Acta Medica Alanya

RESEARCH ARTICLE

ARAŞTIRMA

Acta Medica Alanya

2022;6(3): 293-300

DOI: 10.30565/medalanya.1184894

Risk factors associated with mortality in patients with methanol poisoning: a retrospective study

Metanol zehirlenmesi olan hastalarda mortalite ile ilişkili risk faktörleri: retrospektif bir çalışma

Hakan Aydın[1]*, Fatih Doganay[1], Mehmet Ozgur Erdogan[1], Halil Doğan[1], Attila Beştemir[2], Alpay Tuncar[3]

1. Department of Emergency Medicine, University of Health Sciences Faculty of Medicine, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Türkiye

2. Department of Emergency Medicine, The Minister of Health, Department of Planning, Ankara, Türkiye

3. Department of Emergency Medicine, The Minister of Health, Department of Medical Specialty Board, Ankara, Türkiye

ABSTRACT

Aim: Methanol poisoning (MP) is an significant medical problem worldwide, and despite advances in diagnosis and treatment, the mortality rate in these cases remains high. This study aimed to evaluate the clinical and laboratory factors to determine in-hospital mortality in patients with MP.

Methods: This single-center, retrospective, observational study was conducted with 65 adult MP cases visiting the emergency department (ED) of a tertiary training and research hospital, between January 01, 2017 and February 01, 2022. Data was statistically compared between survivors and non-survivors.

Results: The in-hospital mortality rate was 41.5%. The rate of cases with respiratory distress, low Glasgow coma scale (GCS) (≤8), and delayed arrival to the hospital (>24 hours) was higher in the group of non-survivors compared to the group of survivors. Non-survivors had a higher anion gap (30.5 mEq/L vs. 25.5mEq/L), base excess (-25.0 mmol/L vs. -18.6 mmol/L), lactate (10.2 mmol/L vs. 2.2 mmol/L) levels, and lower pH (6.76 vs. 7.14) and bicarbonate (6.3 mmol/L vs. 10.3 mmol/L) levels than survivors (p<0.001). In ROC analysis, pH (AUC= 0.916) and base excess (AUC=0.915) were blood gas parameters with the highest AUC values in predicting mortality in MP cases. Folate use in the treatment had a statistically significant effect on mortality (P=0.015).

Conclusion: In MP cases, delay in a hospital visit, severe metabolic acidosis, high lactate levels, low GCS on arrival to the ED and no folate therapy, were associated with increased in-hospital mortality rates. Our data will contribute to the clinical management of MP patients and the development of treatment protocols.

Keywords: Methanol, Folic Acid, Acidosis, Anion gap, Alcoholic Intoxication

ÖZ

Amaç: Metanol zehirlenmesi (MZ) dünya çapında önemli bir tıbbi sorundur, tanı ve tedavideki gelişmelere rağmen bu vakalarda ölüm oranı yüksektir. Bu çalışmada MZ olan hastalarda hastane içi mortaliteyi öngörmek için klinik ve laboratuvar faktörlerinin değerlendirilmesi amaçlandı.

Yöntemler: Bu tek merkezli, retrospektif, gözlemsel çalışma, 01 Ocak 2017 ve 01 Şubat 2022 tarihleri arasında üçüncü basamak bir eğitim ve araştırma hastanesinin acil servisini (AS) ziyaret eden yetişkin 65 MZ vakası ile yürütülmüştür. Veriler hayatta olanlar ve hayatta olmayanlar arasında istatistiksel olarak karşılaştırıldı.

Bulgular: Hastane içi ölüm oranı %41,5 idi. Hayatta kalmayanlar grubunda solunum sıkıntısı, düşük GKS (≤8), ve hastaneye geç başvuran (24 saaten sonra) vakalarının oranı, hayatta kalanlar grubuna göre daha yüksekti. Ölen hastaların grubunda yaşayanlara kıyasla daha yüksek anyon açığı (30,5 mEq/L vs. 25,5mEq/L), baz fazlalığı (-25,0 mmol/L vs. -18,6 mmol/L), laktat seviyeleri (10,2 mmol/L vs. 2,2 mmol/L) ve daha düşük pH (6,76 vs. 7,14) ve bikarbonat (6,3 mmol/L vs. 10,3 mmol/L) seviyeleri vardı (p<0.001). ROC analizinde pH (AUC= 0,916) ve baz fazlalığı (AUC=0,915), MZ olgularında mortaliteyi öngörmede en yüksek AUC değerlerine sahip kan gazı parametreleriydi. Tedavide folat kullanımının mortalite üzerinde istatistiksel olarak anlamlı bir etkisi oldu (p=0.015).

