Original Article

Prevalence of clinical and radiologic features in methanol-poisoned patients with and without COVID-19 infection

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Aim: The aim of the current study was to evaluate the prevalence of coronavirus disease (COVID-19) in methanol-poisoned patients admitted to two toxicology academic centers during the COVID-19 outbreak and determine their clinical features and chest/brain computed tomography (CT) findings.

Methods: Methanol-poisoned patients who had been referred during the COVID-19 pandemic were evaluated for signs and symptoms of COVID-19 by chest CT scans and/or polymerase chain reaction test.

Results: A total of 62 patients with confirmed methanol poisoning were enrolled in the study, with a median (interquartile range) age of 35 (28–44) years. Thirty-nine (62.9%) survived. Nine (14.5%) were diagnosed to have COVID-19, of whom four survived. There was a significant correlation between COVID-19 disease and a history of alcohol consumption ($p = 0.036$; odds ratio 1.7; 95% confidence interval, 1.3–2.2). Univariate analysis showed significant differences between infected and noninfected patients regarding their urea and time for first and second hemodialysis sessions, as well as the duration of ethanol administration.

Conclusions: In conclusion, during the pandemic, specific attention should be paid to patients with a history of alcohol ingestion and elevated creatinine, loss of consciousness, and severe acidosis as these signs/symptoms could be present in both COVID-19 and methanol poisoning, making differentiation between the two challenging.

Key words: COVID-19 disease, methanol poisoning, outbreak, SARS-CoV-2 infection

INTRODUCTION

METHANOL IS MAINLY used as a solvent in industry. It is not a toxic substance, per se. In fact, detrimental effects of methanol are exerted through its conversion into formaldehyde and formic acid.[1] Signs and symptoms of methanol poisoning include headache, vertigo, altered visual acuity, nausea, vomiting, loss of consciousness, coma, and death. It can also cause necrosis of the ophthalmic nerve, leading to permanent visual sequelae as well as neurological damage.[1,2] The most common route of methanol poisoning is drinking adulterated alcoholic beverages supplied by illegal producers. However, there are also reports of methanol poisoning due to accidental or occupational exposure.[3,4]

Alcohol consumption is prohibited in Iran due to religious restrictions. Methanol poisoning outbreaks happen occasionally in this country, but they tend to occur more frequently and on a larger scale when different crises make access to alcohol even more difficult.[5] In Iran, an outbreak of

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methanol poisoning was triggered by the coronavirus disease (COVID-19) pandemic in early March 2020 (Fig. 1).[5] People believed that drinking alcohol would prevent this infection.[6] The outbreak was found to be so huge when it was announced that the death toll due to methanol poisoning surpassed the deaths due to COVID-19 in Khuzestan (a province of Iran).[7]

In the current study, we aimed to determine the course and outcome of methanol-poisoned patients who were also infected with severe acute respiratory syndrome corona virus 2

(SARS-CoV-2). As a second aim, we compared alcohol-intoxicated patients with and without COVID-19 to determine the possible risk factors that could help considering this diagnosis in our patients. Brain and chest computed tomography (CT) scan findings of the patients were also evaluated and reported accordingly.

METHODS

Study design and setting

THIS STUDY WAS retrospectively undertaken between March and June 2020. The data were gathered from patients admitted to two toxicology referral centers in Iran, Loghman Hakim Hospital in Tehran and Alzahra Hospital in Isfahan.

Patient selection

All patients who had been diagnosed with methanol poisoning and had undergone brain or chest CT scanning due to loss of consciousness or respiratory manifestations were enrolled. Diagnosis of methanol poisoning was made by patients' history, detection of acidosis in venous blood gas analysis, and high methanol level (where available). Due to the COVID-19 pandemic, all admitted patients were initially screened to rule in/out COVID-19 based on: (i) history of significant and high-risk exposure to a patient with confirmed or suspected COVID-19 during the 3 weeks prior to admission, and/or (ii) at least one of the following manifestations: radiation contactless body temperature of 37.8°C or higher, respiratory rate of 24 breaths/min or more, cough, shortness of breath, nasal congestion/ discharge, myalgia/ arthralgia, diarrhea/vomiting, headache, or fatigue on admission.

