

Methanol poisoning during COVID-19 pandemic: a multicenter study of northern Iran

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Key words: alcohol consumption, methanol poisoning, COVID-19, metabolic acidosis, dialysis.

Conflicts of interest: the authors have no conflicts of interest to declare.

Funding: the Mazandaran University of Medical Sciences funded the study. The funder had no role in designing the study, collecting, analyzing, and interpreting data, or writing the manuscript.

Contributions: ZZ, JD are involved in the interpretation and collecting of data, writing, and editing of the manuscript. SKhGh, ZN were involved in editing and preparing the final version of the manuscript. AHB submitted of the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

Ethics approval: this research was approved by the Mazandaran University of Medical Science Ethics Committee (No: IR.MAZUMS.IMAMHOSPITAL.REC.1400.094) and was carried out in accordance with the Helsinki Declaration Principles. Informed Consent was obtained from all patients/participants and their legal guardian(s) for study participation.

Data availability: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 19 May 2025.

Accepted: 8 August 2025.

Early view: 10 September 2025.

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Emergency Care Journal 2025; 21:14009

doi:10.4081/ecj.2025.14009

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Abstract

During coronavirus disease 2019 (COVID-19) pandemic, Iran experienced the largest methanol mass poisoning outbreak in the history. Despite advancements in the diagnosis and treatment of Methanol Poisoning (MP), mortality rates remain high. In light of the geographical location and increased travel to this northern province, coupled with the rising consumption of illicit and home-made alcoholic beverages and the associated incidence of methanol poisoning, we undertook an analysis of the demographic characteristics, diagnostic procedures, and treatment approaches among patients hospitalized in five designated hospitals within the region. The data collection period for this study spanned from March 2020 to September 2021. This retrospective and descriptive cross-sectional study is a multicenter study in the western part of Mazandaran province over the initial 18 months of the pandemic to provide a more comprehensive view on MP patients. The diagnosis was based on several factors, including a history of alcohol consumption, visual impairment, altered level of consciousness, and the presence of metabolic acidosis in laboratory tests. The study included 82 patients diagnosed with MP, comprising 74 males (90.2%) and 8 females (9.8%), with an average age of 38.20 ±13.9 years. The majorities (76.8%) resided in urban areas, and most were self-employed. Blurred vision and metabolic acidosis were observed in the majority of the patients. Oral ethanol and dialysis were the primary treatment employed for our patients. Visual complications and severe metabolic acidosis are commonly linked to poor outcomes in MP. A comprehensive analysis of MP patients revealed no significant correlation between treatment type, patient demographics, and outcomes, highlighting the complex and multifaceted nature of this condition.

Introduction

During the initial months of the coronavirus disease 2019 (COVID-19) pandemic, there were reports of methanol mass poisoning outbreaks in Iran, the United States, and Turkey.¹⁻⁵ In Iran, at least 5,876 patients with a mortality rate of 13.61% were reported poisoned in over half of the country's provinces, marking the largest Methanol Poisoning (MP) outbreak in the history.^{2, 6} Children were also reported as being affected by this outbreak.⁴ In Iran, the lack of access to legal and safe alcoholic beverages, along with the shortage of methanol-free sanitizers, and misconceptions about the preventive effects of consuming or gargling alcohol against COVID-19 are considered to be among the main caus-

es.^{2,4,5,7-9} In the United States, MP occurred as a result of ingesting alcohol-based hand sanitizers.³

MP can occur through various routes, including ingestion, inhalation, and skin contact, although ingestion is the most common.^{1,3,10,11} Methanol exerts toxic effects when ingested in quantities as low as 7-8 mL. The estimated lethal dose ranges between 30 and 100 ml; however, cases have been documented in which death occurred following ingestion of only 5 ml, and conversely, recovery was observed in individuals who consumed up to 250-500 mL. The toxic methanol blood concentration is considered to be within the range of 0.2-0.3 mg/mL, while concentrations between 0.8-1 mg/mL are typically associated with a fatal outcome.^{12,13}

MP clinical findings include gastrointestinal manifestations (nausea, vomiting and abdominal pain), Central Nervous System (CNS) symptoms such as confusion, drowsiness, ataxia, and seizures, dyspnea, hyperventilation, and uncompensated metabolic acidosis accompanied by visual disturbances.^{1,3,14} Methanol is rapidly absorbed, distributing throughout the body fluids within 10 minutes.^{1,15} In the liver, methanol is converted to formaldehyde by Alcohol Dehydrogenase (ADH), and formaldehyde is further transformed to formic acid by aldehyde dehydrogenase.¹ The metabolic process of methanol to formic acid takes time, therefore, after 6 to 24 hours, depending on the absorbed amount, uncompensated metabolic acidosis and visual disorders such as blurred vision, photophobia, diplopia, and blindness may begin.^{1,10} Methanol induces ataxia, mild inebriation, and lethargy, while formic acid is responsible for metabolic acidosis, blindness, putamen hemorrhage, coma, and eventually death.¹