Sonuç: MZ olgularında hastaneye başvuruda geçikme, şiddetli metabolik asidoz, yüksek laktat düzeyleri, acil servise gelişte düşük GKS ve folat tedavisi verilmemesi, artan hastane içi mortalite oranları ile ilişkiliydi. Verilerimiz MZ hastalarının klinik yönetimine ve tedavi protokollerinin geliştirilmesine katkıda bulunacaktır.

Anahtar Kelimeler: Methanol, Folik asid, Asidoz, Anyon açığı, Alkol zehirlenmesi

Received: 06.10.2022 Accepted: 22.11.2022 Published (Online): 31,12,2022

*Corresponding Author: Hakan Aydın, Department of Emergency Medicine, University of Health Sciences,Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Türkiye, Phone:+905389789810 drhakanAydin054@gmail.com

ORCID : 0000-0003-3195-1805

To cited: Aydın H. Et al. Risk factors associated with mortality in patients with methanol poisoning: a retrospective study Acta Med. Alanya 2022;6(3):293-300 doi: 10.30565/medalanya.1184894

INTRODUCTION

Methanol, obtained by tree fermentation, is a colorless, volatile, toxic type of alcohol found in a variety of household and industrial products [1]. Although methanol is not very toxic, formaldehyde and formic acid, two of its metabolites, cause most of the toxic effects in methanol poisoning (MP) [2,3]. Acute MP is characterized by a latent period of several hours in which patients are asymptomatic or show mild central nervous system (CNS) depression, followed by nausea, vomiting, abdominal pain, respiratory distress, progressively decreasing vision, progressive encephalopathy, and severe metabolic acidosis [2,3]. MP therapy includes standard supportive care, antidote therapy (ethanol or fomepizole), renal replacement therapy (RRT), folic acid (folate) and buffer (sodium bicarbonate) treatments [2,4].

However, despite improved treatments, high mortality rates are still reported in MP cases [2,5]. The main reason for this is the delayed visit to the hospital and the delayed diagnosis due to difficulties. The main difficulties in diagnosis are the inability in many centers to measure methanol, the lack of specificity of early symptoms and other laboratory data for MP, and the difficulty in obtaining an accurate anamnesis in case of attempted self-harm or substance abuse [2,4,5]. There is often a diagnostic dilemma and it is up to the clinician to consider MP as the etiology of many nonspecific findings, particularly metabolic acidosis. However, among MP cases that we can encounter in the form of outbreaks, it is vital to recognize the critically ill, triage these patients, transfer them to poisoning centers and start their treatment early [5].

This study aims to evaluate demographic, clinical and laboratory data to predict the prognosis of MP cases visiting the emergency department (ED) in the form of isolated episodes or outbreaks, at different times over five years.

MATERIALS AND METHODS

Study design and setting: This single-center, retrospective, observational study was conducted with consecutive MP cases visiting the ED of a tertiary training and research hospital, between January 2017 and February 2022. This hospital is a toxicology center, a level 1 trauma center, a STEMI center and a stroke center with multiple medical and surgical specialties, including an emergency medicine residency. There are 612 beds in the hospital, the annual number of ambulance visits to the ED is approximately 20 000 and the total of ED visits number approximately 300 000 per year.

Approval for this study was obtained from the ethics committee of the research institution. (Date: 07.02.2022, Protocol Number: 2022/42) and was conducted in accordance with the Declaration of Helsinki. The study was retrospective and the requirement for informed assent was waived as a result. Additionally, all personal data has been securely safeguarded (by detaching identifying data from the primary dataset) and made only accessible to academics. An anonymous analysis was done on all the data.

Criteria for inclusion and exclusion: The study included patients admitted to the ED with a diagnosis of MP and at least 18 years old. In addition to a strong history or clinical suspicion, the diagnosis of MP was made when the serum methanol content was more than 20 mg per deciliter or when at least two of the following three symptoms were present:

1. An arteria pH below 7.3.

2. Serum bicarbonate less than 20 mEq/L, and/or

3. Serum osmolar gap of more than 10 mOsm/kg.

Methanol levels cannot be measured in our hospital. However, the methanol level of four patients could be measured with blood samples sent to external centers. Patients younger than 18 years of age, who started their treatment elsewhere and were referred to our hospital, and whose data could not be reached, were excluded from the study.

Data: All patients who visited the ED during the study were scanned from the hospital's electronic medical record system, with their defined diagnoses (preliminary, differential, consultation and definitive diagnosis) during their hospital stay. Physician and nurse notes, consultations, daily follow-ups and laboratory data of patients whose diagnoses included the words "alcohol", "ethanol", "methanol" or "poisoning" were

examined. The data of the patients included in the study were recorded in a pre-designed form. The form included demographic data (age, gender, comorbidities), complaints, vital parameters, consciousness status, alcohol or substance abuse, alcohol administration method and time, laboratory results, radiological imaging reports, patient management and prognosis. Analysis of laboratory data included plasma bicarbonate levels, serum electrolyte levels, liver and kidney function test results, pancreatic enzyme levels, arterial blood gas analysis, cardiac markers and glucose and coagulation parameters. In our study, all vital parameters, laboratory and imaging results, were based on the initial data obtained at the time of arrival of the cases to the ED.

