

PAPER DETAILS

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The predictors of mortality in patients with methyl alcohol intoxication

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ABSTRACT

Aim: Methanol intoxication is a worldwide public health problem. Mortality rates are quite high unless there is early intervention and diagnosis. The aim of this study was to investigate the predictors of mortality in patients with methyl alcohol intoxication.

Material and Method: The study included 18 patients admitted to emergency department of our hospital in 2019-2020, who were diagnosed with methanol intoxication. Laboratory parameters and basic features of the patients were recorded. According to the criteria of 2012 Clinical Practice Guideline for Acute Kidney Injury (AKI), patients were diagnosed with AKI.

Results: The mean age of the patients was 45.7 ± 15.21 years and 72.2% of those were male. The mortality and AKI rate were 38.9% and 44.4%, respectively. In regression analyses, delay in admission to hospital, low Glasgow coma scale score, AKI development and high lactate level were independent predictors of mortality. According to ROC analyses when lactate level was more than 5.75 mmol/L, mortality rate increased more rapidly.

Conclusion: Mortality rate is very high in methanol intoxication. Patients with AKI and high lactate levels should be intervened faster.

Keywords: Acute kidney injury, methyl alcohol intoxication, mortality

INTRODUCTION

Methanol is a substance that has industrial use and is liquid at room temperature. Rarely, cases of methanol poisoning occur due to illegal alcohol consumption, accidental, or suicidal exposure. Methanol is not a toxic substance; however, methanol is converted into formaldehyde by the enzyme alcohol dehydrogenase and subsequently, converted into formic acid by a reaction with the enzyme aldehyde dehydrogenase. The metabolites create toxic effects such as high anion gap metabolic acidosis, and damage to many cells particularly the basal ganglia and the optic nerve. If intervention is not relatively quick, the clinical picture proceeds to coma and death (1). The aim of this study was to investigate the predictors of mortality in patients with methyl alcohol intoxication.

MATERIAL AND METHOD

The study was approved by the Clinical Researches Ethics Committee of the Ankara Training and Research Hospital (Date: 17.09.2020, Decision No: 14.08.2020/E-20/393).

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 18 patients admitted to emergency department of our hospital in 2019-2020, who were diagnosed with methanol intoxication. Since the level of methanol was not screened in our hospital, the diagnosis was performed with the presence of metabolic acidosis ($\text{pH} < 7.25$) with increased anion gap ($\text{AG} > 20$), in which other causes were excluded and anamnesis from patients and their relatives and clinical findings. Patients' clinical and demographic features (age, gender, chronic diseases, chronic alcohol users, alcohol type (handmade or not), complaints, time from alcohol exposure to admission to hospital, interventions in hospital (iv. hydration, iv. ethanol, hemodialysis, intubation), acute kidney injury (AKI) development, hospitalization duration, survival status), and laboratory data (blood pH, PCO_2 , bicarbonate, lactate, sodium, potassium, chlorine, serum creatinine at admission and basal creatinine,

albumin, urea, white blood cell, hemoglobin, platelets at admission) were recorded. Hospitalization duration, whether it is the intensive care unit or the service, is the time from the moment of admission to the hospital until leaving the hospital. AKI was defined as an increase in known within 48 hours baseline creatinine greater than 0.3 mg/dl or a baseline creatinine increase of more than 1.5 times, according to the criteria of 2012 Clinical Practice Guideline for AKI.

Statistical Analysis

IBM Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. All data were checked for normality of distribution using the Kolmogorov-Smirnov and Shapiro-Wilk test. Normally distributed data are presented as the mean \pm standard deviation. Non-normally distributed data are represented as the median (inter-quartile range). Independent samples T test, was used to compare parametric continuous variables between groups. Mann Whitney U was employed for the comparison of non-parametric variables. Pearson's X^2 or Fisher's exact were used for categorical variables. Univariate binary logistic regression analyses were performed to detect the factors affecting mortality and AKI. Multivariate regression analyses were not performed due to small sample size. ROC analyses was used to find the cut-off value of parameters found to be significant in binary logistic regression analyses. Survival data were analysed with Kaplan-Meier method and tested for significance using the long rank test.

