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Arterial blood gases and serum cortisol level as predictors for mortality in acute aluminum phosphide poisoned patients: A prospective cohort study

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ABSTRACT

Aluminum phosphide (ALP) is an extremely toxic substance that causes significant morbidity and mortality. Early identification of patients at risk could improve their outcomes. Therefore, this study evaluated the role of serial arterial blood gases and serum cortisol levels in predicting outcomes in patients with acute ALP poisoning. This prospective cohort study included sixty ALP-poisoned patients. Arterial blood gases and serum cortisol levels were assessed at the time of hospital admission, at 6 hours, and at 12 hours after hospital admission. The mortality rate was 55 %. At the time of hospital admission, non-survivors had significantly lower blood pH (7.36 ± 0.08 vs. 7.31 ± 0.09, $p = 0.025$), reduced bicarbonate values (15.67 ± 4.72 vs. 11.44 ± 3.05 mEq/L, $p = 0.001$) and higher serum cortisol levels (41.83 ± 15.93 vs. 58.41 ± 19.61 µg/dL, $p = 0.002$) compared to the survivors. A receiver-operating characteristic (ROC) analysis for the prediction of mortality indicates that the area under the curve (AUC) of blood pH is 0.712 at a cut-off value of ≤ 7.34, with a sensitivity of 75.76 % and a specificity of 66.67 %. At a cut-off value of ≤ 13.5 mEq/L, the AUC of bicarbonate was 0.777, with a sensitivity of 75.76 % and a specificity of 66.67 %. The serum cortisol level exhibited an AUC of 0.737 at a cut-off level of > 45.5 µg/dL, with a sensitivity of 69.70 % and a specificity of 67 %. Therefore, it can be posited that low arterial pH, bicarbonate values, and elevated cortisol levels can predict mortality in acutely poisoned patients with ALP.

1. Introduction

Aluminum phosphide (ALP) is commonly known as grain tablets, easily available under the brand name 'Hoxin' tablet. It is widely used as a grain preservative due to its low cost, high efficacy, and easy availability. Aluminum phosphide has high killing power; even half a tablet can kill a person in a few hours [1].

Aluminum phosphide poisoning is a significant public health problem in Egypt [2]. The ALP tablets have recently emerged as a common method of suicide and are therefore a frequent cause of admission to poison control centers [3]. The documented mortality rate of acute ALP poisoning shows significant variability in the literature, ranging from 40 % to 80 % [4,5].

Upon ingestion of ALP tablets, the interaction of moisture and an acidic environment facilitates the production of toxic phosphine gas. This gas impairs mitochondrial respiration and energy production throughout the body. Moreover, phosphine has been demonstrated to inhibit cytochrome oxidase, thereby inducing oxidative stress and reducing oxygen intake. Consequently, severe acid-base imbalances and tissue hypoxia typically ensure [6]. Therefore, the literature pointed to an association between arterial blood gases (ABG) and outcomes of ALP [7–9].

Patients of acute ALP poisoning present with distinct symptoms such as vomiting, abdominal pain, agitation, tachycardia, tachypnea, acidosis, and hypotension. The clinical course of ALP poisoning begins with nausea and vomiting and progresses to multi-organ failure and death within 24–48 hours after poisoning [10,11]. The common fatal manifestation of acute ALP poisoning is significant metabolic acidosis. Sodium bicarbonate is administered to counteract the acidosis, but the prognosis remains poor [6].

Serum cortisol level is increased in different pathological conditions as a part of the hemostatic mechanism. Exposure to stress conditions such as trauma, hemorrhage, septic shock, infection, and cardiac arrest leads to activation of the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal medullary system. This leads to an increase in the synthesis and release of glucocorticoids from the adrenal cortex and

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catecholamines from the adrenal medulla [12,13]. Thus, it is hypothesized that serum cortisol levels increase as a result of ALP poisoning. Contrary, Farnaghi et al. [14] suggested that cortisol levels did not rise in ALP-poisoned patients. The adrenal cortex may be affected by either shock or the direct toxic effect of phosphine on adrenal cortex cells. Adrenal gland impairment can contribute to the clinical symptoms of ALP poisoning, particularly reduced blood pressure. These conflicting findings raise concerns about the role of serum cortisol in predicting adverse outcomes in patients with ALP poisoning.

