

Prognostic significance of low basal serum creatinine levels in internal intensive care unit patients

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Abstract. – OBJECTIVE: This study aimed to show the relationship between low creatinine level and mortality in the internal Intensive Care Unit (ICU) based on the view that there may be a relationship between low creatinine level and mortality in patients admitted to the ICU.

PATIENTS AND METHODS: This retrospective, single center study was performed in the ICU. Patients older than 18 years who stayed in the ICU for more than 24 hours were included in the study. Patients were evaluated for age, gender, albumin, creatinine levels and length of hospital stay in the analysis. Patients were divided into 7 groups according to serum creatinine levels: group 1: creatinine \leq 0.4; group 2: $0.4 <$ creatinine \leq 0.6; group 3: $0.6 <$ creatinine \leq 0.8; group 4: $0.8 <$ creatinine \leq 1.0; group 5: $1.0 <$ creatinine \leq 1.2; group 6: $1.2 <$ creatinine \leq 1.4; group 7: creatinine $>$ 1.4 mg/dL. Creatinine level of 0.7-0.8 mg/dL was considered as reference and cox regression analysis was performed.

RESULTS: Of 2,359 patients admitted to the ICU, 699 died (29.6%). Mortality relationship according to the accepted creatinine levels of the patients showed a U-shaped distribution, and ICU mortality increased in both low and high creatinine levels. At low creatinine levels (creatinine \leq 0.4 mg/dl), the mortality rate was 71.4% for men and 10.7% for female ($p <$ 0.001). Cox regression analysis showed that group 1 and group 2 increased mortality (HR: 0.721, 95% CI; 0.555-0.936, HR: 0.509, 95% CI; 0.285-0.909, respectively).

CONCLUSIONS: In patients admitted to ICU, lower creatinine acceptance is associated with increased ICU mortality and reduced survival.

Key Words:

Serum creatinine level, Mortality, Intensive Care Unit.

Abbreviations

ICU: Intensive care unit, CI: Confidence Interval, HR: Hazard Ratio, GFR: Glomerular Filtration Rate.

Introduction

Intensive care units (ICU) are special units where serious diseases threatening human life are followed and treated¹. Age, the presence of mechanical ventilation, the severity of the disease and many factors affect morbidity and mortality in ICU patients. Mortality rate in internal ICU patients is reported to range from 14% to 41%²⁻³.

Serum creatinine levels are used to evaluate renal function and glomerular filtration rate (GFR)⁴. Studies⁵ have shown that there is a strong correlation between muscle mass and serum creatinine levels, which can be used for muscle mass measurement. Decreased creatinine levels may be caused by aging, chronic diseases or diet⁶. Low plasma creatinine concentration can be used as a useful marker for measuring skeletal muscle mass and clinically indicates that patients are in deep malnutrition⁷. Mortality has been suggested to increase in patients with basal creatinine concentration less than 0.8 mg/dL. Low basal serum creatinine levels were expressed as an independent risk factor for mortality. The relationship shown was mediated by malnutrition and muscle mass^{7,8}. In addition, in patients with even lower serum creatinine levels, the increase in mortality seems to be maximized⁹.

In this study, we aimed to evaluate the effects of basal creatinine levels on the prognosis of the patients hospitalized in the internal ICU before hospitalization or within the first 24 hours after hospitalization.

Patients and Methods

Our study was performed between January 1, 2013 and April 30, 2017 on patients admitted to Internal ICU. Our study was approved by the Adiyaman University Non-Interventional Clinical

