ORIGINAL INVESTIGATION

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The Relationship Between Acute Kidney Injury and Inflammation-Based Parameters and Mortality in Oncologic Intensive Care Patients

Emre AYDIN[1], Ali Kemal KADIROGLU[1], Fatma YILMAZ AYDIN[2], Ali Veysel KARA[3], Zulfukar YILMAZ[3], Yasar YILDIRIM[3], Mehmet KUCUKONER[4], Abdurrahman ISIKDOGAN[4], Mehmet Emin YILMAZ[3]

[1]University of Dicle School of Medicine, Internal Medicine/ Nephrology/ Intensive Care Unit, Diyarbakır, Turkey

[2]University of Dicle School of Medicine, Internal Medicine Department, Diyarbakır, Turkey

[3]University of Dicle School of Medicine, Internal Medicine/ Nephrology Department, Diyarbakır, Turkey

[4]University of Dicle School of Medicine, Medical Oncology, Diyarbakır, Turkey

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Corresponding Author: Emre Aydin
E mail: emreaydin83@hotmail.com

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ABSTRACT

Background and Aims: Cancer patients are admitted to intensive care units (ICU) due to primary diseases, treatment-related conditions or comorbid diseases. Acute kidney injury (AKI) and infections appear to be factors affecting mortality and morbidity in ICU follow-up. Therefore, in our study, we investigated the effect of AKI and inflammation-based parameters on mortality in cancer patients admitted to the ICU.

Materials and Methods: In this study, 386 patients diagnosed with malignancy hospitalized between 2010 and 2014 in Dicle University Medical Faculty Internal Medicine ICU were included. The study was designed retrospectively. The demographic characteristics and clinical information of the patients were obtained from the files. Subsequently, patients were classified as non- survivors (group 1) and survivors (group 2). Both groups were compared in terms of the presence and stage of AKI by KDIGO definition, neutrophil / lymphocyte ratio (NLR) and platelet / lymphocyte ratio (PLR).

Results: Creatinine, CRP, neutrophil counts were found to be significantly higher and albumin, hemoglobin, platelet and lymphocyte counts were found to be lower in group 1 (n=276) compared to group 2 (n=110). Length of ICU was longer in group 2 patients. There was a positive correlation between mortality and KDIGO stages and NLR. Mortality rate was increased 1.9 fold in KDIGO stage 1, 2.3 fold in stage 2, 2.4 fold in stage 3 and 1.5 fold if NLR>5. There was no statistically significant relationship between PLR and mortality.

Conclusion: The presence of AKI and elevated inflammation-based parameters were associated with mortality in oncologic patients admitted to the ICU.

Keywords: Cancer, acute kidney injury, mortality, intensive care unit

Introduction and Purpose

Cancer is the second most common cause of mortality and morbidity after cardiovascular diseases (1). Therefore, it is an important health problem all over the world (2). According to World Health Organization's 2018 data, it is estimated that there will be approximately 9.6 million cancer-related deaths.

The treatment approach in cancer clinic is mainly surgical intervention, radiotherapy and chemotherapy. Hormone therapies, biological therapy methods and targeted agents are also used for cancer treatment. However, undesirable complications may occur due to all these treatments. Among these, side effects of chemotherapeutic drugs such as acute kidney injury (AKI) and cachexia due to nausea, vomiting and oral intake disorder are frequently observed. When febrile neutropenia develops, patients are susceptible to infections. In addition, complications may occur due to many factors other than treatment. Paraneoplastic syndromes (hypercalcemia, inappropriate ADH release, hypoglycemia, dermatomyositis), tumor lysis syndrome, febrile neutropenia and coagulation abnormalities are the most common disorders that can develop in relation to the type of cancer. Due to all these reasons, cancer patients can be hospitalized in the intensive care unit (ICU). These patients account for approximately 13.5% to 21.5% of all ICU admissions (3). Early admission of these patients to the ICU is associated with better survival rates (4).

Systemic inflammatory response plays a significant role in predicting cancer outcome (5). Measurable blood parameters that demonstrate the inflammatory response includes, cytokines,

leucocytes and their subtypes, platelets and C-reactive protein (CRP). In the last years pre-treatment elevated neutrophil count was found related with worse prognosis in many cancers (6). Especially for high platelet- lymphocyte ratios (PLR) and neutrophil-lymphocyte ratios (NLR) there are lots of trials showing that higher ratio is correlated with poorer prognosis in different types of cancers (7,8).

Increased frequency of infections and inflammatory response are an important reason of AKI in these patients hospitalized in the ICU. AKI is an important part of multi organ failure and has a significant effect on mortality (9).

Therefore, predicting the presence of infection and understanding its relationship with AKI is very important in the clinical course of patients.

