The Value of Clinical, Laboratory and Brain CT Scan Findings in Methanol Toxicity

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Abstract- Methanol poisoning is a severe intoxication that can be fatal. This study aimed to determine the association between clinical and paraclinical findings, particularly brain radiological findings, and the risk of mortality in methanol-poisoned patients. This retrospective cross-sectional study was conducted at the CTD-IRH-MUMS, Mashhad, Iran, from March 2019 to March 2021. Medical and demographic data of adult patients with a confirmed diagnosis of methanol poisoning who had undergone a brain computed tomography (CT) scan were included. A total of 45 methanol-poisoned patients were enrolled in the study, including 36 men (80%) with a mean age of 34.32±13.20 years. Among them, 15 patients (33.3%) had at least one abnormal finding on their brain CT scans. The most frequent finding was diffuse cerebral hemorrhage (n=12, 26.7%), followed by subcortical white matter changes (n=9, 20%), and putaminal hypodensities (n=7, 15.6%). Although abnormal brain CT findings were associated with a higher risk of mortality (OR=4.929, P=0.019), they were not related to any specific type of CT findings. A Glasgow Coma Scale (GCS) score<9 (OR=0.445, *P*=0.003), respiratory rate>19 breaths/min (OR=2.675, *P*=0.006), serum creatinine level>1.8 mg/dL (OR=6.258, *P*=0.009), potassium level>4.3 mEq/L (OR=3.672, *P*=0.006), glucose level (OR=1.011, *P*=0.019), bicarbonate level<11.4 mEq/L (OR=0.872, *P*=0.003), and pH<7.11 (OR=0.001, *P*=0.003) were predictors of mortality with acceptable sensitivity and specificity. Lower GCS, PCO2, and HCO3 levels, along with higher blood pressure, were associated with a higher incidence of pathological brain CT findings. Physicians should consider acidosis, tachypnea, decreased consciousness, and elevated blood glucose and creatinine levels as predictors of mortality or pathological brain CT findings.

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Introduction

Methanol, also known as methyl alcohol, is an essential organic chemical widely used as an industrial, agricultural, and household agent (1). The potentially lethal dose of methanol is reported to be 30 to 240 mL, or 1 g/kg. Methanol exerts its toxic effects through metabolism to formaldehyde and subsequently to formic

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acid, which eventually leads to oxidative injury (2).

Most reported cases of methanol poisoning result from accidental or suicidal ingestion (3,4). The mortality rate in hospitalized patients has ranged from 18% to 30% in previous studies (5-7) A recent cross-sectional study of 795 patients in Iran reported a mortality rate of 10.6% among methanol-poisoned patients during the COVID-19 pandemic (8). The surge of COVID-19 and increased availability of alcohol, besides misinformation, led to an outbreak of methanol poisoning cases, which were likely caused by gargling or drinking alcohol (8-12).

Although in the first 12 to 24 hours post-exposure, presentation can be normal, the most common signs of acute methanol poisoning include a variety of symptoms based on the amount of methanol administration such as weakness, blurred vision, nausea, vomiting, epigastric pain, central nervous system (CNS) depression, stupor, coma, and death (13,14). Considering the neurotoxic effects of methanol metabolites, neuroimaging can play a key role in ruling out differential diagnoses.

Regarding the neurotoxic effects of methanol metabolites on the nervous system, neuroimaging can play a key role to rule out differential diagnoses. Some non-specific findings were reported in the brain imaging of methanol-poisoned patients (15-20). One of the most finding is putaminal necrosis, which may lead to common complication of methanol poisoning, motor dysfunction in survivors (21,22). However, there are a few reports of a relationship between this finding and the mortality of patients.

We conducted the present study to describe an association between the brain CT findings of acute methanol intoxication and the mortality incidence. We also evaluated the predictive value of clinical, laboratory and pathological finding in brain CT scan and mortality rate of methanol poisoned cases.

