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EVALUATION OF INFLAMMATORY MARKERS IN CRITICALLY ILL ICU PATIENTS WITH AND WITHOUT ACUTE KIDNEY INJURY

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ABSTRACT

Objective: Acute Kidney Injury (AKI) is a prevalent condition among patients admitted to the intensive care unit (ICU), with high incidence and increased mortality rates. AKI often induces the elevation of inflammatory biomarkers used for diagnosing infection. This study aimed to investigate changes in inflammatory markers in the setting of AKI.
Methods: This retrospective study included patients admitted to the ICUs of Burdur State Hospital between January 2019 and January 2023. Data from 958 patients were analyzed, and AKI was classified by the Acute Kidney Injury Network (AKIN) criteria. Only creatinine data were used as information on urine output was not available. The cohort was stratified into following groups: no AKI (AKI stage 0), b) creatine levels between 1.60 and 2.50 mg/dL (AKI stage I), creatine levels between 2.51 and 3.99 mg/dL (AKI stage II), and creatine levels above 4 and receiving renal replacement therapy (AKI stage III).
Results: Of the 958 patients, male and female distribution was 55.1% (n= 528) and 44.9% (n= 430) respectively. The median age of the study cohort was 79 years (IQR=18.3 years). Neutrophil-to-lymphocyte ratio, procalcitonin, and C-reactive protein levels were found to increase significantly in direct relation to the severity of AKI ($p<0.001$). Furthermore, in infected patients, these inflammatory biomarkers were found to increase in parallel with the severity of AKI compared to non-infected patients ($p<0.001$).
Conclusion: Inflammatory biomarkers rise as the severity of renal failure increases. The combined use of neutrophil-to-lymphocyte ratio, procalcitonin, and C-reactive protein levels in patients with renal failure would be more effective for diagnosing infection.

Keywords: Infection, Inflammatory Biomarker, Renal Failure, Intensive Care

1. INTRODUCTION

Acute Kidney Injury (AKI) is a clinical condition associated with higher incidence and increased mortality rates in patients admitted to in the intensive care unit (ICU) [1]. Many risk factors such as hypovolemia, shock, sepsis, trauma, nephrotoxic drugs, and the use of radiocontrast agents can cause AKI in the ICU setting [2].

Procalcitonin (PCT) is a precursor of calcitonin released from the C cells of the thyroid gland [3]. It is also a specific biomarker that indicates the inflammatory response in severe bacterial infections [4]. The severity of infection correlates with high PCT levels seen in patients. Moreover, PCT can be used to follow up multiorgan dysfunction syndrome, sepsis, and severe infections [5].

C-Reactive Protein (CRP) is a laboratory parameter that increases with infection and inflammation. This acute-phase reactant is synthesized from the liver in some types of cancer, trauma, infection, and inflammatory events [6]. CRP remains unchanged throughout the day in healthy individuals but begins to rise 3-6 hours after the onset of inflammation, reaching its peak level at 30-90 hours [7].

The neutrophil-to-lymphocyte ratio (NLR) is a new parameter used to define the stress factor in the follow-up of the inflammatory process [8]. Inflammation, which can develop in response to various reasons, causes an increase in neutrophil count and a decrease in monocyte count [9]. Impairment of renal functions leads to changes in NLR as well as serum levels of PCT and CRP [10-12].

The study purpose was to investigate changes in NLR, PCT, and CRP levels in patients with AKI and infection, according to the severity of AKI.

MATERIALS and METHODS

The study included patients who were admitted to the ICUs of Burdur State Hospital between January 2019 and January 2023. Approval for the study was granted by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University. (decision no:227, dated:2023). The patient data were retrospectively reviewed. To be included in the study, patients had to have all three inflammatory parameters (CRP, PCT, and NLR derived from complete blood count) studied and cultures taken at admission. The study excluded patients who were under 18 years old, had an active cancer diagnosis, were admitted to ICU after successful cardiopulmonary resuscitation, had missing data, did not have inflammatory parameters studied and cultures taken simultaneously, and had COVID-19 pneumonia (Figure 1). AKI was classified based on the AKIN criteria, and only creatinine data were used as information on urine output was not available [13]. The patients were divided into following groups: no AKI (AKI stage 0), creatine levels between 1.60 and 2.50 mg/dL (AKI stage I), creatine levels between 2.51 and 3.99 mg/dL (AKI stage II), and creatine levels above 4 and receiving renal replacement therapy (AKI stage III).