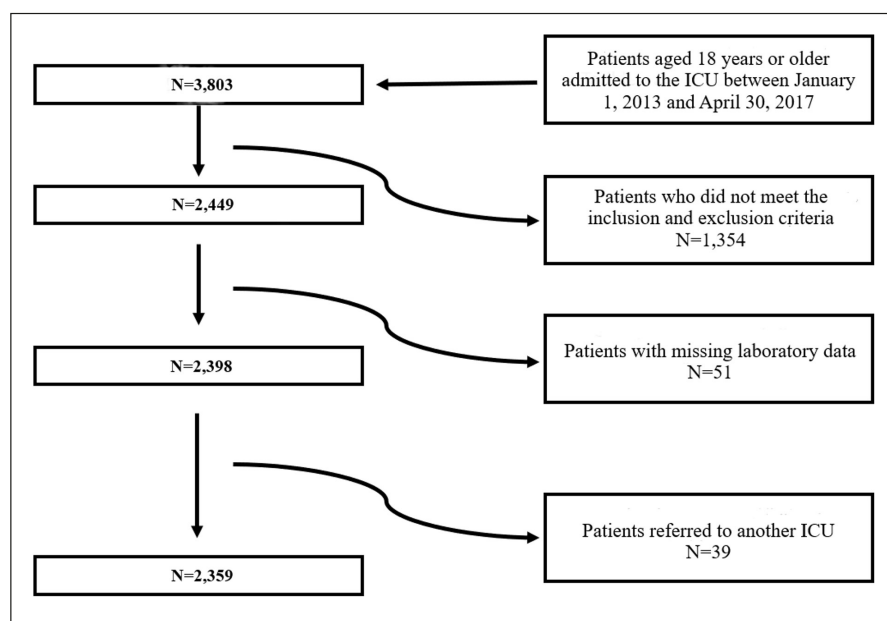


Figure 1. Inclusion of patients in the study.

cal Research Ethics Committee. The search is a cross-sectional, retrospective, descriptive epidemiological study. The study included all adult patients older than 18 years. Patients with creatinine values admitted to the ICU, older than 18 years of age and with more than 24 hours of hospitalization were included in the study. Only the initial acceptance values of patients with multiple ICU admissions were included in the study (Figure 1).

Pregnant patients, patients with end-stage renal disease according to the International Classification of Diseases, 9th revision (International Classification of Diseases, 9th revision) or GFR <15 mL/dk/1.73 m², hemodialysis or peritoneal dialysis were excluded from the study.

Laboratory parameters were obtained from the electronic recording system of our hospital. Primary diagnoses and other diagnoses, if any, which were the reason for admission to the ICU, were recorded. The duration of hospitalization and exit from the ICU (transfer to hospital clinics, discharge or death) were evaluated. Albumin and creatinine values were used in laboratory values. Patients were divided into 7 groups according to serum creatinine levels (group 1: creatinine ≤ 0.4; group 2: 0.4 < creatinine ≤ 0.6; group 3: 0.6 < creatinine ≤ 0.8; group 4: 0.8 < creatinine ≤ 1.0; group 5: 1.0 < creatinine ≤ 1.2; group 6: 1.2 < creatinine ≤ 1.4; group 7: creatinine >1.4 mg/dL). Patients were divided into 3 groups according to albumin levels. Hypoalbuminemia < 3.5, 3.5 ≤ normoalbuminemia ≤ 5, hyperalbuminemia > 5 g/dL. Demographic data, duration of hospitalization, mortality rates

and albumin levels of patients were compared between the creatinine groups.

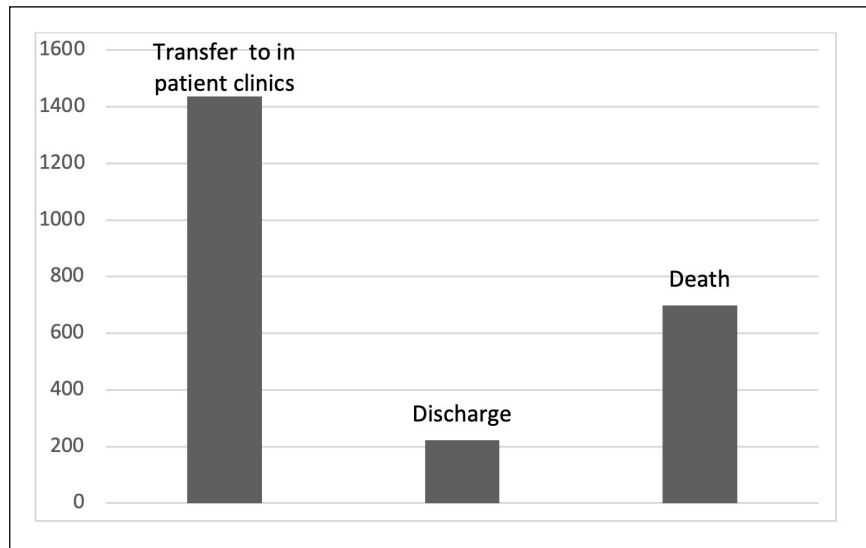
Statistical Analysis

Statistical analysis was performed using SPSS v. 26.0 (IBM Corp., Armonk, NY, USA) package program. Descriptive statistics are summarized as number, percentage, mean and standard deviation, median. The suitability of the variables for normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk tests). Age, albumin, creatinine levels, and hospitalization times of the patients were not normal distribution. Numerical variables that do not show normal distribution were compared between two groups using Mann-Whitney U test and three and more groups using Kruskal Wallis' test. Chi-square analysis was used to compare the ordinal data. Cox regression analysis was used to survival analysis. Male gender, age, albumin levels and creatinine levels were included in the regression model. 0.8-1.0 mg/dL values of creatinine groups were accepted as reference. The regression model fit was significant ($p < 0.001$). In the statistical analyses, comparisons with p -values lower than 0.05 were considered statistically significant.