Materials and Methods

Study design and setting

This retrospective cross-sectional study was designed to investigate the clinical, laboratory, and brain radiological findings in methanol-poisoned patients referred to a tertiary care center in northeastern Iran, the Clinical Toxicology Department of Imam Reza Hospital, affiliated with Mashhad University of Medical Sciences (CTD-IRH-MUMS), Mashhad, Iran, from March 2019 to March 2021. All patients over 18 years old with a definite diagnosis ofmethanol poisoning who underwent a brain computed tomography scan (CT scan) were included in the study by census sampling. Patients who expired before diagnostic investigations or had incomplete medical documentation were excluded from the final analysis. The study protocol was approved by the Mashhad University of Medical Sciences Ethics Committee, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1399.471). The patient information was kept confidential during the investigation by adding codes and deleting their names. All methods were carried out in accordance with the relevant guidelines and regulations.

Data collection

Data were collected using a checklist and evaluating the patient's medical records, laboratory data, and radiologic workup. Demographic characteristics (sex, age, past medical history, admission outcome), type of poisoning (intentional or unintentional), and details regarding the toxic alcohol (type, packaging, and source of supply) were collected. Admission clinical findings including pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), visual impairment, visual acuity, pupillary status, and Glasgow Coma Scale (GCS) score were recorded Laboratory data, including blood ethanol and methanol levels, serum levels of creatinine, urea, sodium, potassium, and calcium, blood glucose (BG), blood gas status, and brain CT findings, were gathered and analyzed. CT scans were independently interpreted by two experts. If there was a disagreement in their reports, the brain CT scan was evaluated by the third expert radiologist. All brain CT scans were performed using a NeuViz Classic 16-slice CT scanner system with a standard protocol.

Statistical analysis

Statistical analysis was conducted using SPSS software version 11.5 (SPSS Inc., Chicago, USA –version 11.5). Descriptive statistics for the demographic characteristics were presented by the median, maximum, minimum, mean, and standard deviation (SD) for quantitative variables and frequency (percentage) for qualitative variables. Fisher's exact test and logistic regression analysis were used to investigate relationships between qualitative variables.

The comparison of quantitative data was performed by independent sample t-test or Mann-Whitney U tests.

For each clinical and laboratory variable, receiver operating characteristic (ROC) curves for mortality and CT findings were generated, and the area under the curve (AUC) with a 95% confidence interval (95% CI) was calculated. Then, the diagnostic sensitivity and specificity

using MedCalc software (version 22.001) were estimated. Variables with AUC>0.7 were identified as potential diagnostics. A *P* less than 0.05 was considered as the significance level.

Results

Based on the study inclusion and exclusion criteria, 45 methanol-poisoned patients were enrolled, of whom 36 (80%) were male. The mean age of the patients was 34.32±13.20 years (range, 18-72 years). Thirty-nine patients (86.7%) had consumed homemade alcohol, 17 (37.8%) obtained it from bootleggers, and 38 (84.4%) stated that there was no registered packaging for the consumed alcohol (Table 1).

Although 36 patients (80%) had no past medical history, hypertension was the most frequent underlying medical condition in the study population (n=3, 6.7%) (Table 2).

Visual impairment (n=26, 57.8%), loss of consciousness (n=25, 55.6%), and nausea and vomiting (n = 21, 46.7%) were the most frequent chief complaints, in descending order. While 16 patients (35.6%) with visual impairment reported blurred vision, normal visual acuity was documented in 13 (28.9%) patients.

Pupillary mydriasis was observed in most patients (n=14, 31.1%) (n=14, 31.1%). The analyzed data revealed that 16 patients (35.6%) expired (Table 2).

The GCS score on admission was 13 to 15 in 19 patients (48.7%). There was a significant difference between GCS levels in survivors and non-survivors (*P*<0.001) groups and the lower GCS was significantly associated with a higher mortality rate (OR=0.445, CI: 0.260-0.763, *P*=0.006) (Table 3). The motor component of the GCS was more critical than the other two components. A GCS score of less than 9 predicted mortality with high sensitivity and specificity (Table 4).

