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Association between pure high anion gap metabolic acidosis and adverse outcomes in acute carbon monoxide poisoning: a preliminary retrospective cohort study

Povezanost čiste metaboličke acidoze sa visokim „anjonskim zjapom“ i nepovoljnih ishoda akutnog trovanja ugljen monoksidom: preliminarna retrospektivna kohortna studija

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Abstract

Background/Aim. Acute carbon monoxide poisoning (ACOP) is a medical emergency, which causes a lack of oxygen in the tissues. The aim of the study was to determine the clinical characteristics of different acid-base disorder phenotypes in ACOP patients, focusing on the association between pure high anion gap (AG) metabolic acidosis and adverse outcomes (AOs). **Methods**. This retrospective study included 124 ACOP patients classified into three phenotypes according to the acid-base analysis: Type 1 (pure high AG metabolic acidosis), Type 2 (mixed acid-base disorders), and Type 3 (other conditions). Clinical indicators and outcomes were compared across groups. Multivariable logistic regression identified independent risk factors for AOs. **Results**. Type 1 phenotype patients [22 (17.74%)] exhibited significantly lower acid-base balance parameters (pH, HCO_3^-, standard base excess) and higher metabolic stress markers (AG, lactate; all $p < 0.05$). They had higher rates of systemic inflammatory response syndrome (SIRS) (72.73% vs. 46.67% and 38.60%) and intensive care unit admission (45.45% vs. 17.78% and 19.30%) than the Type 2 and 3 groups (all $p < 0.05$). Multivariable analysis confirmed the Type 1 phenotype as an independent risk factor for both SIRS [odds ratio (OR): 6.36, 95% confidence interval (CI): 1.486–27.213] and intensive care unit admission (OR: 4.71, 95% CI: 1.102–20.151). **Conclusion**. This preliminary study identifies pure high AG metabolic acidosis as a strong predictor of AOs in ACOP. This readily available arterial blood gas parameter provides a novel perspective for early risk stratification in emergency settings, though its clinical utility requires validation in prospective studies.

Keywords:
acidosis; blood gas analysis; carbon monoxide poisoning; intensive care units; risk assessment; systemic inflammatory response syndrome.

Apstrakt

Uvod/Cilj. Akutno trovanje uglen-monoksidom (*acute carbon monoxide poisoning* – ACOP) je urgentno medicinsko stanje, koje izaziva nedostatak kiseonika u tkivima. Cilj rada bio je da se utvrde kliničke karakteristke različitih fenotipova acido-baznih poremećaja kod pacijenata koji su pretrpeli ACOP, sa fokusom na povezanost između čiste metaboličke acidoze sa visokim „anjonskim zjapom“ (*anion gap* – AG) i nepovoljnih ishoda. **Metode.** Ova retrospektivna studija obuhvatila je 124 pacijenta koja su pretrpela ACOP, svrstana prema rezultatima analiza acido-baznog statusa u tri tipa fenotipa: tip 1 (čista metabolička acidoza sa visokim AG), tip 2 (mešoviti acido-bazni poremećaji) i tip 3 (ostala stanja). Upoređivani su klinički pokazatelji i ishodi između grupa. Za identifikaciju nezavisnih faktora rizika od nastanka nepovoljnih ishoda korišćena je multivarijabilna logistička regresija. **Rezultati.** Pacijenti fenotipa tip 1 [22, (17,74%)] imali su značajno niže vrednosti parametara acido-baznog statusa (pH, HCO_3^-, standardni bazni eksces) i više vrednosti markera metaboličkog stresa (AG, laktat; svi $p < 0,05$). Imali su veću učestalost sindroma sistemskog inflamacijskog odgovora (*systemic inflammatory response syndrome* – SIRS) (72,73% vs. 46,67% i 38,60%, redom) i prijema u jedinicu intenzivne nege (45,45% vs. 17,78% i 19,30%, redom) u odnosu na grupe tipa 2 i tipa 3 (svi $p < 0,05$). Multivarijabilnom analizom potvrđen je fenotip tipa 1 kao nezavisan faktor rizika kako za nastanak SIRS [*odds ratio* (OR): 6,36, 95% *confidence interval* (CI): 1,486–27,213], tako i za prijem u jedinicu intenzivne nege (OR: 4,71, 95% CI: 1,102–20,151). **Zaključak.** Ovom

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preliminarnom studijom identifikovana je čista metabolička acidoza sa visokim AG kao snažan prediktor nepovoljnih ishoda kod ACOP. Kao lako dostupan parametar iz analize gasova arterijske krvi, on u hitnim situacijama pruža novu mogućnost za ranu stratifikaciju rizika u urgentnim stanjima, mada njegova klinička primena zahteva validaciju u prospektivnim studijama.

Ključne reči:
acidoza; krv, analiza gasova; trovanje ugljenmonoksidom; intenzivna nega, odeljenja; rizik, procena; sindrom sistemske zapaljenske reakcije.