The following equation was used to determine the anion gap (AG) in serum:

AG = (Na+ + K+) – (Cl- + HCO3-) (6)

Treatment Protocol: Patients were given the necessary airway, respiratory and circulatory support, following a rapid initial screening assessment, that included mental state and vital signs to establish the urgent steps required to stabilize the patient. Standard supportive care, antidote therapy, elimination therapy, buffer (sodium bicarbonate) and folate are all used in the management of MP [2].

Intravenous (IV) ethanol (10%) was administered as an antidote. Only one patient could get fomepizole, due to a shortage of supply. When arterial pH was below 7.25 or serum bicarbonate was consistently below 20 mEq/L, patients received ethanol treatment intravenously as a 10% solution in 5% glucose (loading dose: 4–8 mL/kg, followed by a maintenance dose of 1-2 mL/kg/h). If necessary, the ethanol infusion rate was increased during hemodialysis (HD) to 2.5–3.0 ml/kg/h. A serial blood gas analysis was carried out roughly every two hours to assess the acidity level and track the medication's effectiveness. HD was performed on cases that met any of the following criteria: abnormality of vision, an initial arterial pH of less than 7.1, an arterial pH that could not be maintained at or above 7.3 or, a decrease in the arterial pH of more than 0.05 unit despite bicarbonate supplementation, worsening of vital signs despite intensive supportive care or renal failure. HD was performed on the patients as quickly as feasible. Since formate or methanol levels cannot be detected, HD was carried out at a high blood flow rate until pH levels returned to normal. Hemodynamically unstable patients (MAP 70 mmHg, GCS ≤8, intubated) or receiving positive inotropic treatment underwent hemodiafiltration (HDF) in the intensive care unit. To treat acidosis in all patients with a pH under 7.3, isotonic saline was given together with an IV bolus of 1 mEq/kg sodium bicarbonate. The infusion rate was customized based on fluid status, baseline pH and serum sodium level. When the arterial pH reached 7.35, the therapy was considered successful and the infusion was halted. As a cofactor treatment, folinic acid was administered. Additionally, thiamine hydrochloride, pyridoxine hydrochloride and cyanocobalamin were given. No patient received any form of gastrointestinal decontamination, such as gastric lavage or Ipecac syrup, or activated charcoal.

Statistical analysis: The statistical analysis of the study's data was conducted using the SPSS for Windows Inc. Version 22 (SPSS Inc.; Illinois, USA) and the MedCalc Statistical Software version 19.0.6. (MedCalc Software bvba, Belgium). Whether the continuous variables were normally distributed or not was calculated using the Shapiro-Wilk test. Non-normally distributed data was compared with the Mann-Whitney U test, and normally distributed data was compared with Student's t-test. Pearson chi-square test was used to compare the categorical results of the patients. Data was provided with means and standard deviations when parametric tests were employed to compare continuous variables. Median (25th and 75th percentiles) values for nonparametric tests were presented. Numbers and percentages (%) values for categorical data were presented. Receiver operating characteristic (ROC) curves were used to compare blood gas parameters to predict in-hospital mortality. The statistical significance level was consented as $p < 0.05$.

RESULTS

The study included 65 MP cases meeting the inclusion and exclusion criteria. Most of the patients were middle-aged (mean: 46.7±13.1 years), male (93.8%) and persistent alcohol drinkers (76.9%).

None of the patients had purchased their drinks from a monopoly dealer. The rate of those who buy drinks containing methanol is 76.9%, while the rate of those who prepare their drinks with the alcohol they buy is 23.1%. All of the patients had been poisoned by the methanol-containing beverages they drank assuming it was alcohol. Three (4.6%) patients had hypertension and one (1.5%) patient had diabetes mellitus. All patients were symptomatic and visual symptoms were the most common clinical feature with 90.8%. The proportion of patients with GCS <15 at the time of ED visit was 55.4% (n=36), and five more patients developed altered consciousness during ED follow-up. Most of the patients were treated with ethanol antidote (84.6%), RRT (IHD [61.5%], HDF [32.3%]), folic acid (58.5%) and bicarbonate (67.7%). A 42-year-old male patient, who was administered fomepizole on the 4th hour of his admission to the ED, died on the 4th day of his hospitalization. The in-hospital mortality rate was 41.5%. In our analysis, there was no statistically significant difference in gender (p=0.636) or mean age (p=0.061) between survivors and non-survivors. In terms of vital parameters, non-survivors had a lower mean arterial pressure (MAP) (86.6 ± 16.6 vs. 97.2 ± 12.0; p=0.042) and higher respiratory rate (23.9 ± 4.3 vs. 17.3 ± 1.7; p <0.001) than survivors. In-hospital mortality rates were 25.0% (n=4) for those visiting the ED within the first 24 hours after oral administration, while 69.2% (n=9) for those visiting after 48 hours. The median hospital stay of non-survivors was 4 (IQR:2-6) days. In addition, the in-hospital mortality rate was 20% (n=8) in patients treated with IHD and 71.4% in patients treated with HDF (P<0.001). However, patients who received folic acid therapy had a lower in-hospital mortality rate than those who did not (28.9% [n=11] vs. 59.3% [n=16]; respectively, p=0.015). Demographic data, vital parameters, clinical findings and treatments of patients grouped in terms of in-hospital mortality, are summarized in Table 1.

