzed. Pre- and postoperative neutrophil-to-lymphocyte ratios, demographic characteristics, renal function parameters, and extracorporeal membrane oxygenation-related data of the patients were recorded. Occurrence and stages of renal injury was determined using the revised Acute Kidney Injury Network and Kidney Disease Improving Global Outcomes criteria.

Results: No significant relationship was found between preoperative neutrophil-to-lymphocyte ratio and renal injury ($p>0.05$). Postoperative neutrophil-to-lymphocyte ratio was higher in patients who developed renal injury, compared to patients without renal injury (8.68 [0.84-42.00] vs. 4.02 [1.04-21.21], respectively, $p=0.004$). When patients were grouped for renal injury stage according to the revised Acute Kidney Injury Network ($p=0.015$) and Kidney Disease Improving Global Outcomes ($p=0.006$) criteria, the patients with more severe renal injury had higher neutrophil-to-lymphocyte ratio. The receiver operating characteristics analysis revealed a cut-off value of 6.71 for the neutrophil-to-lymphocyte ratio for the detection of renal injury. Patients with a value above 6.71 had an odds ratio of 5.941 for occurrence of renal injury.

Conclusion: Postoperative, but not preoperative neutrophil-to-lymphocyte ratio is associated with presence and severity of renal injury in patients under extracorporeal membrane oxygenation support for postcardiotomy shock. Neutrophil-to-lymphocyte ratio is a simple and inexpensive marker of inflammation in this patient population.

Keywords: Extracorporeal membrane oxygenation, inflammation, neutrophil-to-lymphocyte ratio, postcardiotomy shock, renal injury.

ÖZ

Amaç: Bu çalışmada postkardiyotomik şok nedeniyle ekstrakorporeal membran oksijenasyon desteği alan hastalarda nötrofil-lenfosit oranı ve böbrek hasarı arasındaki ilişki araştırıldı.

Çalışma planı: Ocak 2007 - Temmuz 2018 tarihleri arasında merkezimizde postkardiyotomik şok nedeniyle ekstrakorporeal membran oksijenasyon desteği alan ve en az 48 saat hayatta kalan toplam 119 hasta (38 erkek, 81 kadın; ort. yaş 54.4±13.0 yıl; dağılım 24-74 yıl) retrospektif olarak incelendi. Hastaların ameliyat öncesi ve sonrası nötrofil-lenfosit oranları, demografik özellikleri, böbrek fonksiyon parametreleri ve ekstrakorporeal membran oksijenasyona ilişkin verileri kaydedildi. Böbrek hasarının gelişimi ve evreleri revize Akut Böbrek Hasarı Ağı ve Böbrek Hastalığında Küresel Sonuçların İyileştirilmesi kriterlerine göre belirlendi.

Bulgular: Ameliyat öncesi nötrofil-lenfosit oranı ve böbrek hasarı arasında anlamlı bir ilişki saptanmadı ($p>0.05$). Ameliyat sonrası nötrofil-lenfosit oranı, böbrek hasarı gelişen hastalarda, böbrek hasarı olmayan hastalara kıyasla, daha yüksekti (sırasıyla 8.68 [0.84-42.00] ve 4.02 [1.04-21.21], $p=0.004$). Hastalar Akut Böbrek Hasarı Ağı ($p=0.015$) ve Böbrek Hastalığında Küresel Sonuçların İyileştirilmesi ($p=0.006$) kriterlerine göre böbrek hasarı evrelerine ayrıldıklarında, daha ciddi böbrek hasarı olan hastalarda nötrofil-lenfosit oranı daha yüksek bulundu. Alıcı işletim karakteristik analizi ile böbrek hasarı tespitinde nötrofil-lenfosit oranının kesim değeri 6.71 olarak saptandı. 6.71'in üzerinde bir değere sahip hastalarda, böbrek hasarı gelişiminin olasılık oranı 5.941 idi.

Sonuç: Ameliyat öncesi değil fakat, ameliyat sonrası nötrofil-lenfosit oranı, postkardiyotomik şok nedeniyle ekstrakorporeal membran oksijenasyon desteği alan hastalarda böbrek hasarının varlığı ve derecesi ile ilişkilidir. Nötrofil-lenfosit oranı, bu hasta grubunda basit ve ucuz bir enflamasyon belirteçidir.

Anahtar sözcükler: Ekstrakorporeal membran oksijenasyonu, enflamasyon, nötrofil-lenfosit oranı, postkardiyotomik şok, böbrek hasarı.