Inclusion criteria

The patients with one or both of the above-mentioned findings were further evaluated to confirm COVID-19 disease using reverse transcription–polymerase chain reaction (PCR) (W-RR-0479-02; Liferiver Bio-Tech, Shanghai, China) for *E*, *N*, and *Rdrp* genes on nasopharyngeal specimen and/or chest CT scan looking for the typical findings of COVID-19 pneumonitis. An infectious disease specialist made the diagnosis of concomitant COVID-19 in the methanol-poisoned patients.

According to the Radiological Society of North America consensus statement, the typical chest CT scan findings for diagnosis of COVID-19 disease were: (i) peripheral bilateral ground glass opacities and/or consolidation or crazy paving, (ii) multifocal ground glass opacities of rounded morphology and/or consolidation or crazy paving pattern, (iii)

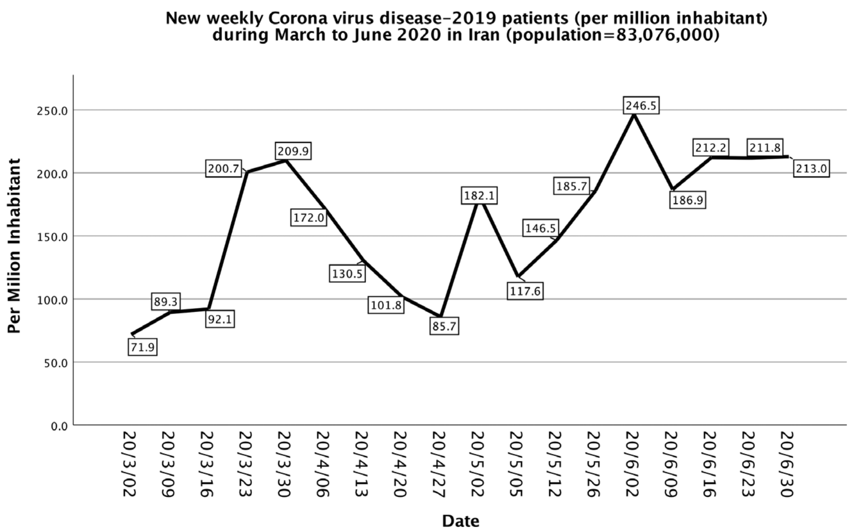

Fig. 1. New weekly COVID-19 cases (per million inhabitants) in Iran (population 83,076,000), March–June 2020.

reverse halo sign or other findings of organizing pneumonia.[8]

The radiologist reported COVID-19 pneumonitis to be positive or negative based on the previous reports on typical CT findings.

Data collection

Data was collected using a questionnaire and by evaluation of the patients' electronic records, laboratory data, and radiologic work-up. The data collected included demographic characteristics (age, sex, intention for alcohol consumption, history of regular alcohol consumption, and history of comorbidities), time and amount of alcohol consumption, time elapsed between alcohol ingestion and hospital presentation/admission, Glasgow Coma Scale (GCS) on admission, signs and symptoms and selected laboratory test results on presentation, need for and time of initiation of ethanol, time and number of sessions of hemodialysis, chest and brain CT scan findings, concurrent COVID-19 and method of its diagnosis (PCR or chest CT scan), duration of hospital stay, and final outcome (death vs. recovery).

Statistical analysis

The data were then analyzed using SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY) by application of the Kolmogorov–Smirnov test, χ^2-test, Mann–Whitney *U*-test, and *t*-test. Kolmogorov–Smirnov was used to evaluate the distribution pattern of the variables. Data with normal distribution are shown using mean ± standard deviation, and nonparametric variables are shown as median and interquartile range. The χ^2-test was used to find significant differences among qualitative variables. To find significant differences among quantitative and nonparametric variables with normal distribution, the *t*-test and Mann–Whitney *U*-test were used, respectively. Significant findings were defined by *p*-values of 0.05 and less.