Brain CT imaging was performed in 78.4% (n=51) and diffusion-weighted magnetic resonance (DW-MRI) imaging was performed in 27.6% (n=18) of the patients, when they presented to the ED. No pathological finding was detected in this imaging. However, intracranial hemorrhage was seen in five cases in the radiological imaging performed between the 3rd and the 5th day following the arrival at the ED. Four patients had pre-dialysis brain CT scans and no pathological findings. Hematoma areas were reported in the bilateral basal cisterns in four patients and in the white matter adjacent to the lateral ventricular in one patient. INR, PT and aPTT values in the blood taken on the same day, as the hemorrhage-detected brain CT of these five patients were within the reference range.

Non-survivors had a greater anion gap (30.5 mEq/L [25.3-38.3] vs. 25.5 mEq/L [22.3-28.0]; p<0.001), higher PCO2 (43.6 [23.4-51.3] vs 29.8 [21.2-36.1]; p=0.015) and lactate (10.2 mmol/L [2.5-12.3] vs. 2.2 mmol/L [1.8-2.9]; p<0.001) levels, and lower pH (6.76 [6.69-7.15] vs. 7.14 [7.10-7.27]; p<0.001), bicarbonate (6.3 mmol/L [5.2-8.8] vs. 10.3 mmol/L [7.0-17.9]; p<0.001) and base excess (-25.0 mmol/L [-34.4 to -21.2] vs -18.6 mmol/L [-22.9 to – -6.5]; p<0.001) than survivors. The ethanol level measured in the blood taken at the time of admission of 47 patients (72.3%) was analysed. Nine patients had ethanol levels above the reference range (0-15 mg/dl). There was no statistically significant difference in mortality between those with and without high initial blood sample ethyl alcohol levels (22.2% [n=2], 39.5% [n=15]; respectively, p=0.455). Only eight cases had diagnoses supported by laboratories, and only one of these patients died. The methanol level in the blood of the deceased patient was 436 mg/dl, and the ethanol level was 131 mg/dl. Analysis of initial laboratory samples of MP cases is summarized in Table 2.

In ROC analysis, pH (AUC= 0.916 [%95 CI: 0.820-0.970]) and base excess (AUC=0.915 [%95 CI: 0.819-0.970) were blood gas parameters with the highest AUC values in predicting mortality in MP cases. The graph of the ROC analysis of blood gas parameters is shown in Figure 1. From the cut-off values determined according to Younden index J, pH ≤6.8 had the highest specificity (%100 [%95 CI:90.7-100]), HCO3 ≤6.7 mmol/L (%85.2 [%95 CI: 66.3-95.8]) and Base excess ≤ -25 mmol/L (85.2 [%95 CI: 66.3-95.8]) were the values with the highest sensitivity (Table 3).

Table 1. Comparison of demographic characteristics, vital parameters, clinical findings, and treatments of survivors and non-survivors.

