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Outcome assessment of acute methanol poisoning: A risk-prediction nomogram approach for in-hospital mortality

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ABSTRACT

Acute methanol poisoning could be associated with high morbidities and fatalities. Stratifying high-risk patients is crucial in improving their prognosis. Hence, this study aimed to identify patients with methanol poisoning at high risk of in-hospital mortality. Also, the risk factors for blindness were assessed. The study included 180 acutely methanol-poisoned patients who received standard medical care. Out of 180 patients, 52 (28.9 %) patients presented with blindness, and 43 (23.9 %) patients died. The predictive model was based on four significant variables, including blindness, mean arterial pressure, serum bicarbonate, and serum creatinine. The presence of blindness and elevated serum creatinine significantly increased the likelihood of mortality by 14.274 and 5.670 times, respectively. Likewise, decreases in mean arterial pressure and serum bicarbonate significantly increased mortality risk by 0.908 and 0.407 times, respectively. The proposed nomogram exhibited excellent discriminatory power (area under the curve (AUC)=0.978, accuracy=93.3 %), which outperforms the AUCs of individual predictors. The provided nomogram is easily applicable with outstanding discrimination, making it clinically helpful in predicting in-hospital mortality in acutely methanol-poisoned patients. Regarding the risk factors for blindness, multivariable regression analysis revealed that delayed time for admission (OR=1.039; 95 % CI=1.010–1.069; p= 0.009) and elevated anion gap (OR=1.053; 95 % CI=1.007–1.101; p= 0.023) were significant risk factors. The current study assists physicians in identifying methanol-poisoned patients with a high probability of mortality or blindness on admission. Future studies are recommended for external validation of the created nomogram, in addition to follow-up for patients with visual impairment.

1. Introduction

Methanol, or methyl alcohol (CH_3OH), is a colorless, volatile, and flammable liquid originating from wood fermentation. It is ubiquitous and widely used in various commercial and industrial products, including washing fluids, paint solvents, fuel, wallpaper, and antifreeze [1,2]. Methanol's low price and apparent similarity to ethanol encourage its use in alcoholic beverage adulteration. Therefore, illicit manufacturing of alcoholic beverages is a global practice, particularly in countries that ban alcohol [3,4]. Accordingly, many methanol poisoning outbreaks have been recorded worldwide, with irreparable morbidities and case fatalities reaching more than 30 % [3,5,6]. Substantially, a dramatic increase in acute methanol poisoning during the COVID-19 pandemic due to misinformation that consuming alcoholic beverages kills the virus and guards against infection [7–10]. Yet, recent literature pointed to increasing methanol poisoning-related morbidities and mortalities in Eastern countries, including Egypt [11–14].

Upon absorption by various routes, methanol is rapidly metabolized in the liver through alcohol dehydrogenase (ADH) to formaldehyde, which is further oxidized to formic acid via aldehyde dehydrogenase (ALDH) [15]. Although the parent methanol compound is less toxic, the highly poisonous metabolites, formaldehyde and formic acid, are

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responsible for methanol-related effects. Subsequently, the initial symptoms may be delayed up to 12–24 hours [16].

Methanol-poisoned patients may present with mild manifestations resembling ethanol intoxication, including headache, GIT upsets, disinhibition, and blurred vision [17]. In severe cases, patients might progress to severe metabolic acidosis, blindness, and deep coma, followed by respiratory and circulatory failure, causing eventual death [18,19]. A triad of high anion gap metabolic acidosis, altered mental status, and visual impairment is highly suggestive of acute methanol poisoning [20].

The diagnosis of methanol poisoning is often challenging because of initial non-specific symptoms, delayed onset of presentation, and lack of patient consciousness that impede proper history-taking [18]. Additionally, patients usually postpone seeking medical intervention for fear of medicolegal inquiries, increasing the probability of poor outcome [10]. Yet, exploring early indicators associated with poor outcome in methanol poisoning has garnered attention to prevent fatalities and other deleterious sequelae [21].

Previous studies have identified many outcome determinants, including delayed hospitalization, decreased consciousness, increased glucose level, metabolic acidosis severity, and hematological parameters [10,11,22,23]. However, limited literature has assessed applicable predictive models incorporating clinical and laboratory parameters.

The nomogram visually represents a statistical model that integrates multiple variables. Incorporating different predictors in a single model allows a thorough assessment of the patient's condition [24]. Using nomograms, the attending physicians may quickly ascertain the likelihood of unfavorable outcome upon admission. Correspondingly, nomograms are a promising forecasting tool in the clinical toxicology field [25–28]. Therefore, the current study aimed to develop a risk-prediction nomogram for in-hospital mortality stratifying high-risk patients with acute methanol poisoning. We also investigated the risk factors for methanol-induced severe visual impairment due to its serious implications on patients' lives.

2. Patient and methods

2.1. Study design and setting

This retrospective cohort study involved gathering the relevant data from the medical records of methanol-poisoned patients admitted to Poison Control Center of Ain Shams University Hospitals (PCC-ASUH) and Tanta University Poison Control Center (TUPCC). These hospitals provide medical care to patients in the Egyptian capital (Cairo) and cities in the Nile Delta region, respectively [29,30]. We conducted the current study from January 2021 to December 2023.

2.2. Inclusion criteria

This study enrolled adult patients (≥18 years) of both sex with acute methanol poisoning who attended PCC-ASUH and TUPCC during the study duration. The diagnosis of acute methanol poisoning relied on a clear history of recent methanol ingestion and identifying methanol containers. Furthermore, the presence of clinical manifestations and laboratory findings of acute methanol poisoning supported the diagnosis [31].

2.3. Exclusion criteria

We excluded patients with an unconfirmed diagnosis of acute methanol poisoning. Besides, patients with ophthalmologic, cardiovascular, respiratory, hepatic, and renal disorders were excluded from the study. Moreover, the study did not include cases with missing data, concomitant head trauma, transferrable patients, attended dead patients, and those who received medical care before admission to poison control centers. As a result of the concurrent ingestion of substances with methanol, we included only the non-significant co-ingestions with mortality outcome.