Furthermore, predicting mortality and identifying factors influencing them is a major concern in ALP. This is mainly because poisoned patients present with unstable but generally reversible situations [15,16]. Therefore, this study aimed to evaluate the role of serial ABG and cortisol levels in predicting mortality in patients with acute ALP poisoning.

2. Patient and methods

2.1. Ethical considerations

Approval was obtained from the Research Ethics Committee of the Faculty of Medicine at Tanta University. Informed written consent was obtained from each patient or their relatives after receiving detailed information about the study (approval number: 35675/8/22). Patients' records and data were kept private and confidential through a coding system.

2.2. Study design, Setting and Location

This was a prospective cohort study that included 60 patients with acute ALP poisoning regardless of sex and age. The patients were admitted to the Tanta University Poison Control Center (TUPCC), Emergency Hospital, Elgharbya governorate, Egypt, between September 2022 and September 2023.

2.3. Eligibility Criteria

This study involved 60 patients of all ages and sexes who were diagnosed with symptomatic acute ALP poisoning, whether deliberate or accidental. The diagnosis was based on clinical manifestations that were suggestive of ALP poisoning and occurred shortly after a single exposure to the compound. The compound was reliably identified based on the container brought by patient attendants. Additionally, the biochemical detection of phosphine gas in gastric aspirate (silver nitrate test) was positive for oral intake [17,18].

We excluded patients who were asymptomatic and presented late (more than 6 hours after ALP exposure). Furthermore, those who were exposed to other toxicants and who received treatment before hospital admission were declined from the study. Patients with chronic diseases, any abnormalities in supra renal glands, septic patients, pregnant or lactating women, and those on corticosteroid therapy were also excluded.

2.4. Data collections

A specially designed sheet was designed to record the relevant data. All patients underwent a comprehensive medical evaluation, including a thorough history, systemic examination, and laboratory investigations. Sociodemographic information, such as age, sex, and residence, as well as toxicological data, such as the route and mode of poisoning and the time elapsed until hospital admission, were collected.

At the time of hospital admission, consciousness level was evaluated by the Glasgow Coma Scale (GCS). While, the severity of ALP poisoning was assessed using the Poison Severity Score (PSS), which is categorized into five levels. The initial level did not manifest any symptoms or indications of poisoning. However, the subsequent level exhibited minor and transient symptoms that resolved spontaneously (mild). The third level exhibited prolonged symptoms (moderate), the fourth level presented life-threatening symptoms (severe), and the fifth level resulted in lethal symptoms, ultimately leading to death [19].

Concerning laboratory assessment, an arterial blood sample was taken for arterial blood gases (ABG) analysis at the time of hospital admission. Venous blood samples were collected and placed in clean, dry centrifuge tubes. The samples were left to stand for 10 minutes before centrifugation to prevent hemolysis and then centrifuged for 10 minutes at 5000 rpm. The serum was then separated and used to estimate the biochemical profile, including sodium (Na), potassium (K), and serum cortisol levels. Additional blood samples were collected at 6 and 12 hours, with ABG analysis and venous samples taken for serum cortisol level measurement, as before (serial measurement). The venous samples were taken at constant times not to assess cortisol levels at specific times of day but to understand cortisol fluctuations.

The human serum cortisol level was measured using a commercial enzyme-linked immunosorbent assay [20] kit provided by Chongqing Biospes Co., Ltd, China (catalogue number: BYEK1446). Normal cortisol levels are typically in the range of 10–20 μg/dL in the early morning, 3–10 μg/dL at 4 p.m., and less than 5 μg/dL after bedtime [21]. A serum cortisol level less than 10 (μg/dL) indicates adrenal insufficiency, while a level between 10 and 33 (μg/dL) indicates critical illness-related corticosteroid insufficiency. Adequate adrenal response is characterized by levels greater than 34 μg/dL [22].