RESULTS

Eighteen patients were included in the study. The mean age of the patients was 45.7 ± 15.21 years, and 72.2 % of those were male. 94.4% of the patients were chronic alcohol users and 94.4% of the patients used handmade alcohol. Time from alcohol exposure to admission to hospital was 39.3 ± 14.7 hours. The most frequent symptoms were loss of consciousness (33.3%), nausea-vomiting (16.7 %) loss of vision (16.7 %), and their combination (33.3%). The patients were found to be hypovolemic on physical examination. 83.3% of the patients underwent hemodialysis. All of the patients who received hemodialysis underwent hemodialysis at the time of admission to the hospital. All of these patients had bicarbonate below 10 meq/L and had severe metabolic acidosis. IV ethanol was administered in 88.8% of patients. Ethanol (10% solution) infusion was given at a load-ing dose of 7.5-8.0 mL/kg for over 1 hour; followed by infusion of 1.0-2.0 mL/kg during follow-up or 2.5-3.0 mL/kg during HD. The ethanol infusion was set to maintain a serum ethanol level above 100 mg/dL. No patient received oral ethanol therapy. 44.4% of the patients were intubated. Hospitalization duration

was 5.72 ± 4.61 days. 38.9% of patients died (**Table 1**). Demographic characteristics and laboratory data of each patient were shown in **Table 2**.

The patients were divided into two groups as survivor and non-survivor. In the non-survivor group, the rates of AKI development and intubation, and the delay in admission to the hospital were higher. In addition, pH and Glasgow coma scale scores were lower, and PCO_2 , lactate and creatinine values were higher in the non-survivor group (**Table 3**). In binary logistic regression analyses, delay in admission to hospital (OR:1.11, 95%CI: 1.008-1.224, P:0.035), low Glasgow coma scale score (OR:0.638, 95%CI: 0.432-0.943, P:0.024), AKI development (OR:0.037, 95%CI:0.03-0.505, P:0.013) and high lactate level (OR:2.11, 95%CI:1.094-4.073, P:0.026) were independent predictors of mortality

Table 1. Patients' clinical and demographic features and laboratory data

Gender (Male)(%)	%72.2
Age (years)	45.7 ± 15.21
Complaints(%)	
Loss of consciousness	%33.3
Nausea-vomiting	%16.7
Loss of vision	%16.7
Both loss of vision and vomiting	%33.3
Chronic alcohol users(%)	%94.4
Alcohol type(%)	
Handmade	%94.4
Commercial	%5.6
Time from alcohol exposure to admission to hospital (hour)	39.3 ± 14.7
Hospital Interventions (%)	
iv. hydration	%100
iv. etanol	%88.8
Hemodialysis	%83.3
Intubation	%44.4
AKI development (%)	%44.4
Hospitalization duration (day)	5.72 ± 4.61
GCS	10.9 ± 3.9
Mortality rate (%)	%38.9
At admission blood pH	7.02 ± 0.21
At admission PCO_2 (mmHg)	32.55 ± 17.96
At admission bicarbonate (mmol/L)	7.98 ± 4.78
At admission lactate (mmol/L)	6.23 ± 4.6
At admission creatinine (mg/dL)	1.16 ± 0.42
At admission urea (mg/dL)	27.16 ± 14.05
At admission sodium (mmol/L)	137.6 ± 4.34
At admission potassium (mmol/L)	5.05 ± 0.87
At admission chlorine (mmol/L)	102.05 ± 4.03
At admission albumin (g/dL)	4.68 ± 0.37
At admission WBC ($10^6/L$)	17622 ± 5868
At admission hemoglobin (g/dL)	15.77 ± 1.88
At admission platelets ($10^6/L$)	288064 ± 124080
At admission Glasgow coma scale score	10.94 ± 3.93
At admission anion gap	29.86 ± 5.57
Basal creatinine (mg/dL)	1.11 ± 1.22