2.4. Sample size calculation

The sample size was calculated based on developing a mortality predictive model following acute methanol poisoning through an equation provided by Peduzzi et al. [32]. The minimum number of patients to include in logistic regression analysis: $N = 10\ k / p$, where k is the number of independent variables, and p is the minor proportion of negative or positive cases in the study population. It was postulated that the regression model for mortality prediction could include a maximum of five independent variables. The proportion of deaths following acute methanol poisoning in the Egyptian population is nearly 0.31 [11]. The minimum calculated sample was $N = 10 \times 5 / 0.31$. In addition, 10 % of the calculated sample size was added to compensate for data incompleteness. Thus, the minimum required sample size in the current study was 177 patients. However, we could obtain 180 patients.

2.5. Data collection

Patients' data were retrieved from PCC-ASUH and TUPCC medical records based on a specially designed sheet. These data included sociodemographics (age, sex, and residence) and poisoning data (history of co-ingestion of substance abuse, intent and place of poisoning, and delay time from exposure to hospital admission). The clinical-related data, including the Glasgow Coma Scale (GCS) and vital signs, were recorded on admission. Additionally, the visual acuity was assessed using standard Snellen charts positioned at a distance of six meters. Severe visual impairment or blindness was considered in patients with visual acuity less than 6/60 by ophthalmological examination [33,34].

The first laboratory findings were also documented, including blood methanol level and arterial blood gas analysis (ABG) results. The random blood glucose, serum electrolytes, serum urea, creatinine, creatine phosphokinase (CPK), and hepatic aminotransferases [aspartate transaminase (AST) and aspartate transaminase (AST)] were measured as well. Accordingly, the anion gap was calculated via the following equation: $AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$ in mmol/L [normal range of anion gap is 10–14 mmol/l] [35]. Likewise, the osmol gap was calculated using the following equation: Serum osmolality–calculated osmolality ((2 × [Na]) + (glucose, in mg/dL)/18 + (blood urea nitrogen, in mg/dL)/2.8) in mosmol/kg [normal osmol gap is between 10 and −10 mosmol/kg] [36].

Furthermore, the hematological indices, including hemoglobin (Hb), hematocrit, white blood cell count (WBCs), platelet count, and red cell distribution width (RDW), as well as the initial electrocardiogram (ECG) findings, were determined.

2.6. Treatment and patient outcome

All patients received standard medical care for acute methanol poisoning. After an initial assessment, all patients received supportive care, including airway protection and sodium bicarbonate therapy of 1–2 mEq/kg for patients with a pH lower than 7.3 to correct metabolic acidosis. Patients were treated with 10 % of ethanol infusion as antidotal therapy. Likewise, a 50 mg IV folic acid was administered to enhance formic acid elimination [31]. Additionally, hemodialysis was performed for patients with the following criteria: visual impairment, persistent arterial pH lower than 7.1, methanol concentration more than 25 mg/dL, deteriorating vital signs, and renal insufficiency [37,38]

We recorded the time before ethanol administration, the number of hemodialysis sessions, the need for vasopressors, the duration of mechanical ventilation (MV), the length of intensive care unit (ICU) admission, and the total hospitalization period. Patients were categorized according to in-hospital mortality into survivors and non-survivors. Furthermore, risk factors for blindness were investigated.

2.7. Statistical analysis

Data were analyzed using the statistical package for the social sciences software program IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA). Pearson's Chi-square test was applied to analyze the categorical variables. Fishers' Exact test was used if more than 20 % of cells had counts less than five. The Shapiro–Wilk test was implemented to test the normality of continuous data. The independent T-test was used to analyze the normally distributed data, while the Mann–Whitney U test was applied to compare the skewed data. The significant parameters ($P < 0.05$) in the bivariate analysis were pooled in a multivariable binary logistic regression analysis after checking for multicollinearity to create a prediction model for mortality. We kept the default probability for stepwise at 0.05 for entry and 0.10 for removal of predictors while performing the regression analysis.

The nomogram was developed to predict in-hospital mortality using STATA/SE 16.0 software and the nomogram program. We utilized a Kattan-style nomogram due to its suitability for binary logistic regression predictive models.

2.8. Internal validation

The created nomogram was subjected to internal validation through a bootstrapping approach, using 1000 samples replicated from the studied patients' samples. This approach calculated bias-corrected and accelerated confidence intervals and prevented model overfitting. The optimism estimate from bootstrapping results was calculated as an average of the coefficients (B) differences. Additionally, the optimism-adjusted discrimination (area under the curve [AUC]) and calibration (Hosmer and Lemeshow fit test) were determined by subtraction the optimism estimate from their respective values. Furthermore, a receiver operating characteristics (ROC) curve analysis was carried out to test the discrimination power of the significant predictors used to create the predictive model.

2.9. Ethical considerations

The study was approved by the Research Ethics Committees of the Faculty of Medicine, Tanta University (IRB: 0010038, FWA: 00022834, Approval Code: 36264PR754/7/24), and the Research Ethics Committees of Faculty of Medicine, Ain Shams University [FWA: 000017585, Approval number: FMASU(R211/2024)]. The present research concurred with the World Medical Association Declaration of Helsinki. The patient's data were handled anonymously, and confidentiality was strictly preserved. Obtaining the informed consent from the patients was waived as data were extracted from medical records.

3. Results

3.1. Patients' characteristics and outcome

The current study included 180 eligible methanol-poisoned patients. Out of them, 52 (28.9 %) patients had severe visual impairment, and the mortality outcome was the fate of 43 (23.9 %) patients.

Table (1) reveals that the median age of non-survivors was significantly higher than in survivors (41 versus 36 years; $p = 0.001$). Almost all (96.1 %) studied patients were males, and 74.4 % were from urban areas with no significant association with mortality ($p > 0.05$).

Regarding the toxicological history, 66.7 % of patients ingested methanol outdoors, which was significantly linked with mortality ($p = 0.019$). Although 90.6 % of patients intentionally ingested methanol, no significant difference was observed between survivors and non-survivors regarding poisoning manner. Likewise, the median time between methanol ingestion and patients' presentations was 18 hours without substantial association with mortality. Furthermore, co-ingestions were noted in 9.4 % of patients without a significant impact on patient outcome ($p > 0.5$), as shown in Table (1).