Introduction

Acute carbon monoxide (CO) poisoning (ACOP) represents a significant global public health challenge, characterized by persistently high morbidity and mortality rates. ACOP typically results from exposure to CO generated by the incomplete combustion of carbon-containing fuels in enclosed or poorly ventilated spaces. Common sources include malfunctioning domestic gas heaters, coal stoves, charcoal grills, portable generators, vehicle exhaust in garages, and occupational exposure in industrial settings [1–2]. The 2021 Global Burden of Disease Study reported approximately 28,900 deaths globally attributable to unintentional ACOP that year, with significant regional variations in mortality highlighting the ongoing severity of the situation and the urgent need for effective control strategies [3]. The pathophysiological core of ACOP is tissue hypoxia. CO not only reduces the blood's oxygen-carrying capacity by forming carboxyhemoglobin (COHb) but also directly inhibits the mitochondrial respiratory chain, triggering oxidative stress (OS) and energy metabolism dysfunction, ultimately leading to internal environment disturbances [4–6]. In this context, arterial blood gas (ABG) analysis is a key tool for assessing acid-base balance, with parameters such as pH, bicarbonate, and the anion gap (AG) becoming crucial for determining the prognosis of critically ill patients [7–8].

High AG metabolic acidosis (MA) is a common metabolic disturbance in ACOP, primarily due to lactate accumulation from tissue hypoxia [9]. However, current research has predominantly focused on evaluating the overall acid-base status or the prognostic value of individual biochemical markers [10, 11], lacking a refined differentiation of acid-base disorder phenotypes. A key knowledge gap exists regarding whether there are essential differences in clinical characteristics and prognostic significance between pure high AG MA and mixed acid-base disorders [12, 13]. Although the Glasgow Coma Scale (GCS) score and COHb level are classic indicators for assessing severity, it remains to be elucidated whether the specific phenotype of pure high AG MA remains an independent predictor of adverse outcomes (AOs) after adjusting for these known risk factors [14, 15]. This limitation results in a lack of precise evidence in current guidelines for individualized risk stratification and intervention based on different metabolic phenotypes [4].

To address this gap, this study aims to employ the clinically commonly used three-step method for analyzing acid-base disorders to finely classify the acid-base status of ACOP patients at admission. It will focus specifically on pure high AG MA to clarify its clinical characteristics and its association with AOs. The study hypothesizes that in ACOP patients, pure high AG MA, compared to mixed acid-base disorders, can more independently and strongly predict the development of systemic inflammatory response syndrome (SIRS) and the need for intensive care unit (ICU) admission, thereby providing a novel perspective for early risk stratification that goes beyond traditional indicators.

Therefore, the aim of this study was to generate evidence to improve the identification of critically ill ACOP patients and guide precise management.

Methods

Study design and participants

This single-center retrospective cohort study was approved by the Ethics Committee of Bozhou People's Hospital, Bozhou, China (No. BoYiLunShen 263, from November 03, 2025) and conducted in accordance with the Declaration of Helsinki and relevant ethical guidelines. Consecutive adult patients with ACOP admitted to the Emergency Department of our Hospital between December 2022 and December 2024 were enrolled.

Inclusion criteria were as follows: age ≥ 18 years; confirmed ACOP diagnosis based on a clear history of CO exposure, clinical symptoms, and laboratory tests; COHb level > 5% at admission; and availability of complete ABG analysis, electrolyte panel, lactate measurement, clinical data, laboratory results, and follow-up outcomes obtained immediately upon admission.

Exclusion criteria were: pre-existing chronic organ dysfunction (e.g., chronic heart failure, chronic renal failure, cirrhosis), chronic metabolic diseases (e.g., diabetic ketoacidosis, renal tubular acidosis), or autoimmune diseases; prehospital treatments that could significantly alter acid-base balance or laboratory parameters (e.g., high-flow oxygen therapy, mechanical ventilation, fluid resuscitation for acid-base correction); concomitant conditions such as other toxin poisonings, major trauma, acute infections, or recent surgery, and incomplete clinical, laboratory, or outcome data precluding acid-base phenotyping or statistical analysis.

A final cohort of 124 patients was included.

Acid-base disorder phenotyping

Acid-base disorder phenotyping was performed *via* a standardized three-step physiological algorithm using admission pre-oxygenation ABG analysis and electrolyte panel data to characterize acid-base patterns that support early, rapid emergency decision-making [16, 17]. First, the primary acid-base disorder has been determined based on pH, partial pres-

sure of arterial carbon dioxide ($PaCO_2$), and hydrogen carbonate (HCO_3^-). Subsequently, AG is calculated as AG = $Na^+ + K^+ - Cl^- - HCO_3^-$, with AG > 16 mmol/L defining high-AG MA. Finally, the adequacy of respiratory compensation is assessed using Winter's formula. If the measured $PaCO_2$ fell within the range of the predicted $PaCO_2 \pm 2$ mmHg, respiratory compensation was deemed appropriate, and the case was classified as Type 1 (pure high AG MA). If the measured value fell outside this range, it indicated the presence of a mixed respiratory component, and the case was classified as Type 2 (mixed disorder). Accordingly, the final classification was: Type 1 (pure high AG MA) – elevated AG with appropriate respiratory compensation; Type 2 (mixed disorder) – presence of any two or more primary acid-base disorders; Type 3 (other) – all other simple disorders and cases without significant acid-base derangement, excluding Type 1. To ensure objectivity and reliability, all phenotyping results were independently and blindly assessed by two clinicians. Any discrepancies were resolved by a third senior physician for final adjudication. This classification method adheres to established physiological principles [18, 19].

