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Research

The Role of Neutrophil Gelatinase-associated Lipocalin as a Predictive Biomarker of Acute Kidney Injury in Patients Undergoing Major Abdominal Surgery

Majör Abdominal Cerrahi Geçiren Hastalarda Akut Böbrek Hasarının Prediktif Biyobelirteci Olan Nötrofil Gelatinaz İlişkili Lipokalinin Rolü

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ABSTRACT

Objective: The current study investigates the development of acute kidney injury (AKI) in patients undergoing major abdominal surgery via earlier determination of the rise in neutrophil gelatinase-associated lipocalin (pNGAL) compared to that in creatinine.

Methods: In this prospective observational study, 60 patients aged between 18 and 65 undergoing major abdominal surgery were selected for the investigation after obtaining ethics committee approval. Patients who did not meet the age criteria, had liver and kidney failures, severe cardiac and respiratory distress, used angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs, developed postoperative respiratory failure, cardiogenic and septic shock, relapse in the 1st 24 h, and those who underwent emergency surgery were excluded from the study. Leukocyte and creatinine values (preoperatively and at 24 and 48 h postoperatively), pNGAL (at 0 h intraoperatively and 6 h and 24 h postoperatively), lactate values (at 0 h intraoperatively and 24 h and 48 h postoperatively), and urine output value (at 24 and 48 h postoperatively) were evaluated.

Results: Of the 60 patients, 9 (15%) showed increased pNGAL values at 6 h postoperatively; however, increased creatinine values and decreased urine output values were observed at 48 h postoperatively. Thus, AKI development was detected at an early stage. The change in leukocyte and lactate values was not statistically significant.

Conclusion: pNGAL was proven to be an early predictive biomarker of AKI in patients undergoing major abdominal surgery.

Keywords: Major abdominal surgery, acute kidney injury, plasma NGAL (neutrophil gelatinase-associated lipocalin), creatinine

ÖZ

Amaç: Çalışmanın amacı majör abdominal cerrahi geçiren 60 hastada plazma nötrofil jelatinaz ilişkili lipokalin (pNGAL) değerinin kreatinin değerinden daha erken dönemde akut böbrek hasarının (ABH) geliştiğini belirlemesini araştırmaktır.

Gereç ve Yöntem: Etik kurul onayı alınan, 18-65 yaş arası, Amerikan Anesteziyoloji Derneği I-III, majör abdominal cerrahi geçiren 60 hasta seçildi. Preoperatif, postoperatif 24. ve 48. saatte lökosit, kreatinin; intraoperatif 0. saat, postoperatif 6. ve 24. saatte pNGAL; intraoperatif 0. saat, postoperatif 24. ve 48. saatte laktat değerlerine bakıldı, postoperatif 24. ve 48. saatlerde saatlik idrar çıkışları değerlendirildi.

Bulgular: Altmış hastadan 9'unda (%15) plasma NGAL seviyesi postoperatif 6. saatte yükselmiş olsada, kreatinin değerleri postoperatif 48. saatte artmış oldu, postoperatif saatlik idrar çıkışları 0,5 cc/kg altına düşmüş oldu. Böylece, gelişen ABH erken dönemde tespit edilmiş oldu. Lökosit ve laktat değerlerindeki değişim istatistiksel olarak anlamlı bulunmadı.

Sonuç: Majör abdominal cerrahi geçiren hastalarda plasma NGAL'nin akut böbrek hasarının en erken prediktif biyobelirteci olduğu kanıtlanmıştır. Postoperatif 2 aylık takip süresinde hastalarda renal replasman terapisi veya ölüm insidansı saptanmamıştır.

Anahtar Kelimeler: Majör abdominal cerrahi, akut böbrek hasarı, plazma NGAL (nötrofil getalinaz ilişkili lipokalin), kreatinin

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INTRODUCTION

Major abdominal surgery is a procedure performed via the intraperitoneal approach under general anesthesia (1). The pathogenesis of postoperative acute kidney injury (AKI) after major abdominal surgery is complex and differs from that observed after cardiac or vascular surgery. It involves fluid loss, neuroendocrine response to general anesthesia and surgery itself, injury-induced inflammation, urinary tract obstruction, and intra-abdominal pressure (2).

Surgery is the leading cause of AKI in hospitalized patients and may account for 40% of AKI cases (3). AKI is most common after cardiac surgery, followed by general and thoracic surgeries (4). The incidence of AKI in patients undergoing major abdominal surgery may reach 35% (4).