Among the vital signs, only the respiratory rate was significantly associated with mortality (OR=2.675, 95% CI: 1.325-5.395, *P*=0.006) (Table 3). Furthermore, patients who presented with dyspnea had a significantly higher mortality rate (OR=20.0, 95% CI: 2.009-199.73, *P*=0.005). A respiratory rate of more than 19 cycles/min could predict mortality with high sensitivity and specificity (Table 4).

The mean blood methanol level was 21.12±33.11 mg/dL, the blood ethanol level was 19.94±20.96 mg/dL, and the mean pH was 7.20±0.21 (Table 5). The non-survivors' cases had higher creatinine, potassium, and glucose blood levels, and lower PH, and HCO3 serum levels (Table 5). Higher levels of potassium (OR=3.672, 95% CI: 1.443-9.345, *P*=0.006), glucose (OR=1.011, 95% CI: 1.002-1.020, *P*=0.019), and creatinine (OR=6.258, 95% CI: 1.59-24.58, *P*=0.009), along with lower levels of HCO3 (OR=0.872, 95% CI: 0.797-0.953, *P*=0.003) and pH (OR=0.001, 95% CI: 0.00-0.109, *P*=0.003), were associated with a higher risk of mortality (Tables 4 and 5). However, the exact the blood PCO2 level was not a suitable predictor of mortality. Based on the data recorded on patients' documents, 18(40%) cases underwent emergency dialysis, and 7(15.6%) of them underwent the second time hemodialysis. The median time of the first dialysis was 14 hours (IQR=6-24) post-hospitalization, and the median time of the second dialysis was 24 hours (IQR=12-46) post-hospitalization.

Among the 45 brain CT scans evaluated, 15 patients (33.3%) had at least one abnormal finding on tomography. The most frequent abnormal findings were diffuse cerebral hemorrhage (n=12, 26.7%), subcortical white matter changes (WMCs) (n=9, 20%), and putaminal hypodensities (n=7, 15.6%). Other less prevalent abnormalities included cerebellar hypodensity, as well as intraventricular, intracranial, and putaminal hemorrhages (Table 6).

Although logistic regression analysis predicted the mortality rate of methanol poisoning based on the presence of abnormal brain CT findings (OR=4.929, 95% CI: 1.297-18.733; *P*=0.019), there was no significant relationship between any specific type of brain CT finding and mortality (*P*>0.05) (Table 6). The frequency of various types of brain CT findings was not different in both sexes, patients with and without convulsion, nausea and vomiting, and respiratory distress.

The presence of significant pathological findings on brain CT was more likely in patients with higher systolic blood pressure (OR=1.037, 95% CI: 1.003-1.072, *P*=0.035), lower PCO2 (OR=0.940, 95% CI: 0.8920.991, *P*=0.022), and lower HCO3 levels (OR=0.923, 95% CI: 0.854-0.997, *P*=0.042) (Table 7). Hypocapnia (PCO2<32.4 mmHg) was a sensitive indicator of the presence of various pathological findings on brain CT scans in methanol-poisoned patients (Table 4).

Table 1. Type of intoxication, and the route of the alcohol preparation of the methanol-poisoned patients

		frequency (percentage)
Type of Intoxication	Incidental	39(86.7)
	Unknown	6(13.3)
The route of alcohol preparation	Alcohol Dealer	17(37.8)
	Unknown	17(37.8)
	Illegal Seller	6(13.3)
	Cosmetics Store	2(4.4)
	Peddler	2(4.4)
	Drug store	1(2.2)

Table 2. Clinical presentations, underlying diseases, and outcomes of the methanol-poisoned patients