For the quantitative variables with significant differences, the receiver operating characteristic curve test was applied to find the best simultaneous sensitivity and specificity.

Ethical approval and consent to participate

Need for informed consent was waived by our local ethics committee due to the retrospective nature of the study. This study was approved by our local ethics committee in Shahid Beheshti University of Medical Sciences (reference code: IR.SBMU.RETECH.REC.1398.872). All study procedures were carried out in accordance with relevant guidelines and regulations. The study was undertaken in accordance with the Basic and Clinical Pharmacology and Toxicology policy for experimental and clinical studies.[9]

RESULTS

A TOTAL OF 62 patients with confirmed methanol poisoning were enrolled into the study (Fig. 2), of whom 49 (79%) were men. The median (interquartile range) age was 35 (28, 45) years (range, 17–70 years). Thirty-nine (62.9%) patients survived and 23 (37.1%) died. The median duration of hospitalization was 3 (2, 7) days.

Sixty patients (96.8%) had ingested alcoholic liquids and two (3.2%) had consumed alcoholic sanitizers. Three (4.8%) mentioned that they had consumed alcohol to disinfect themselves, of whom one survived. The intent of drinking was not clarified in 33 cases (53.2%). The other 26 cases (41.9%) had drunk alcohol for recreational purposes. Of the patients, 27 (65.9%) had a positive history of regular alcohol consumption and 14 (34.1%) had no history; the remainder had not provided data in this regard. Of the patients who survived, 18 (69.6%) had a history of regular alcohol consumption and seven (30.4%) had no history (p = 0.571); data were insufficient in 21 cases. Of three patients who had ingested alcohol to disinfect against COVID-19, one had history of regular alcohol use (p = 0.209).

In our series, nine (14.5%) patients were diagnosed with SARS-CoV-2 infection. Diagnosis of infection were made by spiral chest CT scan in seven (77.8%) patients and by PCR in two (22.2%). Among infected patients, four survived and five died; however, there was no significant difference in mortality rates between SARS-CoV-2-infected and noninfected patients (p = 0.272). Seven of nine (77.8%) SARS-CoV-2-infected patients had positive history of regular alcohol consumption. This history was positive in 20 of 53 (37.7%) noninfected cases. There was a significant correlation between COVID-19 and history of alcohol consumption (p = 0.036; odds ratio 1.7; 95% confidence interval, 1.28-2.25). Univariate analysis showed significant differences between infected and noninfected patients regarding their urea level and time for first and second hemodialysis sessions, as well as the duration of ethanol administration as an antidote (Table 1).

Chest CT scan was carried out in 56 patients with 36 (69.2%) having normal chest CT findings and 20 (30.8%) with abnormal findings. In nine cases (16.1%), changes were due to COVID-19 infection. Of those with COVID-19 chest CT findings, four survived (P = 0.256). Prevalence of each of the radiologic findings of chest CT scan is provided in Table 2.