AKI is defined as a rapid deterioration of kidney function, with an increase in serum creatinine or a decrease in the urine output (5). AKI is common in hospitalized patients and has a significant impact on in-hospital mortality, length of hospital stay, healthcare costs, chronic kidney disease (CKD) progression, and increased risk of cardiovascular disease (6,7). Recently, although there has been a decrease in mortality rates, mortality increases as the severity of AKI increases, and it can reach up to 60% in critically ill patients (8).

The most common cause of AKI is sepsis, whereas the second most common cause is surgery (9). Chronic diseases, such as CKD, diabetes mellitus, and chronic obstructive pulmonary disease are associated with the development of AKI (10).

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein that is synthesized in the bone marrow during granulocyte maturation (9). NGAL is also an early indicator of tubular damage (11). This study aimed to detect AKI in the early stage of its development by evaluating NGAL and show the potential of NGAL as an early biomarker of AKI in patients undergoing major abdominal surgery.

The incidence of AKI varies between 1% and 7% in all hospitalized patients and 30% and 50% in intensive care patients. Especially in intensive care patients, the mortality rate is very high (up to 50%). Moreover, 20%-50% of surviving patients with AKI may subsequently develop CKD, 5% may develop end-stage renal disease, and finally may develop the need for renal replacement therapy (RRT) (12).

In patients with impaired renal autoregulation, an intraoperative mean arterial pressure of 60 mmHg may lead to decreased renal perfusion and AKI development (13). Intraoperative hypotension lasting for more than 1 min significantly increases the risk of postoperative AKI (13).

NGAL, also known as lipocalin-2, siderocalin, oncogeneprotein 24p33, uterocalin, and alpha-2 microglobulin-associated protein, is a 25-kD protein comprising 178 amino acids. It was first identified as a protein covalently bound to the gelatinase of neutrophils (14). NGAL is expressed in insignificant amounts in many human tissues, including the kidney tissue, but increases markedly because of epithelial damage (15). In the body, NGAL mRNA is normally found in many tissues such as those of the bone marrow, uterus, prostate, salivary gland, stomach, colon, trachea, lung, liver, and kidney (16).

NGAL can also be markedly increased in most types of cancer (28) and has bacteriostatic properties (17).

METHODS

After obtaining the approval of the ethics committee (Marmara University Faculty of Medicine Clinical Research Ethics Committee- protocol code: 09.2021.74, date: 08.01.2021) and obtaining written consent from the patients our study included 60 patients [American Society of Anesthesiology (ASA) status I-III] aged between 18 and 65 who underwent major abdominal surgery under general anesthesia.

Patients having an age beyond the specified age range, liver and kidney failures, severe cardiac and respiratory distress, using angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs, those who developed postoperative respiratory failure, cardiogenic and septic shock, and relapsed in the 1st 24 h were excluded from the study.

All the patients included in our study underwent the same anesthesia induction procedure (2 mg/kg propofol/1-2 mcg/kg remifentanil/0.6 mg/kg rocuronium bromide). Additionally, desflurane inhalation and intravenous remifentanil infusion were used for anesthesia maintenance. Maintenance fluid was administered to the patients intravenously at a rate of 10-12 mLl/kg/h without fluid restriction.

Creatinine, lactate, and leukocyte values were measured preoperatively and postoperatively at 24 and 48 h using the blood samples of the patients. For measuring NGAL values, approximately 3 mL of venous blood sample was collected preoperatively at 0 h and postoperatively at 6 and 24 h into an ethylenediaminetetraacetic acid-containing tube and centrifuged for 15 min at 3000 rpm in a centrifuge (Nüve NF800, REF: Z10.NF 800). The plasma portion of the

centrifuged blood was placed in an Eppendorf tube and stored in a -20 °C freezer until plasma NGAL value analysis was conducted.

The hourly urine output was measured at 24 and 48 h postoperatively, and the glomerular filtration rate (GFR) and creatinine clearance (CrCl) value of the patients were calculated.

Patients' age, gender, body weight, ASA status, lactate, creatinine, leukocyte, NGAL, Kidney Disease Improving Global Outcomes (KDIGO) stages and postoperative hourly urine output were recorded in the patient evaluation form.