	Variables		Frequency (%)	
Chief complain		Seizure	3(6.7)	
		Impaired Consciousness	25(55.6)	
		Nausea and Vomiting	21(46.7)	
		Alcohol Breath	17(37.8)	
		Gastric Pain	10(22.2)	
		Shortness of Breath	6(13.3)	
	Visual Impairment	blurred vision	16(35.6)	26(57.8)
		Scotoma	2(4.4)	
		Halos Vision	2(4.4)	
		Color Vision Deficiency	1(2.2)	
		Others	5(11.1)	
Vision Acuity		Normal	13(28.9)	
		Counting fingers	2(4.4)	
		Hand Motion	2(4.4)	
		Light Perception	1(2.2)	
		Light Imperceptions	1(2.2)	
		Un-assessable	8(17.8)	
Status of Pupils		Normal	12(26.7)	
		Mydriasis	14(31.1)	
		Miosis	7(15.6)	
		Not Reactive to Light	1(2.2)	
		Un-assessable	1(2.2)	
Underlying disease/ co-morbidity		Hypertension	3(6.7)	
		Diabetes Mellitus	2(4.4)	
		Seizure	2(4.4)	
		Face Trauma	2(4.4)	
		Psychological Complications	1(2.2)	
		Renal Lithiasis	1(2.2)	
		Chronic Kidney Disease (CKD)	1(2.2)	
		Cardiovascular Disease	1(2.2)	
		Chronic Obstructive Pulmonary Disease (COPD)	1(2.2)	
		Tramadol abuse	1(2.2)	
		Opioid dependent	2(4.4)	
Outcome		Discharged	21(46.7)	
		Death	16(35.6)	
		Discharged by Personal Consent	8(17.8)	

Table 3. The association between patients' clinical manifestations and the risk of mortality in the methanol poisoned patients

			Comparing		Logistic regression	
variable	**Outcome**	**Mean (SD)**	**Median (Min-Max)**	**PV**	**OR(95%CI)**	**PV**
GCS total	Survivors	13.16(2.14)	14.00(8-15)		0.445(0.260-0.763)	0.003
	Non-survivors	5.86(3.21)	4.5(3-13)	<0.001NP		
	Total	10.54(4.36)	11.0(3-15)			
GCS (EYE)	Survivors	3.4(0.76)	4.00(2-4)		0.052(0.007-0.373)	0.003
	Non-survivors	1.0(0.65)	1.00(1-3)	<0.001		
	Total	2.72(1.17)	3.00(1-4)			
GCS (Verbal)	Survivors	4.12(0.971)	4.00(2-5)		0.147(0.044-0.495)	0.002
	Non-survivors	1.79(1.051)	1.00(1-4)	<0.001		
	Total	3.28(1.5)	3.00(1-5)			
GCS (Motor)	Survivors	5.60(0.707)	6.00(4-6)		0.184(0.066-0.509)	0.001
	Non-survivors	2.57(1.604)	2.5(1-6)	<0.001 NP		
	Total	4.51(1.83)	5.00(1-6)			
Systolic blood pressure	Survivors	123.5(17.43)	120.00(90-160)	0.739 NP		0.658
	Non-survivors	127.0(34.84)	121.00(60.185)		1.006(0.979-1.035)	
	Total	124.60(23.78)	120.50(60-185)			
Diastolic blood pressure	Survivors	76.34(11.17)	73.00 (55-110)	0.338	1.025(0.975-1.078)	0.334
	Non-survivors	80.83(18.07)	80.00(50-120)			
	Total	77.66(13.47)	77.00(50-120)			
Pulse rate	Survivors	91.24(16.57)	88.00(60-126)	0.372 NP		0.264
	Non-survivors	99.38(29.96)	95.00(50-163)		1.018(0.987-1.050)	
	Total	93.76(21.56)	89.00(50-163)			
Respiratory rate	Survivors	17.59(1.74)	18.00(12-21)	0.001	2.675(1.325- 5.395)	0.006
	Non-survivors	20.67(3.87)	20.00(17-32)			
	Total	18.49(2.87)	18.00(12-32)			

NP=Nan parametric test

Table 4. Sensitivity and Specificity of different clinical and laboratory findings of methanol poisoned patients for mortality and brain CT findings