Results

The mean age of the patients was 66.7 ± 19.5 years (median 73 years). Of the patients included in the study, 50.8% were male ($n = 1,199$) and

Figure 2. Patients' final status.



49.2% (n = 1,160) were female. The mean ICU stay was 8.0 ± 10.2 days (median 5 days, range 1-139 days). Most patients (69%, n = 1,628) remained in the ICU for 1 week or less, while 31% (n = 731) stayed longer. 29.6% (n = 699) of the patients had died. However, 60.9% (n = 1,437) of the surviving patients were transferred to inpatient clinics and 9.5% (n = 223) were discharged on the same day after exiting the ward (Figure 2).

Creatinine was ≤ 0.4 mg/dL in 1.8% (n = 42), $0.4 < \text{creatinine} \leq 0.6$ mg/dL in 18% (n = 424), $0.6 < \text{creatinine} \leq 0.8$ mg/dL in 31.2% (n = 737), $0.8 < \text{creatinine} \leq 1.0$ mg/dL in 15.3% (n = 362), $1.0 < \text{creatinine} \leq 1.2$ mg/dL in 8.4% (n = 198), 1.2

$< \text{creatinine} \leq 1.4$ mg/dL in 4.3% (n = 101), and $\text{creatinine} > 1.4$ mg/dL in 20.9% (n = 495) of the patients (Figure 3).

There was a difference between the creatinine groups in terms of age ($p < 0.001$). The mean age of group 1 and 2 was lower than group 4, group 5, group 6 and group 7 ($p < 0.05$). The mean age of group 3 was smaller than group 4, group 5, group 6 and group 7 ($p < 0.05$). The mean age of group 4 was greater than group 1, group 2 and group 3 ($p < 0.05$). The mean age of group 5 was greater than group 1, group 2 and group 3 ($p < 0.05$). The mean age of group 6 was greater than group 1, group 2 and group 3 ($p < 0.05$). The mean age of

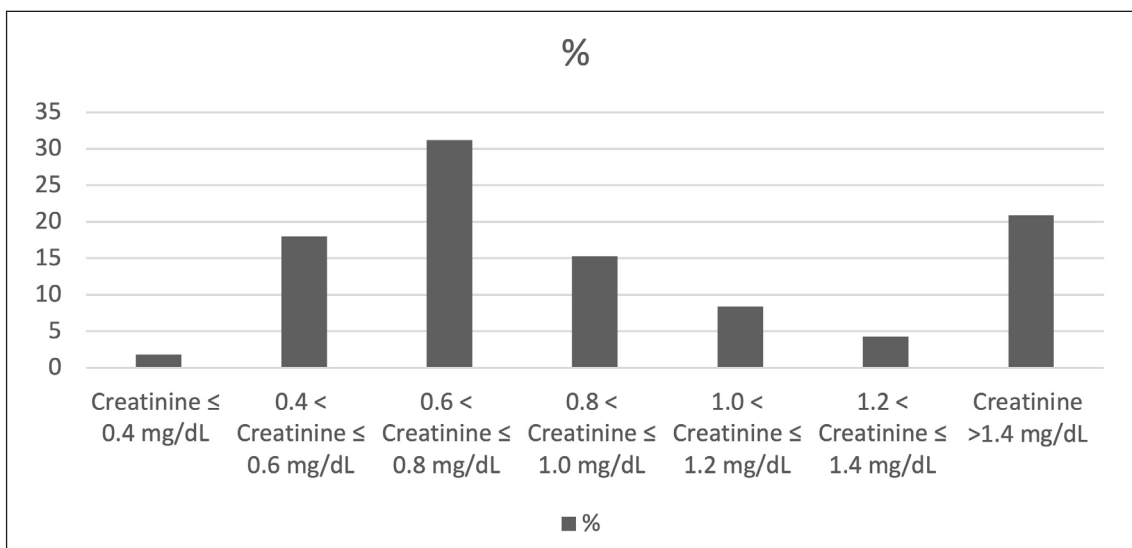


Figure 3. Distribution of patients according to creatinine categories.