Data collection and outcome definition

Data were extracted from the hospital electronic medical records and were classified into several categories: baseline characteristics, clinical and laboratory parameters, and clinical outcomes. Baseline characteristics included age, sex, height, weight, smoking history, alcohol use, and comorbidities (e.g., hypertension, coronary artery disease, and diabetes mellitus). Clinical and laboratory parameters on admission consisted of the following: vital signs (temperature, heart rate, respiratory rate, blood pressure); GCS score (calculated as the average of independent assessments by two emergency physicians); ABG parameters (pH, $PaCO_2$, HCO_3^-); electrolytes (Na^+, Cl^-, K^+); AG, lactate, COHb, complete blood count, liver and kidney function tests; and myocardial injury, which was defined as elevated cardiac troponin I (cTnI ≥ 0.05 ng/mL). The final category included clinical outcomes. Primary outcomes were the occurrence of SIRS and the need for ICU admission. SIRS was diagnosed when at least two of the following criteria were met [20]: temperature > 38 °C or < 36 °C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg; white blood cell count > 12×10^9/L or < 4×10^9/L, or > 10% immature bands. SIRS was monitored continuously during the first 6 hrs of hospitalization, and its occurrence was recorded as a binary outcome. ICU admission was defined as transfer to the ICU for intensive monitoring and treatment due to critical illness within 6 hrs of emergency department presentation.

Treatment protocol

All patients received uniform institutional care: high-flow oxygen (10–15 L/min) immediately upon arrival, followed by hyperbaric oxygen therapy as routine standard care for all confirmed ACOP cases. No patient received bicarbonate or alkalinizing agents to correct acidosis. Mechanical ventilation and vasopressors were used only for standard indications. Treatment modality was identical across all phenotype groups and was not analyzed as a covariate.

Statistical analysis

As an exploratory retrospective cohort study analyzing associations between acid-base phenotypes and outcomes in ACOP, the sample size was determined by the consecutive eligible cases available during the study period. We acknowledged that the sample size, particularly for the Type 1 subgroup, might limit statistical power. A *post-hoc* power analysis using Demidenko's formula [21] was performed to contextualize the findings. For the primary outcome (ICU admission), based on an odds ratio (OR) of 3.60 from univariate analysis, an alpha of 0.05, and 80% power, the calculated required sample size was approximately 180. With 124 included patients, the achieved power was approximately 64%. For the secondary outcome (SIRS), the required sample size was approximately 128, corresponding to an achieved power of 79%. Analyses were performed using SPSS 26.0. Normally distributed continuous data are presented as mean ± standard deviation and compared using one-way analysis of variance – ANOVA (with *post-hoc* testing if variances were equal); non-normally distributed data are presented as median (first quartile – Q1, third quartile – Q3) and compared using the Kruskal-Wallis *H* test. Categorical data are presented as numbers (percentages) and compared using the chi-square (χ^2) or Fisher's exact test. Correlations were assessed using Spearman's rank correlation. Variables with $p < 0.1$ in univariate logistic regression were entered into multivariable logistic regression models (using the stepwise method; entry $\alpha = 0.05$; removal $\alpha = 0.10$) to identify independent risk factors. A two-sided $p < 0.05$ was considered statistically significant.

Results

Comparison of baseline characteristics and clinical indicators across the three groups

The 124 ACOP patients were classified into three acid-base phenotype groups: Type 1 – pure high AG MA [22 (17.74%)], Type 2 – mixed acid-base disorders [45 (36.29%)], and Type 3 – other conditions [57 (45.97%)]. No statistically significant differences were observed among the three groups regarding age, sex, BMI, vital signs, or baseline laboratory indicators (all $p > 0.05$), indicating comparability at baseline.

Significant differences were found among the groups in acid-base balance, metabolic, and inflammatory markers (all $p < 0.05$). Specifically, patients with the Type 1 phenotype exhibited characteristic features of severe MA with a high AG: they had the lowest pH and HCO_3^- levels, and the highest AG values (e.g., pH: Type 1: 7.33 vs. Type 2: 7.39 vs. Type 3: 7.41; AG: Type 1: 25.20 mmol/L vs. Type 2: 20.99 mmol/L vs. Type 3: 16.78 mmol/L). Concurrently, lactate levels were significantly higher in the Type 1 group com-

pared to the other two groups (median: 5.20 mmol/L vs. 3.80 mmol/L vs. 2.20 mmol/L, respectively) (Table 1).

