CAN ACUTE KIDNEY INJURY BE DIAGNOSED USING BIOMARKERS IN INTENSIVE CARE PATIENTS?

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ABSTRACT

Introduction: and Objective*: Recent clinical trials have examined several biomarkers, which are suggested to allow an early diagnosis of AKI. Considering that the following molecules will allow an early diagnosis of AKI, we examined neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL-18), cystatin C (Cys-C), and kidney injury molecule-1 (KIM-1)in the urine samples and compared the levels of these molecules with the serum creatinine levels.*

Material and method*: 27 patients who developed AKI and 27 patients who did not develop AKI, were included in the study. AKI and non-AKI groups namely , according to the RIFLE criteria. The urine samples from the patients were collected on the 1st, 3rd, and 7th days to study the levels of NGAL, IL-18, cystatin C, and KIM-1 as the biomarkers.*

Results*: A significant difference was observed between the AKI and the non-AKI groups in terms of the APACHE II scores ($p<0.001$). A moderately negative and significant correlation at the level of $p<0.05$ was determined between the APACHE II scores and the day of ARF development ($p=0.041, r= -0.403$). As regards to the biomarker levels, we studied, statistically significant differences were identified in the AKI and non-AKI groups in the IL-18 levels on all of the three days which the tests were performed ($p=0.042$, $p=0.008$, $p<0.0001$ respectively). However, Cys-C levels measured on the 1st, 3rd, and 7th days were not statistically significantly different in the AKI or non-AKI groups ($p=0.625$, $p= 0.074$, $p=0.061$ respectively).*

Conclusion*: NGAL can be a valuable biomarker to detect the development of AKI in the early phase in ICU admissions. NGAL and KIM-1 can be consecutively used for the early diagnosis of AKI. IL-18 can be used for the early diagnosis of AKI and it is a valuable biomarker.*

Keywords*: KIM-1, Cystatin C, NGAL, IL-18, APACHE II score, intensive care unit.*

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Introduction

Acute renal failure (ARF) is a heterogeneous and complex process with high morbidity and mortality. It is common among the ICU patients[(1)]. It can develop due to several different reasons such as sepsis, surgical interventions, low cardiac output, hypovolemia, or drug toxicity. These causative factors are encountered commonly during the follow-up of the patients in the ICU[(2,3)]. The diagnosis of acute renal failure is made with the elevated serum creatinine levels and decreased urine output.

The elevated levels of serum creatinine and the decreased levels of urine output used in making the diagnosis lead to delays in the treatment. The major limitation is the delay in the elevation of serum creatinine levels following the real decrease in the glomerular filtration rate (GFR). The delays in making the diagnosis of acute renal failure lead to consecutive delays in the treatment and preventive measures to be executed, particularly in patients in intensive care units and in older adult patients. Recent clinical trials have examined several biomarkers that are suggested to allow an earlier

diagnosis of ARF[4,5]. In this study, we included the patients admitted to our hospital's ICU due to various etiologies, but we excluded the patients with histories of acute or chronic renal failure, kidney transplantation, or renal replacement therapy. Using the RIFLE criteria, the patients were assigned into two groups, namely, the group of patients who developed ARF (AKI group) and the group of patients who did not develop ARF (non-AKI group). APACHE II scale is one of the scoring systems used in patients treated in ICU and this scale's scores were calculated for each patient in the study. Considering that the following molecules would allow an early diagnosis of ARF, we examined neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL-18), cystatin C (Cys-C), and kidney injury molecule-1 (KIM-1) in the urine samples and compared the levels of these molecules with the serum creatinine levels.

Material and method

The approval for compliance with the ethical rules was obtained from Ordu University Clinical Research Ethical Committee (Decision number:15/24; Date: 23.02.2017). The signed informed consent forms were collected from the relatives of the eligible patients for the study. The study was conducted in compliance with the Helsinki declaration during the period starting with the commencement of the study till its finalization. Consisting of 27 patients who developed AKI and 27 patients who did not develop AKI, a total of 54 patients, who were admitted to the intensive care unit of our hospital between April 1, 2017 and December 31, 2017 were included. Patients older than 18 and younger than 90 years old were included in the study. The exclusion criteria were as follows:

- Patients with chronic renal insufficiency,
- Pediatric patients,
- Patients with a malignant pathology,
- Patients younger than 18 or older than 90 years old,
- Patients who died in the first 24 hours of admission or patients who had been admitted for follow-up for a duration less than 24 hours,
- Patients with a history of prior renal replacement therapy,
- Patients with a history of acute or chronic kidney disease,
- Patients who underwent renal transplantation.