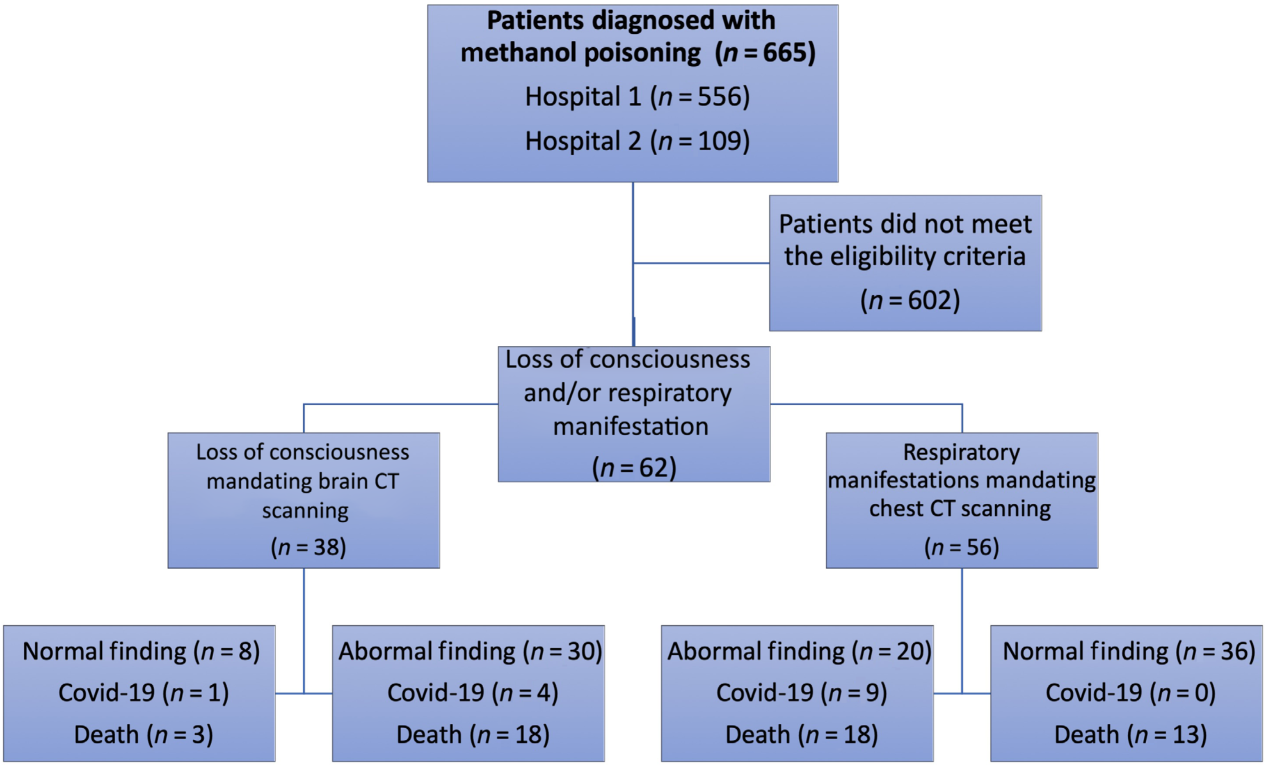

Fig. 2. Selection algorithm of 62 cases of methanol poisoning at two toxicology centers in Iran. CT, computed tomography.

Table 1. Variables with significant group difference in methanol-poisoned patients (COVID-19-infected vs. noninfected cases)

	p-value[a]	Odds ratio	95% confidence interval	
Comorbidities	0.024	8.500	1.500	50.000
History of alcohol consumption	0.036	0.741	0.593	0.926
Abnormal chest CT scan	<0.001	4.300	2.500	7.200
Urea (<40 mg/dL)	0.004	0.050	0.010	0.480
Delay in first dialysis (<13.5 h)	<0.001	0.013	0.001	0.179
Delay in second dialysis (>20.5 h)	0.001	6.300	2.200	17.900
Duration of taking maintenance ethanol (>17 h)	0.007	3.500	1.800	6.900

Abbreviation: CT, computed tomography.
[a]Fisher's exact test.

Figure 3 depicts chest CT scans of a patient with bilateral peripheral ground glass infiltrations.

Brain CT scan was undertaken in 38 (61.2%) patients, of whom 30 (78.9%) had abnormal findings.

Prevalence of each radiologic finding of brain CT scan is shown in Table 3. Five of nine infected patients had undergone brain CT scan and only one had normal CT.

There were no significant differences between patients with or without COVID-19 regarding the presence of abnormal brain CT findings (p = 0.999). Patients' selected laboratory data is shown in Table 4.

Variables with significant difference between survivors and nonsurvivors in univariate analysis are shown in Table 5.