Variable	prediction	Associated criterion	Sensitivity (95% CI)	Specificity (95% CI)	+ likelihood ratio (95% CI)	Area under the ROC curve (AUC)	Significance level P (Area=0.5)
GCS	mortality	≤9	85.71 (57.2-98.2)	96.00 (79.6-99.9)	21.43 (3.10-147.97)	0.96	<0.0001
Respiratory rate	mortality	>19	75.00 (42.8-94.5)	89.66 (72.6-97.8)	7.25 (2.37-22.22)	0.83	<0.0001
Creatinine	mortality	>1.8	53.33 (26.6-78.7)	96.43 (81.7-99.9)	14.93 (2.06-108.38)	0.82	<0.0001
HCO3	mortality	≤11.4	62.50 (35.4-84.8)	89.66 (72.6-97.8)	6.04 (1.94-18.83)	0.77	0.0016
PH	mortality	≤7.11	62.50 (35.4-84.8)	93.10 (77.2-99.2)	9.06 (2.26-36.39)	0.76	0.0052
PCo2	Cerebellar Hypo-densities	≤32.4	100.00 (15.8-100.0)	75.61 (59.7-87.6)	4.10 (2.39-7.03)	0.76	0.0001
PCO2	CT finding	≤36.2	71.43 (41.9-91.6)	68.97 (49.2-84.7)	2.30 (1.22-4.35)	0.75	0.0015
PCO2	Diffuse Cerebral Hemorrhage	≤36.2	81.82 (48.2-97.7)	68.75 (46.8-81.4)	2.62 (1.46-4.70)	0.78	0.0005
PCO2	Putamen Hypo-densities	≤34.4	83.33 (35.9-99.6)	77.78 (60.8-89.9)	3.75 (1.85-7.61)	0.83	0.0001
PCO2	Subcortical White Matter Changes	≤32.4	75.00 (34.9-96.8)	82.86 (66.4-93.4)	4.38 (1.91-10.04)	0.84	<0.0001
Potassium	mortality	>4.3	75.00 (47.6-92.7)	88.89 (70.8-97.6)	6.75 (2.24-20.35)	0.79	0.0007

Table 5. The association between patients' laboratory data and the risk of mortality in the methanol poisoned patients

		Compare means			Logisric regression	
variable	**outcome**	**Mean(SD)**	**Median(Min-Max)**	**PV**	**OR(95%CI)**	**PV**
Creatinine	Survivors	1.03(0.440)	0.900(0.5-2.4)	0.007 NP	6.258(1.59-24.58)	0.009
	Non-survivors	2.26(1.58)	1.85(0.8-6.0)			
	Total	1.48(1.16)	1.05(0.5-6.0)			
Urea	Survivors	30.25(13.64)	29.5(10-66)	0.089 NP	1.03(0.993-1.069)	0.109
	Non-survivors	60.62(66.28)	35.00(14-250)			
	Total	41.30(43.12)	29.50(10-250)			
sodium	Survivors	140.1(3.16)	140.00(135-149)	0.708 NP	0.972(0.864-1.094)	0.637
	Non-survivors	139.25(8.31)	140.00(128-163)			
	Total	139.80(5.56)	140.00(128-163)			
potassium	Survivors	4.02(0.69)	4.00(3-6.7)	0.001	3.672(1.443-9.345)	0.006
	Non-survivors	4.95(1.03)	4.90(3.6.60)			
	Total	4.36(0.94)	4.20(3-6.70)			
calcium	Survivors	8.74(0.48)	8.80(8.0-9.6)	0.63 NP	0.170(0.29-0.992)	0.49
	Non-survivors	7.75(1.13)	7.5(6.0-9.6)			
	Total	8.37(0.90)	8.50(6.0-9.6)			
Glucose	Survivors	123.5(52.78)	111.50(64.0-287.0)	0.031 NP	1.011(1.002-1.020)	0.019
	Non-survivors	193.0(108.10)	108.0(49.0-365.0)			
	Total	148.92(83.52)	115.0(49.0-365.0)			
PH	Survivors	7.29(0.11)	7.31(70.5-7.45)	0.004 NP	0.001(0.000015 - 0.1.09)	0.003
	Non-survivors	7.05(0.28)	7.06(6.61-7.48)			
	Total	7.21(0.22)	7.28(6.61-7.48)			
PCO2	Survivors	42.49(13.75)	39.30(14.1-78.4)	0.302	0.978(0.938-1.021)	0.314
	Non-survivors	37.73(17.58)	38.2(9.8-70.9)			
	Total	40.79(15.15)	39.30(9.8-70.9)			
HCO3	Survivors	21.13(6.78)	22.10(4.00-29.1)	0.001	0.872(0.797-0.953)	0.003
	Non-survivors	12.34(8.95)	8.85(2.7-30.6)			
	Total	18.00(8.64)	1940(2.70-29.1)			