The patient was managed according to the standard protocol of the TUPCC. It encompassed treatment of the airway, breathing, and circulation. Intravenous fluids, monitored by central venous pressure, and intravenous vasopressors were employed for the management of hypotension and refractory shock. The potential use of sodium bicarbonate for the correction of metabolic acidosis was considered. Moreover, a magnesium sulfate infusion of 1 g was administered intravenously every hour for the initial 3 hours, followed by 1–1.5 g every 6 hours for a duration of 24 hours. The gastric contents were aspirated and removed before proceeding with gastric lavage. A gastric lavage was conducted using a solution of 50 mL of paraffin oil and 50 mL of 8.4 % sodium bicarbonate. The lavage solution was administered via the tube and subsequently extracted after 3–5 minutes. The gastric lavage was performed repeatedly until the aspirate was clear[9].

The need for an intensive care unit (ICU) admission was primarily for hemodynamic stabilization, respiratory support, mechanical ventilation, and meticulous care of comatose patients [23].

2.5. Study Outcome

The current study aimed to predict mortality by serial arterial blood gases and serum cortisol levels. Thus, the patients were categorized as survivors and non-survivors.

2.6. Statistical analysis

The data were analyzed using IBM SPSS software package version 20.0, developed by IBM Corp in Armonk, NY. The normality of the distribution of variables was assessed using the Kolmogorov-Smirnov, Shapiro, and D′Agostino tests. The mean and standard deviation (SD) were used to present the normally distributed data. Paired sample t-tests and analysis of variance were performed, and if the ANOVA test was significant, a Post Hoc Test (adjusted Bonferroni) was conducted. Categorical variables were expressed as counts and percentages. The Chi-square test (specifically, the Fisher or Monte Carlo variant) was used to evaluate comparisons across groups for categorical data. The study determined the appropriate cut-off value, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) for each predictor using the receiver operating characteristics (ROC) curve. The AUC was graded as follows: excellent (0.90–1), good (0.80–0.90), fair (0.70–0.80), and poor (0.60–0.70). The level of significance was set at

$P < 0.05$.

3. Result

Sixty-seven patients were admitted to TUPCC with a diagnosis of acute ALP during the study period. Out of these patients, 6 patients were referred from other hospitals, three patients had co-ingestion of other toxicants, three patients had no ALP poisoning manifestations, two patients presented late after 12 hours from the exposure, one pregnant female, and one patient had chronic kidney disease. Sixty patients met the inclusion criteria and were divided into two groups: survivors (27 patients; 45 % of patients) and non-survivors (33 patients; 55 % of patients) (Fig. 1).

The sociodemographic and toxicological data were comparable between both groups without any statistical differences. Among the non-survivors, the highest percentages of patients were females, aged less than 20 years of suicide intention by oral intake. The majority of non-surviving patients required ICU admission and mechanical ventilation more frequently than the survivors ($p < 0.001$). The duration of hospital stays was significantly prolonged for survivors compared to non-survivors (26.4 ± 5.37 vs 24.4 ± 13.47, $p = 0.0015$, Table 1).

Compared to the survivor group, the non-survivor exhibited higher incidences of hypotension, abnormal ECG changes, a lower serum Na level, and higher random blood sugar ($p = 0.001$, 0.022, 0.018, and 0.016, respectively). All the survivors were fully conscious while the non-survivors suffered from mildly disturbed consciousness. According to the poison severity score, most of the non-survivors were severely poisoned patients (Table 2).

Table 3 shows the ABG analysis at the time of hospital admission, at 6 hours, and at 12 hours after hospital admission. The non-survivors had statistically lower blood pH, $PaCO_2$ levels, and HCO_3 levels compared to the survivors. Furthermore, along with serial measurements of ABG, there were statistical increases in blood pH, $PaCO_2$ levels, and HCO_3 levels but still lower than the survivors. The serum cortisol level was higher in non-survivors compared to survivors at the time of admission (58.41 ± 19.61 vs 41.83 ± 15.93 μg/dL, respectively, $p = 0.002$) and after 6 hours post-admission (69.53 ± 16.04 vs 54.75 ± 16.93 μg/dL, $p = 0.003$). The highest incidence of non-survivors had sufficient normal cortisol levels at the time of admission, at 6 hours and 12 hours postadmission.