Table (2) illustrates the results of the initial clinical examination. A significantly higher percentage (46.5 %) of non-survivors presented with severe visual impairment compared to survivors (23.4 %; $p = 0.003$). The median score of the GCS of the non-survivors was significantly lower than survivors (4 *versus* 13; $p < 0.001$). Similarly, some vital signs' mean/median values were significantly lower in non-survivors. These vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), temperature, and respiratory rate ($p < 0.001$). Conversely, both groups' median heart rate was within normal ranges, with no significant mortality association. Additionally, ECG abnormalities were significantly higher among non-survivors ($p < 0.001$), with a significant association between mortality and the existence of sinus tachycardia and inverted T wave ($p = 0.002$ and 0.003, respectively).

Considering laboratory investigations, the mortality was significantly associated with higher methanol levels ($p = 0.005$). The non-survivors had significantly acidic blood status, presenting with lower pH and HCO_3, as well as a higher base deficit, $PaCO_2$, anion gap, and osmolar gap than survivors ($p < 0.001$). Furthermore, The mortality was significantly associated with increased serum sodium and blood glucose levels, liver transaminases, renal function tests (urea and creatinine), CPK, and some hematological parameters (hematocrit, RDW, WBCs, and platelet count), as illustrated in Table (3).

Table (4) displays the relationship between different treatment modalities of acute methanol poisoning and mortality. A substantially higher percentage of non-survivors received inotropes/vasopressors

Table 1
Sociodemographic and toxicological characteristics of methanol-poisoned patients.

		Mortality				Total n=180		p value
		Survivors n=137 (76.1 %)		Non-survivors n=43 (23.9 %)				
Age (years)	Minimum- Maximum	19.0–80.0		24.0–54.0		19.0–80.0		0.001*
	Median (IQR)	36.0 (27.0–43.0)		41.0 (36.0–45.0)		37.0 (29.0–44.0)		
Sex	Male	131	95.6 %	42	97.7 %	173	96.1 %	0.470
	Female	6	4.4 %	1	2.3 %	7	3.9 %	
Residence	Urban	104	75.9 %	30	69.8 %	134	74.4 %	0.420
	Rural	33	24.1 %	13	30.2 %	46	25.6 %	
Place of exposure	Outdoors	85	62.0 %	35	81.4 %	120	66.7 %	0.019*
	Home	52	38.0 %	8	18.6 %	60	33.3 %	
Manner of Poisoning	Intentional	121	88.3 %	42	97.7 %	163	90.6 %	0.077
	Accidental	16	11.7 %	1	2.3 %	17	9.4 %	
Delay (hours)	Median (IQR)	18 (10–27)		17 (12–24)		18 (11–26)		0.588
Co-ingestion of substances of abuse		11	8.0 %	6	14.0 %	17	9.4 %	0.244
	Opioids	6	4.4 %	2	4.7 %	8	4.4 %	0.610
	Benzodiazepine	5	3.6 %	2	4.7 %	7	3.9 %	0.673
	Cannabis	3	2.2 %	3	7.0 %	6	3.3 %	0.149

* Significant at $p < 0.05$, IQR: interquartile range

Table 2
Initial clinical and electrocardiographic findings of methanol-poisoned patients.

		Mortality		Total n=180	*p* value
		Survivors n=137 (76.1 %)	Non-survivors n=43 (23.9 %)		
Blindness	N, (%)	32 (23.4 %)	20 (46.5 %)	52 (28.9 %)	0.003*
GCS	Median (IQR)	13 (11−14)	4 (3−6)	11 (8−13)	<0.001*
Heart rate (beat/min)	Median (IQR)	88 (77−98)	92 (75−125)	90 (77−110)	0.183
SBP (mmHg)	Median (IQR)	110 (100−130)	80 (70−90)	100 (90−130)	<0.001*
DBP (mmHg)	Median (IQR)	70 (60−80)	40 (40−50)	70 (50−80)	<0.001*
MAP (mmHg)	Mean± SD	85.89 ±17.05	55.50±18.47	78.63±21.67	<0.001*
Respiratory rate (breath/min)	Median (IQR)	26 (22−32)	12.0 (8.0–16.0)	24 (11.5–32)	<0.001*
Temperature	Mean± SD	37.0±0.3	36.7±0.4	36.9±0.4	<0.001*
ECG abnormalities n (%)		59 (43.1 %)	36 (83.7 %)	95 (52.8 %)	<0.001*
	Sinus tachycardia	31 (22.6 %)	20 (46.5 %)	51 (28.3 %)	0.002*
	Sinus bradycardia	10 (7.3 %)	7 (16.3 %)	17 (9.4 %)	0.130
	Atrial Fibrillation	5 (3.6 %)	0 (0.0 %)	5 (2.8 %)	0.340
	Prolonged QTc	3 (2.2 %)	1 (2.3 %)	4 (2.2 %)	1.00
	ST changes	8 (5.8 %)	6 (14.0 %)	14 (7.8 %)	0.103
	Inverted T wave	1 (0.7 %)	5(11.6 %)	6 (3.3 %)	0.003*

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; ECG: Electrocardiographic
*Significant at p <0.05, IQR: interquartile range, SD: standard deviation

Table 3
Laboratory investigations of methanol-poisoned patients.