AKI: Acute kidney injury, GCS: Glasgow coma scale score

Table 2. Demographic and laboratory data of each patient

No	Gender	Age	Outcome	Complaints	Hospital Interventions	Time*	AKI	Time**	ph	PCO ₂	HCO ₃	Lactate	Anion Gap	Creatinine admission	Basal creatinine	GCS
1	F	42	R	Loss of vision, Nausea,vomiting	Hydration, HD	24	-	12.00	7.06	15.20	4.10	3.90	33.10	.92	.90	13
2	M	46	D	Loss of vision, Nausea,vomiting	Hydration, HD Intubation	48	+	9.00	6.94	69.00	3.90	8.20	38.10	1.10	.70	14
3	M	33	R	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol	24	-	4.00	7.13	17.20	5.50	2.40	32.30	1.01	.95	13
4	M	43	R	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol	24	+	4.00	7.18	17.20	6.20	6.20	34.60	1.18	.73	14
5	M	47	R	Nausea,vomiting	Hydration	24	-	1.00	7.23	34.00	17.00	1.90	28.10	.87	.91	13
6	M	19	R	Nausea,vomiting	Hydration	24	-	1.00	7.25	18.80	18.00	1.70	20.00	.90	.94	14
7	M	39	R	Nausea,vomiting	Hydration	24	-	1.00	7.25	33.90	18.10	2.20	23.30	.88	.89	13
8	F	23	R	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol	24	-	4.00	7.13	15.00	5.20	1.30	29.00	.72	.85	14
9	F	41	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	48	+	1.00	6.58	53.40	4.70	14.00	37.40	1.80	.90	8
10	F	33	D	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol, Intubation	24	+	13.00	6.71	48.20	5.70	11.80	38.30	1.36	.80	13
11	F	38	R	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	48	+	14.00	6.95	24.10	5.10	4.00	34.70	.90	.53	7
12	M	68	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	60	+	1.00	7.00	62.30	11.00	10.00	27.00	1.04	6.00	7
13	M	60	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	60	+	4.00	6.95	29.50	6.70	5.30	24.30	1.17	.60	7
14	M	71	R	Loss of vision	Hydration, HD iv.Ethanol	48	-	10.00	7.19	22.40	8.30	1.70	22.70	.82	.92	14
15	M	39	D	Loss of consciousness	Hydration,HD iv.Ethanol, Intubation	48	+	4.00	6.72	29.00	4.50	11.50	32.50	1.58	.82	3
16	M	58	R	Loss of vision	Hydration, HD iv.Ethanol	48	-	4.00	7.25	15.40	7.30	8.60	26.70	.85	.88	13
17	M	42	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	60	+	12.00	6.71	59.40	5.00	15.00	30.00	1.36	.79	3
18	M	71	R	Loss of vision	Hydration, HD iv.Ethanol	48	+	4.00	7.16	22.00	7.50	2.60	25.50	2.42	.93	14.

F: Female, M:Male, R:Recovery, D:Death, HD: Hemodialysis, Time* (day): Time from alcohol exposure to admission to hospital, AKI: Acute kidney injury Time** (hour): Time from the moment of admission to the hospital until leaving the hospital, GCS: Glasgow coma scale score

Table 3. The comparison of demographic and laboratory data between survivor and non-survivor group

	Survivor group (n:11)	Non-survivor group (n:7)	P
Gender (female) (%)	27.3	28.6	0.676
Age (year)	42 (25)	42 (21)	0.791
Chronic alcohol users (%)	100	85.7	0.389
Alcohol type (Handmade) (%)	90.9	100	0.611
AKI (%)	27.3	100	0.004
Hemodialysis (%)	72.7	100	0.202
Intubation (%)	9.1	100	<0.001
Time* (hour)	24 (24)	48 (12)	0.002
Blood ph	7.18 (0.12)	6.72 (0.24)	<0.001
Bicarbonate (mmol/L)	7.3 (11.8)	5 (2.2)	0.104
Anion gap	28.1 (9.8)	32.5 (11.1)	0.126
PCO ₂ (mmHg)	18.8 (8.7)	53.4 (32.8)	<0.001
Lactate (mmol/L)	2.4 (2.3)	11.5 (5.8)	<0.001
Creatinine (mg/dL)	0.9 (0.16)	1.36 (0.48)	0.008
Basal Creatinine (mg/dL)	0.9 (0.08)	0.8 (0.2)	0.211
WBC (10 ⁶ /L)	9260 (7220)	19090 (9970)	0.008
Hemoglobin (g/dL)	14.3 (1.9)	17.4 (3.7)	0.049
Hospitalization duration (day)	4 (9)	4 (11)	0.791
GCS	13 (1)	7 (10)	0.027