Table 4 displays the serum cortisol levels among patients requiring ICU admission. At the time of hospital admission and 6 hours post-admission, patients requiring ICU admission had significantly higher cortisol levels compared to those who did not require ICU admission ($p = 0.002$ and 0.027 respectively).

According to the receiver operating characteristic (ROC) curve, the area under the curve (AUC) for evaluating pH level as a predictor of mortality was 0.712, while that of the $PaCO_2$ level was 0.629 at a cut-off value of ≤ 7.34, and ≤ 25 respectively. The ROC curve evaluation of HCO_3 level as a predictor of mortality revealed an AUC of 0.777 with a cut-off value of ≤ 13.5. The ROC curve evaluation of cortisol levels as predictors of mortality yielded an AUC of 0.737 at cut-off values of > 45.4 μg/dL (Table 5 and Fig. 2).

4. Discussion

Acute ALP poisoning is associated with a high risk of morbidity and mortality. Early identification of these high-risk patients is important. Thus, the search for prognostic factors is a major concern in clinical toxicology. However, most of the applied prognostic scores for acutely intoxicated patients are often complicated in nature which challenges its applicability [24]. Therefore, this study aimed to assess the role of serial arterial blood gases and serum cortisol levels in predicting mortality in patients with acute ALP poisoning.

In the current study, the mortality rate was 55 % agreed with different literature. Where the reported mortality rates range from 40 % to 80 % [6,2,3,5,15].

The majority of the included patients were less than 20 years old with suicidal oral intake. The characteristics of our patients were similar to those of previous studies in the same community [18,25–28]. These age groups are more susceptible to social and psychological stress, emotional problems, confrontations with others, and educational problems, which may increase their likelihood of committing suicide [29]. As our poison control center is located in a rural governorate, the highest percentage of patients studied came from nearby rural areas, with relatively rapid arrival at our hospital at 1.75 hours after exposure.

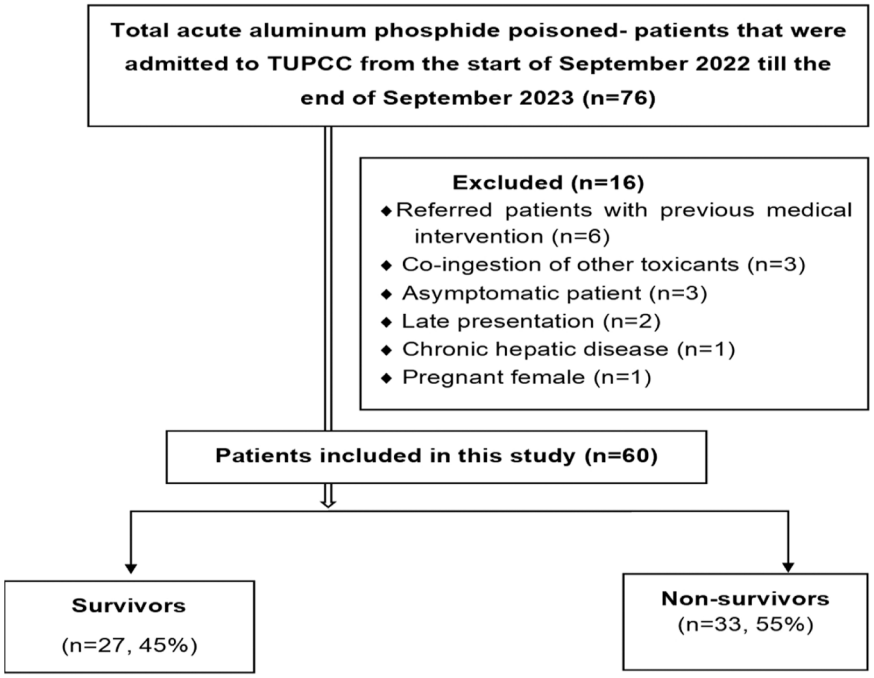

Fig. 1. Flow chart of patients with acute aluminum phosphide poisoning.