Statistical Analysis

Minimum sample size was calculated for obtaining the area under the receiver operating characteristic (ROC) curve. While an area under the ROC curve for a variable at the value of 0.500 indicates that the variable has no discriminative power, a value of ≥0.800 indicates excellent discrimination. In this context, it is assumed that the minimum area value required for statistical significance is 0.800. For this calculation, the ratio of subjects developing/not developing an incident is also important. Based on the study conducted by Shavit et al. (18), this ratio was accepted as 10/64. On the basis of these values, it was calculated that at the value of α=0.05, the minimum sample size required to reach 80% power should be 45.

RESULTS

Baseline and Intraoperative Characteristics

Table 1 shows the patients mean age, weight and gender. The increase in the urine output observed at 48 h postoperatively was statistically significant compared to that of the subjects at 24 h postoperatively.

Table 2 shows that the change in the creatinine values of the subjects was statistically significant (p=0.001). Because of the evaluations, the decrease observed in the values at 24 h postoperatively compared to those observed preoperatively and the increase in the values at 48 h postoperatively compared to those at 24 h postoperatively were found to be statistically significant (p<0.001, p=0.033, respectively).

The change observed in the GFR values of the patients over time was statistically significant (p=0.001). The increase observed in the values at 24 h postoperatively compared to those observed preoperatively and the decrease in the values at 48 h postoperatively compared to those at 24 h postoperatively were found to be statistically significant (p<0.001, p=0.036, respectively).

The change observed in the CrCl values of the subjects was found to be statistically significant (p=0.001). The increase in the values observed at 24 h postoperatively compared to those observed preoperatively was statistically significant (p<0.001, p<0.001, respectively).

The change observed in the lactate values of the subjects was found to be statistically significant (p=0.003). The analyses showed that the increase observed in the values at 24 and 48 h postoperatively values compared to those at 0 h intraoperatively was statistically significant (p=0.002, p=0.020, respectively).

Even though we had only one group in our study, we decided conditionally to divide the patients into two groups according to pNGAL value. Table 3 shows that the subjects with an NGAL value <90 ng/mL at postoperative 6 h and 24 h were found to have normal creatinine values. All the subjects with an NGAL value >90 ng/mL at postoperative 6 h and 24 h were classified as AKI class I and II based on their creatinine values. Patients with NGAL values >90 ng/mL had a higher tendency to be included in AKI class I and II based on their creatinine values (p<0.001).

Furthermore, 3.9% of the subjects with an NGAL value <90 ng/mL had hourly urine output values <0.5 cc/kg/h, whereas all cases with an NGAL value >90 ng/mL had hourly urine output values <0.5 cc/kg/h. It was found that the percentage of subjects with hourly urine output values <0.5 cc/kg/h was higher than that of those with NGAL values >90 ng/mL (p<0.001). In those with NGAL values < 90 ng/mL, the increase in the values observed at 48 h postoperatively compared to those at 24 h postoperatively was statistically significant (p=0.010). In those with NGAL values >90 ng/mL, the change observed in the urine output values at 48 h postoperatively compared to that at 24 h postoperatively was not statistically significant (p>0.05).

Table 1. Data on identifying features

(n=60)	Minimim-maximum	Mean ± SD
Age (years)	20-65	50.77±12.44
Weight (kg)	43-90	68.25±9.70
	n	**%**
Gender		
Female (number)	24	40
Male (number)	36	60
ASA (number =60)		
I	7	11.6
II	42	70
III	11	18.4

ASA: American Society of Anesthesiologists, SD: Standard deviation

Table 2. Data on laboratory results

	WBC ($x10^3/\mu L$)	CRE (mg/dL)	GFR (mL/minute/1.73 m^2)	CrCl (mL/minute)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Preoperatively	7.54±3.59	0.75±0.21	102.15±20.77	112.47±35.88
Postoperative 24	10.5±4	0.68±0.23	107.32±21.19	124.97±38.24
Postoperative 48	9.68±3.58	0.75±0.32	101.8±25.62	117.98±40.08
Test value, p	**F=14.883, p<0.001**	**F=7.831, p=0.001**	**F=7.510, p=0.001**	**F=6.779, p=0.001**

WBC: White blood cell, CRE: Creatinine, GFR: Glomerular filtration rate, CrCl: Creatinine clearance, SD: Standard deviation

Table 3. Relationship between NGAL and creatinine values and hourly urine output

	NGAL <90 ng/mL	NGAL> 90 ng/mL	Test value, p
	n (%)	n (%)	
Creatinine			**χ^2=52.941, p<0.001**
Normal	51 (100)	0	
AKI I & II	0	9 (100)	
Hourly urine output (cc/kg/h)			**χ^2=47.166, p<0.001**
Postop 24 h	0.74±0.35	0.62±0.06	**t=1.011, p=0.314**
Postop 48 h	0.9±0.46	0.48±0.01	**t=2.713, p=0.008**
Normal	49 (96.1)	0	
<0.5 cc/kg/h	2 (3.9)	9 (100)	

NGAL: Neutrophil gelatinase-associated lipocalin, Fisher's Exact test: p<0.05

In those with NGAL values <90 ng/mL and those with NGAL values >90 ng/mL, the change observed in creatinine values over time was statistically significant (p<0.001, p<0.001, respectively) (Table 4).