Table I. Age, hospitalization duration and gender distribution of patients according to creatinine groups.

Creatinine levels	Creatinine levels							P
	Group 1 Cr ≤ 0.4	Group 2 0.4-0.6	Group 3 0.6-0.8	Group 4 0.8-1.0	Group 5 1.0-1.2	Group 6 1.2-1.4	Group 7 Cr>1.4	
Age ^a	56 ± 24	61 ± 21	62 ± 21	69 ± 18	73 ± 15	73 ± 14	71 ± 13	<0.001
Gender ^b Male	14 (33.3)	145 (34.2)	374 (50.7)	226 (62.4)	114 (57.6)	66 (65.3)	260 (52.5)	<0.001
Hospitalization Duration ^a	18.7 ± 23.5	9.6 ± 11.3	6.4 ± 7.3	7.4 ± 8.6	7.3 ± 8.7	7.8 ± 7.1	9.1 ± 12.2	<0.001
Albumin ^a	2.7 ± 0.5	2.7 ± 0.5	2.8 ± 0.5	2.8 ± 0.6	2.7 ± 0.5	2.6 ± 0.5	2.5 ± 0.5	<0.001
Mortality ^b	13 (31.0)	98 (23.1)	144 (19.5)	101 (27.9)	68 (34.3)	41 (40.6)	234 (47.3)	<0.001

Cr: Creatinine, ^aKruskal-Wallis' test, ^bChi-square test.

group 7 was greater than group 1, group 2 and group 3 ($p < 0.05$). There was a significant difference in creatinine groups in terms of gender distribution ($p < 0.001$). The proportion of female patients in group 1 ($p = 0.022$) and group 2 ($p < 0.001$) was higher than in male patients. Gender distribution was similar in group 3 ($p = 0.958$) and group 7 ($p = 0.234$). The proportion of male patients was higher in group 4 ($p < 0.001$), group 5 ($p = 0.047$) and group 6 ($p = 0.003$). Duration of hospitalization was found to be different between creatinine groups ($p < 0.001$). Duration of hospitalization in group 1 was longer than group 3 ($p < 0.05$), in group 2 was longer than in group 3 and group 4 ($p < 0.05$), in group 3 it was shorter than in group 2 and group 7 ($p < 0.05$), in group 4 was shorter than in group 2. Albumin levels differed

between creatinine groups. Group 2 had lower albumin levels than group 3, higher than group 7 ($p < 0.05$); group 3 had higher albumin levels than groups 6 and 7 ($p < 0.05$); group 4 had higher albumin levels than group 7; albumin level of group 5 was higher than that of group 7 ($p < 0.05$), albumin level of group 6 was lower than that of group 3 ($p < 0.05$) (Table I).

Mortality rates varied between creatinine groups. Mortality graph according to creatinine levels was U-shaped. High mortality at low creatinine levels showed a decrease in normal creatinine values and increased again at high creatinine levels. Mortality rates were 47.3% in group 7, 40.6% in group 6, 34.3% in group 5, 31% in group 1, 27.9% in group 4, 23.1% in group 2, 19.5% in group 3 (Figure 4).