Table 1
Sociodemographic and toxicological data, the need for ICU, mechanical ventilation, and total duration of hospital stays among patients with acute ALP poisoning (n = 60 patients).

Variables		Total (n = 60)	Survivor group (n = 27)	Non-survivor group (n = 33)	p-value
Age, years, n (%)	≤ 20	29 (48.3 %)	13 (48.1 %)	16 (48.5 %)	0.559
	20–29	19 (31.7 %)	12 (44.4 %)	7 (21.2 %)	
	≥ 29	12 (20 %)	2 (7.4 %)	10 (30.3 %)	
	Median (IQR)	20 (18 – 25)	20 (18 – 30)	20 (18 – 24)	
Sex, n (%)	Male	32 (53.3 %)	18 (66.7 %)	14 (42.4 %)	0.061
	Female	28 (46.7 %)	9 (33.3 %)	19 (57.6 %)	
Residence, n (%)	Urban	16 (26.7 %)	9 (33.3 %)	7 (21.2 %)	0.291
	Rural	44 (73.3 %)	18 (66.7 %)	26 (78.8 %)	
Route of administration, n (%)	Oral	58 (96.7 %)	27 (100 %)	31 (93.9 %)	0.497
	Inhalation	2 (3.3 %)	0 (0 %)	2 (6.1 %)	
Mode of poisoning, n (%)	Suicidal	58 (96.7 %)	27 (100 %)	31 (93.9 %)	0.497
	Accidental	2 (3.3 %)	0 (0 %)	2 (6.1 %)	
Delay time, hours	Median (IQR)	1.75 (1−2)	2 (1 – 2)	1.50 (1 – 2)	0.158
Need for ICU	n (%)	38 (63.3 %)	7 (25.9 %)	31 (93.9 %)	< 0.001*
Need for mechanical ventilation	n (%)	36 (60 %)	7 (25.9 %)	29 (87.9 %)	< 0.001*
Total duration of hospital stays, hours	Mean ± SD	24.9 ± 11.9	26.4 ± 5.37	24.4 ± 13.47	0.015*

n: number; Min: minimum; Max: maximum; ICU: intensive care unit; IQR: interquartile range; SD: standard deviation;
* : p-value significant < 0.05.

Table 2
Clinical data and laboratory investigations among patients with acute ALP poisoning (n = 60 patients).

		Total (n = 60)	Survivors (n = 27)	Non-survivors (n = 33)	p-value
Pulse, b/m, Mean ± SD.		98.75 ± 20.22	93.11 ± 15.48	103.4 ± 22.59	0.547
Respiratory rate, c/m, Mean ± SD.		27.78 ± 6.13	27.11 ± 4.57	28.33 ± 7.18	0.447
Systolic blood pressure, mmHg, Mean ± SD.		79.8 ± 14.6	84.8 ± 15.3	74.4 ± 11.9	0.009*
Diastolic blood pressure, mmHg, Mean ± SD.		47.5 ± 11.5	52.2 ± 11.6	42.4 ± 9.26	0.001*
Blood pressure, n (%)	Normal	10 (16.7 %)	9 (33.3 %)	1 (3.0 %)	< 0.001*
	Hypotension	42 (70.0 %)	18 (66.7 %)	24 (72.7 %)	
	Undetected	8 (13.3 %)	0 (0.0 %)	8 (24.2 %)	
ECG, n (%)	Normal	28 (46.7 %)	17 (63.0 %)	11 (33.3 %)	0.022*
	Abnormal	32 (53.3 %)	10 (37.0 %)	22 (66.7 %)	
AST, U/L, Mean ± SD.		22.56 ± 11.65	22.30 ± 9.61	22.77 ± 13.23	0.601
ALT, U/L, Mean ± SD.		22.17 ± 10.24	22.89 ± 9.45	21.58 ± 10.95	0.625
Urea, mg/dL, Mean ± SD.		29.35 ± 5.22	28.37 ± 4.73	30.15 ± 5.52	0.191
Creatine, mg/dL, Mean ± SD.		0.99 ± 0.19	0.97 ± 0.15	1.01 ± 0.21	0.416
Serum sodium, mg/dL, Mean ± SD.		141.8 ± 5.51	143.6 ± 6.34	140.2 ± 4.25	0.018*
Serum potassium, mg/dL, Mean ± SD.		3.54 ± 0.53	3.59 ± 0.54	3.50 ± 0.52	0.534
Random blood sugar, mg/dL, Mean ± SD.		164.1 ± 65.62	148.1 ± 71.93	177.2 ± 57.82	0.016*
WBCs × 10^3, cell/L Mean ± SD.		8.78 ± 3.50	8.93 ± 2.69	8.65 ± 4.09	0.308
GCS, Mean ± SD.		14.73 ± 0.71	15.0 ± 0.0	14.52 ± 0.91	0.004*
PSS	**Moderate**	27 (45.0 %)	16 (59.3 %)	11 (33.3 %)	0.045*
	Severe	33 (55.0 %)	11 (40.7 %)	22 (66.7 %)	