Analysis of clinical outcomes revealed that the Type 1 phenotype group had the highest incidence of adverse events. Both the incidence of SIRS (72.73%) and the rate of ICU admission (45.45%) were significantly higher in the Type 1 group compared to the Type 2 (SIRS: 46.67%; ICU admission: 17.78%) and Type 3 groups (SIRS: 38.60%; ICU admission: 19.30%) (intergroup comparisons, all $p < 0.05$) (Table 1).

Correlation analysis of major clinical indicators

Spearman correlation analysis revealed significant associations among key clinical indicators (Table 2). The Type 1

Table 1

Comparison of baseline characteristics and clinical indicators among ACOP patients with different acid-base phenotypes

Variable	Reference ranges	Type 1 (n = 22)	Type 2 (n = 45)	Type 3 (n = 57)	*p*-value
Age, years	–	55.0 (44.5, 71.8)	58.0 (50.0, 70.0)	55.0 (46.0, 68.0)	0.741
Gender					
male	–	7 (31.80)	22 (48.90)	30 (52.60)	0.246
BMI, kg/m²	–	23.95 (22.98, 26.53)	23.53 (21.48, 26.84)	24.22 (22.04, 27.04)	0.646
Temperature, °C	36.0–37.4	36.50 (36.50, 36.60)	36.60 (36.40, 36.80)	36.5 (36.50, 36.60)	0.585
Heart rate, bpm	60.0–100.0	95.00 (86.00, 104.50)	82.00 (76.00, 108.00)	85.00 (78.00, 98.00)	0.284
Respiratory rate, breaths/min	12.0–20.0	19.00 (16.30, 20.00)	18.00 (16.00, 21.00)	18.00 (15.00, 20.00)	0.622
Systolic BP, mmHg	90.0–139.0	118.00 (104.50, 129.50)	129.00 (118.00, 144.00)	127.00 (116.00, 139.00)	0.081
Hypertension	–	6 (27.30)	14 (31.10)	15 (26.30)	0.862
Diabetes mellitus	–	3 (13.60)	3 (6.70)	6 (10.50)	0.635
GCS score	–	11.00 (8.00, 13.00)	12.00 (8.00, 14.00)	13.00 (9.00, 15.00)	0.158
COHb, %	–	28.40 (20.20, 40.70)	21.20 (13.20, 34.80)	27.50 (14.30, 33.40)	0.352
pH	7.35–7.45	7.33 (7.31, 7.36)	7.39 (7.34, 7.43)	7.41 (7.38, 7.44)	< 0.001
HCO_3^-, mmol/L	22.00–27.00	15.45 (14.10, 17.20)	19.50 (16.40, 23.50)	21.10 (20.00, 23.00)	< 0.001
AG, mmol/L	8.00–16.00	25.20 (23.08, 26.46)	20.99 (18.67, 25.18)	16.78 (15.44, 18.37)	< 0.001
Lactate, mmol/L	0.50–2.20	5.20 (2.92, 8.38)	3.80 (2.00, 5.50)	2.20 (1.70, 3.30)	< 0.001
WBC count, $\times 10^9$/L	4.00–10.00	14.12 (10.94, 21.23)	11.74 (8.97, 15.81)	10.43 (8.21, 13.55)	0.030
Hemoglobin, g/L	130.0–175.0	143.50 (124.00, 154.00)	136.00 (120.00, 155.00)	133.00 (125.00, 144.00)	0.563
Creatinine, μmol/L	57.0–97.0	56.60 (47.70, 79.50)	65.30 (48.90, 94.10)	59.40 (48.30, 69.30)	0.391
ALT, U/L	10.0–40.0	25.00 (20.00, 40.50)	30.00 (20.00, 47.00)	21.00 (17.00, 33.00)	0.050
Albumin, g/L	40.0–55.0	45.90 (40.80, 48.00)	43.90 (39.90, 45.90)	41.50 (39.30, 45.30)	0.048
Myocardial injury	–	14 (63.60)	20 (44.40)	22 (38.60)	0.133
SIRS	–	16 (72.73)	21 (46.67)	22 (38.60)	0.024
ICU admission	–	10 (45.45)	8 (17.78)	11 (19.30)	0.026

ACOP – acute carbon monoxide poisoning; n – number; BMI – body mass index; bpm – beats *per* minute; BP – blood pressure; GCS – Glasgow Coma Scale; COHb – carboxyhemoglobin; AG – anion gap; WBC – white blood cell; ALT – alanine aminotransferase; SIRS – systemic inflammatory response syndrome; ICU – intensive care unit.