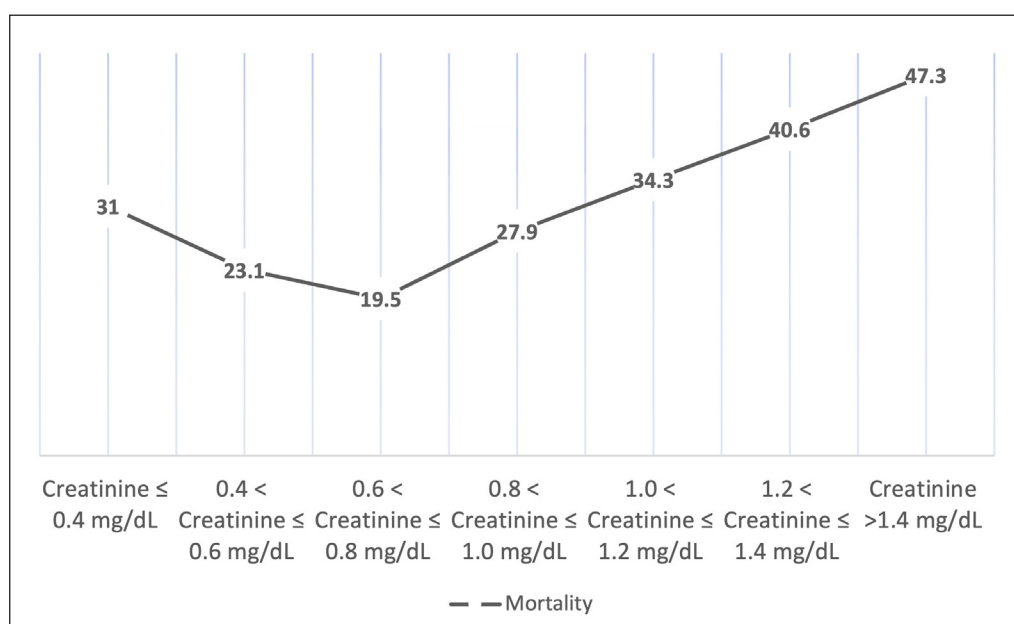


Figure 4. Mortality rates according to creatinine groups.

Table II. Distribution of patient diagnoses according to creatinine groups.

Creatinine levels	Creatinine levels							Total number of patients
	Group 1 Cr ≤ 0.4 (n=42)	Group 2 0.4-0.6 (n=424)	Group 3 0.6-0.8 (n=737)	Group 4 0.8-1.0 (n=362)	Group 5 1.0-1.2 (n=198)	Group 6 1.2-1.4 (n=101)	Group 7 Cr >1.4 (n=495)	
Cardiovascular	8 (19.0)	108 (25.5)	201 (27.3)	97 (26.8)	71 (35.9)	36 (35.6)	199 (40.2)	720
Pulmonary	15 (35.7)	73 (17.2)	142 (19.3)	81 (22.4)	34 (17.2)	17 (16.8)	79 (16.0)	441
Neurological	5 (11.9)	82 (19.3)	117 (15.9)	69 (19.1)	40 (20.2)	17 (16.8)	89 (18.0)	419
Gastrointestinal	5 (11.9)	65 (15.3)	113 (15.3)	56 (15.5)	27 (13.6)	17 (16.8)	60 (12.1)	343
Musculoskeletal	1 (2.4)	24 (5.7)	31 (4.2)	10 (2.8)	5 (2.5)	2 (2.0)	12 (2.4)	85
Toxication	2 (4.8)	14 (3.3)	34 (4.6)	9 (2.5)	2 (1.0)	0	0	61
Nephrological	0	2 (0.5)	11 (1.5)	8 (2.2)	2 (1.0)	3 (3.0)	27 (5.5)	53
Psychiatric	1 (2.4)	10 (2.4)	18 (2.4)	5 (1.4)	3 (1.5)	1 (1.0)	2 (0.4)	40
Ear diseases	0	7 (1.7)	11 (1.5)	4 (1.1)	3 (1.5)	1 (1.0)	6 (1.2)	32
Oncologic	1 (2.4)	8 (1.9)	10 (1.4)	5 (1.4)	0	2 (2.0)	3 (0.6)	29
Blood diseases	0	7 (1.7)	6 (0.8)	4 (1.1)	1 (0.5)	1 (1.0)	2 (0.4)	21
Genitourinary	1 (2.4)	3 (0.7)	5 (0.7)	5 (1.4)	3 (1.5)	1 (1.0)	4 (0.8)	22
Endocrinological	0	5 (1.2)	6 (0.8)	2 (0.6)	1 (0.5)	0	5 (1.0)	19
Traumata	0	1 (0.2)	11 (1.5)	0	0	0	0	12
Metabolic	3 (7.1)	1 (0.2)	2 (0.3)	1 (0.3)	3 (1.5)	0	1 (0.2)	11
Dermatological	0	2 (0.5)	4 (0.5)	1 (0.3)	0	0	2 (0.4)	9
Allergy	0	0	0	0	1 (0.5)	0	1 (0.2)	2
Other	0	12 (2.8)	15 (2.0)	5 (1.4)	2 (1.0)	3 (3.0)	3 (0.6)	40
<i>p</i>	<0.001	0.008	<0.001	0.811	0.130	0.920	<0.001	

Cr: Creatinine.