		All patients	Survivor	Non-survivor	p
Male, n (%)		61 (93.8)	35 (92.1)	26 (96.3)	0.636
Age, years, mean ± SD		46.7 ± 13.1	44.1 ± 13.4	50.3 ± 11.8	0.061
Vital parameters, mean ± SD					
MAP, mmHg		92.8 ± 14.9	97.2 ± 12.0	86.6 ± 16.6	0.042
Pulse, n/min		85.5 ± 12.4	85.1 ±11.0	86.2 ± 14.3	0.706
Tempatura, oC		36.5 ± 0.23	36.5 ± 0.22	36.4 ± 0.23	0.437
SpO2, %		94.0 ± 4.7	96.4 ± 2.5	90.5 ± 5.0	<0.001
Glasgow coma score, n (%)					
≤8		19 (29.2)	3 (7.9)	16 (59.3)	<0.001
9-14		17 (26.2)	10 (26.3)	7 (25.9)	
15		29 (44.6)	25 (65.8)	4 (14.8)	
Complaints, n (%)					
Visual disturbances		59 (90.8)	32 (84.2)	27 (100)	0.037
Gastrointestinal symptoms		42 (64.6)	26 (68.4)	16 (59.3)	0.447
Dyspnea		20 (30.8)	5 (13.2)	15 (55.6)	<0.001
Alcohol consumption habit, n (%)		50 (76.9)	27 (71.1)	23 (85.2)	0.183
Drug misuse and addiction, n (%)		11 (16.9)	5 (13.2)	6 (22.2)	0.337
Time from exposure to hospital arrival, hours, n (%)					
<24		16 (24.6)	12 (31.6)	4 (14.8)	0.044
24-48		36 (55.4)	22 (57.9)	14 (51.9)	
>48		13 (20.0)	4 (10.5)	9 (33.3)	
Door-to-diagnosis time, h, median (IQR)		1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.672
Mechanical ventilation		34 (52.3)	7 (18.4)	27 (100)	<0.001
Treatment, n (%)		Treatment, n (%)	Treatment, n (%)	Treatment, n (%)	
RRT	IHD	40 (61.5)	32 (84.2)	8 (29.6)	<0.001*
	HDF	21 (32.3)	6 (15.8)	15 (55.6)	
Folate		38 (58.5)	27 (71.1)	11 (40.7)	0.015
Ethanol antidote		55 (84.6)	33 (86.8)	22 (81.5)	0.555
Bicarbonate		44 (67.7)	17 (44.7)	27 (100)	<0.001
Door-to-treatment time, h, Median (IQR)					
IHD or HDF		5.0 (3.0-8.0)	5.5 (3.8-9.0)	4.5 (3.0-7.0)	0.221
Folate		13.0 (6.0-16.8)	14.0 (6.0-18.0)	6.0 (6.0-9.5)	0.124
Ethanol		4.0 (2.0-5.0)	4.0 (2.0-4.0)	3.5 (1.0-6.5)	0.905
Bicarbonate		1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	0.564

HDF: Hemodiafiltration, h: hours, IHD: Intermittent hemodialysis, RRT: Renal replacement treatment, SD: Standart division, MAP: Mean Arterial Pressure, SpO2: Oxygen saturation by pulse oximetry, Door-to-diagnosis time: Time from admission to the emergency department to diagnosis of methanol poisoning, Door-to-treatment time: Time from arrival in the emergency department to the start of treatment.*Statistical comparison was made between patients who performed IHD and HDF

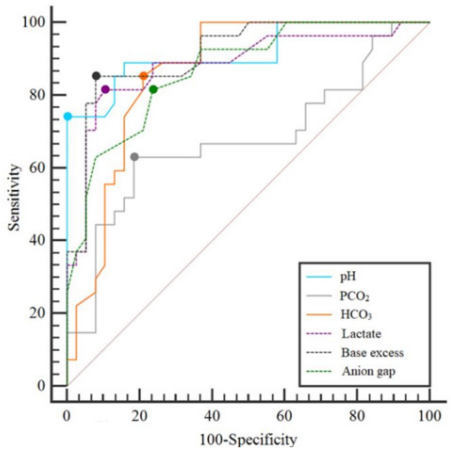

Figure 1: The receiver operating characteristic curve of arterial blood gas analysis parameter

Table 2. Comparison of laboratory parameters of survivors and non-survivors.

Laboratory parameters	Survivor, Median (IQR)	Non-survivor, Median (IQR)	P
pH	7.14 (7.10-7.27)	6.76 (6.69-7.15)	<0.001
PCO2 (mmHg)	29.8 (21.2-36.1)	43.6 (23.4-51.3)	0.015
HCO3 (%)	10.3 (7.0-17.9)	6.3 (5.2-8.8)	<0.001
Lactate (mmol/L)	2.2 (1.8-2.9)	10.2 (2.5-12.3)	<0.001
Base Excess (mmol/L)	-18.6 (-22.9 to -6.5)	-25.0 (-34.4 to -21.2)	<0.001
Anion gap (mEq/L)	25.5 (22.3-28.0)	30.5 (25.3-38.3)	<0.001
HS-Trop T (ng/l)	4.6 (2.0-9.8)	18.6 (14.0-25.1)	0.096
CK (U/L)	155 (97-430)	167 (128-379)	0.984
INR	1.18 (1.04-1.22)	1.38 (1.08-1.63)	<0.001
PTZ (sn)	15.2 (13.6-15.8)	17.9 (14.1-21.8)	<0.001
aPTT (sn)	30.1 (27.8-32.9)	32.4 (29.9-36.6)	<0.001
Glucose (mg/dl))	117 (98-145)	159 (156-215)	<0.001
Creatinine (mg/dl)	0.91 (0.74-1.09)	1.79 (1.37-2.55)	<0.001
AST (U/L)	35.5 (29.8-76.1)	34.1 (25.1-39.7)	0.001
ALT (U/L)	31.1 (24.8-48.7)	18.1 (12.0-29.0)	0.627
Amilaz (U/L)	75 (56-120)	119 (64-211)	0.032
Lipase (U/L)	43 (26-76)	73 (42-105)	0.042
Potassium (mmol/L)	4.6 (3.9-5.7)	5.1 (5.1-5.6)	0.001
Sodium (mmol/L)	140 (136-144)	145 (142-147)	0.001
Calcium (mg/dl)	8.51 (7.95-9.47)	8.62 (7.61-10.18)	0.139
Chloride (mmol/L)	109 (105-112)	111 (108-116)	0.108
Ethanol (mg/dl)	8.0 (2.25-25.8)	5.0 (0.0-7.5)	0.097