In those with NGAL values <90 ng/mL and those with NGAL values >90 ng/mL, the change observed in CrCl values was found to be statistically significant (p<0.001, p<0.001, respectively). The decrease in the values observed at 48 h postoperatively compared to those observed preoperatively and at 24 h preoperatively was found to be statistically significant (p<0.001, p<0.001, respectively) (Table 5).

In those with NGAL values <90 ng/mL; the change in lactate values was found to be statistically significant (p=0.012). The increase in the values observed at 24 h postoperatively compared to those observed at 0 h intraoperatively was statistically significant (p=0.006). In those with NGAL values >90 ng/mL, the change observed in lactate values over time was not statistically significant (p>0.05).

The graph of the change in plasma NGAL values of the patients over time shows that the values tended to increase at 6 and 24 h postoperatively compared to 0 h (Figure 1).

Concerning the change in the creatinine values of the patients over time, they decreased at 24 h postoperatively in 60 patients, but they tended to increase at 48 h postoperatively (Figure 2).

When NGAL and creatinine values of all subjects were compared, it was found that NGAL values increased after 6 h postoperatively and creatinine values increased at 48 h postoperatively (Figure 3).

DISCUSSION

This study investigated the efficacy of plasma NGAL in predicting AKI, hemodialysis, and mortality in patients undergoing major abdominal surgery. It was found that NGAL values measured at 6 and 24 h postoperatively were higher than those measured at 0 h intraoperatively and postoperative creatinine values increased later. Therefore, it has been proven that NGAL has a more predictive value in diagnosing AKI in patients undergoing major abdominal laparotomy surgery than creatinine. Additionally, it enables AKI detection at the early stage (at 6 h postoperatively).

In another study by Teixeira et al. (19) that included 450 patients undergoing major nonvascular abdominal

surgery, the incidence of postoperative AKI in the first 48 h after surgery was 22.4% and AKI was associated with the incidence of in-hospital mortality. In our study, AKI was observed in 15% of the 60 patients; however, RRT was not performed in these patients.

We conducted this study because the relationship between postoperative AKI and the need for long-term dialysis and/or decreased kidney function has only been investigated in patients who had undergone prior hepato-biliary, pancreatic, and cardiac surgeries (20) but not in those who had undergone major abdominal surgery.

In AKI, the initiating mechanism and subsequent response to injury decrease the recovery of the basal structure and function of the kidneys (21). In our study, it was proven that AKI can also develop after major abdominal surgery.

AKI is one of the most common critical diseases with high morbidity and poor prognosis. Its causes are extremely complicated, and it is linked to conditions such as hypovolemia, decreased cardiac output, nephrotoxic drug use and urinary tract obstruction (5). In our study, to protect the patients from hypovolemia, a pleth variablitiy index (PVI) device was used. The PVI value was kept between 5 and 13, and intravenous fluids were administered at a rate of 10-12 cc/kg/h.

Hypoxia caused by by different reasons can lead to inflammation, oxidative stress, immune system activation, and cell death (22). AKI is a common complication that may occur after abdominal surgery. AKI development after abdominal surgery causes a 3.5-fold increase in mortality in patients (23). Although AKI developed in 9 of the 60 patients included in our study, the incidence of death was not observed during the 2-month postoperative follow-up.

Numerous studies in the literature have shown that the most important risk factor for AKI development after abdominal surgery is preoperative renal failure. Other risk factors include dehydration, intra-abdominal hypertension, blood transfusion, and nephrotoxic drug use (24). We took care that the patients included in our study did not have kidney failure and did not use any nephrotoxic drug.