		Mortality		Total n=180	*p* value
		Survivors n=137 (76.1 %)	Non-survivors n=43 (23.9 %)		
Methanol level (mg/dL)	Median (IQR)	100 (65−178)	160 (110−230)	120 (65.5–185)	0.005*
pH	Mean± SD	7.13±.14	6.75±.22	7.04±.23	<0.001*
$PaCO_2$ (mmHg)	Median (IQR)	35 (28–41.7)	59 (42−69)	38 (29–52.5)	<0.001*
HCO_3 (mmol/L)	Median (IQR)	10.6 (8.4–14)	5 (3.8–7)	9 (6.9–11.7)	<0.001*
Lactate (mmol/L)	Mean± SD	3.4±1.7	10.2±2.3	5.0±3.4	<0.001*
Base deficit (mmol/l)	Median (IQR)	6.9 (4.3–14)	25.0 (23.4–28.7)	12.7 (4.9–20.3)	<0.001*
Anion gap (mmol/l)	Mean± SD	23.4±5.4	37.8±3.9	26.8±8.0	<0.001*
Osmolar gap (mosmol/kg)	Mean± SD	22.5±4.0	34.3±3.9	25.3±6.4	<0.001*
Serum sodium (mmol/L)	Mean± SD	138.9± 3.3	141.5±4.5	139.6±3.8	<0.001*
Blood glucose (mg/dL)	Median (IQR)	123 (101−150)	189 (147−212)	129 (107−165)	<0.001*
Serum potassium (mmol/L)	Mean± SD	4.1±.6	4.1±.9	4.1±.7	0.690
Urea (mg/dl)	Median (IQR)	32 (26.0–38.0)	45 (34−76)	35 (27.0–43.0)	<0.001*
Creatinine (mg/dl)	Mean± SD	1.2±.3	1.8±.7	1.3±.5	<0.001*
AST (U/l)	Median (IQR)	36 (23−45)	68 (43−138)	40.5 (28−58)	<0.001*
ALT (U/l)	Median (IQR)	26 (20−34)	61 (30−98)	27.5 (22−48)	<0.001*
CPK (U/l)	Median (IQR)	275 (187.0–389.0)	1455 (1088–3689)	324 (203−605)	<0.001*
Hemoglobin (g/dl)	Mean± SD	14.9±2.1	15.4±1.6	15.0±2.0	0.096
Hematocrit (%)	Mean± SD	45.2±5.8	47.3±5.5	45.7±5.8	0.038*
RDW (fL)	Mean± SD	13.6±.9	17.1±1.2	14.4±1.8	<0.001*
WBCs ($\times 10^9$/L)	Median (IQR)	11.0 (8.9–14.6)	18.0 (14.8–20.5)	12.0 (9.3–17.3)	<0.001*
Platelets count ($\times 10^9$/L)	Mean± SD	272.9±49	319.4±45.4	284.0±52	<0.001*

PaO_2: Partial arterial oxygen pressure; $PaCO_2$: Partial arterial carbon dioxide pressure; HCO_3: Bicarbonate; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CPK: Creatine Phosphokinase; RDW: Red Cell Distribution Width; WBCs: White Blood Cells
*Significant at p <0.05, IQR: interquartile range, SD: standard deviation

Table 4
Treatment modalities of methanol-poisoned patients.

		Mortality		Total n=180	*p* value
		Survivors n=137 (76.1 %)	Non-survivors n=43 (23.9 %)		
Inotropes/Vasopressors	n (%)	29 (21.2 %)	38(88.4 %)	67(37.2 %)	<0.001*
Folic acid	n (%)	112(81.8 %)	33(76.7 %)	145(80.6 %)	0.469
Lag time before ethanol administration (hours)	Median (IQR)	24.0 (13.5–39.0)	24.5 (16.0–49.0)	24.0 (14.0–39.5)	0.336
Number of hemodialysis sessions	Median (IQR)	1.0 (.0–1.0)	1.0 (.0–2.0)	1.0 (.0–2.0)	0.748
Length of ICU stay (days)	Median (IQR)	2.0 (1.5–2.8)	3.5 (2.0–5.5)	2.0 (1.5–3.2)	<0.001*
Mechanical ventilation duration (days)	Median (IQR)	.0 (.0−.0)	3.5 (2.0–5.5)	.0(.0–2.0)	<0.001*
Length of hospital stay (days)	Median (IQR)	3.0 (2.4–4.0)	3.5 (2.0–5.5)	3.0 (2.4–4.0)	0.178

* Significant at p <0.05, IQR: interquartile range

than survivors (88.4 % versus 21.2 %; $p < 0.001$). However, no significant difference was observed between the two groups regarding lag time before ethanol administration, hemodialysis session numbers, and folic acid treatment ($p > 0.05$). Although the durations of MV and ICU admission were significantly prolonged in non-survivors ($p < 0.001$). There was no significant difference in the total hospitalization period between the two groups (p =0.178).

3.2. Risk prediction nomogram for in-hospital mortality

Table (5) demonstrates the development of a risk-prediction model for mortality in acute methanol poisoning using the multivariable logistic regression analysis. The predictive model was based on four significant variables, including blindness, MAP, HCO_3, and serum creatinine (Fig. 1). The presence of blindness and elevated serum creatinine significantly increased the likelihood of mortality by 14.274 and 5.670 times, respectively. Likewise, decreases in MAP and HCO_3 significantly increased mortality risk by 0.908 and 0.407 times, respectively. Accordingly, the proposed nomogram formula was generated using the odds values of significant variables as follows: (14.274) presence of blindness+ (5.670) serum creatinine+ (0.908) MAP+ (0.407) HCO_3. Fig. (2) shows an example of the calculated mortality probability of a methanol-poisoned patient using the developed nomogram. First, each predictor's value is determined on its scale. Then, perpendicular lines are drawn from these values to assess each predictor score. The scores of all predictors are summed to calculate the total scale value. Lastly, a perpendicular line is drawn from the total score scale to the probability scale to assess methanol-poisoned patients' mortality risk.

Fig. (3A) revealed that the ROC curve analysis of the numerical nomogram independent predictors (MAP, HCO3, and serum creatinine) was significantly associated with mortality ($p < 0.001$). Serum HCO_3 at cut-off ≤7.2 mmol/L had the best discriminatory power (AUC= 0.919, with 95 % CI of AUC= 0.869–0.954), with 81.40 % sensitivity and 90.51 % specificity. Also, MAP had good discriminatory power (AUC= 0.889, with 95 % CI of AUC= 0.827–0.951), with 76.74 % sensitivity and 89.05 % specificity at cut-off ≤63.33 mmHg. Meanwhile, serum creatinine had AUC= 0.784, with 95 % CI of AUC= 0.717–0.842, with 65.12 % sensitivity and 89.05 % specificity at cut-off >1.5 mg/dl. The pairwise comparison revealed that serum HCO_3 had significantly better discriminatory power than serum creatinine (p= 0.004). However, the proposed nomogram revealed the highest AUC=0.978 and an overall accuracy of 93.3 %, which outperforms the AUCs of individual predictors constituting the nomogram, as shown in Fig. (3**B**).