aPTT: Activated partial thromboplastin time, CK-MB: Creatinine kinase, HCO3: Bicarbonate, HS-Trop T: High Sensitivity Troponin T, INR: International normalized ratio, PTZ: Prothrombin time, PCO2: Partial Pressure of Carbon Dioxide.

Table 3. Cut-off values for the maximum sensitivity, specificity, PLR, NLR, PPV, and NPV of the arterial blood gas parameters.

	AUC (%95 CI)	Cut-off	Sens. (%95 CI)	Spec. (%95 CI)	PLR (%95 CI)	NLR (%95 CI)	PPV (%95 CI)	NPV (%95 CI)
pH	0.916 (0.820-0.970)	≤6.8	74.1 (53.7-88.9)	100 (90.7-100.0)		0.26 (0.1-0.5)	100 (83.2-100)	84.4 (70.5-93.5)
PCO2	0.678 (0.550-0.788)	>37.4	62.9 (42.4-80.6)	81.6 (65.7-92.3)	3.42 (1.6-7.1)	0.45 (0.3-0.8)	70.8 (48.9-87.4)	75.6 (59.7-87.6)
HCO3	0.865 (0.757-0.937)	≤6.7	85.2 (66.3-95.8)	78.9 (62.7-90.4)	4.05 (2.1-7.6)	0.19 (0.07-0.5)	74.2 (55.4-88.1)	88.2 (72.5-96.7)
Lactate	0.855 (0.781-0.950)	>5.9	81.5 (61.9-93.7)	89.5 (75.2-97.1)	7.74 (3.0-19.9)	0.21 (0.09-0.5)	84.6 (65.1-95.6)	87.2 (72.6-95.7)
Base Excess	0.915 (0.819-0.970)	≤-25	85.2 (66.3-95.8)	92.1 (78.6-98.3)	10.79 (3.6-32.3)	0.16 (0.06-0.4)	88.5 (69.8-97.6)	89.7 (75.8-97.1)
Anion Gap	0.868 (0.762-0.939)	>28	81.5 (61.9-93.7)	76.3 (59.8-88.6)	3.44 (1.9-6.3)	0.24 (0.1-0.5)	71.0 (52.0-85.0)	85.3 (68.9-95.0)

HCO_3: Bicarbonate, NPV: Negative likelihood ratio, NPV: Negative predictive values, PLR: Positive likelihood ratio, PPV: Positive predictive values.

DISCUSSION

In this study, 65 MP cases who visited the ED of a toxicology center over a 5-year period were analyzed. The in-hospital mortality rate was statistically higher in those who visited the ED late and had low GCS and respiratory distress at the time of arrival to the ED. In terms of laboratory, high anion gap metabolic acidosis and high lactate levels were associated with mortality in MP cases. Folate treatment had a statistically significant positive effect on mortality.

The incidence of MP is likely to be underestimated, given the difficulty of making an accurate diagnosis and the lack of diagnostic equipment such as format or methanol level. The mortality rate in MP cases remains high despite medical interventions such as ethanol, bicarbonate and hemodialysis, so clinicians continue to seek appropriate methods

to identify patients at high risk of poor outcomes and develop treatment modalities that will give the best prognosis [7,8].

Methanol poisoning cases occur as isolated episodes or epidemics in different geographies and periods [1,5,9]. In this study, a significant portion of MP cases (78.5%) consisted of patients in three different outbreaks (March 2017, March 2020, and December 2020). The last two MP outbreaks coincided with the COVID-19 pandemic as of the date of their outbreak [10].

After oral administration, methanol reaches peak concentration within 30 to 60 minutes [11]. In contrast, methanol metabolism is slow (8 mg·dl·h) and long latent periods of up to 96 hours can occur, especially if the antidote is ingested with ethanol [12,13]. In our study, the mortality rate in patients who were treated by visiting the ED within the first 24 hours following oral administration was considerably lower than in those who visited later.