NP=Nan parametric test

Table 6. Frequency of Brain CT scan findings of the methanol poisoned patients and the relationship with mortality

CT-scan findings	Number (%)	OR (95%CI)	P-Value
Abnormal Brain CT-scan Findings	15(33.33)	4.929(1.297-18.733)	0.019
Diffuse Cerebral Hemorrhage	12(26.66)	3.733(0.939-14.837)	0.061
Subcortical White Matter Changes	9(20)	2.841(0.638-12.654)	0.171
Putamen Hypo-densities	7(15.55)	2.889(0.557-14.980)	0.206
Intra Cranial Hemorrhage	4(8.88)	1.929(0.245-15.185)	0.533
Putamen Hemorrhage	3(6.66)	0.900(0.075-10769)	0.934
Cerebellar Hypo-densities	2(4.44)	1.867(0.109-32.009)	0.667

OR=Odds ratio for mortality, CI= 95% Confidence interval

Table 7. The association between patients' clinical manifestations and laboratory data with the risk of positive brain CT findings in the methanol poisoned patients

		Compare means			Logistic regression	
variable	**CT finding**	**Mean(SD)**	**Median(Min-Max)**	**PV**	**B(CI)**	**PV**
GCS	Positive	9.58(4.21)	9.50(3-15)	0.368	0.929(0.795-1.09)	0.359
	Negative	10.96(4.33)	13.00(3-15)			
Systolic blood pressure	Positive	136.21(26.97)	130.50(100-185)	0.023	1.037(1.003-1.072)	0.035
	Negative	118.79(20.1)	12.00(60-160)			
Diastolic blood pressure	Positive	80.36(19.26)	78.50(50-120)	0.463 NP	1.023(0.974-1.074)	0.358
	Negative	76.26(9.35)	75.00(55-95)			
Pulse rate	Positive	103.29(24.53)	95.00(78-163)	0.041	1.034 (0.999-1.071)	0.059
	Negative	89.0(18.59)	88.00(20-126)			
Respiratory rate	Positive	19.36(3.84)	18.00(12-23)	0.166	1.192(0.906-1.568)	0.211
	Negative	18.04(2.18)	18.00(16-32)			
Creatinine	Positive	1.62(1.01)	1.30(0.6-4.2)	0.583	1.161(0.688-1.960)	0.577
	Negative	1.41(1.25)	1.00(0.5-6.0)			
Urea	Positive	37.80(20.99)	30.0(10-86)	0.704	0.997(0.981-1.013)	0.699
	Negative	43.13(51.23)	29.00(10.0-250.0)			
sodium	Positive	138.4(8.18)	137.00(128-163)	0.243	0.922(0.803-1.057)	0.244
	Negative	140.5(3.56)	141.00(132-149)			
potassium	Positive	4.45(1.05)	4.15(3-6.60)	0.682	1.154(0.592-2.251)	0.675
	Negative	4.32(0.89)	4.60(3.0-6.7)			
calcium	Positive	8.67(0.72)	8.65(7.5-9.6)	0.551	1.480(0.434-5.027)	0.530
	Negative	8.29(0.98)	8.50(6.0-9.6)			
Glucose	Positive	164.07(96.95)	118(83-365)	0.410	1.0003(0.996-1.011)	0.402
	Negative	141.07(76.46)	112.0(49-315)			
PH	Positive	7.176(0.234)	7.21(6.71-7.48)	0.522	0.390(0.023-6.570)	0.514
	Negative	7.221(0.211)	7.30(6.61-7.45)			
PCO2	Positive	33.04(12.65)	34.40(9.80-52.60)	0.013	0.940(0.892-0.991)	0.022
	Negative	44.68(14.99)	42.55(17.30-78.40)			
HCO3	Positive	14.21(9.10)	17.00(3.40-30.60)	0.036	0.923(0.854-0.997)	0.042
	Negative	19.90(7.87)	21.250(2.70-32.40)			