The proposed nomogram was subjected to internal validation using a bootstrapping method. The model has excellent discrimination with an adjusted AUC of 0.778. A bias-corrected calibration was conducted with an accepted adjusted Hosmer and Lemeshow fit test of 0.698. Additionally, the calibration curve consistently demonstrates high correlations between the actual and predicted probabilities, as shown in Fig. (4).

3.3. Risk factors for severe visual impairment (blindness)

Univariate regression analysis was conducted to determine the risk factors of methanol poisoning-related blindness. Clinical variables, including delayed hospitalization, decreased GCS, and respiratory rate, were significantly associated with visual impairment (p =0.004, 0.008, and 0.033, respectively). Additionally, laboratory parameters, including acidic blood status (decreased pH and increased $PaCO_2$, base deficit, anion gap, and osmol gap), as well as elevated CPK, WBCs, and platelets count, were significantly associated with severe visual impairment (p <0.05). However, out of these variables, it was found that delayed time for admission (OR=1.039; 95 % CI=1.010–1.069; p = 0.009) and elevated anion gap (OR=1.053; 95 % CI= 1.007–1.101; p = 0.023) were the significant determinants for blindness by multivariable regression analysis. Noticeably, each hour of delay time increased the probability of blindness by 1.039 times, and the increase in anion gap by one millimole/liter increased the likelihood of blindness by 1.053 times, as illustrated in (Table 6).

4. Discussion

Although acute methanol poisoning has significant life-threatening outcome and long-lived morbidities, the early identification of its prognostic determination is a challenging matter [21]. Accordingly, researchers have exerted efforts to stratify patients with a high probability of adverse outcome on admission to improve their prognosis, especially in emergencies with limited hospital resources. Therefore, we aimed to establish a validated risk prediction nomogram for in-hospital mortality and precise risk assessment for visual impairment.

In the current study, 23.9 % of methanol-poisoned patients died. Nevertheless, Egyptian studies by Abdelwahab et al., 2022 [11] and Eweda and Hasab Elnabi 2023 [12] reported slightly higher mortality percentages (31 and 34.3 %, respectively). Furthermore, much higher mortality rates (55 % and 61.3 %) of methanol outbreaks were recorded during the COVID-19 pandemic in Iran [8] and Malaysia [39], respectively. Conversely, studies conducted in Saudi Arabia [40] and the USA [41] demonstrated lower fatality incidences (17.4 % and 6.5 %, respectively).

The contradictory results of mortality rates among studies were attributed to geophysical and social diversity, as well as variance in patient poisoning characteristics [42]. Additionally, methanol-poisoned patients might hesitate to seek medical care in countries where alcohol consumption is socially and legally prohibited [4,43]. This explanation could illuminate the relatively higher methanol-related mortality percentages in Egypt compared with Western countries. On the other hand, developed countries possess resources that enable immediate implementation of methanol detoxification modalities that achieve favorable outcomes [44].

We considered statistical and clinical perspectives while selecting the nomogram predictors for anticipating mortality in methanol poisoning. From a statistical point of view, blindness, MAP, HCO_3, and serum creatinine were significantly associated with mortality, with an overall accuracy of 93.3 % and excellent discriminatory power (AUC=0.978). From a clinical standpoint, the developed nomogram assessed various toxicological parameters, including symptoms (blindness), clinical examination (MAP), and laboratory investigations (HCO_3 and serum creatinine), ensuring a thorough patient evaluation. Furthermore, as previously proven in the literature, all predictors were relevant to the severity of methanol poisoning.

Visual disturbances are the key features of acute methanol poisoning,

Table 5
Multivariable logistic regression analysis for developing a prediction model for mortality following acute methanol poisoning.

	Beta coefficient	*p* value	AOR	95 % CI AOR	BCa 95 % CI	Accuracy	Nagelkerke R^2	*p* value
Blindness	2.658	.004*	14.274	2.285–89.168	.590–6.440	93.3 %	82 %	<0.001*
MAP (mmHg)	−.097	<0.001*	.908	.863–.954	−.151-(−.084)			
HCO_3 (mmol/L)	−.899	<0.001*	.407	.262–.633	−1.214-(−.891)			
Serum creatinine (mg/dl)	1.735	.032*	5.670	1.156–27.822	.321–3.752			
AUC (95 % CI): 0.978 (0.960–0.996)								
Adjusted AUC:0.778								
Hosmer and Lemeshow fit test: 0.898								
Adjusted Hosmer and Lemeshow fit test: 0.698								

MAP: mean arterial pressure; HCO_3: Bicarbonate; AOR: adjusted odds ratio; CI: confident interval; AUC: area under the curve; BCa: bias-corrected accelerated
*: significant at $p < 0.05$.

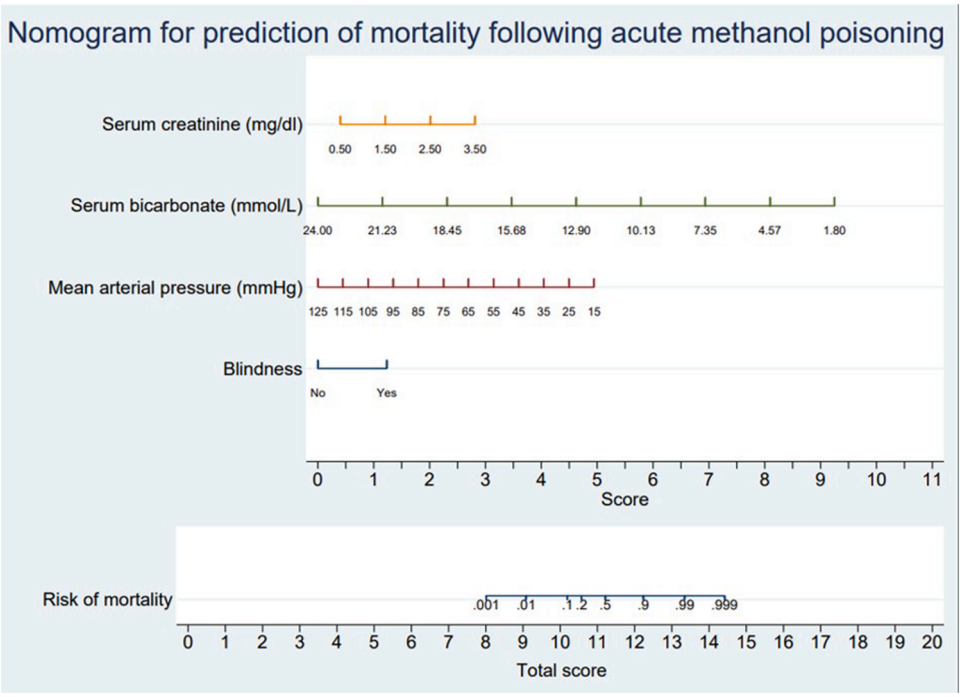

Fig. 1. Risk-prediction nomogram for prediction of in-hospital mortality among methanol-poisoned patients.