***Note*: Data are presented as median (first quartile, third quartile) or as numbers (percentages). Comparisons among groups were performed using the Kruskal-Wallis *H* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. For detailed definitions of Types 1–3, see the Methods section.**

Table 2

Spearman correlation coefficient matrix of major clinical indicators and outcomes in patients with ACOP

Variable	SIRS	Type 1	ICU admission	GCS Score	COHb	Lactate
SIRS	–					
Type 1	0.231*	–				
ICU admission	0.237**	0.241**	–			
GCS score	-0.416**	-0.127	-0.506**	–		
COHb	0.082	0.117	0.653**	-0.428**	–	
Lactate	0.484**	0.280**	0.423**	-0.467**	0.478**	–

ACOP – acute carbon monoxide poisoning; SIRS – systemic inflammatory response syndrome; ICU – intensive care unit; GCS – Glasgow Coma Scale; COHb – carboxyhemoglobin; n – number.

***Note*: The data in the table represent Spearman correlation coefficients (ρ). *$p < 0.05$, ** $p < 0.01$ (two-tailed test). For brevity, sample size (n = 124) and non-significant *p*-values are not shown in the table. "Type 1" refers to the pure high anion gap metabolic acidosis phenotype.**

acid-base phenotype (pure high AG MA) showed significant positive correlations with the occurrence of SIRS (ρ = 0.231, $p < 0.05$), ICU admission (ρ = 0.241, $p < 0.01$), and lactate levels (ρ = 0.280, $p < 0.01$, more precise: $p = 0.002$). This indicates a significant association between this phenotype and systemic inflammatory response, critical outcomes, and the degree of tissue hypoxia. However, no significant correlation was found between the Type 1 phenotype and the GCS score (ρ = -0.127, $p = 0.162$) or COHb levels (ρ = 0.117, $p = 0.199$), suggesting that the critical nature of the Type 1 phenotype appears to be independent of traditional indicators of consciousness impairment and poisoning severity. In contrast, traditional critical illness indicators such as lactate, GCS score, and COHb showed stronger correlations with each other and with both SIRS and ICU admission (all $p < 0.001$).

Analysis of risk factors for intensive care unit admission

Univariate logistic regression identified multiple variables associated with ICU admission ($p < 0.1$) (Table 3). Multivariable analysis further identified three independent predictors: Type 1 phenotype [OR: 4.71, 95% confidence interval (CI): 1.102–20.151, $p = 0.037$], GCS score (OR: 0.76, 95% CI: 0.618–0.940, $p = 0.011$), and COHb (OR: 1.12, 95% CI: 1.054–1.200, $p < 0.001$). Hemoglobin showed a trend (OR: 1.03, 95% CI: 0.997–1.067, $p = 0.077$). Heart rate and white blood cell count did not demonstrate independent predictive value.

Analysis of risk factors for systemic inflammatory response syndrome occurrence

Univariate logistic regression analysis demonstrated that the Type 1 phenotype (pure high AG MA) was significantly associated with the development of SIRS in patients with ACOP ($p < 0.012$). Variables with $p < 0.1$ in the univariate analysis were subsequently included in a multivariable logistic regression model. After multivariable adjustment, Type 1 phenotype remained the strongest independent predictor (OR: 6.36, 95% CI: 1.486–27.213, $p = 0.013$), alongside GCS score (OR: 0.79, $p = 0.008$), hypertension (OR: 0.14, $p = 0.006$, protective), hemoglobin (OR: 1.03, $p = 0.050$), creatinine (OR: 1.02, $p = 0.025$), ALT (OR: 1.04, $p = 0.033$) and myocardial injury (OR: 3.76, $p = 0.023$). The magnitude of this association is presented in Table 4, indicating that this specific acid-base disorder phenotype possesses independent predictive value for the onset of SIRS.

Table 3

Risk factors for intensive care unit admission

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Type 1 phenotype	3.64	1.372–9.662	0.009	4.71	1.102–20.151	0.037
GCS score	0.68	0.582–0.796	< 0.001	0.76	0.618–0.940	0.011
COHb, %	1.15	1.089–1.219	< 0.001	1.12	1.054–1.200	< 0.001
Gender						
male	2.16	0.918–5.057	0.078	–	–	–
Heart rate, bpm	1.03	1.006–1.054	0.012	–	–	–
WBC count, $\times 10^9$/L	1.10	1.029–1.178	0.006	–	–	–
Hemoglobin, g/L	1.05	1.022–1.076	< 0.001	1.03	0.997–1.067	0.077
Albumin, g/L	1.08	1.012–1.161	0.022	–	–	–
Age, years	1.00	0.973–1.020	0.748	–	–	–
BMI, kg/m²	0.98	0.883–1.091	0.725	–	–	–
Temperature, °C	1.00	0.282–3.562	0.997	–	–	–
Respiratory rate, breaths/min	1.02	0.936–1.101	0.708	–	–	–
Systolic BP, mmHg	0.99	0.976–1.013	0.552	–	–	–
Hypertension	0.45	0.157–1.298	0.140	–	–	–
Diabetes mellitus	1.10	0.278–4.375	0.890	–	–	–
Creatinine, μmol/L	1.00	0.992–1.015	0.578	–	–	–
ALT, U/L	1.00	0.984–1.021	0.809	–	–	–
Total bilirubin, μmol/L	1.06	0.985–1.132	0.128	–	–	–
Myocardial injury	1.69	0.732–3.910	0.218	–	–	–

OR – odds ratio; CI – confidence interval; GCS – Glasgow Coma Scale; COHb – carboxyhemoglobin; bpm – beats *per* min; WBC – white blood cell; BMI – body mass index; BP – blood pressure; ALT – alanine aminotransferase.