The patients with creatinine levels within normal limits at the time of admission were included in the study. The amount of 24-hour urine output was taken for evaluation. The creatinine levels of the patients on the day of admission to the intensive care unit (ICU) were accepted as the baseline values. The creatinine values were tested routinely during the follow-up of the patients in the ICU. Accepting the first day of admission in the ICU as the 1st day, the creatinine values obtained on the 1st, 3rd, and 7th days were recorded. The patients were assigned into two groups, namely the study group (AKI group) and the control group (non-AKI group) according to the RIFLE criteria. The age, gender, medications, existing diagnoses, reasons for hospitalization, and the APACHE II scores of the patients were recorded. The creatinine levels obtained on the day of admission to the ICU and the routine follow-up creatinine test results on the 1st, 3rd, and 7th day were recorded. Furthermore, the 1st, 3rd, and 7th day urine samples were collected from the patients to test for the biomarkers, which are NGAL, IL-18, cystatin-C, and KIM-1.

Biochemical Analysis

The urine samples collected from the patients on the day of admission and the 1st, 3rd, and 7th days were centrifuged without delays at 3000 rpm for 5 minutes The supernatant was taken off and stored at -80˚ C until the day of the analysis. On the day of the analysis, the frozen samples were thawed at room temperature. The samples were manually examined with Creatinine Roche Modular® DPP for creatinine, with Human NGAL (Neutrophil Gelatinase-Associated Lipocalin) ELISA Kit for NGAL, with Human Kidney Injury Molecule-1 (KIM-1) ELISA Kit for KIM-1, with Human IL-18 Platinum ELISA for IL-18, and with Human Cys-C (high-sensitivity Cystatin C) ELISA Kit for cystatin-C.

Statistical Analysis

The data were analyzed using the SPSS 21.0 (for Windows) software package. In order to compare the two groups for the gender frequencies, Pearson chi-square test was used. The comparison of the two groups for the mean ages, APACHE II scores, and for the urine levels of KIM-1, IL-18, cystatin C, and NGAL was performed with Mann Whitney U-test (MWU). Kruskal Wallis test was used to assess the distribution of the biomarkers according to the primary diagnoses of the patients.

The correlations of the biomarkers with each other in the study and control groups were analyzed with correlation analysis. The data were expressed in means ± SD. The probability values below 0.05 were accepted as statistically significant.

Results

This study included 27 patients in the AKI group and 27 patients in the non-AKI group, making a total of 54 patients. Of the 54 patients, 21 (38.88%) were females and 33 (61.11%) were males. The gender distributions of the AKI and non-AKI groups were not statistically significantly different (p=0.68). The mean age was 57.38 ± 16.2 and the median age was 54.5 (18-84) in the AKI group. On the other hand, the mean age was 55.21 ± 17.28 and the median age was 60 (19-82) in the non-AKI group. Statistically, there was not a significant difference between the mean ages of the AKI and non-AKI groups (p=0.771) (Table 1).

	AKI Group	Non-AKI Group
Mean Age	57.38±16.2	55.21±17.28
Median (min-max)	54.5 (18-84)	60 (19-82)

Table 1: The age distribution in the AKI and Non -AKI groups.

The mean APACHE II score of the AKI group was 27.25 ± 9.75 and the median APACHE II score was 25 (9-43). The mean APACHE II score of the non-AKI group was 15.85 ± 5.61 and the median score was 14 (6-28). The APACHE II scores of the two groups were significantly different (p<0.001) (Table 2).

The APACHE II scores	AKI	Non-AKI
Mean	27.25 ± 9.75	15.85 ± 5.61
Median (min-max)	25 (9-43)	14 (6-28)

Table 2: The APACHE II scores of the AKI and non-AKI groups
Mann-Whitney U test MWU=190.5 p<0.001

The assessment of the distributions of biomarkers and APACHE II scores according to the primary diagnoses (sepsis, hypotension-ischemia, medication-associated, and others) of the patients demonstrated that there were no significant differences between the two groups. The evaluation of the distribution of the days of AKI development according to the primary diagnoses demonstrated that AKI developed significantly earlier in the sepsis and hypotension patients (p = 0.018, Table 3).