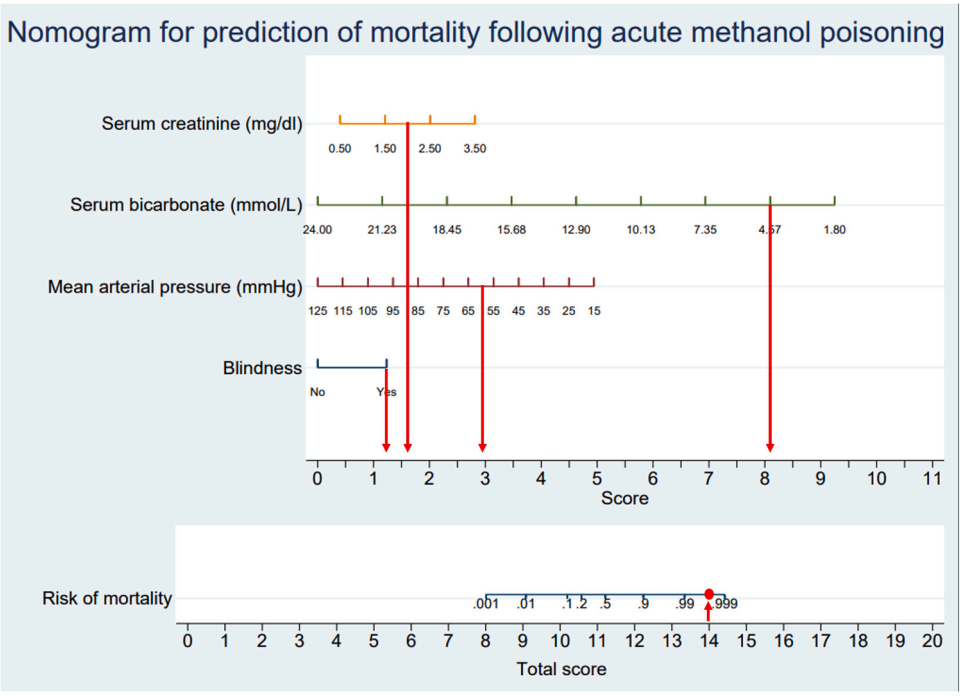

Fig. 2. Applying the nomogram to predict the probability of in-hospital mortality of a 40-year-old male patient with acute methanol poisoning. He was presented with blindness. On-admission, parameters included MAP = 60 mmHg, HCO_3 = 4.5 mmol/L, and serum creatinine = 1.9 mg/dl. The probability was calculated: blindness, MAP, HCO_3, and serum creatinine correspond to 1.3, 3, 8.1, and 1.6 points, respectively. The result of the summation of these points is 14, which means > 99 % risk of mortality.

ranging from blurred vision "snowstorm" to complete blindness, with incidences of 29–77 % [23,45]. Accordingly, in the current study, 28.9 % of methanol-poisoned patients were presented with severe visual impairment (blindness). Likewise, Elbastawesy et al., 2022 declared that one-third of their patients had visual sequelae [14]. Furthermore, Gheshlaghi et al., 2023 demonstrated that 33.33 % of methanol-poisoned patients experienced initial visual acuity deficits, which was substantially associated with long-term visual impairment and optic disc atrophy [33].

The main toxic metabolite of methanol (formic acid) inhibits cytochrome C oxidase, resulting in histotoxic hypoxia and impairing tissue oxygen [46]. Subsequently, the characteristic methanol-inducing ocular toxicity is attributed to the selective vulnerability of the optic nerves and the retina to hypoxia due to their relatively low number of mitochondria

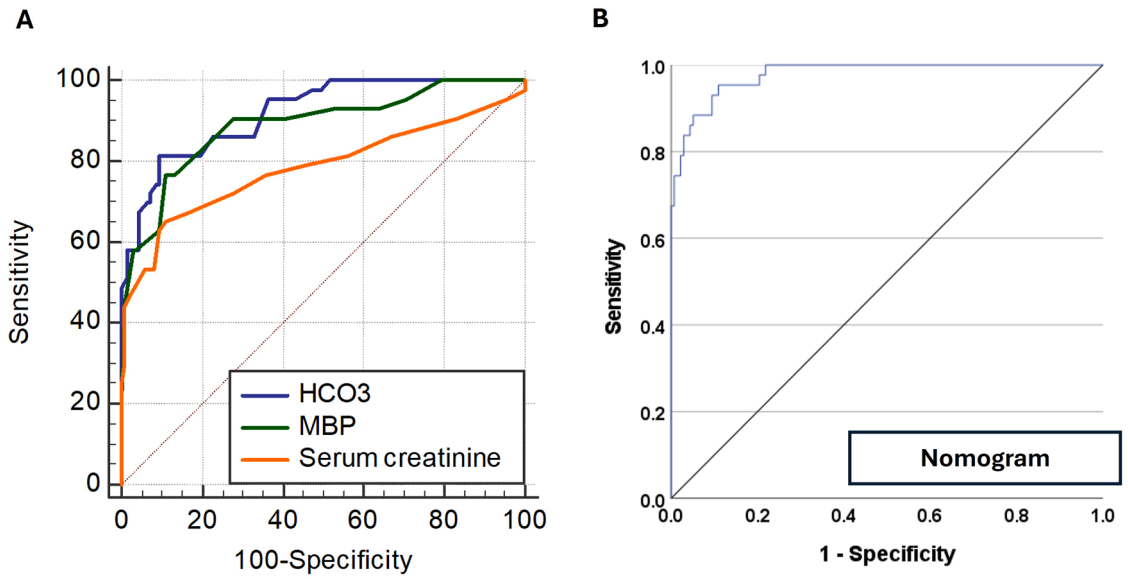

Fig. 3. **(A)** ROC curves for the quantitative predictors from the logistic regression model (MAP, HCO_3, and serum creatinine) predicting in-hospital mortality among methanol-poisoned patients.; **(B)** ROC curves testing the performance of the developed nomogram.