***Note*: Variables with $p < 0.1$ in univariate analysis were entered into multivariate analysis using the stepwise method (entry $\alpha = 0.05$, removal $\alpha = 0.10$). Blood gas parameters (pH, $PaCO_2$, HCO_3^-, AG, lactate) were excluded from regression analysis due to causal inclusion relationships with the metabolic acidosis phenotype. A dash (–) indicates the variable was not included in the final multivariate model.**

Table 4

Risk factors for systemic inflammatory response syndrome

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Type 1 phenotype	3.66	1.323–10.119	0.012	6.36	1.486–27.213	0.013
GCS score	0.76	0.676–0.864	< 0.001	0.79	0.662–0.941	0.008
Gender						
male	2.49	1.208–5.137	0.013	–	–	–
Hypertension	0.39	0.171–0.895	0.026	0.14	0.035–0.562	0.006
Hemoglobin, g/L	1.05	1.025–1.072	< 0.001	1.03	1.000–1.060	0.050
Creatinine, μmol/L	1.03	1.014–1.049	< 0.001	1.02	1.003–1.046	0.025
ALT, U/L	1.05	1.024–1.083	< 0.001	1.04	1.003–1.070	0.033
Albumin, g/L	1.10	1.024–1.188	0.010	–	–	–
Myocardial injury	6.45	2.940–14.140	< 0.001	3.76	1.201–11.747	0.023
Diabetes mellitus	0.33	0.086–1.296	0.113	–	–	–
COHb, %	1.02	0.987–1.046	0.278	–	–	–
Age, years	1.00	0.976–1.016	0.691	–	–	–
BMI, kg/m²	1.01	0.920–1.098	0.911	–	–	–
Systolic BP, mmHg	1.00	0.980–1.012	0.645	–	–	–
Total bilirubin, μmol/L	1.02	0.954–1.084	0.601	–	–	–

OR – odds ratio; CI – confidence interval; GCS – Glasgow Coma Scale; ALT – alanine aminotransferase; COHb – carboxyhemoglobin; BMI – body mass index.

***Note*: Variables with $p < 0.1$ in univariate analysis were entered into multivariate analysis using the stepwise method (entry $\alpha = 0.05$, removal $\alpha = 0.10$). Blood gas parameters (pH, $PaCO_2$, HCO_3^-, AG, lactate) were excluded from regression analysis due to causal inclusion relationships with the metabolic acidosis phenotype. Systemic inflammatory response syndrome (SIRS) component variables (temperature, heart rate, respiratory rate, white blood cell count) were excluded from SIRS-related regression analyses due to definitional overlap with the outcome. A dash (–) indicates the variable was not included in the final multivariate model.**

Discussion

This preliminary study indicates that ACOP patients presenting with pure high AG MA upon admission face a significantly elevated risk of developing SIRS and requiring ICU admission. Despite the limited sample size, the core value of this study lies in being the first to utilize standardized physiological phenotyping to reveal the independent prognostic role of compensatory failure in ACOP. We have clearly identified this phenotype as a critical clinical manifestation in ACOP. Multivariable analysis demonstrated that even after adjusting for factors like GCS score and COHb level, it remained a strong independent risk factor for both SIRS (OR: 6.36) and ICU admission (OR: 4.71). This directly links the core pathophysiology of ACOP–tissue hypoxia and metabolic failure–to clinical risk, providing a key metabolic indicator for identifying high-risk patients in the emergency setting [5, 9].

The Type 1 phenotype signifies that the patient has entered a vicious cycle of tissue hypoxia and compensatory failure. CO not only reduces oxygen-carrying capacity by forming COHb but also directly inhibits mitochondrial cytochrome c oxidase, leading to lactate accumulation, the primary cause of elevated AG [4–6]. The weak positive correlation observed between the Type 1 phenotype and lactate levels ($\rho = 0.280$, $p = 0.002$) in univariate analysis supports this pathological mechanism. Its "pure" nature–indicating appropriate respiratory compensation–suggests that despite maximal compensatory effort, the acidosis remains uncorrected, pointing to the extreme severity of the hypoxia and metabolic disturbance [16, 17]. Multivariable analysis further confirmed this phenotype as an independent predictor of AOs, consistent with findings from Wang et al. [9] and Kimmel and Alscher [13].