High lactate values in the blood reflect tissue microcirculation failure. Previous studies have shown that high lactate values are a risk factor in critically ill patients (25). Lactate values in the blood may be affected by conditions such as intraoperative tissue ischemia, postoperative coagulation, acute inflammatory response, and sepsis (26). In our study, although the intraoperative lactate values of the patients were not high, the change observed over time was found to be statistically significant. The analyses showed that the increase observed in the values at 24 and 48 h postoperatively compared to those at 0 h intraoperatively was statistically significant (p=0.002, p=0.020, respectively). Conversely, the change observed in the values at 48 h postoperatively compared to those at 24 h postoperatively was not significant (p>0.05).

The endotoxin load released because of the occurrence of intestinal ischemia, visceral perfusion disorder, and portal endotoxemia during abdominal surgery activates the proinflammatory response, resulting in endothelial damage,

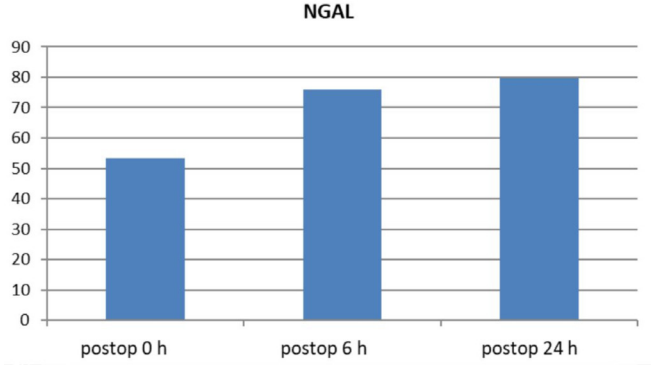

Figure 1. Change in plasma NGAL values over time
NGAL: Neutrophil gelatinase-associated lipocalin

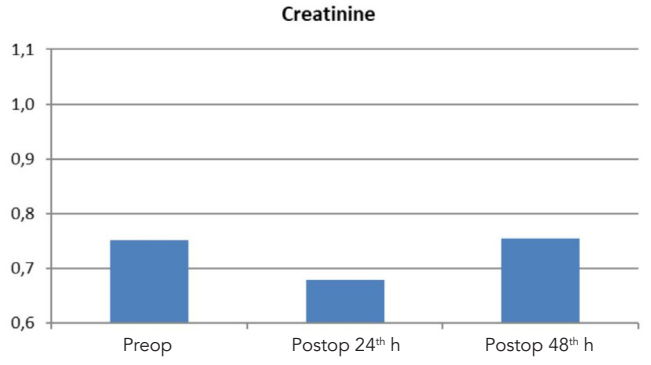

Figure 2. Change in serum creatinine value over time

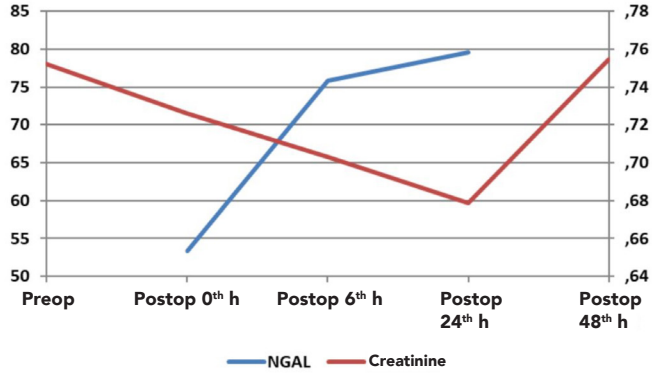

Figure 3. Comparison of the changes in plasma NGAL and creatinine values over time
NGAL: Neutrophil gelatinase-associated lipocalin

Table 4. Relationship between NGAL values and change in creatinine

Creatinine (mL/minute)	NGAL <90 ng/mL	NGAL> 90 ng/mL	Test value, p
	Mean ± SD	Mean ± SD	
Preoperatively	0.75±0.22	0.75±0.13	**t=-0.073, p=0.942**
Postop 24 h	0.68±0.24	0.7±0.16	**t=0.265, p=0.791**
Postoperative 48 h	0.65±0.22	1.32±0.24	**t=8.406, p<0.001**
Test value, p	**F=11.550, p<0.001**	**F=152.943, p<0.001**	

NGAL: Neutrophil gelatinase-associated lipocalin, SD: Standard deviation, Generalized linear mixed model: p<0.05

Table 5. Comparison of NGAL and CrCl

CrCl (mL/minute)	NGAL<90 ng/mL	NGAL>90 ng/mL	Test value, p
	Mean ± SD	Mean ± SD	
Preoperatively	110.69±36.57	122.56±31.67	**t=0.837, p=0.404**
Postoperative 24 h	122.82±35.68	137.11±51.28	**t=1.090, p=0.277**
Postoperative 48 h	126.53±36.28	69.56±22.67	**t=-4.518, p<0.001**
Test value, p	**F=10.776, p<0.001**	**F=61.923, p<0.001**	