Diagnosis	Number	Day of ARF development ± SD	p
Sepsis	15	1.5 ± 1.1	
Hypotension-ischemia	7	1.7 ± 0.4	0.018
Medication-associated	2	6±0.3	
Other	3	2±1.8	

Table 3: The distribution of the day of ARF development according to the primary diagnoses.
Kruskal Wallis Analysis
χ^2*=7.038 p=0.018*

In the AKI group, the assessment of the relation of the biomarkers and the APACHE II scores with the ARF development time showed that there was a significant and moderately negative correlation only between the APACHE II scores and the days of AKI development (p=0.041, r=-0.403,). Furthermore, the correlations of the biomarkers with each other were analyzed in the AKI group. The correlation between the 1st day IL-18 and 1st-day Cystatin-C levels was strong and significant at the level of p<0.01 (p= 0.004). Secondly, the correlation between the 1st day IL-18 and the 1st day KIM-1 levels were moderate and significant at the level of p<0.05 (p=0.039). Finally, the correlation between the levels of NGAL and KIM-1 both on the 3rd day was moderate and significant at the level of p<0.05 (p=0.026) (Table 4).

	NGAL 1st day	IL-18 3rd day	Cys-C 3rd day	KIM-1 3rd day
NGAL 1st day	-	-0.325	0.014	-0418 *
IL-18 3rd day	-0.345	-	0.540 **	0.41
Cys-C 3rd day	0.014	-0.540**	-	0.198
KIM-1 3rd day	-0.418 *	0.39	0.198	-

Table 4: The correlation of biomarkers with each other in the AKI group.
*** p<0.01 * p<0,05.*

The correlation of the biomarkers with each other was studied in the non-AKI group, too. It was identified that the 1st day KIM-1 levels were correlated to both the 3rd day KIM-1 levels and the 1st-day IL-18 levels. This correlation was moderate and significant at the level of p<0.05 (p=0.23).

The 1st day KIM-1 levels were also significantly and strongly correlated to the 3rd day KIM-1 levels and the 3rd day IL-18 levels at the level of p<0.01 (p=0.003). There was a significant and moderate correlation of the 1st day IL-18 at the level of p<0.01 (p=0.002) (Table 5).

	KIM-1 1st day	KIM-1 3rd day	KIM-1 7th day	IL-18 1st day	IL-18 3rd day
KIM-1 1st day	-	0.277	0.39*	0.35*	-0.091
KIM-1 3rd day	0.277	-	0.799**	0.479**	0.52**
KIM-1 7th day	0.39*	0.799**	-	0.593**	0.216
IL-18 1st day	0.35*	0.479**	0.593	-	0.054
IL-18 3rd day	-0.091	0.52**	0.216	0.054	-

Table 5: The correlation of biomarkers with each other in the non-AKI group.
*** p<0.01 * p<0.05.*

Among the biomarkers tested in this study, the levels of IL-18 were statistically significantly different between the AKI and non-AKI groups on all of the three days of measurement (1st, 3rd, and 7th days) (p=0.042, p= 0.008, p<0.0001 respectively). On the other hand, the levels of Cys-C were not statistically significantly different between the AKI and non-AKI groups on any of the days of measurement (1st, 3rd, and 7th days) on the comparison (p=0.625, p= 0.074, p=0.061 respectively). The NGAL levels of were significantly different between the two groups only on the first day of measurement (p = 0.029). On the other hand, the levels of KIM-1 were only significantly different between the two groups only on the 7th day of measurement (p = 0.038). These findings suggest that IL-18 has the highest specificity to make a diagnosis of AKI. Our results are summarized in Figure 1 and Figure 2.

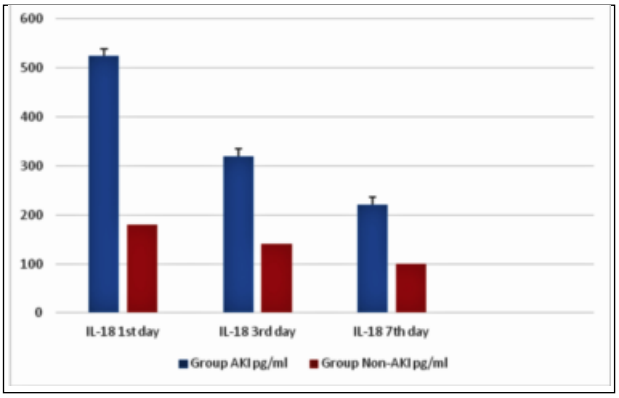

Fig. 1: IL-18 levels of both groups on the 1st, 3rd, and 7th days.