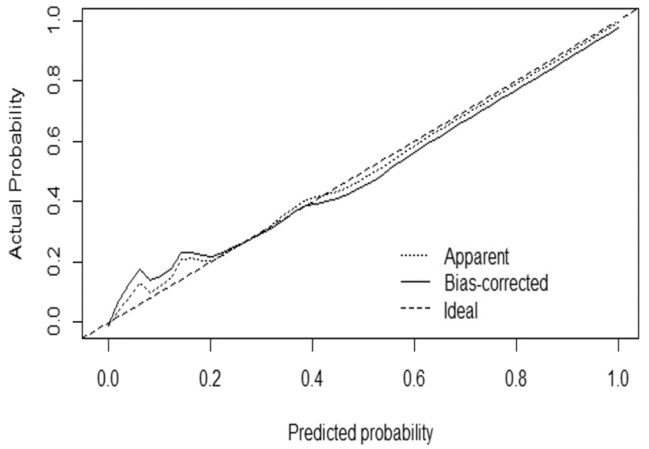

Fig. 4. Calibration curve testing the accuracy of the developed nomogram in predicting in-hospital mortality among methanol-poisoned patients.

and limited energy reserves [16]. Furthermore, the rich blood supply and high metabolic demand of ocular tissue may promote formic acid diffusion, inducing serious injury due to their location in the end-vascular zone perfusion [47]. Thus, formic acid targets the retro-laminar section of the optic nerve and the optic disc, resulting in optic disc edema, myelin sheath damage, direct axonal injury, as well as vacuolization in the retinal pigment epithelium and photoreceptor inner segments [15,48,49].

Many previous studies found a significant association between visual impairment, methanol poisoning severity, and in-hospital mortality [20, 21,50]. Accordingly, the current study proved that the presence of blindness was one of the nomogram predictors with the highest odds ratio, where the patients who presented with blindness on admission are 14 times at risk of mortality.

It is noteworthy that visual impairment might occur up to 72 hours after methanol ingestion [51]. Therefore, it is critically important to recognize red flags associated with blindness in methanol poisoning [52]. The current study pointed to delayed presentation and increased anion gap as the most influential risk factors for methanol-induced blindness, which complied with Shen et al., 2023 [48], who declared that delayed admission and degree of acidosis influenced the prognosis of visual acuity following methanol poisoning.

Table 6
Univariate and multivariable regression analysis for risk assessment of blindness in acute methanol poisoning.

	Odds ratio	95 % CI	*p* value
Univariate regression analysis			
Age (Years)	1.005	0.975–1.036	0.729
Sex (male)	2.508	0.294–21.363	0.400
Co-ingestion	1.028	0.343–3.080	0.960
Delay time (days)	1.041	1.013–1.070	0.004*
ECG abnormalities	1.849	0.953–3.856	0.069
GCS	0.889	0.815–0.969	0.008*
Heart rate (beat/min)	1.004	0.990–1.019	0.561
MAP (mmHg)	0.986	0.971–1.001	0.068
Respiratory rate (Breath/min)	0.972	0.947–0.998	0.033*
Methanol level (mg/dL)	1.002	0.998–1.007	0.298
pH	0.194	0.048–0.795	0.023*
$PaCO_2$ (mmHg)	1.032	1.011–1.054	0.003*
HCO_3 (mmol/l)	0.970	0.903–1.042	0.408
Lactate (mmol/l)	1.089	0.995–1.193	0.065
Base deficit (mmol/l)	1.041	1.004–1.080	0.031*
Anion gap (mmol/l)	1.062	1.020–1.107	0.004*
Osmol gap (mosmol/kg)	1.072	1.019–1.127	0.008*
Serum creatinine (mg/dL)	1.797	0.991–3.259	0.054
CPK(U/L)	1.00	1.00–1.001	0.004*
Hemoglobin (g/dl)	0.769	0.830–1.148	0.768
WBCs ($\times 10^9$/L)	1.065	1.008–1.125	0.026*
Platelets ($\times 10^9$/L)	1.012	1.005–1.019	<0.001*
Multivariable regression analysis			
Delay time (days)	1.039	1.010–1.069	0.009*
Anion gap (mmol/l)	1.053	1.007–1.101	0.023*
Accuracy 76.4 %			
Hosmer and Lemeshow test 0.185			

GCS: Glasgow Coma Scale; MAP: mean arterial pressure; $PaCO_2$: Partial arterial carbon dioxide pressure; HCO_3: Bicarbonate; CPK: Creatine Phosphokinase; WBCs: White Blood Cells; *Significant at $p < 0.05$; CI: confidence interval

The prolonged prehospital time in acute methanol poisoning is due to the unique pathophysiology, which is time-consuming, involving the production of formic acid from the parent compound. Additionally, local norms and legislation could contribute to further delayed seeking medical support in methanol-poisoned patients [50]. Alternatively, some patients had misconceptions of initial methanol poisoning as a non-serious condition, indicating medical intervention [46]. The current

study found that the median time between methanol ingestion and admission to poison centers was 18 hours. However, other studies conducted by Yousefinejad et al., 2020 [23] and Sharif et al., 2021 [53] reported a more prolonged prehospitalization period of 24 hours in patients with acute methanol poisoning.

An in-depth look at the pathophysiology of acute methanol poisoning reveals that delayed presentation, increased anion gap, and severe visual impairment are interconnected. The delayed admission is often associated with formic acid buildup and a subsequent increase in lactic acid formation from anaerobic cellular respiration. The accumulating formic acid and lactate are responsible for the increased anion gap in acute methanol poisoning [15]. Consequently, increased acidity enhances formic acid diffusion to the cells, aggravating its disastrous visual effects [54,55]. Similarly, Mishra et al., 2022 [56] and Jafarizadeh et al., 2023 [46] identified a significant correlation between acidosis and initial as well as final visual impairment. Accordingly, the anion gap was used as an early methanol prognostic indicator as it correlated well with formate levels [22].