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Extracorporeal membrane oxygenation (ECMO) is a mode of mechanical support used in the treatment of cardiogenic or respiratory shock. The course of the patient under ECMO support can be complicated by many adverse events, among which acute kidney injury (AKI) is the most frequently reported complication.^[1] Its incidence has been reported as high as 74% in the literature.^[2] Acute kidney injury during ECMO treatment, sometimes termed ECMO-associated kidney injury (EAKI), brings about more inotrope and transfusion requirements,^[3] and is associated with a higher mortality.^[4,5]

An appreciable inflammatory response is initiated with the placement of ECMO. The release of proinflammatory cytokines, activation of the coagulative cascades, the complement system, and lymphocytes result in endothelial injury and impaired microcirculation, leading to end-organ damage.^[6] The inflammatory milieu triggers the endothelium, lymphocytes, and platelets, causing neutrophil infiltration of tissues and inflammatory insult into organs.^[6] This and other factors including preexisting multisystemic disease, ischemia-

reperfusion damage, hemolysis are involved in the pathogenesis of EAKI.^[3]

The neutrophil-to-leukocyte ratio (NLR) has been implicated in oncology, neurology, and cardiovascular diseases as a surrogate of inflammatory state associated with responsiveness to treatment, disease severity, and adverse events.^[7-13] Recently, the NLR has been shown to have a predictive value for mortality in patients supported with ECMO.^[14]

In the present study, we aimed to evaluate NLR in patients under ECMO support for postcardiotomy shock and to investigate the possible relationship between the NLR and renal injury.

PATIENTS AND METHODS

Between January 2007 and July 2018, a total of 138 patients received ECMO for postcardiotomy shock in our center. Nineteen patients who died within the first 48 h of ECMO were excluded. Finally, 119 patients (38 males, 81 females; mean age 54.4±13.0 years; range, 24 to 74 years) who received ECMO support for postcardiotomy shock were retrospectively analyzed.

Table 1. Demographic and clinical characteristics of patients

Characteristics	n	%	Mean±SD
Age (year)			54.4±13.0
Gender			
Female	81	68.1	
Male	38	31.9	
Hypertension	56	47.1	
Diabetes mellitus	37	31.1	
ECMO duration (days)			6.8±5.8
ECMO site			
Peripheral	32	26.9	
Central	87	73.1	
Acute kidney injury	96	80.7	
Renal replacement therapy	54	45.4	
Hemodialysis duration (days) (n=54)	8.57	9.05	
AKIN stage			
0	23	19.3	
1	17	14.3	
2	17	14.3	
3	62	52.1	
KDIGO stage			
0	23	19.3	
1	19	16.0	
2	18	15.1	
3	59	49.6	

SD: Standard deviation; ECMO: Extracorporeal membrane oxygenation; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease Improving Global Outcomes.

Those with a known history of renal failure were excluded. A written informed consent was obtained from the patient. The study protocol was approved by the institutional Academic Review Board (Decision No: 28001928-508.01). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Pre- and postoperative NLR for each patient was recorded along with parameters of renal function before and after ECMO treatment. Difference in pre- and postoperative NLR denoted an arithmetic difference of the calculated values. Demographic characteristics, preexisting chronic diseases, method of ECMO placement, and postoperative renal function parameters for all patients were recorded. In addition, ECMO-related data were recorded including the site of insertion (central or peripheral) and duration of ECMO support.

The patients were initiated on veno-arterial (VA) ECMO via heparin-coated arterial and venous cannulas either through the ascending aorta and right atrium or peripherally through the femoral artery and vein. A centrifugal blood pump sustained flow at 3 to 4 L/min. The ECMO circuit was primed with 600 mL of balanced Ringer's solution. The target mean arterial pressure was >60 mmHg and the target hemoglobin level was >7 g/dL.

Definitions

The revised Acute Kidney Injury Network (AKIN)^[15] and Kidney Disease Improving Global Outcomes KDIGO^[16] criteria were used to classify patients into respective AKI and KDIGO stages of renal failure. Early renal failure was defined as renal failure within 72 h of ECMO initiation. The highest serum creatinine level within the first 72 h, urine output during this period, and renal replacement therapy (RRT) requirement were recorded.

Statistics

Statistical analysis was performed using the (Number Cruncher Statistical System) (NCSS) version 2007 software (NCSS LLC, Kaysville, UT, USA).

Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. The Mann-Whitney U and Kruskal-Wallis H tests were used for the comparison of groups without normal distribution. The Kruskal-Wallis H test with Dunn's test was applied for post-hoc analysis of the groups. The Pearson's chi-square test was used to compare the groups with categorical data. To estimate a cut-off value for variables, diagnostic tests and Receiver Operating Characteristics (ROC) curve were used. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 96 (80.7%) developed AKI during the first three days of treatment. Demographic and clinical characteristics of the patients are summarized in Table 1.

There was no statistically significant difference in the preoperative NLR with respect to the presence of AKI according to either AKIN or KDIGO criteria, while a significant relationship between postoperative NLR and presence of early kidney injury was observed (Table 2). The patients who developed early kidney injury according to either AKIN or KDIGO criteria had higher NLR compared to the patients without early kidney injury. The difference between the pre- and postoperative NLR was also higher in the patients with AKI.