NGAL: Neutrophil gelatinase-associated lipocalin, SD: Standard deviation, CrCl: Creatinine clearance, Generalized linear mixed model: p<0.05

followed by vasoconstriction, microvascular occlusion, and leukocyte congestion. Immune activation resulting from AKI causes systemic inflammatory changes (27). In our study, the change observed over time in white blood cell counts of the patients with AKI was not found to be statistically significant (p>0.05).

In their randomized study, Gözce et al. (28) reported that monitoring biomarkers in the blood of critically ill patients undergoing major noncardiac surgery significantly reduced the incidence of class II and severe AKI. In our study, according to the creatinine values, 10% (n=6) of the cases had class I AKI, 5% (n=3) had class II AKI, and 15% (n=10) patients in total were found to develop AKI. It was observed that in 15% (n=9) of the patients, the cut-off value of NGAL increased (>90 units).

In severe AKI cases, RRT may be necessary to maintain blood volume, electrolytes, and acid-base balance. The use of RRT in critically ill patients is increasing over time. It has been observed that 10%-15% of critically ill patients require RRT, resulting in increased incidence of mortality and length of hospital stay (29). In our study, RRT was not performed, and none of the patients had died during the 2-month postoperative follow-up.

NGAL is synthesized by intestinal, liver, and lung tissue and can be detected in blood plasma. In healthy adult individuals, the normal plasma NGAL value is considered as 50-90 ng/mL (20,30). Although there are studies investigating different cut-off values of NGAL in the literature, the cut-off value for NGAL values measured in our study was deemed >90 ng/mL, and AKI developed in 9 (15%) out of 60 patients.

Mishra et al. (31) founded that plasma and urine NGAL values increased within 2 h postoperatively in 71 pediatric patients who had undergone open heart surgery and cardiopulmonary bypass, and AKI developed in patients within 24-72 h postoperatively. In our study, NGAL values were normal in 60 patients at 0 h intraoperatively and increased above 90 ng/mL at 6 and 24 h postoperatively in 9 patients. Creatinine and hourly urine output values at 48 h postoperatively were evaluated by the KDIGO classification and indicated class I and II AKI. Thus, it has been proven that NGAL values show an early response (at 6 h postoperatively) compared to creatinine values.

Study Limitations

The survival of the patients included in our study was evaluated at 48 h postoperatively, and patient follow-up was conducted until 2 months postoperatively, which could have been conducted for a longer time. In our study, NGAL values were measured at 0 h intraoperatively and 6 and 24 h postoperatively; however, there are some studies in the literature that have used different intervals for performing measurements like at 0 h intraoperatively; at 2h, 6 h, 24h, 48 h, and 72 h postoperatively. Since our study was conducted

in a single center, it limited the social evaluation of how effective a major laparoscopic surgery is on AKI. The lack of a definite cut-off value for NGAL in studies in the literature can be cited as another limitation. Furthermore, our study was conducted on patients undergoing major abdominal surgery, but it could also have included patients undergoing more elaborate surgeries. Not measuring intra-abdominal pressure during surgery can also be considered another limitation.

The most important advantage of our study is that plasma NGAL enabled the detection of AKI at an early stage. Measuring the plasma NGAL values at 0 h and considering it as a baseline value is another advantage. The third advantage of our study is that it was done by a single team.

CONCLUSION

It has been proven that compared to creatinine, NGAL is more efficient in predicting the development of AKI in patients undergoing major abdominal laparotomy. Additionally, it predicts AKI development in the early stage (at 6 h postoperatively).

ETHICS

Ethics Committee Approval: Approval for this study was obtained from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (protocol code: 09.2021.74, date: 08.01.2021).

Informed Consent: Written informed consent was obtained from the patients.

Authorship Contributions

Surgical and Medical Practices: A.M., M.O.E., S.Ü.Z., Concept: A.M., M.O.E., S.Ü.Z., Design: A.M., M.O.E., S.Ü.Z., Data Collection or Processing: A.M., S.Ü.Z., Analysis or Interpretation: A.M., M.O.E., S.Ü.Z., Literature Search: A.M., Writing: A.M., M.O.E., S.Ü.Z.

Conflict of Interest: No conflict of interest was declared by the authors.

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