Statistical Analysis

First, we presented the frequencies and percentages of categorical variables used in this study. We checked whether continuous variables follow a normal distribution via Shapiro-Wilk's normality test. Normally distributed variables were presented through mean and standard deviations. In similar manner, non-normally distributed variables were represented through median and interquartile range (IQR). To compare categorical variables between non-survivors and discharged patients, the chi-square test was used, and Fisher's exact test was applied when is needed. Independent sample t test and Mann-Whitney U test were applied for variance analysis. Which test to choose was decided according to whether the data showed a normal distribution or not.

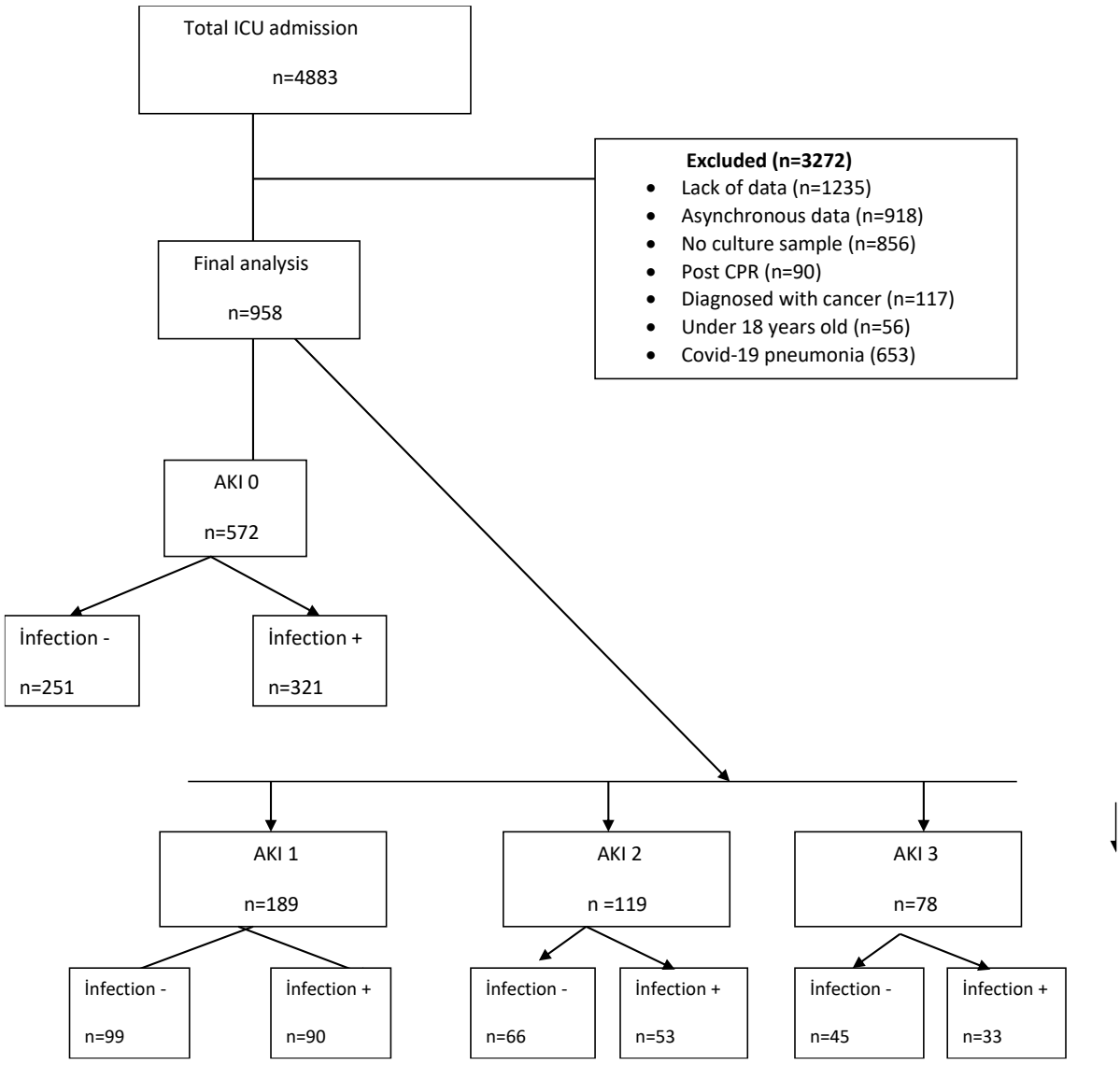


Figure 1. Flow chart of study

Table 1. Comparison of patient characteristics by the severity of acute kidney injury