DISCUSSION

LACK OF EDUCATION on ethanol consumption was highlighted in Iran when a rumor spread in the public and hit our health system. Some people believed that alcohol consumption could disinfect them against COVID-19. In a market providing the goods only illegally, producing adulterated or in the best scenario, low-quality beverages, is

Table 2. Chest computed tomography results in methanol-poisoned patients in Iran with and without COVID-19 infection

Radiologic pattern/frequency	COVID-19 patients (n = 9)	Non-COVID-19 patients (n = 47)	p-value	OR (95% CI)
Ground glass opacity	9 (100.0)	2 (4.1)	<0.001	23.50 (6.10, 91.20)
Crazy paving	0 (0.0)	0 (0.0)	–	–
Consolidation	4 (44.4)	7 (14.9)	0.063	–
Reticulation	0 (0.0)	0 (0.0)	–	–
Nodular infiltration	1 (11.1)	1 (2.0)	0.298	–
Reverse halo	0 (0.0)	0 (0.0)	–	–
Lymphadenopathy	0 (0.0)	0 (0.0)	–	–
Pleural effusion	0 (0.0)	1 (2.0)	0.999	–
Peripheral/subpleural	6 (66.7)	1 (2.0)	<0.001	0.01 (0.01, 0.12)
Central/ peribronchovascular	2 (22.2)	0 (0.0)	0.023	0.78 (0.55, 1.10)
Unilateral left	0 (0.0)	0 (0.0)	–	–
Unilateral right	1 (11.1)	1 (2.0)	0.289	–
Bilateral	6 (66.7)	9 (19.1)	0.008	0.12 (0.02, 0.57)

Note: Data are shown as n (%).
Abbreviations: –, not applicable; CI, confidence interval; OR, odds ratio.

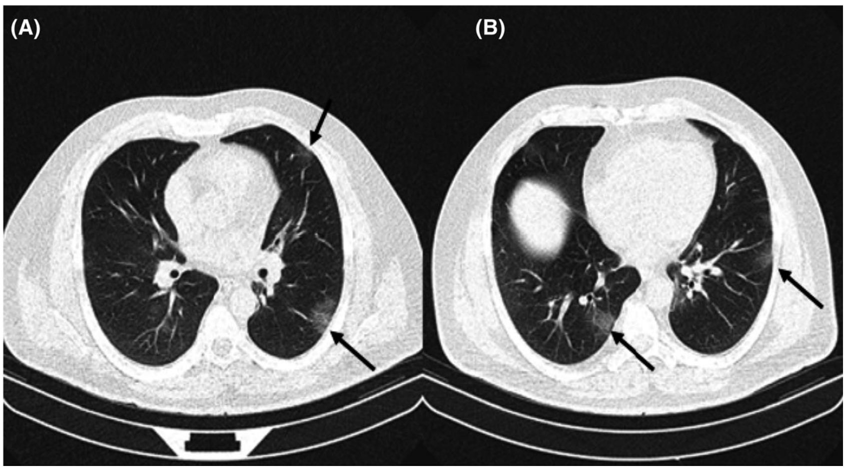

Fig. 3. Chest computed tomography scan of a patient with COVID-19 infection and methanol poisoning. Two axial sections (A, B) depict bilateral peripheral ground glass opacities (black arrows).

quite possible. This caused a huge outbreak of methanol poisoning in the country along with the COVID-19 epidemic.[6] There were people who drank sanitizers and even pure methanol to disinfect themselves. Three patients in our series had consumed alcohol for this purpose. Additionally, the mortality rate among patients who had a history of alcohol consumption was approximately 41% versus 50% in patients without a background of alcohol consumption. It can be imagined that this difference is due to the use of alcohol from a market inundated with low-quality and adulterated alcoholic beverages because of the increase in the demand for alcohol-based disinfectants. Also, it can be assumed that these patients had drunk even more detrimental beverages, including sanitizers, to reach the abovementioned goal.