NP=Nan parametric test

Discussion

The current study was conducted on methanol-poisoned patients to verify the association between clinical presentations and brain CT scan findings. All patients in the current study were poisoned after consuming alcoholic beverages, with the main complaints of visual and consciousness impairment, nausea, and vomiting, respectively. Visual impairment affected about 60% of the patients. Among them, 61.5% stated that they have blurred vision. Prevalence of various presentations in the current study (Table 2) is similar to Mahdavi et al., study that was a multi-center study on methanol poisoned cases from all parts of Iran (8). In a review study, blurred vision combined with intact consciousness was identified as a strong indicator of methanol intoxication (23). The visual acuity in the most cases of the current research was normal (28.9%). Considering the pupils' status, most patients had mydriasis, consistent with multiple studies reporting mydriasis, including delayed or non-reactive mydriasis to light, as a common presentation in Methanol-poisoned cases (23-25). Ocular symptoms of methanol poisoning are considered the consequence of retinal and optic nerve damage caused by the inhibition of cytochrome oxidase activity and mitochondrial impairment (26,27).

In our study, lower GCS levels were significantly associated with fatal outcomes (OR=0.445). Other studies also mentioned that a lower GCS<8-9 is a predictor of poor prognosis in methanol-poisoned patients (6,8,22,23,28).

According to our results, the higher levels of creatinine, potassium, glucose, and lower levels of PH and bicarbonate were associated with higher mortality risk, consistent with previous cross-sectional studies (16, 22,23,28,29). In a case series study of 51 methanol-poisoned patients from Norway, severe metabolic acidosis (pH<6.90, base defect>28 mmol/L), and elevated pCO2 level were significant predictors of poor prognosis in these cases (6). The difference in the predictive role of PCO2 might be due to the differing mean levels between our study and the Norwegian study (52.62 mmHg vs. 99.75 mmHg). Respiratory arrest, hyperglycemia, and delayed hospital admission were recognized as risk factors for poor prognosis in methanol-poisoned patients in a retrospective cross-sectional study conducting in Sanandaj, Iran, over eight years (30). Interestingly, a study from Iran on 95 methanol-poisoned patients over seven years claimed that hyperglycemia could be a valuable prognostic factor (31) which was in line with our finding that higher blood glucose was associated with fatal outcomes .

A study from the Czech Republic on 46 methanol-poisoned patients announced the higher prevalence of hemorrhagic brain lesions among radiological abnormalities, which was similar to our study. They mentioned that those with hemorrhagic brain lesions were more acidemic and had higher levels of glycemia and lactacidemia on admission than those without hemorrhages (32).

Regarding the guidelines, subjects with serum methanol levels higher than 20 mg/dl are considered as methanol-poisoned patients (27). In our study, the mean detected methanol level was 21.12±33.11 mg/dL, less than previous studies (6,29,33). Although high blood methanol levels were regarded as poor prognostic factors in a retrospective case series study of 147 methanol-poisoned patients in Estonia (34), it could not be counted as a prognostic factor according to some other investigations (22,23). This disparity can be explained by different ingested methanol amounts and delay hospital admission. Since methanol is metabolized to formic acid over time, serum methanol levels may not accurately reflect the severity of toxicity (35). Formic acid is a sensitive marker for methanol poisoning confirmation. While formic acid levels≥50 mg/dl have been linked to extreme toxicity, a 90% mortality risk has been pointed out in patients with≥315 mg/dl formic acid (2,36).