Postoperative NLR was also significantly different according to the AKIN and KDIGO stages, when the patients were staged according to these respective criteria (Table 3). The number of the patients with AKI was identical using both criteria. However, the stage of AKI varied in three patients using both criteria and a statistically significant difference was found between the groups for different disease stages. Post-hoc analysis with the Dunn's test also revealed a significant difference.

A cut-off value of 6.71 was calculated for an NLR value distinguishing the presence of early renal injury

Table 2. Pre- and postoperative NLR according to presence of early kidney injury

	Early Kidney Injury (-) (n=23)		Early Kidney Injury (+) (n=96)		<i>p</i>
	Median	Min-Max	Median	Min-Max	
Preoperative NLR	3.51	1.07-31.60	2.97	0.11-31.73	0.6185
Postoperative NLR	4.02	1.04-21.21	8.68	0.84-42.00	0.004*
Difference in NLR	-0.07	-16.48-18.41	3.90	-21.55-38.36	<0.001**

NLR: Neutrophil-to-lymphocyte ratio; AKI: Acute kidney injury; Min: Minimum; Max: Maximum; * *p*<0.05; ** *p*<0.001 (Mann-Whitney U test).

Table 3. Postoperative NLR according to AKI stage using AKIN and KDIGO criteria

	AKI stage				<i>p</i>
	0	1	2	3	
AKIN					
n (%)	23 (19)	17 (14)	17 (14)	62 (52)	0.015*
Median	4.02	7.33	8.15	8.74	0.002**
Minimum-Maximum	1.04-21.21	0.08-28.84	0.94-27.33	1.08-42.0	
KDIGO					
n (%)	23 (19)	19 (16)	18 (15)	59 (50)	0.006*
Median	4.02	6.76	7.81	8.82	0.005**
Minimum-Maximum	1.04-21.21	0.08-28.84	0.94-27.33	1.08-42.0	

NLR: Neutrophil-to-leukocyte ratio; AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease Improving Global Outcomes; * Kruskal-Wallis test; ** Dunn's post-hoc test.

under ECMO. The ROC curve is shown in Figure 1. A cut-off value of 6.71 for NLR in distinguishing the presence of early renal injury was significant with $p=0.001$, with an area under curve of 0.693 with a sensitivity of 67.71% and a specificity of 73.91% (Table 4). An odds ratio of 5.941 was calculated for the risk of renal injury in the patients whose NLR was above 6.71.

DISCUSSION

The present study examined the possible relationship between the inflammatory status of patients via NLR as a surrogate marker of inflammation and development of early AKI under ECMO support. The

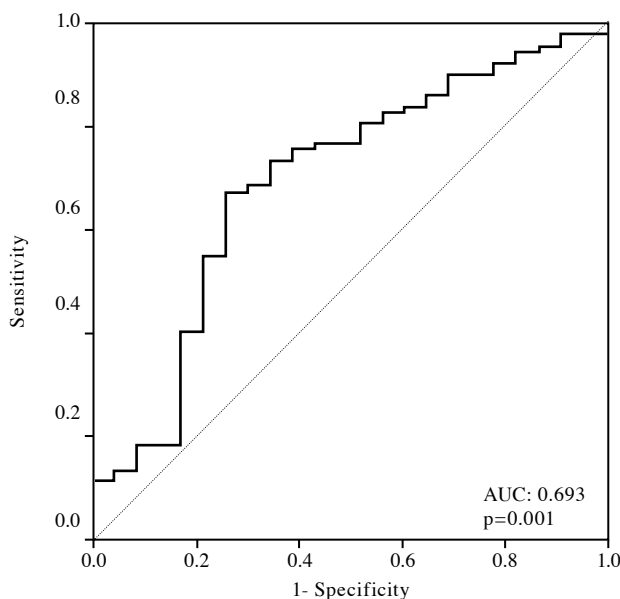


Figure 1. Receiver operating characteristics curve for Neutrophil-to-lymphocyte ratio and presence of renal injury.

AUC: Area under curve.

indication for ECMO in all included patients was postcardiotomy shock and AKI occurred in 81% of the patients.