The frequency of primary diagnosis was found to change according to creatine groups ($p < 0.001$). In group 1 ($p < 0.001$), group 2 ($p = 0.008$), group 3 ($p < 0.001$) and group 7 ($p < 0.001$), significant differences were observed in primary diagnoses, but not in groups 4, 5 and 6. Pulmonary diseases were most common in group 1 (35.7%), while cardiovascular system diseases were the most common in other groups (Table II).

The age of male patients varied according to creatinine groups ($p < 0.001$). The mean age of group 2 was lower than that of groups 5, 6 and 7 ($p < 0.05$), and the mean age of group 3 was lower than that of groups 5, 6 and 7 ($p < 0.05$). There was no significant difference between the other groups. The duration of hospitalization in male patients varied between creatinine groups ($p < 0.001$). The duration of hospitalization of group 1 was longer than in group 3, 4, 5 and 6 ($p < 0.05$), and the duration of hospitalization of group 2 was longer than in group 3 ($p < 0.05$). There was no significant difference between the other groups. Albumin levels of male patients differed between creatinine groups ($p < 0.001$). Group 2 had higher albumin levels than those of group 7 ($p < 0.05$), group 3 had

higher albumin levels than those of group 7 ($p < 0.05$), group 4 had higher albumin levels than those of group 7 ($p < 0.05$). The albumin level of group 5 was higher than that of group 7 ($p < 0.05$). There was a significant difference between the creatinine groups in male patients ($p < 0.001$). The mortality of group 1 was 71.4%, for group 7 was 49.2%, for group 6 was 45.5%, for group 5 was 32.5%, for group 4 was 25.7%, for group 2 was 23.4%, and for group 3 was 20.1% (Figure 5).

The age of the female patients varied according to the creatinine groups ($p < 0.001$). The mean age of group 1 was lower than group 5 ($p < 0.05$), the mean age of group 2 was lower than group 4, 5, 6 and 7 ($p < 0.05$), and the mean age of group 3 was lower than group 4, 5, 6 and 7. Mean age of group 5 was higher than group 7 ($p < 0.05$). There was no significant difference between the other groups. The duration of hospitalization in female patients varied between creatinine groups ($p < 0.001$). The duration of hospitalization of group 2 was longer than in group 3 ($p < 0.05$) and the duration of hospitalization of group 3 was lower than in group 7 ($p < 0.05$). There was no significant difference between the other groups. The albumin level of the

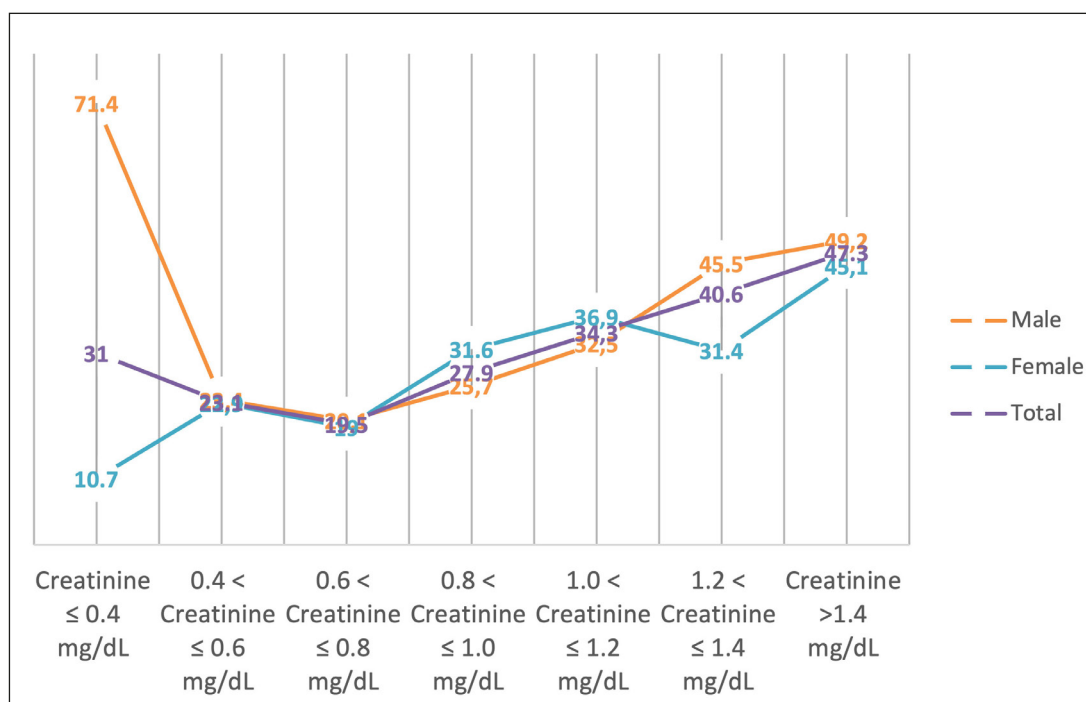


Figure 5. Mortality rates by gender.