As previously well known, profound metabolic acidosis is one of the diagnostic features of acute methanol poisoning with substantial association with poisoning severity. Consequently, serum bicarbonate level was included in the nomogram as one of the mortality predictors. The significant alternation of blood gas parameters (pH, HCO_3, PCO_2, lactate) to the acidic direction indicates cellular and tissue breakdown [15]. Likewise, HCO_3 was proposed as one of the early significant mortality predictors by Gulen et al., 2020 [20], Kayali et al.2022 [15]. and Eweda and Hasb Elnabia 2023 [12]. Accordingly, Sharif et al., 2023 [26] identified decreased HCO_3 as the main parameter of the nomogram predicting ICU admission in alcohol-poisoned patients.

Mean arterial pressure is one of the parameters reflecting the hemodynamic stability of poisoned patients. Therefore, this study considered diminished MAP as one of the model mortality predictors, as previously reported by Aydın et al.2022 [22]. The recorded hypotension could be one of the disastrous effects of acidosis that impedes myocardium contractility and induces arterial vasodilation [57].

Furthermore, Mansour et al., 2018 [13], Eweda and Hasb Elnabia 2023 [12], and Sasani et al., 2024 [17] emphasized a significant relationship between mortality and hypotension with compensatory tachycardia, highlighting them as alarming signs of poor outcome, among methanol-poisoned patients. Consistently, our study revealed a significant association between ECG abnormalities, including sinus tachycardia and inverted T wave, with mortality. ECG abnormalities could be attributed to direct ionic channel blockage and repolarization abnormalities by toxic formaldehyde metabolites [58–60].

Acute kidney injury (AKI) was one of the methanol poisoning sequelae that was strongly associated with mortality and multiorgan failure. Accordingly, previous studies reported that AKI ranged from 16 % to 66.0 % in methanol-poisoned patients [16,61–63].

According to Thongprayoon et al., the primary mechanism for AKI in methanol poisoning is the evolution of sepsis, although this process is still unknown [62]. Several causes are suggested for sepsis-induced AKI, including reduced renal perfusion and impaired microcirculation following notable hypotension, as well as the release of systemic inflammatory mediators producing renal tubular damage. Rhabdomyolysis is another postulated mechanism for AKI, where the low pH of tubular urine could enhance the precipitation of both myoglobin and hemoglobin in the renal tubules, producing tubular obstruction [62]. Another proposed mechanism is pancreatitis-induced AKI through releasing pancreatic enzymes and inflammatory mediators from necrotic pancreatic tissue, causing direct nephrotoxicity [62].

The high reported AKI incidences could explain the significant association between initial serum creatine and mortality in methanol-poisoned patients, which is consistent with previous studies conducted by Mansour et al., 2018 [13], Aydın H et al.2022 [22], and Eweda and Hasb Elnabia 2023 [12]. Consequently, serum creatine was one of the mortality predictors in the currently developed nomogram with a high odds ratio that increased the likelihood of mortality 5.670 times. Likewise, a systematic review and meta-analysis by Gheshlaghi et al., 2024 have identified serum creatinine as one of the strongest predictors of mortality methanol poisoning out of 15 potential factors [42].

Our study outperforms earlier studies that predicted methanol poisoning outcome. Previous studies predicted methanol unfavorable outcomes collectively as they included both two major adverse events (visual impairment and mortality) within the same category [14,23]. Also, other studies predicted in-hospital mortality in acute methanol poisoning using traditional statistical methods such as regression models and/or ROC analyses; these statistical approaches did not include results validation, in addition to their difficult applicability in clinical settings [10,13,17,22]. Recently, Rahimi et al., 2024 generated a machine learning-driven model that accurately predicted methanol poisoning outcomes with an AUC=0.947 [21]. However, not all attending physicians are familiar with applying artificial intelligence-based tools and might face technical difficulties. Alternatively, our nomogram has approximately similar excellent predictive capabilities (AUC=0.978) for predicting in-hospital mortality among methanol-poisoned patients. Furthermore, its graphical presentation allows attending toxicologists to apply this predictive tool easily.

Regarding visual impairment, a considerable portion of enrolled patients suffered from blindness on admission. Thus, we explored factors associated with blindness rather than generating a predictive model. The current study indicated that methanol-poisoned patients who presented late or had elevated anion gap were at higher risk for blindness.

5. Strengths and limitations

The current findings allow for the identification of methanol-poisoned patients with high probabilities of mortality or blindness. As regards mortality prediction, a nomogram was developed that accurately estimated the probability of in-hospital mortality of methanol-poisoned patients. Additionally, risk factors of blindness were identified. The main limitation of the current study was the inability to follow up for the patients after hospital discharge, particularly those with visual impairment. Accordingly, further studies are recommended to follow up for methanol-poisoned patients to assess the long-term outcome. Also, external validation of the created nomogram is warranted to verify the model's generalizability.

6. Conclusions

Notably, methanol poisoning is a global problem that has deleterious outcome. We observed a higher mortality and visual impairment frequency that mandate critical risk evaluation. As a result, timely risk assessment of unfavorable outcome promotes effective interventions and reduces lifelong visual sequelae. Our study addresses the knowledge gap and challenging matter in predicting outcome of acute methanol poisoning. Implementing four variables-based nomogram, including blindness, MAP, HCO_3, and serum creatinine, yielded robust discrimination and practical application for predicting in-hospital mortality. Furthermore, the elapsed time from exposure to hospitalization and increased anion gap are the significant risk factors for blindness. Identifying these determinants may revolutionize risk assessment techniques, assist clinical decision-making during the treatment course, and minimize the likelihood of visual disabilities.

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Author statement

We the undersigned declare that this manuscript is original, has not

been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Walaa G. Abdelhamid: Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ghada N. El-Sarnagawy:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zahraa Khalifa Sobh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None

Data Availability

Data will be made available on request.

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