Renal injury under ECMO results from an interplay of several patient-related and ECMO-related mechanisms. Implicated factors include progression of preexisting multisystemic diseases, pre-ECMO management, alterations in the renal macro/microvasculature, ischemia-reperfusion, hemolysis and oxidative stress, disruption of the glycocalyx, impaired renal autoregulation, nephrotoxic medications, and iatrogenic coagulation abnormalities.^[3] The period under cardiopulmonary bypass in the preceding operation through inflammatory and non-inflammatory mechanisms with the hemodynamically unstable period, before the initiation of ECMO threatens the renal function, and AKI is a common presence in postcardiotomy shock before ECMO implantation.^[17] The double-edged sword of ECMO is that the patient hemodynamics and kidney perfusion are augmented in exchange for the loss of pulsatile flow, hemolysis, ischemia-reperfusion damage, and systemic inflammatory response, resulting in an impaired renal function.^[3,17,18]

Proinflammatory cytokines are released with the activation of coagulative and complement cascades. Neutrophil activation is a key element of the increased inflammatory response to ECMO.^[17] As a result of increased neutrophil infiltration and inflammatory insult from activated endothelium, lymphocytes, and platelets, the kidney suffers from endothelial injury and impaired microcirculation.^[3,6]

Defining renal injury is a challenge in many studies. The revised AKIN criteria are accepted as a validated definition and used widely in the literature.^[19] The AKIN criteria along with the Risk, Injury, Failure,

Table 4. ROC curve for a cut-off value of 6.71

	Diagnostic scan				ROC curve		<i>p</i>	
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under curve		95% CI
Postoperative NLR	≥6.71	67.71	73.91	91.55	35.42	0.693	0.567-0.819	0.001*

ROC: Receiver operating characteristics; CI: Confidence interval; NLR: Neutrophil-to-lymphocyte ratio; * 0.001 (ROC analysis).

Loss, and End-stage renal failure (RIFLE) and KDIGO have been used to examine prognostic parameters under ECMO and allows for reproducible classification which aids in studying AKI.^[18,19] Furthermore, higher stages of renal injury were associated with worse survival under ECMO, and one study found the KDIGO criteria to have better outcome prediction than the RIFLE and AKIN classifications.^[20]

The immune response to the initiation of ECMO has detrimental consequences. Endothelial dysfunction, end-organ damage, and increased mortality are the results of different pathways that are activated in response to the ECMO circuitry.^[6] Accordingly, a higher NLR was shown to be a predictor of poor outcome in ECMO patients of different indications, presumably as it mirrors a maladaptive immune response to ECMO.^[14]

On the other hand, we found no correlation between the preoperative NLR in postcardiotomy shock patients undergoing cardiac surgery and kidney injury within the first three days of ECMO initiation. We, therefore, cannot conclude that preoperative NLR is a predictor for postoperative AKI. This finding indicates that the preoperative NLR of an immunologically unprovoked patient undergoing elective cardiac surgery does not reflect their potential inflammatory response. Our study population was not comprised of heart failure patients whose distinctive inflammatory milieu might alter the postoperative course and end-organ status. Intraoperative variables and a new-onset inflammatory response might play a more prominent role in the development of AKI in postcardiotomy shock patients. This is reflected by the higher difference in NLR from the preoperative values in patients with AKI. A more profound change in the inflammatory status parallels its detrimental results on the kidney.

In the present study, the NLR cut-off value as calculated by the ROC analysis was 6.72, which is higher than cut-off values reported in the literature.^[7-9,11,13] We believe this is due to our association of EAKI with postoperative NLR where these ratios are higher with the inflammatory response in place, as opposed to the preoperative period, when

the NLR is lower before any inflammatory stimulus.

Postoperative NLR was associated with AKI developing within 72 h of ECMO initiation. This association is still valid, when AKI is defined with both the AKIN and KDIGO criteria. This relationship can be explained with a higher postoperative NLR, suggesting a more profound immune reaction after ECMO placement. Furthermore, NLR was higher with a more severe AKIN or KDIGO disease stage. A more profound immune response could, therefore, be cause a more severe damage to the renal function.

In general, NLR is a valuable and simple parameter which can provide an insight into the frequently emerging risk of kidney injury. This relationship may translate into an association with mortality in the longer term. In future studies, the relationship between the NLR and mortality and other adverse events under ECMO can be investigated. Further studies may also address into the correlation of other markers of inflammation and adverse events with ECMO.

The limitations of the study include its retrospective design and single-center involvement. Another point worth mentioning is that while this study focused on postcardiotomy shock cases and therefore involved a set of patients with a homogenous mechanism of inflammatory response, operation type and intraoperative variables that could influence kidney injury were not separately analyzed. Future research can be directed towards clarifying the effects of operative variables to the resulting NLR and AKI.

In conclusion, the neutrophil-to-lymphocyte ratio is a simple and inexpensive marker of inflammation and the increase after the initiation of extracorporeal membrane oxygenation treatment is correlated with early renal injury. A higher neutrophil-to-lymphocyte ratio is associated with a more severe renal injury. The severity of a new-onset inflammatory response in postcardiotomy shock may be responsible for early kidney injury after the initiation of extracorporeal membrane oxygenation support.

Declaration of conflicting interests

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