female patients was different among the creatinine groups ($p < 0.001$). The albumin level of group 2 was lower than in group 3, higher than in group 7, and the albumin level of group 3 was higher than that in groups 4, 6 and 7 ($p < 0.05$). There was a significant difference between the creatinine groups in female patients ($p < 0.001$). Mortality of group 7 was 45.1%, for group 5 was 36.9%, for group 4 was 31.6%, for group 6 was 31.4%, for group 2 was 22.9%, for group 3 was 19.0%, for group 1 was 10.7% (Figure 5).

Among the factors affecting survival, the model formed when hypoalbuminemia, age, gender and creatinine levels were included was found to be significant ($p < 0.001$, $\chi^2 = 85.7$). Hypoalbuminemia and gender were not decisive of survival in the regression model. Since the lowest mortality rate was observed in group 3, it was accepted as a reference in the regression model. According to this, it was seen that group 1, group 2 and group 7 decreased survivals, group 4 had no effect on survival and groups 5 and 6 increased survival (Table III).

Table III. Analysis of factors affecting mortality.

Variable	β	p	HR	95% CI	
Hypoalbuminemia	-0.283	0.163	0.754	0.507-1.121	
Age	0.009	0.002	1.009	1.003-1.015	
Male	-0.055	0.480	0.946	0.812-1.103	
Creatinine					
Group 1	≤ 0.4 mg/dL	-0.328	0.014	0.721	0.555-0.936
Group 2	0.4-0.6 mg/dL	-0.676	0.023	0.509	0.285-0.909
Group 3	0.6-0.8 mg/dL	---	---	---	---
Group 4	0.8-1.0 mg/dL	0.146	0.266	1.157	0.895-1.496
Group 5	1.0-1.2 mg/dL	0.343	0.021	1.409	1.053-1.886
Group 6	1.2-1.4 mg/dL	0.442	0.013	1.556	1.097-2.205
Group 7	>1.4 mg/dL	-0.451	<0.001	0.305	0.275-0.643

Since the lowest mortality rate was observed in group 3, it was accepted as a reference in the cox regression model. β ; beta, HR; hazard ratio, CI; confidence interval.

Discussion

There is a great evidence that creatinine elevation increases mortality in ICU patients¹⁰⁻¹². However, limited data are available on the effect of low creatinine levels on patients' clinical settings.

Creatinine is produced non-enzymatically by creatine and creatine phosphatase. 95% of creatinine is found in muscles¹³. Creatinine production is lower in patients with low muscle mass. Correlation of serum creatinine levels with muscle mass suggests that creatinine may also be used for skeletal muscle measurements⁵, and that low serum creatinine levels may be associated with mortality in patients followed up in the ICU. Although there are studies evaluating the effect of low serum creatinine levels on ICU mortality, data on this issue are limited^{7,14}.

Our first remarkable finding was that when patients were separated according to their creatinine levels, the mortality rate had a U-shaped curve. Intensive care unit mortality, which was 31% at low creatinine levels, decreased to the lowest level when creatinine levels were normal, and it was seen that mortality increased linearly as creatinine levels increased. In addition, creatinine levels were low in female patients and mortality was 10%, and 70% in male patients. Other studies have shown that low creatinine levels increase mortality. In-hospital mortality drew a U-shaped graph according to creatinine levels similar to study by Thongprayoon et al¹⁵. Mortality at low creatinine level (< 0.4 mg/dL) was 20.1%, at normal creatinine level (0.6-0.8 mg/dL) 7.8%, and at high creatinine levels (> 1.4 mg/dL), mortality increased again to 28%. When divided by gender, the lowest mortality in male patients was 0.9-1.0 mg/dL. Mortality was found to be increased in patients with creatinine levels below 0.4 mg/dL and in patients with creatinine values above 1.4 mg/dL. In females, the lowest mortality was observed between 0.5-0.8 mg/dL. Similarly, mortality was found to be higher in patients with creatinine levels below 0.4 mg/dL and above 1.4 mg/dL. When 0.9-1.0 mg/dL was accepted as a reference, creatinine level below 0.4 mg/dL increased the mortality in males by 4.12 to 4.27 times and in females by 2.46-2.77 times. Similarly, the one-year mortality in male patients was 30.4% in the lowest creatinine group and 20.1% in female. Our findings were similar to these results. However, in this study, mortality rates were lower because of inpatients in other clinics and not inpatients in the ICU. The difference between genders may be due to the fact that men have more muscle mass than women¹⁴.