b/m: beat/minute; c/m: cycle/minute; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECG: electrocardiograph; WBCs; white blood cells; GCS: Glascow Coma Score; PSS: Poison Severity Score; SD: standard deviation; n: number;
* : p-value significant < 0.05.

Among our non-survivors, most were hypotensive, with undetected blood pressure, and abnormal ECG findings. The patients who did not survive were more hemodynamically unstable than survivors. According to the literature, cardiotoxic symptoms manifest in 60–100 % of patients poisoned by ALP. Hypotension, shock, arrhythmias, myocarditis, and pericarditis are the common manifestations [5,30]. The mechanism of cardiotoxicity in these patients involves both the direct toxic effects of phosphine gas and the impact of metabolic acidosis on the myocardium. The phosphine gas inhibits cytochrome oxidase and impairs oxidative phosphorylation, which results in cellular damage and the subsequent induction of cell death [31]. Furthermore, the cardiac instability could be due to volume depletion, myocardial depression, and adrenal insufficiency [11,32].

In this study, the non-survivors had significantly higher blood glucose levels compared to the survivors. Hyperglycemia could be caused by the glucose-counterregulatory hormone cortisol. Mehrpour et al. [33] attributed that to the activation of cortisol, glucagon, and adrenaline release, suppression of insulin, inhibition of hepatic glucogenesis, and impairment of hepatic glycogenolysis. Furthermore, hyperglycemia is harmful to critically ill patients [34].

As a consequence of hypotension and circulatory collapse, there is a reduction in blood flow to essential organs, which can lead to changes in mental alertness [32]. In the current study, Glasco coma score and poison severity score were significantly associated with non-survivors. Shadnia and colleagues [21] reported that patients poisoned with ALP remain conscious until the late stages of poisoning. Most non-survivors were classified as severe based on poison severity scores. Poison severity score was initially used for a time limit and had a questionable score.

Previous research [11,24] considered the PSS to be a significant prognostic score in ALP poisoning; however, ElMehy et al. [35] indicated that the PSS was less valid than the PGI score that included pH < 7.25, GCS < 13 and impaired SBP < 90 mmHg. They attributed this limitation to the static nature of the PSS, which limits its usefulness in monitoring the patient's condition. It includes the most detrimental values on admission, which is contrary to the principles of care and monitoring of the poisoned patient.

In the current study, arterial blood gases were significantly lower in non-survivors compared to survivors. According to the ROC curve analysis, a blood pH level of ≤ 7.34 and a bicarbonate level of ≤ 13.5 mEq/L could predict mortality. Similarly, Shadnia et al. [21] and

Table 3
Serial measurements of arterial blood gases and serum cortisol levels among patients with acute ALP poisoning (n = 60 patients).