The triad of visual impairment, gastrointestinal symptoms, and metabolic acidosis has been suggested as characteristic indicators of MP.^{16, 17} However, simultaneous ethanol consumption may alter the presentation and delay the onset of symptoms.¹⁴ Clinical diagnosis of MP may be established when symptoms like visual disturbances, headache, dizziness, nausea, vomiting, and increased osmolar and anion gap concentrations are present. Prompt intervention in cases of methanol poisoning is critical.¹⁵ Methanol toxicity commonly leads to hypotension, primarily through vasodilation, and is often accompanied by vomiting. Consequently, fluid resuscitation with intravenous crystalloids is frequently required. Due to methanol's rapid gastrointestinal absorption and its poor affinity for activated charcoal, gastrointestinal decontamination is generally not recommended.¹⁸ Nonspecific symptoms emphasize the significance of laboratory tests in diagnosing MP.¹⁴ Following initial resuscitation, the most crucial therapeutic measures involve correcting acidosis, administering folic acid, inhibiting ADH, and, if necessary, resorting to hemodialysis.^{1,3,19} Inhibiting ADH with fomepizole and ethanol is possible; however, considering the fewer side effects, fomepizole is preferable.^{1,19} Indications for initiating hemodialysis in methanol poisoning include the presence of severe metabolic acidosis (pH<7.25 and anion gap >30 mEq/L), evidence of end-organ damage such as visual disturbances, CNS involvement, or renal dysfunction, progressive deterioration of vital signs despite conservative management, significant electrolyte abnormalities, and methanol serum concentrations exceeding 50 mg/dL – even in the absence of acidosis or overt clinical symptoms.¹ The combination of fomepizole and hemodialysis has been proven to be both safe and effective.¹⁵ Corticosteroids are recommended to prevent visual complications and reduce mortality, although further research is warranted.^{1, 9} Despite advancements in the diagnosis and treatment of methanol poisoning, mortality rates remain high.^{9, 14}

According to reports, there was a mass outbreak of MP in Mazandaran, Iran, with an initial mortality rate of 34.3%, ranking

second-highest in the country within the first month of the COVID-19 pandemic.^{2, 6} In this study, we conducted a multicenter cross-sectional survey in the western part of Mazandaran province over the initial 18 months of the pandemic to provide a more comprehensive view.

Materials and Methods

This research is a retrospective and descriptive cross-sectional study that was approved by the Mazandaran University of Medical Science Ethics Committee (No. IR. MAZUMS. IMAM HOSPITAL. REC.1400.094) and carried out in accordance with the ethical guidelines of the Helsinki Declaration Principles. Additionally, written informed consent was obtained from all participants or their legal guardians.

Table 1. Demographic and clinical characteristics of patients.

Demographic and clinical features	Frequency (%) Mean±SD
Age	38.20±13.9
Gender	
Male	74 (90.2)
Female	8 (9.8)
Marital status	
Single	29 (35.4)
Married	53 (64.6)
Education	
Illiterate	2 (2.4)
Elementary	31 (37.8)
Secondary (High school)	31 (37.8)
Collegiate level	18 (22.0)
Residence	
Rural	19 (23.2)
Urban	63 (76.8)
Occupation	
Unemployed	17 (20.7)
Employee	9 (11.0)
Self-employee	56 (68.3)
Clinical findings	
Nausea/vomiting	31 (37.8)
Blurred vision	76 (92.7)
Decreased LOC	9 (11)
Shortness of breath	24 (29.3)
Seizure	5 (6.1)
Headache	2 (2.4)
Metabolic acidosis	82 (100)
Laboratory tests	
pH	7.09±0.21
PCO ₂	36.25±17.2
HCO ₃	10.5±5.66
BS (mg / dL)	140±38
BUN (mg/dL)	28±14
Cr (mg/dL)	1.1±0.8
Na (mEq/L)	139±8
K (mEq/L)	3.8±1.03
Treatment	
Ethanol	55 (67.1)
Dialysis	80 (97.5)

BS, Blood sugar, BUN, Blood urea nitrogen, Cr, Creatinine, Na, Sodium, K, Potassium, LOC, level of consciousness

The selection of samples for this study involved patients who were diagnosed with MP. The diagnosis was based on several factors, including a history of alcohol consumption, visual impairment, altered level of consciousness, and the presence of metabolic acidosis in laboratory tests. The study included patients admitted to five specific hospitals in the western region of Mazandaran province, which is located in northern Iran. The data was obtained for research purposes in the period from March 2020 to September 2021.