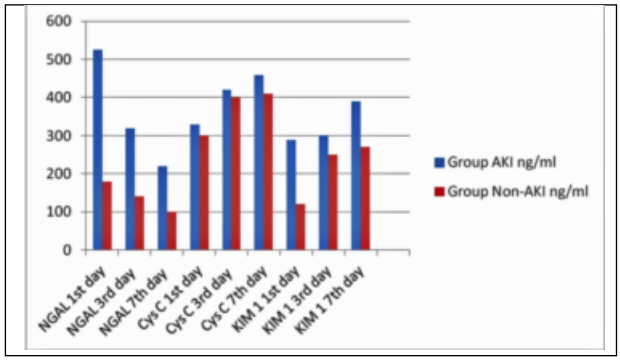

Fig. 2: The mean levels of NGAL,Cys C,KIM -1 biomarkers on the 1st, 3rd, and 7th days.

Discussion

In our study, the IL-18 levels were significantly higher in the AKI group compared to the non-AKI group. While there were no significant differences in the levels Cys-C between the groups, the NGAL levels were significantly different only on the 1st day. Finally, the levels of KIM-1 were significantly different between the two groups on the 7th day.

According to RIFLE criteria, the incidence of ARF in ICU ranges from 25% to 36%[6-8]. Despite the advances in the medical treatments, ARF has a course with high morbidity and mortality rates[9, 10]. The prognosis is usually quite unfavorable with 40-80% mortality rates in intensive care units[11,12]. The fact that the diagnosis is based on the levels of creatinine leads to delays in the diagnosis[13,14]. The plasma and urine levels of NGAL, urine Cys-C, IL-18, and KIM-1 are the early biomarkers in the diagnosis of ARF. These biomarkers have been studied in various clinical conditions (e.g; following the cardiac surgeries, contrast agent administration, and kidney transplantations)[15,16].

A study conducted by Arsalan M. et al. evaluated the urine levels of KIM-1, NGAL, and IL-18 in the postoperative 2nd, 4th, and 12th hours in the patients who developed AKI and in the patients who did not develop AKI after a transcatheter aortic valve implantation (TAVI). They found that 17 of the 66 TAVI patients developed AKI. The statistical analysis revealed that there were no statistically significant differences between the two groups in the levels of these three biomarkers. The authors suggested that these recent renal biomarkers (KIM-1, IL-18, and NGAL) have any predictive values[17]. On the other hand, in our study, we found that the IL-18 levels on each of the three days of measurement were statistically significantly higher in the AKI group compared to the non-AKI group.

Our study differed from the study of Arsalan M. et al., in other findings as well. In our study, the levels of NGAL on the 1st day and the levels of KIM-1 on the 7th day were statistically different. Arsalan M.et al. performed these measurements of the levels of these biomarkers in the early postoperative period, whereas, in our study, the measurements were performed on the 1st, 3rd, and 7th days after admissions to the ICU. The differences in our results may result from the differences in the times of measurements.

Cho YS et al . have studied the plasma NGAL levels in 231 patients whose spontaneous circulation recovered after cardiopulmonary resuscitation. They measured the plasma NGAL levels in the first 48 hours (the measurements were performed twice, one at the end of the resuscitation and one at the end of 48 hours following the resuscitation). The authors classified 170 patients who did not develop AKI or who developed stage 1 AKI as the non-AKI group and 61 patients who developed advanced stages of AKI as the AKI group. They found higher levels of NGAL in the group with advanced stages of AKI. They found that patients with high serum NGAL levels had higher SOFA scores, too, with higher mortality rates. The authors reported that plasma NGAL levels had a high predictive value for estimating the advanced stages of AKI and the mortality[18].

Our study findings are partially in line with those of the Cho YS et al. study. In our study, APACHE II scores were higher in the group of patients who developed AKI compared to the non-AKI group. In addition, the 1st-day NGAL levels were statistically different between the two groups in our study. However, unlike Cho YS et al. study which evaluated the plasma NGAL levels, the urine levels of NGAL were measured in our study. We are of the opinion that the results of our study were not in alignment with the results of Cho et al. study may be due to this condition[18].