Seven patients in the SARS-CoV-2-infected group had positive history of alcohol consumption. For a person who regularly drinks alcohol in a society where alcohol use is

Table 3. Brain computed tomography results in methanol-poisoned patients in Iran

	Involvement		
	Unilateral	Bilateral	None
Putaminal hypodensity	1 (2.6)	23 (60.5)	14 (36.8)
Putaminal hemorrhage	2 (5.3)	10 (26.3)	26 (68.4)
Subcortical WM hypodensity	0 (0.0)	15 (39.5)	23 (60.5)
ICH	2 (5.3)	2 (5.3)	34 (89.4)
IVH	4 (10.5); 1 (2.6) lateral ventricle; 1 (2.6) 4th ventricle; 2 (5.3) with hemorrhage in all brain ventricles		34 (89.5)
Diffuse cerebral edema	12 (31.6)		26 (68.4)
Cerebellar hypodensity	0 (0.0)	1 (2.6)	37 (97.4)

Note: Data are shown as *n* (%).
Abbreviations: ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; WM, white matter.

prohibited, the alcoholic drinks are usually supplied by someone who is supposed to be a constant reliable seller.

However, adverse changes in the market due to the COVID-19 pandemic had resulted in difficulties accessing alcohol even among these drinkers with reliable sources of alcohol provision. Unfortunately, not only had alcohol consumption failed to achieve the desired effect of disinfecting these patients against COVID-19 infection, but also it likely increased their vulnerability for COVID-19 pneumonitis. This group of patients had experienced a vicious cycle of outcomes, acquiring the severe form of the infection leading to hospitalization, with five out of nine deaths.

In our cases, drinking history, elevated urea level, presence of comorbidities (see Table 1), delay in both first and second dialysis sessions, and increased time of need for maintenance ethanol therapy was more prevalent in SARS-CoV-2-infected patients.

Urea has been recognized as a prognostic factor for mortality due to pneumonia.[10,11] It has also been a prognostic factor for mortality due to COVID-19.[12] The blood urea nitrogen (BUN) / creatinine ratio has been suggested as an appropriate index for prediction of severity and mortality in COVID-19.[13] It has been reported that the new coronavirus can directly infect kidney cells through angiotensin-converting enzyme 2 receptors.[14] Activation of these receptors can lead to activation of the renin–angiotensin–aldosterone system, resulting in vasoconstriction and decreased glomerular filtration and reduced BUN filtration. Activation of the renin–angiotensin–aldosterone system also promotes sodium and water reabsorption in glomerular tubes, leading to passive reabsorption of BUN, leading to an elevated level of urea.[15,16]

In our study, prevalence of comorbidities was significantly higher in the SARS-CoV-2-infected group. There are a variety of reports on the detrimental role of comorbidities on patients' survival with this infection.[17,18] Thus, it can be hypothesized that the presence of comorbidities in cases of methanol poisoning necessitates hospital admission and intensive medical care.

In the current study, the first and second rounds of dialysis were significantly delayed in patients with COVID-19, which could be due to more prominent signs and symptoms of infection compared to signs of methanol intoxication.

It has been reported that SARS-CoV-2 infection causes acute respiratory distress syndrome, septic shock, and metabolic acidosis.[19] Presence of severe metabolic acidosis is one of the main indications for dialysis in methanol-poisoned patients,[20] and metabolic acidosis could be due to exacerbation of COVID-19 in these patients. This diagnosis could be even harder to make when metabolic acidosis is persistent after the first session of dialysis in methanol poisoning.

This hypothesis seems to be acceptable as five out of nine patients with COVID-19 died.

In our cases, putaminal hypodensity (63.2%) was the most prevalent central nervous system finding in brain CT followed by subcortical white matter hypodensity (39.5%), cerebral edema (31.6%; Figure 4A), and putaminal hemorrhage (31.6%; Figure 4B). These findings are in agreement with previous studies.[21,22]

Although basal ganglia and subcortical white matter changes are not specific for diagnosis of methanol poisoning, these findings can serve as appropriate diagnostic

Table 4. Laboratory test results in methanol-poisoned patients in Iran with and without COVID-19 infection