In 2007, it was observed that mortality was U-shaped, similar to our findings in a study conducted by Cartin-Ceba et al⁷. The same pattern of dispersion was monitored for the length of stay in the ICU. In this study, unlike our study, not only patients in the internal ICU but all patients in the ICU were included. The peak creatinine concentration measured at the first 24 hour of ICU admission was evaluated instead of the creatinine level at admission in the study conducted by Udy et al¹⁶. Similarly, mortality rates according to creatinine levels were U-shaped.

It is known that serum creatinine level decreases in cases such as decreased production, pregnancy, chronic liver disease, and increased clearance. Among these reasons, decrease in muscle mass is prominent in critical patients because of its prognostic significance¹⁷. It is known that serum creatinine levels decrease especially in malnourished patients due to the low muscle mass¹⁴. It has been reported¹⁴ that the length of hospital stay increases and survival rates decrease in patients with poor nutritional status and low muscle mass.

In addition to creatinine levels, albumin levels were also effective in mortality. In our study, the mortality rate was 32.3% in patients with hypoalbuminemia and 9.6% in patients with normoalbuminemia. There are many studies^{18,19} confirming the relationship between albumin levels and mortality. Along with creatinine, albumin is also an indicator of nutritional status. However, a number of causes such as changes in intravascular volume, acute infection, inflammation, liver function, and loss of protein alter albumin levels²⁰.

In our study, ICU mortality was 29.7%. However, patients staying in ICU for more than 24 hours were included in the study. Therefore, it can be said that mortality rates are higher than normal. On the other hand, elderly patients hospitalized in the ICU and comorbid diseases increase the mortality rates of the internal ICU. In a multicenter study²¹ conducted in Europe, ICU mortality rates were reported as 19.1%. Differences between ICU mortality in literature may be caused by the level of development of countries, the level of development of hospitals, the presence of ICU, the different criteria for admission to ICU, and the reporting of mortality rates in different time periods.

Limitations

Our study has some limitations such as being a retrospective study, the diversity of hospitalization diagnoses of ICU patients and the heterogeneity in terms of admission diagnoses of the ICU.

There are many factors that have an impact on ICU mortality. However, the other parameters that had an impact on mortality were not evaluated in our study. We think that these factors include treatment practices that affect creatinine levels and patient diagnoses. However, these reasons were not evaluated in our study.

Conclusions

In our study, mortality tended to increase in patients admitted to ICU with low serum creatinine level. It was observed that the mortality rates at low creatinine level decreased in normal creatinine levels and increased again when creatinine levels were above normal, causing a U-shaped mortality graph. Although the effect of elevated creatinine levels associated with acute or chronic kidney injury on mortality is well known, the effect of low creatinine levels on mortality is not clear. Our study expanded data on the effect of low creatinine levels on mortality in ICU patients.

It is important to know or predict patients who will have a high mortality rate in order to reduce the mortality of patients followed up in the ICU. Therefore, mortality should be predicted in patients with low serum creatinine levels. Adding creatinine levels to systems developed for mortality estimation in patients will improve mortality estimation.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

None.

Informed Consent

Not applicable.

Ethics Approval

Our study was approved by the Adiyaman University Non-Interventional Clinical Research Ethics Committee (20.06.2017; 2017/5-8), which was conducted in compliance with the 2013 version of the Helsinki Declaration.

Authors' Contribution

Research conception and design: Ayşe Şahin Tutak, Hakan Aydın; Data acquisition: Hakan Aydın; Review of patients'

clinical information: Ayşe Şahin Tutak; Data analysis and interpretation: Hüseyin Avni Findikli; Statistical analysis: Hüseyin Avni Findikli; Drafting of the manuscript: Ayşe Şahin Tutak, Hakan Aydın; Critical revision of the manuscript: Ayşe Şahin Tutak; Approval of final manuscript: Ayşe Şahin Tutak, Hakan Aydın.

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