Based on these data, in this study; we evaluated the relationship between the stages of KDIGO and inflammation-based parameters and mortality in oncologic patients hospitalized in Internal Medicine ICU's between 2010 and 2014.

Material and Methods

In this study, first of all, 450 patients who were histopathologically diagnosed as malignancy admitted to Dicle University Medical Faculty Internal Medicine ICU's between 2010 and 2014 were reviewed retrospectively. Approval was obtained from the Dicle University ethics committee (14.05.2015 / 239). The study exclusion criteria were: age under 18 year-old, patients without histopathologic diagnosis, patients with chronic kidney damage / failure, terminal patients, cardiogenic shock, severe malnutrition. 64 patients were excluded due to exclusion criteria. The demographic characteristics (age, sex), etiology, cancer types, length of ICU stay and results were recorded of 386 patients were obtained from the patient files. Complete blood count (CBC) values, including the hemoglobin, platelet, neutrophil count, lymphocyte count at ICU admission were evaluated. In addition, serum albumin levels, CRP were recorded. Serum creatinine levels were evaluated at ICU admission and after 48 hours. AKI diagnosis criteria was assumed to be ≥0,3mg/dl increase in the serum creatinine level in 48 hours. Subsequently, patients were classified as non- survivors (group 1) and survivors (group 2). These groups were compared in terms of the presence and stage of AKI (KDIGO Stage-1-2-3), platelet / lymphocyte ratio (PLR), neutrophil / lymphocyte ratio (NLR), length of ICU stay and outcomes.

Patients were evaluated with the presence or absence of AKI by KDIGO stage (10), Neutrophil / Lymphocyte Ratio ≤5 or> 5 and Platelet / Lymphocyte Ratio <150, 150-300, ≥300 (11).

Statistical analysis of the results was performed using SPSS (Statistical Package for Social Sciences) 18.0 software (SPSS Inc, Chicago, IL). The variables were examined visually (histogram and probability graphs) and by analytical methods (Kolmogorov-Smirnov / Shapira-Wilk tests) for normal distribution. Descriptive analyzes were examined using mean and standard deviations for normally distributed variables. For the variables with normal distribution, comparisons between groups were made using Student's t test. The differences between the groups in terms of frequency were compared using Chi-Square tests. Univariate and multivariate analyzes were used to determine the increased mortality-related characteristics of the patients. Kaplan-Meier Method was used for survival and compared using log rank analysis. Multivariate Cox Regression analysis was used for mortality related variables analysis. The condition which was below 5% of the type 1 error level was interpreted as a statistically significant.

Results

A total of 386 malignant patients were included in the study, of which 246 were males (63.7%) and 140 were females (36.3%). The mean age of the patients was 59.89 ± 14.06 and the mean length of ICU stay was 7.84 ± 7.32 days. It was determined that AKI developed in 50.5% of the patients. Among the patients included in the study, 37% (n = 143) had lung malignancy, 14.8% (n = 57) had stomach malignancy, 11.7% (n = 45) had breast malignancy and the remaining 36.5% (n = 141) had other malignancies. The distribution of patients with malignancies is presented in Table 1.

Table 1. The diagnostic distribution of malignant diseases

Diagnosis	n	%
Lung cancer	143	37
Gastric cancer	57	14.8
Breast cancer	45	11.7
Liver-Gall bladder cancer	29	7.5
Colorectal cancer	24	6.2
Prostate cancer	23	6.0
Ovarian cancer	22	5.7
Pancreatic cancer	15	3.9
Brain cancer	13	3.4
Head and Neck cancer	11	2.8
Lymphoma	4	1
Total	386	100

Admission diagnoses of patients were respiratory failure in 33.67% (n = 130), confusion in 25.38% (n = 98), diarrhea and AKI due to oral intake disorder in 16.83% (n = 65), febrile neutropenia in 5.95% (n = 23), pneumonia in 5.44% (n = 21), sepsis in 4.40% (n = 17) and 8.26% (n = 32) in other reasons.

Serum creatinine, CRP and neutrophil levels were higher and serum albumin, hemoglobin, platelet, lymphocyte and length of ICU stay were lower in Group 1 than Group 2 ($p < 0.05$). The comparison of the two groups in terms of demographic, characteristic and laboratory parameters is shown in Table 2.

The mean value of the patients length of ICU stay was 7.84±7.32 days. According to the results of Kaplan-Meier analysis, the mortality rate was significantly higher in patients with Neutrophil / Lymphocyte ratio > 5 ($p < 0.001$) and AKI ($p < 0.001$) (Figure 1-2).