Consistent with the literature, a high anion gap metabolic acidosis during the predialysis period was found in our study to be an important prognostic factor in MP cases [5]. Metabolic acidosis in MP has been associated with formic acid accumulation in the early stage [3,14]. In the next period, increased lactic acid production in tissues as a result of inhibition of mitochondrial cytochrome-c oxidase by formic acid, contributes to both anion gap and acidosis [2,15]. In our study, the group of non-survivors had higher median serum lactate values compared to the survivors. Decreased pH due to increased lactate production results in decreased renal excretion of formic acid and increased diffusion of formic acid across the blood-brain barrier [13]. This causes CNS depression [16]. In our study, the presence of low GCS and coma at the time of arrival to the ED was associated with increased mortality, consistent with the literature [8,17]. In our study, 19 (29.2%) of 65 patients were in a coma (GCS<8) when they arrived at the ED, and 16 of these patients died. Besides, as pH decreases, inhibition of cytochrome oxidase becomes stronger and cellular damage accelerates [18]. The putamen is highly susceptible to the resulting cytotoxic hypoxemia [19]. However, brain CT imaging is often normal when performed within the first 24 hours after methanol ingestion [20]. In our study, no pathology was detected in the brain CT and DW-MRI imaging performed at the time of arrival to the ED, however, intracranial hemorrhage was detected in five patients in the imaging performed in the later period. Although it is not routinely recommended in MP cases, neuroradiological imaging of patients who visit the ED with the complaint of changing consciousness is important.

Low Ph levels, low GCS and high formate levels have been reported among poor prognostic indicators. Our hospital cannot measure formate levels, however our study's relationship between folate treatment and mortality was statistically significant. This may be due to the effect of folate on formate metabolism in the early stages of poisoning. In addition, the anion gap can be used in centers where the formate level cannot be measured. Hovda et al. reported that anion gaps and serum formate concentrations were well correlated at admission [21]. Our study observed a higher anion gap in the non-survival group compared to the survivors. Anion and osmolar gaps (OG) can be used in diagnosing and triaging MP cases [21]. However, when calculating the osmolar gap in MP cases, the effect of ethanol, which is likely to be swallowed together with methanol and used in the treatment as an antidote, should not be overlooked. It has also been reported that OG decreases and AG increases as time progresses in MP [21]. The time factor must be taken into account when interpreting these examinations.

The primary purpose of RRT in MP cases is to rapidly remove both main alcohols and toxic acid metabolites. IHD is a preferred treatment modality over HDF because of its faster toxin clearance [22]. As in our study, HDF is generally preferred in hemodynamically unstable patients [23]. The mortality rate in patients who underwent HDF was higher in our study, than in patients who underwent IHD. The reason for this may be that HDF is preferred in patients for unstable before predialysis. Antidote treatment was administered to 86.1% of the patients in our study. Intravenous ethanol was administered to all patients who received antidote treatment except one, because ethanol is an antidote that we can easily access in our hospital compared to fomepizole. However, ethanol has some side effects such as sedation

and respiratory depression. In our study, a statistically significant relationship between the use of ethanol in treatment and mortality could not be established. Dialysis was performed on the patients who visit our ED shortly after starting ethanol treatment. Although ethanol treatment was continued during dialysis, the desired therapeutic level may not have been reached because the ethanol level could not be monitored [12, 24].

Study Limitations: First, this study was designed retrospectively and some patients for whom methanol poisoning was not suspected may have been overlooked. Second, there was a relatively limited number of MP patients and a limited number of cases had a laboratory-confirmed (methanol level >20 mg/deciliter) diagnosis of MP. Diagnosis of a significant group of patients is based on clinical features, other laboratory tests and blood gas analysis. Furthermore, the timing and quality of their interventions may differ.

CONCLUSION

According to the study, low GCS on arrival at the ED, delay in hospital visits, high anion gap metabolic acidosis and elevated lactate levels, were all associated with higher in-hospital mortality rates for MP patients. The use of folate can be considered in treating all MP patients due to its advantages on mortality.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Funding sources: The authors declare that this study has received no financial support

Ethics Committee Approval: This study was approved by the University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital research ethics committee (Date: 07.02.2022, number: 2022/42)

ORCID and Author contribution: **H.A. (0000-0003-3195-1805):** Concept and Design, Data collection, Literature search, Analysis and Interpretation, Manuscript Writing, Critical Review. **F.D. (0000-0003-4720-787X):** Design, Analysis and interpretation. **M.Ö.E. (0000-0001-7325-6646):** Concept, Design, Data Collection. **H.D. (0000-0003-4751-030X):** Literature search, Review, Editing, Supervision. **A.B. (0000-0003-0986-9039):** Critical Review, Editing, Supervision. **A.T. (0000-0002-3889-819X):** Literature search, Manuscript Writing, Critical Review.

Peer-review: Externally peer reviewed.