Time* Time from alcohol exposure to admission to hospital, AKI: Acute kidney injury, WBC: White blood cell, GCS Glasgow coma scale score

Table 4. Binary logistic regression analysis of risk factors affecting mortality

Parameters	β	OR	95% CI	P
Gender	0.065	1.067	0.129-8.793	0.952
Age	0.010	1.010	0.947-1.077	0.770
Complaint	-2.303	0.1	0.006-1.544	0.09
Time*	0.105	1.111	1.008-1.224	0.035
AKI development	-3.296	0.037	0.003-0.505	0.013
Hospitalization time	0.046	1.047	0.848-1.292	0.671
Glasgow coma scale score	-0.449	0.638	0.432-0.943	0.024
Blood pH	-28.45	0.00	0.00-1740	0.120
Bicarbonate	-0.124	0.807	0.560-1.163	0.251
PCO ₂	0.216	1.241	0.986-1.562	0.06
Lactate	0.747	2.111	1.094-4.073	0.026
WBC	0.001	1	1-1	0.051
Hemoglobin	0.596	1.815	0.956-3.446	0.069
Platelets	0.001	1	1-1	0.086

* time from alcohol exposure to admission to hospital, WBC: White blood cell

(Table 4). The Kaplan-Meier analyses disclosed that AKI patients suffered lower cumulative survival than non-AKI patients (Figure 1). In ROC analyses it was found that mortality increased significantly when lactate level exceeded 5,75mmol/L (Figure 2). Regression analyses revealed that intubation (OR:12, 95 CI%:1.294-111.32, P:0,029), high lactate (OR:1,445, 95%CI:1.045-1.998, P:0,026) and hemoglobin levels (OR:2,527,95%CI:1.108-5.766, P:0,028) were independent risk factors for the development of AKI,

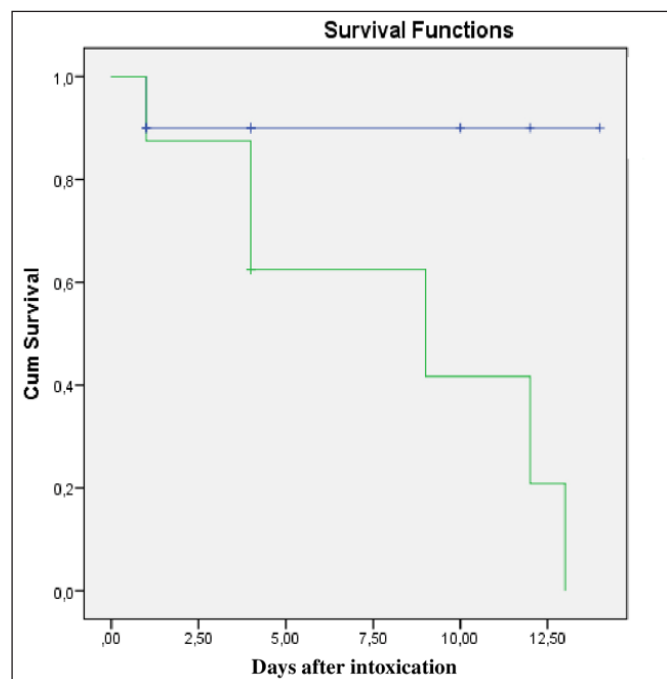


Figure 1. Kaplan-Meier analysis. Acute kidney injury patients (green line) suffered from lower cumulative survival than non-acute kidney injury patients (blue line) (log rank test, chi-square:3.845 p:0.048)