A key aspect of this study is its distinction between the prognostic implications of pure vs. mixed high-AG MA. The "pure" nature of the Type 1 phenotype implies that respiratory compensation has reached its maximum capacity yet fails to correct the acidosis, indicating that the MA has exceeded physiological compensatory limits, leading to a decompensated vicious cycle of hypoxia-lactate accumulation-worsening acidosis. In contrast, the Type 2 (mixed) phenotype encompasses various scenarios such as over-compensation, under-compensation, or combination with other acid-base disorders, resulting in complex pathological significance that may dilute the critical signal of a high AG. Consequently, its prognostic value is considerably lower than that of the pure phenotype.

This study addresses a gap in previous research, which often focused on overall acid-base status or single parameters [10, 11], by confirming the independent prognostic value of pure high AG MA. This aligns with findings in critical care: Mochizuki et al. [22] reported higher mortality with metabolic acidemia than with respiratory acidemia, and Canova et al. [23] confirmed MA as an independent risk factor for in-hospital mortality. Our study focuses this understanding specifically on ACOP, deepening the knowledge of acid-base disorders in this condition. Furthermore, the high incidence of SIRS in Type 1 patients is consistent with the systemic inflammatory state seen in septic patients in the emergency department [24] and

supports the mechanism proposed by Simonsen et al. [5] wherein CO poisoning triggers OS and inflammatory responses, thereby completing the pathophysiological chain of ACOP.

In clinical practice, rapid acid-base phenotyping using admission blood gas analysis is simple, immediate, and incurs no additional cost, making it well-suited for emergency department use. Identifying patients with the Type 1 phenotype should prompt initiation of more intensive monitoring and treatment, including early hemodynamic monitoring, assessment of eligibility for advanced respiratory support, optimization of hyperbaric oxygen therapy schedules, and lactate clearance therapy, thereby enabling precise intervention. Future research should involve large-scale, multicenter prospective studies to validate the predictive power of this phenotype, explore targeted personalized treatment strategies, and clarify its impact on improving patient outcomes, thereby providing an evidence base for updating clinical guidelines.

Limitation of the study

This study has several limitations. First, its single-center retrospective design and relatively small sample size limit statistical power, resulting in wide CIs for the ORs in the multivariable analysis. The conclusions should therefore be considered hypothesis-generating and require validation in larger prospective multicenter studies. Second, the retrospective design is susceptible to unmeasured confounding factors. Specifically, data on CO exposure duration, transport time to hospital, and prehospital treatments (e.g., oxygen administration by emergency medical services, fluid resuscitation) were not systematically documented in electronic medical records and thus could not be included in the analysis. These factors may significantly influence the severity of poisoning and subsequent outcomes. Their absence reflects an inherent limitation of retrospective emergency department studies, and future prospective studies should incorporate standardized prehospital data-collection protocols. Third, the study focused only on short-term outcomes (SIRS, ICU admission) and lacked follow-up on long-term neurological sequelae and mortality [12], preventing a comprehensive assessment of the phenotype's long-term value. Finally, constrained by data availability in the emergency setting, SIRS rather than the sequential organ failure assessment – SOFA score was used to define the inflammatory response; biomarkers of inflammation and OS were not measured [5, 9]; the efficacy of different treatments across phenotypes was not analyzed [15]; and the generalizability of the single-center data requires verification [14].

Conclusion

Ultimately, pure high anion gap metabolic acidosis represents a critical phenotype in acute carbon monoxide poisoning and is a strong independent predictor for the development of systemic inflammatory response syndrome and the need for intensive care unit admission. This readily available parameter from routine blood gas analysis provides a crucial metabolic perspective for identifying high-risk patients, stratifying risk, and guiding intensive treatment in the emergency department, holding significant clinical value. This study enriches the evidence base concerning acid-base disorders in acute carbon monoxide poisoning, provides a reference for refining clinical guidelines, and lays the groundwork for subsequent prospective research.