Table 2. Demographic, clinical and laboratory characteristics of the groups

Parameters	All cases (n=386)	Non-Survivors (n=276)	Survivors (n=110)	p
Age (years)	59.89±14.06	59.94±14.39	59.77±13.28	0.913
Gender (M/F)	246/140	166/110	80/30	**0.020**
Creatinine (mg/dl)	1.64±1.56	1.93±1.70	0.91±0.76	**<0.001**
Albumin(g/dl)	2.14±0.59	2.03±0.54	2.39±0.57	**<0.001**
CRP (mg/dl)	13.57±10.25	14.48±10.15	11.33±10.13	**0.006**
Hemoglobin (g/dl)	10.15±2.02	10.01±1.99	10.51±2.06	**0.029**
Platelet (10^3/uL)	215.17±148.86	201.00±152.51	250.70±133.46	**0.003**
Neutrophil (10^3/uL)	11.72±11.68	12.72±12.76	9.22±7.88	**0.008**
Lymphocyte (10^3/uL)	1.04±0.88	0.98± 0.90	1.20±0.80	**0.027**
Platelet lymphocyte ratio	380.52±551.61	406.41±619.80	314.97±312.50	0.143
Neutrophil lymphocyte ratio	23.18±93.62	28.15±109.99	10.58±11.63	0.097
Length of ICU stay (days)	7.84±7.32	6.90±6.84	10.21±7.96	**<0.001**

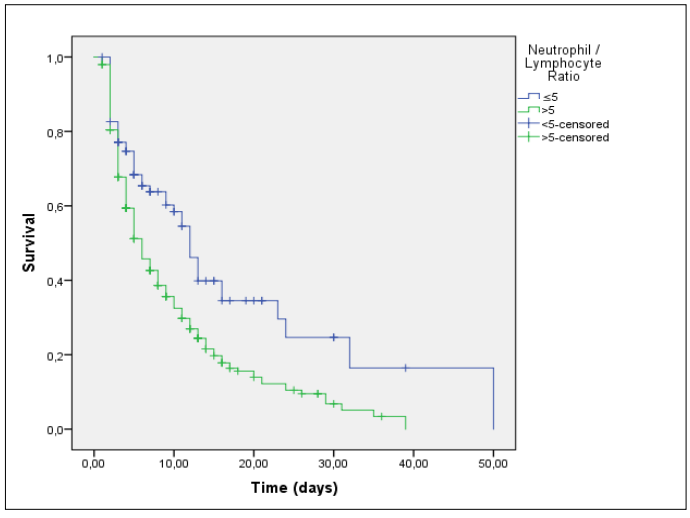

Figure 1. Kaplan-Meier survival analysis for neutrophil / lymphocyte ratio.

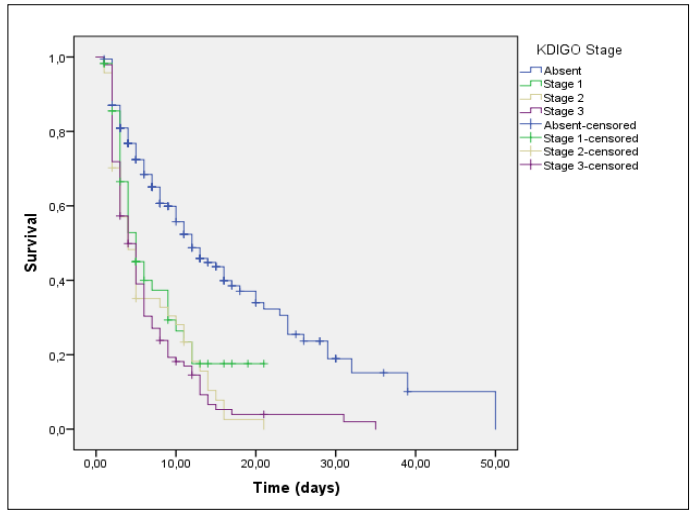

Figure 2. Kaplan-Meier survival analysis for KDIGO Stage.

Table 3. Multivariate cox regression analysis for death

Variables	HR	%95 CI	p
AKI			
Reference			
KDIGO Stage 1	1.969	1.34-2.88	**<0.001**
KDIGO Stage 2	2.325	1.61-3.35	**<0.001**
KDIGO Stage 3	2.440	1.81-3.28	**<0.001**
NLR (≤5 vs. >5)	1.515	1.10-2.08	**0.011**
PLR	1.095	0.853-1.40	0.476

AKI: Acute Kidney Injury; HR: hazard ratio; CI: confidence interval; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio

When evaluated by multivariate COX regression analysis, the risk of death was 1.96 fold higher in KDIGO Stage 1 patients, 2.32 fold higher in KDIGO Stage 2 patients and 2.44 fold higher in KDIGO Stage 3 patients compared to those without AKI. By COX regression analysis, in patients with a neutrophil / lymphocyte ratio ≤5, the mortality rate was 1.51 fold higher than those with a neutrophil / lymphocyte ratio> 5. No statistically significant difference was found between groups for PLR (Table 3).