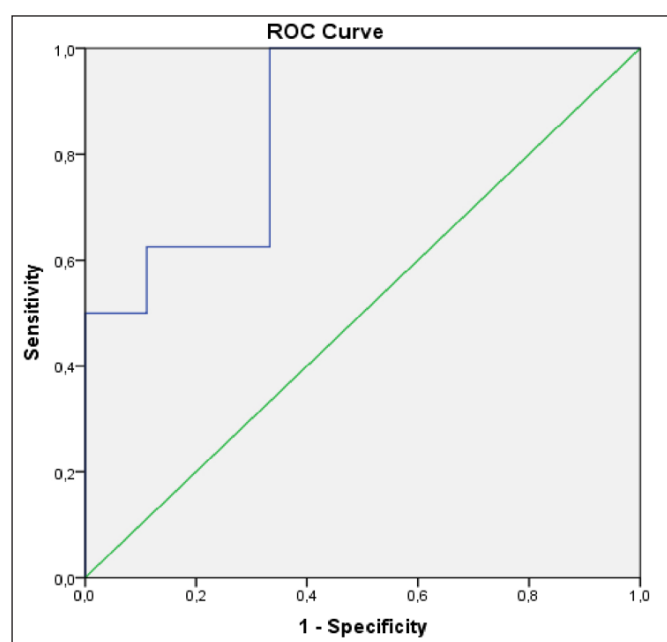


Figure 3. ROC (Receiver operating characteristic) curve analysis of hemoglobin level affecting acute kidney injury development in patients with methanol intoxication. Area under the ROC curve:0.861, %95 CI (Confidence interval):0.684-1,P:0,012 sensitivity:66.6%, specificity:62.5%

(Table 5). According to ROC analyses if hemoglobin and lactate levels were more than 15,6g/dL and 5,75mmol/L, respectively AKI developed more rapidly (Figure 3,4).

DISCUSSION

There is a latent period in methanol intoxication until the formation of metabolites and the manifestation of their toxic effects. The amount of methanol taken, the route of intake, and whether or not ethanol is taken

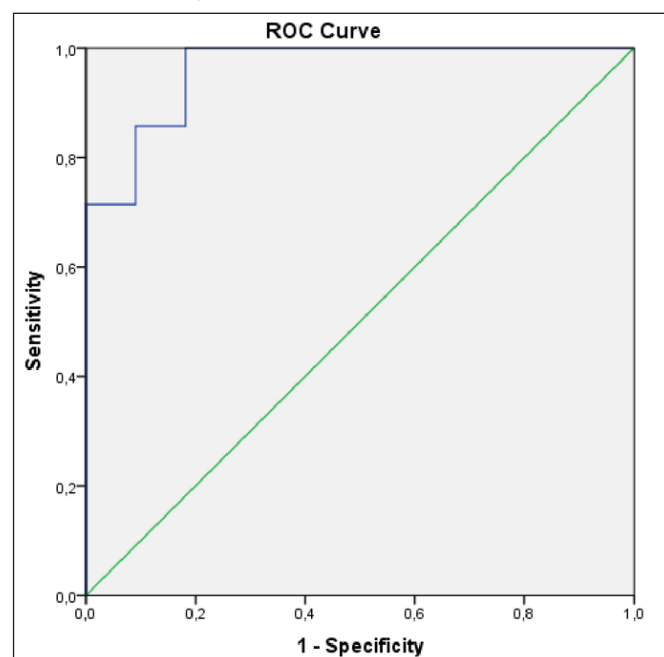


Figure 2. ROC (Receiver operating characteristic) curve analysis of lactate level affecting mortality in patients with methanol intoxication. Area under the ROC curve:0.961, %95CI (Confidence interval):0.881-1, P:0,001 sensitivity:81.8%, specificity:85.7%)

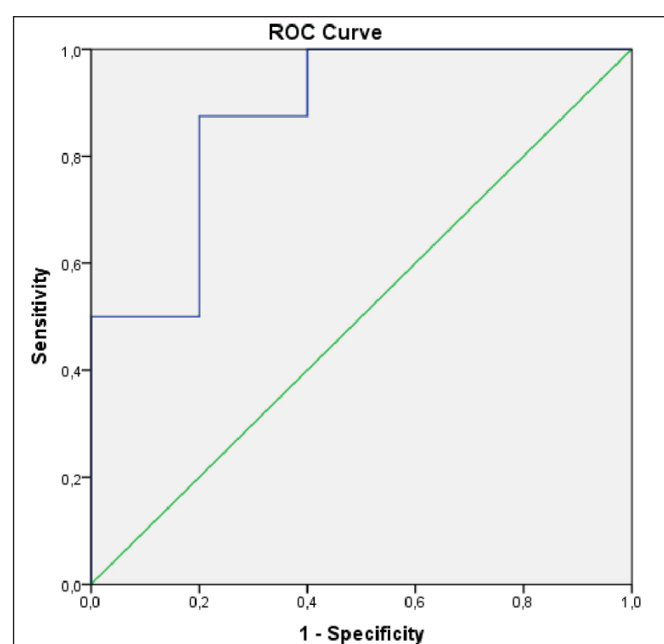


Figure 4. ROC (Receiver operating characteristic) curve analysis of lactate level affecting acute kidney injury development in patients with methanol intoxication. Area under the ROC curve:0.875, %95 CI(Confidence interval):0.713-1, P:0,008 sensitivity:80%, specificity:75%)