Hemodialysis may reduce the patient's hospital stay through elimination of methanol and formic acid and correcting metabolic acidosis (37). In the current study, 40% of patients underwent emergency dialysis, while 15.6% underwent second-time hemodialysis. In a cross-sectional study of 795 methanol-poisoned patients from different provinces of Iran during the COVID-19 pandemic, a higher rate of second-time hemodialysis was found in non-survivor than survivor groups (8). In a retrospective study on 30 methanol-poisoned patients in Tehran, Iran, 14(46%) had undergone hemodialysis by the median time interval of 4 hours after hospitalization, of whom four patients died. However, no significant association was found between hemodialysis and patient outcomes (7). In another retrospective cohort study from the U.S. on 603 methanol-poisoned patients, about 40% needed life-supporting treatments for renal failures, such as hemodialysis (38).

In the present study, most patients had normal CT findings, but among those with abnormalities, diffuse cerebral hemorrhage was the most prevalent, followed by subcortical white matter changes and putamen hypodensities. We observed a significant correlation between abnormal brain CT findings and the methanol

poisoning mortality rate (OR=4.929), while none of the specific CT findings was associated with a higher risk of mortality. Previous studies have reported distinctive brain radiological manifestations in methanol intoxication, including brain and cerebellar edema, subarachnoid and intracerebral hemorrhage, putaminal and cerebral white matter hypodensities, and focal lesions in the cerebellum, globus pallidus, and hypothalamus (15-17,39,40). Basal ganglion necrosis is now acknowledged as the most radiological characteristic presentation in methanol-poisoned patients (41-43), especially the putamen (hemorrhagic or non-hemorrhagic) necrosis that has been widely reported as a CT and/or MRI manifestation (21,44,45). In a cross-sectional study from Iran, 40 patients out of 516 participants underwent CT scanning, and it was declared that the putaminal or subcortical white matter hemorrhage could be regarded as a mortality indicator in methanol-poisoned patients (22). Also, a cohort study in Iran on 42 methanol-poisoned patients reported bilateral putaminal hypodensity as the most common CT presentation and insisted that there was a significant association between necrosis of insular subcortex white matter and putaminal hemorrhage and the poor prognosis of methanol poisoning (16). Surprisingly, a case report of methanol toxicity from Turkey did not present any pathological feature of the basal ganglia MRI (46).

In the current study, we assessed the association of clinical manifestations, laboratory findings, and radiological presentations with mortality due to methanol poisoning. It was revealed that lower GCS (<9), higher respiratory rate (>19 cycles/min), higher levels of creatinine (1.8mg/dl), potassium (4.3 mEq/L), and glucose, and lower levels of PH (<7.11) and bicarbonate (<11.4 mEq/L) could be considered key indicators of mortality.with efficient sensitivity and specificity. The presence of abnormal brain CT findings was associated with a higher mortality risk (4.929), but none of the specific CT findings was associated with fatal outcomes. These findings can help physicians in the early and effective triage and treatment of methanol-poisoned patients based on their clinical and subclinical manifestations. The high prevalence of methanol poisoning in Iran and the paucity of research on this topic highlight the necessity of conducting further large-scale studies to explain the prognostic factors in methanol poisoning.

Limitations

Although our study had several strengths, including there were some limitations in this study.

The osmolar gap and formic acid levels were not evaluated due to a lack of laboratory equipment, even though they were reported as valuable indicators (2,35).

The retrospective cross-sectional design of the study may limit the ability to establish causality between variables, and future studies would benefit from a prospective design. However, nearly all of the similar studies were done retrospectively (7,16,29,30,32,39).

Despite the availability of data for most of the patients, the long-term outcomes of patients could not be determined as it was a cross-sectional study.

We only evaluated the clinical, paraclinical, and outcome of the patients who have undergone the brain CT scan, thus we mostly evaluated moderate to severe cases.

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