Discussion

ICU admission complications of cancer patients may be related to cancer, treatment or comorbid diseases. In addition, the most common reasons for admission are respiratory failure requiring ventilator support, renal failure requiring renal replacement therapy, neurological disorders and septic shock requiring vasopressor support (12,13). In our study, ICU hospitalization indications were respiratory failure, confusion, AKI due to diarrhea and oral intake disorders, and febrile neutropenia, respectively.

There are many studies showing that AKI increases mortality in ICU patients. In a study by Ostermann et al, it was shown that there was a relationship between AKI and mortality in patients hospitalized in ICU and a relationship was found between RIFLE classification and prognosis (14). Based on these data, we evaluated

the relationship between AKI and mortality in oncologic patients hospitalized in ICU according to KDIGO classification. We detected that AKI developed in 195 (50.51%) of 386 malignancy patients. In patients with AKI, we classified the patients as Stage 1 - Stage 2 - Stage 3 using KDIGO classification. AKI is known to be a common complication in cancer patients in the ICU. Yang et al. have seen worse prognosis in patients admitted to ICU with AKI or developing AKI in ICU. (12) Survival expectancy is less (15). In patients with lung cancer who were hospitalized in the ICU, the risk of mortality was significantly higher in patients with AKI than in patients without AKI (16). In another study by Bagshaw et al., it was shown that mortality was significantly increased in patients with cancer and AKI compared to patients with AKI alone. In addition, one-year survival in 38 AKI patients with cancer was 15.8%, whereas one-year survival was 40.1% in 202 patients AKI without cancer (17). Therefore, early detection and treatment of AKI, especially in this patient group, is vital to reduce mortality. In our study, the presence and advanced stages of AKI seem to be closely related to mortality.

The presence of inflammation in ICU patients is another factor associated with mortality (18). In addition, cancer-related inflammation has been shown to be a predictor of progression and survival over the past 10 years (19).Therefore, it is important to evaluate systemic inflammatory response markers such as easily accessible leukocytes, neutrophils, lymphocytes, platelets, or parameters derived from these markers such as NLR, PLR, which are routinely examined to show cancer-related inflammation (20,21). Ohno et al. found that increased NLR was associated with bad outcomes in urologic malignancies (22). Walsh SR et al. in their study, preoperative NLR> 5 in patients with colorectal cancer reported that it has a prognostic value in survival, regardless of age, gender and tumor diameter. (23). Azab B et al. showed that high NLR is a predictor of mortality in breast cancer patients (24). In a similar study, Proctor MJ et al. found a close relationship between NLR and total survival in a large population of patients with multiple cancers ($p < 0.001$) (25). In our study, although there was no statistically significant difference in NLR between the groups, it was found that having NLR> 5 increased the mortality 1.5 fold compared to those with ≤5 ($p = 0.011$).We interpreted the absence of NLR difference between the groups as a result of the fact that the majority of our cases is in the advanced stage of their malignancies.

PLR may be another prognostic indicator in cancer patients and there are many studies on this in literature. Kemal Y et al. showed that in lung cancer patients high PLR is associated with worse prognosis and can be used as a useful biomarker such as NLR in determining prognosis. (26), Kim E.Y. et al. showed that in gastric cancer patients, NLR is more significant than PLR in predicting overall survival. (NLR: $p = 0.023$ PLR: $p = 0.788$) (27). Giakoustidis A. et al. demonstrated that the role of NLR and PLR after pancreatic ductal adenocarcinoma resection is important in shaping treatment and predicting survival. In the same study, coexistence of high NLR and PLR was found to be associated with lower survival, but elevated NLR was a more important independent predictor than PLR (28). These studies have shown that PLR is not as valuable as NLR in predicting prognosis in malignancies. In our study, PLR was not different between groups ($p = 0.476$) and mortality predictor ($p = 0.143$).

Renal dysfunction prolongs the length of ICU stay, making it difficult for the patient to administer life-saving chemotherapy and this affects the long-term prognosis of patients (29-31).

Conclusion

In summary, a high NLR is associated with mortality in the oncologic patient group, and NLR may serve as an important prognostic biomarker in predicting mortality. Another factor related to mortality is the presence of AKI and the advanced stages of AKI. Therefore, early diagnosis and treatment of AKI is important in these patients.

AUTHOR CONTRIBUTIONS:

Concept: EA,AKK, AI, MEY; **Design:** EA,ZY,YY; **Supervision:** AKK,MEY; **Resources:** EA,FYA; **Materials:** EA, FYA; **Data Collection and/or Processing :** EA,FYA; **Analysis and/or Interpretation:** MK,ZY; **Literature Search:** EA,AVK; **Writing Manuscript:** EA, FYA; **Critical Review:** EA, AKK, FYA,AVK,ZY,YY,MK, AI, MEY

Ethics Committee Approval: Approval was obtained from the Dicle University ethics committee (14.05.2015 / 239)

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