Acknowledgement: No acknowledgement

REFERENCES

1. Rostrup M, Edwards JK, Abukalish M, Ezzabi M, Some D, Ritter H, et al. The methanol poisoning outbreaks in Libya 2013 and Kenya 2014. PloS One 2016;11(3):e0152676. PMID: 27030969
2. Barceloux DG, Randall Bond G, Krenzelok EP, Cooper H, Allister Vale J. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40:415–46. PMID: 12216995
3. McMartin KE, Makar AB, Martin G, Palese M, Tephly TR. Methanol poisoning. I. The role of formic acid in the development of metabolic acidosis in the monkey and the reversal by 4-methylpyrazole. Biochem Med 1975;13:319-33. PMID:2163
4. McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Brit J Clin Pharmacol. 2016;81(3):505-15. PMID: 26551875
5. Gulen M, Satar S, Avci A, Acehan S, Orhan U, Nazik H. Methanol poisoning in Turkey: Two outbreaks, a single center experience. Alcohol. 2020;88:83-90. PMID: 32702502
6. Aabakken L, Johansen KS, Rydningen EB, Bredesen JE, Ovrebo S, Jacobsen D. Osmolal and anion gaps in patients admitted to an emergency medical department. Hum Ex Toxicol. 1994;13:131-4. PMID: 7908810
7. Mahieu P, Hassoun A, Lauwerys R. Predictors of methanol intoxication with unfavourable outcome. Human Toxicol. 1989;8(2):135-7. PMID: 2501214
8. Liu JJ, Daya MR, Carrasquillo O, Kales SN: Prognostic factors in patients with methanol poisoning. J Toxicol Clin Toxicol. 1998;36:175-81. PMID: 9656972
9. Paasma R, Hovda KE, Hassanian-Moghaddam H, Brahmi N, Afshari R, Sandvik L, et al. Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes – a multicenter study. Clin Toxicol (Phila). 2012;50(9):823–831. PMID: 22992104
10. Hassanian-Moghaddam H, Zamani N, Kolahi AA, McDonald R, Hovda KE. Double trouble: methanol outbreak in the wake of the COVID-19 pandemic in Iran—a cross-sectional assessment. Crit Care, 2020;24(1),402. PMID: 32646475
11. Becker CE. Methanol Poisoning. J Emerg Med. 1983;1(1):51–8. PMID: 6386968
12. Jacobsen D, McMartin KE. Antidotes for methanol and ethylene glycol poisoning. J Toxicol Clin Toxicol. 1997;35(2):127–43. PMID: 9120880
13. Jacobsen D, Webb R, Collins TD, McMartin KE. Methanol and formate kinetics in late diagnosed methanol intoxication. Med Toxicol Adverse Drug Exp. 1988;3(5):418–23. PMID: 3193890
14. Sejersted OM, Jacobsen D, Ovrebo S, Jansen H. (1983). Formate concentrations in plasma from patients poisoned with methanol. Acta Med Scand. 1983;213(2):105-10. PMID: 6837328
15. Kruse, J.A. Methanol Poisoning. Intensive Care Med. 1992;18(7):391–7. PMID: 1469176
16. Smith SR, Smith SJM, Buckley BM. Lactate and Formate in Methanol Poisoning. Lancet 1982;1(8271):561–2. doi: 10.1016/S0140-6736(82)92067-0. PMID: 6120412
17. Kute VB, Godara SM, Shah PR, Gumber MR, Goplani KR, Vanikar AV, et al . Hemodialysis for methyl alcohol poisoning: a single-center experience . Saudi J Kidney Dis Transpl. 2012;23(1):37–43. PMID: 22237216
18. Liesivuori J, Savolainen H. Methanol and Formic Acid Toxicity: Biochemical Mechanisms. Pharmacol Toxicol. 1991;69(3):157–63. PMID: 1665561
19. Hantson P, Duprez T, Mahieu P. Neurotoxicity to the Basal Ganglia Shown by Magnetic Resonance Imaging (MRI) Following Poisoning by Methanol and Other Substances. J Toxicol Clin. Toxicol. 1997;35(2):151–61. PMID: 9120884
20. Kuteifan K, Oesterle´ H, Tajahmady T, Gutbub AM. Laplatte G. Necrosis and Haemorrhage of the Putamen in Methanol Poisoning Shown on MRI. Neuroradiology 1998;40(3):158–60. PMID: 9561519
21. Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: Epidemiology, clinical features, and prognostic signs. J Intern Med 2005;258(2):181-90. PMID: 16018795
22. Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015;43(2):461–72. PMID: 25493973
23. Zakharov S, Rulisek J, Nurieva O, Kotikova K, Navratil T, Komarc M, et al . Intermittent versus continuous renal replacement therapy in acute methanol poisoning: comparison of clinical effectiveness in mass poisoning outbreaks. Ann Intensive Care. 2017;7(1):77. PMID: 28730555
24. Hantson P, Wittebole X, Haufroid V. Ethanol therapy for methanol poisoning: Duration and problems. Eur J Emerg Med. 2002;9(3):278-9. PMID: 12394629