REFERENCES

1. *Bleecker ML.* Carbon monoxide intoxication. Handb Clin Neurol 2015; 131: 191–203. DOI: 10.1016/B978-0-444-62627-1.00024-X.
2. *Weaver LK.* Carbon monoxide poisoning. Undersea Hyperb Med 2020; 47(1): 151–69. DOI: 10.22462/01.03.2020.17.
3. *GBD 2021 Carbon Monoxide Poisoning Collaborators.* Global, regional, and national mortality due to unintentional carbon monoxide poisoning, 2000-2021: results from the Global Burden of Disease Study 2021. Lancet Public Health 2023; 8(11): e839–49. DOI: 10.1016/S2468-2667(23)00185-8.
4. *Hampson NB, Piantadosi CA, Thom SR, Weaver LK.* Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. Am J Respir Crit Care Med 2012; 186(11): 1095–101. DOI: 10.1164/rccm.201207-1284CI.
5. *Simonsen C, Magnusdottir SO, Andreasen JJ, Wimmer R, Rasmussen BS, Kjaergaard B,* et al. Metabolic changes during carbon monoxide poisoning: An experimental study. J Cell Mol Med 2021; 25(11): 5191–201. DOI: 10.1111/jcmm.16522.
6. *Dent MR, Rose JJ, Tejero J, Gladwin MT.* Carbon Monoxide Poisoning: From Microbes to Therapeutics. Annu Rev Med 2024; 75: 337–51. DOI: 10.1146/annurev-med-052422-020045.
7. *Sanagustín MN, Osredkar J.* Blood gas analysis: Clinical applications, interpretation and future directions (Review). Med Int (Lond) 2025; 6(1): 7. DOI: 10.3892/mi.2025.291.
8. *Castro D, Patil SM, Zubair M, Keenaghan M.* Arterial Blood Gas. In StatPearl [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.
9. *Wang W, Huang H, Xiong X, Ye C, Huang J, Ling YA.* Multidimensional metabolic profiling in carbon monoxide poisoning: acid-base disturbances correlate with neurological severity. Biomarkers 2025; 30(5): 363–70. DOI: 10.1080/1354750X.2025.2551303.
10. *Aykut A, Günsoy E, Karabulut BÖ, Aktaş RS, Öncül MV, Karabulut AE.* Serum lactate and carboxyhemoglobin as predictors of hyperbaric oxygen therapy in carbon monoxide poisoning: a retrospective study. BMC Emerg Med 2025; 25(1): 252. DOI: 10.1186/s12873-025-01410-w.
11. *Doğruyol S, Akbaş I, Tekin E, Doğruyol M.* Carbon monoxide intoxication in geriatric patients: How important are lactate values at admission? Hum Exp Toxicol 2020; 39(6): 848–54. DOI: 10.1177/0960327120903484.
12. *Rahimi M, Aghabiklooei A, Nasouhi S, Mashayekhian M, Ghoochani A, Yousefi Y,* et al. A 5-year Assessment on Carbon Monoxide Poisoning in a Referral Center in Tehran-Iran. Int J Prev Med 2019; 10: 116. DOI: 10.4103/ijpvm.IJPVM_338_18.
13. *Kimmel M, Alscher MD.* Disorders of the acid-base balance and the anion gap. Dtsch Med Wochenschr 2016; 141(21): 1549–54. (German) DOI: 10.1055/s-0042-109042.
14. *Mattiuzzi C, Lippi G.* Worldwide epidemiology of carbon monoxide poisoning. Hum Exp Toxicol 2020; 39(4): 387–92. DOI: 10.1177/0960327119891214.

15. *Liao WC, Cheng WC, Wu BR, Chen WC, Chen CY, Chen CH,* et al. Outcome and prognostic factors of patients treated in the intensive care unit for carbon monoxide poisoning. J Formos Med Assoc 2019; 118(4): 821–7. DOI: 10.1016/j.jfma.2018.09.005.
16. *Berend K, de Vries AP, Gans RO.* Physiological approach to assessment of acid-base disturbances. N Engl J Med 2015; 372(2): 193–5. DOI: 10.1056/NEJMc1413880.
17. *Morikawa MJ, Ganesh PR.* Acid-Base Interpretation: A Practical Approach. Am Fam Physician 2025; 111(2): 148–55.
18. *Hopkins E, Sanvictores T, Sharma S.* Physiology, Acid Base Balance. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
19. *Cao Y, Wang M, Yuan Y, Li C, Bai Q, Li M.* Arterial blood gas and acid-base balance in patients with pregnancy-induced hypertension syndrome. Exp Ther Med 2019; 17(1): 349–53. DOI: 10.3892/etm.2018.6893.
20. *Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M,* et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801–10. DOI: 10.1001/jama.2016.0287.
21. *Demidenko E.* Sample size determination for logistic regression revisited. Stat Med 2007; 26(18): 3385–97. DOI: 10.1002/sim.2771.
22. *Mochizuki K, Fujii T, Paul E, Anstey M, Uchino S, Pilcher DV,* et al. Acidemia subtypes in critically ill patients: An international cohort study. J Crit Care 2021; 64: 10–7. DOI: 10.1016/j.jcrc.2021.02.006.
23. *Canova TJ, Lipps K, Dahiya G, Hillerson DB, Kashani KB, Jentzer JC.* Admission Acid-Base Status and Mortality in Cardiac Intensive Care Unit Patients. J Intensive Care Med 2026; 41(7): 670–82. DOI: 10.1177/08850666251399182.
24. *Henning DJ, Puskarich MA, Self WH, Howell MD, Donnino MW, Yealy DM,* et al. An Emergency Department Validation of the SEP-3 Sepsis and Septic Shock Definitions and Comparison With 1992 Consensus Definitions. Ann Emerg Med 2017; 70(4): 544–52.e5. DOI: 10.1016/j.annemergmed.2017.01.008.

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