All individuals with MP from March 2020 to September 2021 in the selected hospitals were included in the study through a census approach. Patients admitted to the hospital with a history of alcohol consumption and a diagnosis of MP was included in this study. The exclusion criteria were a diagnosis of ethanol toxicity or the unavailability of complete patient records. The study parameters were recorded based on a provided questionnaire and clinical symptoms, including visual impairment, altered level of consciousness, dyspnea, chest pain, nausea/vomiting, abdominal pain, and laboratory findings. Data analysis was performed using SPSS version 21, based on data from all patients entered into the study from the beginning. Initially, variables were categorized into quantitative and qualitative categories, and then data from the study was analyzed using chi-squared and Fisher's exact tests.

Results

In total, 82 patients with MP were enrolled in this study. Among the patients, 74 (90.2%) were male, and 8 (9.8%) were female, with an average age of 38.20 ± 13.9 years. 53 patients (64.6%) were married, and 29 patients (35.4%) were single. Furthermore, 31 patients (37.8%) had under diploma, while 18 patients (22%) had a university education. Among them, 56 patients were self-employed, 9 were employed, and 17 patients were unemployed. It is noteworthy that 76.8% of the patients resided in urban areas, while 23.2% lived in rural areas (Table 1).

In total, 31 patients (37.8%) presented with symptoms of nausea and vomiting, 76 patients (92.7%) experienced blurred vision, 9 patients (11%) exhibited altered level of consciousness, 24 patients

(29.3%) reported shortness of breath, 5 patients (6.1%) had seizures, and 2 patients (2.4%) complained of headaches. All patients displayed metabolic acidosis and the laboratory tests revealed that the average blood pH of the patients was 7.09 ± 0.21 , with an average PCO_2 of 36.25 ± 17.2 , and an average HCO_3^- of 10.5 ± 5.66 . In this study, 12 patients (14.6%) required intubation, while 80 patients (97.5%) underwent dialysis. Among the 82 patients evaluated, none received fomepizole therapy due to its unavailability. Treatment was administered to 55 patients (67.1%) based on symptomatic presentation and the availability of oral ethanol, as summarized in Table 1. Of the 82 patients enrolled in this study, 6 (7.3%) experienced visual complications, while 65 (79.3%) were discharged without any adverse outcomes. Unfortunately, 11 patients (13.4%) succumbed to the poisoning. No significant association was observed between the treatment type and patient outcomes and demographic characteristics (age, gender, education level, residency, and job status) ($p > 0.05$) (Table 2).

Discussion

In this 18-month study, we reported cases of hospitalized patients diagnosed with MP across five selected hospitals in north-west of Iran. The reporting timeframe started from the beginning of the COVID-19 pandemic in Iran and likely included some patients as part of the MP outbreak. Given that Mazandaran province is a popular tourist destination in Iran, it is conceivable that some patients were travelers. The majority of our patients were male (90.2%), with visual impairments (92.7%), and residents of urban areas (76.8%), aligning with previous studies in the country.^{2,6,7,9,20-23} All patients in our sample exhibited metabolic acidosis, but anion gap and osmolality were not reported, which were expected to be elevated.¹ Western Mazandaran faces shortages in hospital and laboratory equipment, and some necessary tests, such as methanol and ethanol levels in the blood and medications for MP, like fomepizole and intravenous ethanol, are not readily available in hospitals. Given various limitations in therapeutic options, all patients underwent dialysis. In our study, the majority of patients were discharged from the hospital without specific com-

Table 2. Methanol poisoning outcome and correlation between demographic characteristics.

Demographic features	Death (n=11)	Visual complications (n=6)	Without complication (n=65)	p
Gender				
Male	9 (12.1)	6 (8.1)	59 (79.7)	0.459
Female	2 (25)	0 (0.0)	6 (75)	
Marital status				
Single	1 (3.4)	1 (3.4)	27 (93.1)	0.70
Married	10 (18.8)	5 (13.1)	38 (71.6)	
Education				
Illiterate	0 (0)	0 (0.0)	2 (100)	0.578
Elementary	6 (19.3)	1 (3.2)	31 (77.4)	
Secondary (High school)	2 (6.4)	4 (12.9)	25 (80.6)	
Collegiate level	3 (16.6)	1 (5.5)	14 (77.7)	
Residence				
Urban	9 (14.2)	5 (7.9)	49 (77.7)	0.830
Rural	2 (10.5)	1 (5.2)	16 (84.2)	
Occupation				
Unemployed	2 (11.7)	1 (5.8)	14 (82.3)	0.906
Employee	2 (22.2)	1 (11.1)	6 (66.9)	
Self-employee	7 (12.5)	4 (7.1)	45 (80.3)	

plications, but 7.3% experienced visual complications, and 13.4% unfortunately passed away. The mortality rate and complications in the western part of the province were lower than in the central region, possibly due to the referral of critically ill patients from across the province to the central region.⁹