Variables	Total (n:958)	AKI Stage 0 (n:572)	AKI Stage 1 (n:189)	AKI stage 2 (n:119)	AKI stage 3 (n:78)	P
Age	79 (18-99)	78 (18-99)	82 (25-99)	83 (25-96)	75,5 (24-97)	<0,001
APACHE 2	20 (8-44,9)	19(8-44,9)	22 (12-40)	22 (9-40)	24 (14-43)	<0,001
SOFA	7 (1-17)	5 (1-16)	8 (2-17)	9 (3-15)	10 (4-14)	<0,001
PRC	0,64 (0,01-100)	0,24 (0,01-100)	1,12 (0,06-100)	3,66 (0,1-100)	3,45 (0,08-100)	<0,001
CRP	81,92 (0,01-350)	59,31 (0,01-350)	100 (0,1-350)	135 (2,2-350)	135,1 (2,02-350)	<0,001
NLR	10,09 (0,4-508)	9 (0,4-508)	9 (0,50-60)	15 (1,8-100)	13,3 (1,5-52,1)	<0,001

Chart 1. Procalcitonin levels by the severity of acute kidney injury and infection status

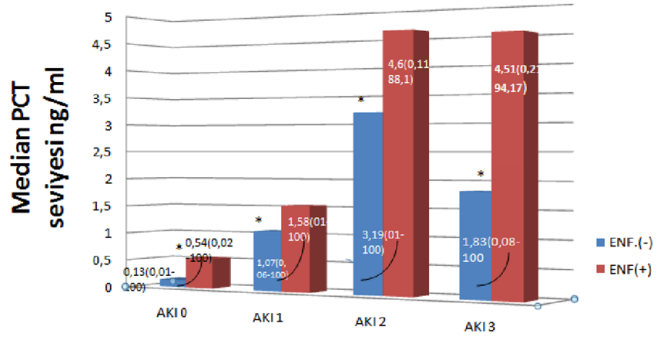


Chart 2. C-reactive protein levels by the severity of acute kidney injury and infection status

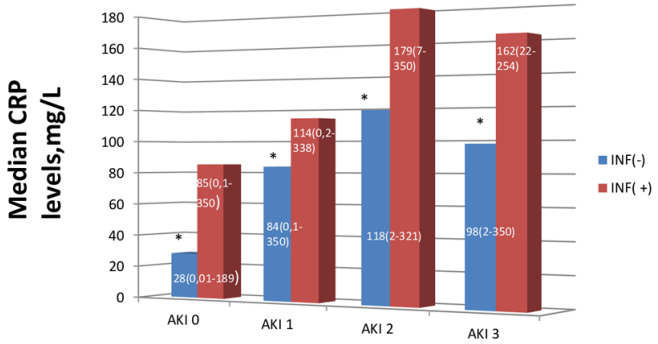
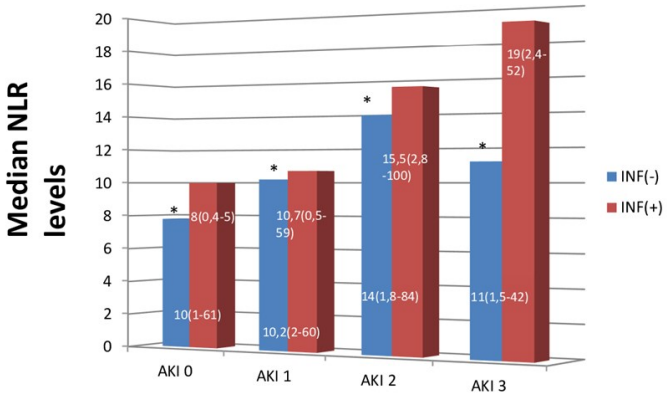


Chart 3. Neutrophil-to-lymphocyte ratios by the severity of acute kidney injury and infection status



RESULTS AND DISCUSSION

The study included 958 patients, of whom 55.1% (n= 528) were male and 44.9% (n= 430) were female. The median age of the study group was 79 years (IQR= 18.3 years). During the intensive care follow-up, 57.1% (n= 495) of the patients died, while 48.3% (n= 463) were discharged. The patients were grouped in four considering their creatinine levels. All inflammatory markers increased significantly as the severity of AKI increased (p<0.001), as shown in Table 1.