A study conducted by Nejat M. et al. in intensive care patients evaluated the urine levels of NGAL, KIM-1, IL-18, Cys-C, and GGT (Gamma-Glutamyl Transpeptidase). The authors performed the measurements at two different time points in the first 48 hours of intensive care unit admissions. They did not find any differences in the levels of NGAL and GGT in neither of the time points which the measurements were performed. However, they found significantly high levels of KIM-1, IL-18, Cys-c in the AKI group compared to the non-AKI group. Our study results are similar to these findings in the literature[19].

Lippi I et al. compared the levels of KIM-1 and GGT levels in the urine samples of healthy dogs and of the dogs with chronic kidney diseases. Compared to the healthy dogs, the urine KIM-1 and GGT levels were remarkably higher in the dogs with chronic kidney disease. The authors reported that the use of these two biomarkers were favorable both in making the diagnosis and predicting the prognosis of AKI[20]. Our study is a clinical study and the GGT levels were not studied. In our study, particularly the KIM-1 levels on the 7th day were found to be significant statistically. We are also of the opinion that KIM-1 has an important place in the early diagnosis of AKI.

Jelinek MJ. et al. have studied the urine NGAL and Cys-C levels in the cisplatin chemotherapy receiving cancer patients who developed AKI and who did not develop AKI. They found that the urine levels of Cys-C and NGAL were significantly higher in the AKI group compared to the non-AKI group[21]. Our study findings were partially in line with those of the study of Jelinek MJ et al. We did not find the Cys-C levels to be significantly different in the AKI group compared to the non-AKI group. However, our study's NGAL results showed similarities to the reports in the literature.

Wang C. et al. have studied the urine levels of NGAL and IL-18 in 103 patients following aorto-coronary bypass surgery. The urine samples of the patients were collected prior to the bypass surgery and in the 12th, 24th, 48th, and 72nd hours after the bypass surgery. 22 of these patients have developed AKI with higher urine NGAL and IL-18 levels in the period after the bypass surgery. Wang C et al. reported that particularly IL-18 had a 90.91% sensitivity and 91.36% specificity. They also obtained similar results with NGAL. The authors also reported that the IL-18 levels were elevated in the earlier periods and persisted in these higher levels during longer periods compared to the levels of NGAL. They emphasized that IL-18 was more favorable in making the diagnosis and in monitoring the prognosis of AKI[22]. Our results are completely in line with the results of Wang C. et al. In our study too, we found that IL-18 had a higher diagnostic specificity.

Sterling M et al. have studied the urine NGAL and IL-18 levels in pediatric patients who developed AKI as a result of nephrotoxicity but who were not required to be treated in the ICU. They reported that both urine IL-18 and NGAL levels

were involved in the making the diagnosis of nephrotoxicity-associated AKI earlier[23]. Our study was conducted with adult subjects who were hospitalized in the intensive care unit. Although our study population and the age group of the patients were different, our results are completely in alignment with the results of Sterling M. et al.

In the review article by Andreucci M et al., they emphasized the importance of urinary biomarkers in the early diagnosis of contrast-ınduced acute kidney injury. The authors stated that serum creatinine level and acute kidney injury could be diagnosed in days, but biomarkers could be diagnosed with contrast-induced acute kidney injury within hours. The authors reported the diagnostic value of KIM-1, IL-18, Cys-C, NGAL, N-Acetyl-b-d-glucosaminidase, microalbumin, Liver-type Fatty Acid-Binding Protein, Midkine, Netrins, Gamma-glutamyl transpeptidase and alkaline phosphatase biomarkers[24]. Similarly to our study, IL-18 was more sensitive than other biomarkers.

In conclusion, the APACHE II scores are valuable in predicting the prognosis of AKI diagnosed according to RIFLE criteria. The calculation of the APACHE II score is simple and practical, and it can be used as a predictor of the development of AKI. It is important to be cautious for the development of AKI in patients with sepsis and with hypotension-ischemia patients. The volume status should be strictly monitored in these patients and the intensive care specialists should be in close collaboration with the nephrologists in monitoring these patients. NGAL can be a valuable biomarker to diagnose the development of AKI at early stages in ICU admissions. Also, NGAL and KIM-1 can be consecutively used for an early diagnosis of AKI. IL-18 can be used for the early diagnosis of AKI and is a valuable biomarker.

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