In Iran, access to official records on MP has consistently been limited.²⁴ A study that analyzed forensic mortality data in Tehran clearly demonstrated a 16.5% increase in deaths related to MP during the first three months after the onset of the pandemic.²⁵ Other studies reported 800 deaths were observed nationwide, with 22 deaths in the pediatric population.^{4,6} In mass outbreaks of MP, it is often observed that the peak of cases occurs in the early days. There have been reports of unpublished data indicating that a single emergency room experienced over 200 cases of MP within a single week. This highlights the urgency and importance of early identification and seeking assistance from relevant authorities.^{14,26}

The MP outbreak in the early days of the COVID-19 pandemic is believed to have stemmed from two primary causes. Firstly, a rise in unstructured leisure time, decreased sports activity resulting from gym closures, and mass encouragement for the public to stay at home caused increased alcohol consumption. This led to a higher incidence of MP in a country where legal and safe alcohol sales are prohibited.^{25,26} Furthermore, the extensive spread of misinformation regarding the prevention of COVID-19—specifically the use of alcohol-based beverages and sanitizers through consumption or gargling—prompted individuals to adopt such hazardous practices. However, due to the legal prohibition of the production, distribution, and consumption of alcoholic beverages in Iran, along with the prevalence of illicit and homemade alternatives, many resorted to black market sources, thereby exposing themselves to severe health risks associated with methanol-contaminated substances. Additionally, as the pandemic surged in the country, sanitizers became scarce in the market. According to local news, the heightened demand for ethanol prompted bootleggers to eliminate the color from industrial alcohols containing pyridine (to discourage consumption) using bleach, before selling them as regular ethanol to Iranians.^{2,3,5-8,26}

It's noteworthy that sanitizers containing methanol were not exclusive to Iran. In July 2020, the FDA recalled at least 75 sanitizers containing methanol from across the United States.¹⁵ Furthermore, the prolonged use of methanol-containing sanitizers can be absorbed through the skin.¹¹

MP is associated with numerous complications and high mortality, necessitating rapid diagnosis and treatment to prevent permanent consequences and death.¹ Various factors contribute to delayed diagnosis, including religious or societal taboos on alcohol consumption and nonspecific presentation of poisoning.^{14,27} In Iran, the lack of proper laboratory equipment for measuring toxic alcohol concentrations and their metabolites, as well as serum osmolality and chloride levels for calculating anion gap and serum lactate levels, also plays an effective role in diagnostic delays.^{1,24} Another factor during the early months of the pandemic was the fear of COVID-19, which likely deprived victims of alcohol poisoning from timely diagnosis and treatment.⁶ Limited access to appropriate treatment is another reason, despite the addition of fomepizole to the essential drugs list of the World Health Organization (WHO), its availability in Iran is limited.^{24,28}

Although COVID-19 may no longer dominate our concerns, the emergence of other widespread infectious diseases remains a possibility. In such circumstances, it is crucial for responsible governmental bodies to take decisive actions. This involves countering the circulation of misinformation and unsafe behaviors in society through education and increased public awareness. On one hand,

they should strive to provide accurate information, and on the other hand, by supplying safe, methanol-free sanitizers, they can reduce the risk of MP. Moreover, MP outbreaks were prevalent in Iran long before the COVID-19 pandemic. Comprehensive education on toxic alcohols and MP, coupled with training healthcare professionals for timely and effective responses, along with providing appropriate hospital equipment across all regions, can contribute significantly. Lastly, acknowledging the reality of alcohol consumption in Iran, the government must assume a responsible role in regulating its use. Implementing these measures is essential to prevent tragic events, such as the methanol mass poisoning outbreak of 2020.^{5,14,21,22}

Limitations

The explicit and implicit legal restrictions on accessing and publishing hospital records of MP cases pose a significant barrier to conducting a thorough clinical evaluation and obtaining detailed imaging findings. The inability to obtain an accurate medical history from patients, often stemming from fear of familial judgment and legal repercussions under country's laws, significantly influences the nature and urgency of their presentation at the emergency department. The inadequate availability of hospital laboratory equipment in the healthcare system has hindered the provision of comprehensive and precise diagnosis and treatment procedures for patients with MP.

Conclusions

MP poses a significant challenge to both individual and social health globally. Despite efforts to promptly diagnose and treat affected individuals, the mortality rate associated with MP remains a cause for concern. In Iran, one contributing factor to the morbidity and mortality related to MP is the delay in seeking treatment due to the fear of legal consequences. However, based on our study, no significant correlation was found between the type of treatment, patient outcomes, and demographic characteristics. It is worth noting that timely recognition of the outbreak and the involvement of experienced specialists can play a crucial role in mitigating the impact of visual complications and severe metabolic acidosis.

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