Furthermore, the patients were grouped in two based on their blood culture positivity. The analyses of the infected and non-infected groups revealed that PCT levels increased in direct relation to the severity of AKI, as demonstrated in Chart 1 (p<0.001). Similarly, the comparison of the infected and non-infected groups in terms of CRP levels yielded a significant increase in CRP with increasing severity of AKI, as shown in Chart 2 (p<0.001).

Moreover, the comparison of the infected and non-infected groups by NLR levels showed that NLR levels increased in parallel with the severity of AKI in groups, as shown in Chart 3 (p<0.001).

This study investigated the changes in NLR and serum levels of CRP and PCT according to the AKI severity in critically ill ICU patients with AKI and infection. Overall, the study results suggested an increase in serum levels of inflammatory markers with the deterioration of kidney functions, and in the case of infection, an increase in NLR, PCT, and CRP levels with the increasing severity of AKI.

AKI arises due to a multitude of causes. The most frequent causes include sepsis and systemic inflammation, reperfusion injury from ischemia resulting from reduced renal blood flow, and the use of nephrotoxic drugs [14]. AKI is more prevalent, particularly in intensive care units, with reported rates ranging from 13% to 78% in various studies [15]. This study revealed that 40% of patients admitted to our intensive care unit had AKI.

CRP and PCT are the commonly used inflammatory markers for infection follow-up in ICUs. The half-life of PCT has been reported to be 22-29 hours, and in the case of bacterial infection, it starts to rise 4 hours following infection, reaching its peak level at 12-24 hours, while CRP tends to rise later and may take up to 2-3 days to reach the peak level [16].

Renal failure affects the inflammatory process as well as the biomarkers used for diagnosing inflammatory processes caused by various reasons. Serum PCT levels have been found to be significantly higher in chronic kidney disease (CKD) patients without a history of dialysis or infection, compared to healthy individuals [17]. Since PCT has a low molecular weight of 13 kilodaltons and its renal elimination is impaired in renal dysfunction, its serum level is affected. The high level of PCT in patients with impaired renal function may be due to delayed elimination [18].

Several studies have reported that PCT is a better marker than CRP for demonstrating infection in patients with impaired renal function [19-21]. However, contrary to these studies, Park et al. reported that CRP was effective in demonstrating infection in patients with renal failure and that PCT had no superiority over CRP [22]. Our study showed that both PCT and CRP were affected by renal failure, with a statistically significant increase in serum levels of both markers in the presence of infection in patients with renal failure.

Various studies have evaluated the role of PCT levels in renal failure. Heredia-Rodríguez et al. reported that while PCT levels may be high in AKI patients, they cannot be used to differentiate between infected and uninfected patients [23]. Nakamura et al. also reported that the diagnostic value of PCT may be low in the diagnosis of sepsis in patients with renal failure [10]. However, in their studies categorizing the level of renal failure, Huang et al. found that PCT serum level increased as the severity of AKI increased in both infected and uninfected patients [24]. The results of our study revealed an increase in the serum level of PCT with the increasing severity of AKI. Moreover, infected patients had significantly higher PCT levels compared to non-infected patients. We are of the opinion that PCT is an effective marker to evaluate infection in patients with AKI.

On the other hand, Cosentino et al. found that the CRP level increased as the severity of AKI increased [11]. Similarly, our study also demonstrated an increase in the serum levels of CRP as the severity of AKI increased, with infected patients having significantly higher levels of CRP compared to non-infected patients.

Catecholamine levels increase in response to infections and physiological stress, resulting in an increase in neutrophil count and a decrease in lymphocyte count. Studies have reported that the neutrophil-to-lymphocyte ratio (NLR) increases in response to stress after six hours [8-25]. Erdem et al. found that NLR increases in AKI and decreases when renal function improves [12]. Chen et al. showed that NLR is an independent marker of the severity of AKI and can be used to classify AKI early in critically ill patients in intensive care [26]. They also reported a significantly higher incidence of severe AKI (stage 2-3) in patients with a high NLR [27]. We observed a statistically significant increase in NLR as the AKI stage increased. Additionally, as the AKI stage increased, the infected group had higher serum NLR levels than the uninfected group.

Our study has following drawbacks; (1) the study had a retrospective, single-center design, (2) although we classified the severity of renal failure according to the AKIN criteria, we could not evaluate urine output data, so we only considered creatinine levels.

CONCLUSION

As the severity of renal failure increases, inflammatory biomarkers such as PCT, CRP, and NLR increase as well. Thus, we suggest that the combined use of these markers in the clinical setting would be more effective in diagnosing infection in patients with renal failure.

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