	COVID 19-infected patients (*n* = 9)	Noninfected patients (*n* = 53)	*p*-value	Survivors (*n* = 39)	Nonsurvivors (*n* = 23)	*p*-value	Total (*n* = 62)
Methanol level[a,b] (mg/dL)	10.4	21.1	0.139	19.3	22.3	0.402	20.4
(SD of mean)	4.2–16.7	11.8–31.2		12.4–26.2	8.8–35.9		10.6–30.2
(min–max)	6.0–14.9	8.0–54.7		10.9–33.9	6–54.7		6.0–54.7
Creatinine[a,c] (mg/dL)	1.5	1.4	0.251	1.3	1.6	0.004	1.4
IQR	1.3–1.9	1.2–1.7		1.1–1.5	1.4–1.9		1.2–1.7
(min–max)	1.2–28	1-2.5		1–28	1.1–2.5		1–28
Urea[a,b] (mg/dL)	45.5	27	0.013	28	31.5	0.423	29
IQR	37.2–89.2	22–36		21–38	22.2–46.2		22–42
(min–max)	23–108	4.4–77		4–108	16–77		4.4-108
pH	7.08	7.10	0.956	7.14	6.9	0.000	7.09
IQR	7.05–7.12	6.83–7.19		7.04–7.29	6.72–7.09		6.8–7.19
(min–max)	6.72–7.33	6.56–7.60		6.61–7.60	6.56–7.13		6.56–7.60
pCo_2[a] (mmHg)	26	26.4	0.868	26.2	29	0.600	26.4
IQR	17.4–33.0	18.2–36.1		18.2–34.3	16.7–45		18–34.9
(min–max)	14.1–58.4	6.3–112.2		6.3–51	11.8–112.2		6.3–112.2
HCO_3[a] (mEq/L)	9.3	8.8	0.603	10.4	6.5	0.001	8.8
IQR	8–13.25	5.8–13.4		7.9–14.2	4.9–8.8		6–13.4
(min–max)	6.5–14	3.5–29		4.5-–29	3.5–25.5		3.5–29
Base D/E[a] (mEq/L)	−20.550	−22	0.873	−18	−27	0.012	−22
IQR	−25.1–9.2	−28.8–9.6		−23.6–4.5	−30.5–22.2		−28.3–13.0
(min–max)	−20.6–17	−35.7–32.7		−33.7–32.7	−35.7–17		−35.7–32.7
Na[b] (mEq/L)	138.6	139.4	0.623	138.3	140.5	0.044	139.3
(SD of mean)	133.0–143.1	135.5–143.3		134.5–142.0	136.6–144.4		135.3–143.2
(min–max)	134–147	130–150		130–147	134–150		130–150
K[b] (mEq/L)	4.6	4.6	0.995	4.6	4.8	0.244	4.6
(SD of mean)	3.5–5.7	3.8–5.5		3.7–5.4	3.9–5.7		3.8–5.5
(min–max)	2.6–5.7	3.2–6.9		3.3–6.9	2.6–6.9		2.6–6.9
Glucose[b] (mg/dL)	184.6	185.4	0.982	177.4	199.6	0.415	185.3
(SD of mean)	142.0–227.2	87.8−283.1		79.5–275.4	116.1–283.2		93.8–279.1
(min–max)	118–243	66−464		66-416	95–464		66–464

Abbreviations: IQR, interquartile range; min, minimum; max, maximum; SD, standard deviation.
[a]Subject to missing data.
[b]Mean.
[c]Median.

tools in patients who have consumed alcohol and are referred with loss of consciousness. However, these findings can also be present in conditions including hypoxic–ischemic damage, carbon monoxide inhalation, and acute cyanide poisoning.[23,24] The possibility of methanol poisoning should be considered based on the patient's history. In addition, diffuse cerebral edema on brain CT was significantly correlated with increased mortality in our cases.

Our analysis showed that elevated creatinine and sodium levels, loss of consciousness (GCS < 12), and acidosis are related to the need for intensive therapy (need for antidiuretic hormone blocker and second session of hemodialysis) and, consequently, the final outcome.