concomitantly causes this period to extend from 12 to 72 hours (1). In the current study, patients were admitted to the hospital after a mean of 39 hours due to nausea, vomiting, or loss of vision. Six patients were brought to the hospital with loss of consciousness. Since these patients had severe metabolic acidosis, they were immediately underwent hemodialysis. Hemodialysis is a method that enables the rapid removal of both methanol and its metabolites from the body. In a study by Lachance et al. (2), using the formula of $3.390 \times (\ln(\text{initial methanol concentration}(\text{MCI})/4))$ for women and $3.534 \times (\ln(\text{MCI}/4))$ for men, the safe level of 4 mmol/L methanol was found to be achieved in 141 minutes and 147 minutes in women and men, respectively. Since methanol levels could not be monitored in our hospital, a standard 240-minutes hemodialysis program was applied to the patients. In the blood tests taken after hemodialysis, the metabolic picture was observed to be recovered.

Another treatment method in methanol intoxication is the intravenous application of fomepizole or ethanol; both of which inhibit the alcohol dehydrogenase enzyme and prevent the formation of its metabolites (1). The enzyme affinity of fomepizole is 500-1000 times higher than ethanol. However, it is considered an expensive treatment, and ethanol is also known to have 10 times more enzyme affinity than methanol. Since there was no fomepizole in our hospital, intravenous ethanol was applied.

In methanol intoxication, the mortality rates are quite high if the patients are not intervened early. In a case series, the mortality was observed to range from 0 to 48% (3-17). In the current study, the mortality rate was determined as 38.9 % and it was observed that delay in admission to hospital, lower Glasgow coma scale score, high lactate level, and AKI development were independent predictors of mortality. Similar to our study, Chang et al. (17), reported that a significant relationship was found between mortality and AKI in patients with methanol intoxication. In the comparison of the two groups with and without AKI, it was emphasized that mortality and intubation rates were high in the AKI group. In this study, where it was stated that the patients did not have hemoglobinuria or myoglobinuria, it was stated that intubation may play a role in the development of AKI by triggering the release of cytokines (17). There have been publications suggesting that cytokines released during intubation affect kidney function (18,19). In various past studies, AKI rate was shown to range from 15.4 to 66% (17,20,21). In current study, we found that 44.4% of patients developed AKI and a significant relationship between AKI development and intubation, high lactate and hemoglobin levels. The high hemoglobin level was interpreted as an indicator of the volume deficiency caused

by vomiting of the patients. When lactate level exceeded 5,75 mmol/L, both AKI and mortality rates increased rapidly. In methanol intoxication, methanol metabolites may have a direct effect on the tubule in the development of AKI, and they may also damage the kidney by triggering hemoglobinuria and myoglobinuria. In a study by Velvet et al. (21) hydropic changes in the proximal tubule were demonstrated in kidney biopsies of patients who died due to methanol intoxication. In addition, in this study, hemoglobinuria and myoglobinuria were detected in the patients living and it was stated that this may play a role in the development of AKI.

CONCLUSION

Delay in admission to hospital, lower Glasgow coma scale score, high lactate level, and AKI development were independent predictors of mortality. Intubation, high lactate, and hemoglobin levels were risk factors of AKI development. Therefore, patients should be recognized early and aggressively treated to avoid mortality. Nevertheless, the retrospective nature of the study, small sample size, and absence of urine output, urinalysis, creatinine kinase and methanol measurements limit the certainty of our conclusions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Clinical Resarches Ethics Committee of the Ankara Training and Research Hospital (Date: 17.09.2020, Decision No: 14.08.2020/E-20/393).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: All authors declare no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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