There are reports on the prevalence of acute kidney injury (AKI) in patients with methanol poisoning as an indicator of poorer outcome.[25,26] Acute kidney injury could result in the worsening of acidosis and higher peaks of formate levels. The etiology of AKI incidence in methanol-poisoned patients has been connected to either the direct effect of methanol and its metabolite formic acid or as a consequence of poisoning, including myoglobinuria or hemodialysis.[27]

Table 5. Variables with significant group difference (survivors vs. nonsurvivors) among methanol-poisoned patients in Iran

	p-value	Odds ratio	95% confidence interval	
			Lower	Upper
Need for second dialysis	0.030	3.611	1.109	11.763
Receiving loading ethanol	0.007	0.488	0.360	0.663
Receiving maintenance ethanol	0.007	0.488	0.360	0.663
GCS (<12/15)	0.000	10.900	2.600	45.600
Blood pressure (<120 mmHg)	0.019	4.000	1.200	13.400
Creatinine (>1.45 mg/dL)	0.004	5.600	1.700	18.600
pH (<7.08)	0.001	7.400	2.200	24.000
HCO_3 (<8.9 mEq/L)	<0.001	10.800	3.000	39.200
Base deficit/excess (<−22.150)	0.002	11.300	2.300	54.500
Duration of hospitalization (>3 days)	0.003	8.700	2.000	37.800
Diffuse cerebral edema on brain CT	0.003	16.000	1.797	142.438

CT, computed tomography; GCS, Glasgow Coma Scale.

By this explanation, elevated creatinine level could be a prognostic factor of a possible AKI leading to an exacerbated poisoning.

Our findings relating low GCS and severe acidosis to higher mortality are compatible with former studies. Other factors, including need for second dialysis, are indicative of the severity of poisoning in these patients. Interestingly, radiologic findings and even outcome showed no correlation with methanol level, and brain damage on CT scan did not increase the mortality risk.

CONCLUSION

IN PATIENTS WITH concurrent methanol poisoning and COVID-19, higher urea level is more common, making the patients more susceptible to delayed medical care, which could influence their outcome. Among patients with methanol poisoning, specific attention should be paid to those with elevated creatinine, loss of consciousness, and severe acidosis.

ACKNOWLEDGMENTS

NONE.

DISCLOSURE

APPROVAL OF THE research protocol**:** This study was approved by our local ethics committee at Shahid Beheshti University of Medical Sciences (reference code: IR.SBMU.RETECH.REC.1398.872).

Informed consent: Need for informed consent was waived by our local ethics committee due to the retrospective nature of the study.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

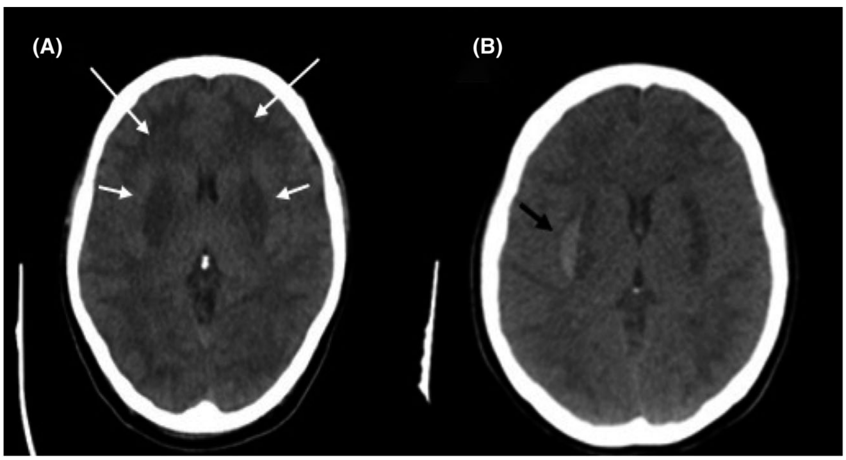

Fig. 4. Brain computed tomography scans in two patients with methanol poisoning. A, Bilateral putaminal (short white arrows) and white matter hypodensity (long white arrows). B, Bilateral putaminal hypodensities accompanied by right-lateral hemorrhage (black arrow).

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