		Total (n = 60)	Survivor (n = 27)	Non-survivor (n = 33)	p-value
pH, Mean ± SD.	**At admission**	7.33 ± 0.09	7.36 ± 0.08	7.31 ± 0.09	0.025*
	At 6 hours	7.40 ± 0.06	7.39 ± 0.06	7.41 ± 0.06	0.314
	At 12 hours	7.46 ± 0.07	7.48 ± 0.07	7.42 ± 0.07	0.027*
	p-value	< 0.001*	< 0.001*	< 0.001*	
$PaCO_2$, mmHg, Mean ± SD.	**At admission**	23.68 ± 7.34	24.94 ± 6.06	22.65 ± 8.20	0.232
	At 6 hours	27.95 ± 8.29	31.68 ± 9.15	23.89 ± 4.73	0.001*
	At 12 hours	33.29 ± 5.98	35.28 ± 5.72	29.46 ± 4.56	0.003*
	p-value	< 0.001*	< 0.001*	0.031*	
HCO_3, mEq/L, Mean ± SD.	**At admission**	13.35 ± 4.40	15.67 ± 4.72	11.44 ± 3.05	< 0.001*
	At 6 hours	20.84 ± 5.36	23.95 ± 5.03	17.45 ± 3.29	< 0.001*
	At 12 hours	24.96 ± 7.36	27.30 ± 7.54	20.44 ± 4.46	0.005*
	p-value	< 0.001*	< 0.001*	< 0.001*	
Cortisol level, μg/dL, Mean ± SD.	**At admission**	50.95 ± 19.74	41.83 ± 15.93	58.41 ± 19.61	0.002*
	At 6 hours	61.83 ± 17.96	54.75 ± 16.93	69.53 ± 16.04	0.003*
	At 12 hours	58.10 ± 26.91	51.93 ± 28.11	69.11 ± 21.32	0.149
	p-value	< 0.001*	< 0.001*	< 0.001*	

SD: standard deviation; n: number; $PaCO_2$: partial pressure of carbon dioxide; HCO_3: bicarbonate level;
* : p-value significant < 0.05.

Table 4
Relation between serum cortisol levels and the need for ICU admission among patients with acute ALP poisoning (n = 60 patients).

Cortisol levels Mean ± SD.	Not need ICU admission	Need ICU admission	**U**	**p**
at admission	(n = 22) 40.60 ± 16.97	(n = 38) 56.94 ± 18.90	219.0*	0.002*
at 6 hours	(n = 21) 55.17 ± 15.78	(n = 27) 67.01 ± 18.10	177.0*	0.027*
at 12 hours	(n = 21) 53.94 ± 27.30	(n = 18) 62.95 ± 26.37	151.0	0.294

Min: minimum; Max: maximum; ICU: intensive care unit; n: number;
* : p-value significant < 0.05

Farzaneh et al. [36], have supported our findings that low pH and HCo_3 levels are reliable indicators of mortality among patients with acute ALP poisoning. Also, Wahdan and Khalifa [7] observed that a blood pH level of ≤ 7.28 was an indicator of mortality in acute ALP-poisoned patients. Furthermore, Sagah and Elhawary [8] reported that blood pH levels of ≤ 7.33, bicarbonate level of ≤ 12.6 mEq/L, and $PaCO_2$ ≤ 27 mmHg could be predictors of mortality in ALP poisoning.

Metabolic acidosis is considered a key indicator of ALP poisoning. It arises as a consequence of tissue hypoxia and the accumulation of lactic acid, which results from the reduction in cellular respiration brought about by phosphine's deleterious impact on mitochondrial activity[5]. Metabolic acidosis has been demonstrated to elevate the risk of mortality by diminishing myocardial contractility, which can ultimately result in cardiogenic shock [6,9]. Thus, repeated arterial blood gas analysis is a crucial aspect of the management of ALP, offering invaluable insights into the patient's metabolic status, respiratory function, and overall condition. Timely identification of metabolic acidosis and respiratory distress through arterial blood gas monitoring can significantly impact the efficacy of therapy and enhance survival rates in patients affected by this poisoning.

Serum cortisol levels were statistically increased on serial follow-up measurements and were significantly high among non-survivors and in patients who required ICU admissions. Chugh and colleagues [37] studied the effects of ALP on the adrenal cortex in a group of 30 ALP-poisoned patients. A significant increase in plasma cortisol levels, exceeding 37.73 μg/dL, was recorded, and postmortem histopathologic examination revealed mild to moderate changes in the adrenal glands. In 10 % of patients, the adrenal cortex was significantly affected, resulting in blood cortisol levels not exceeding the normal range (less than 25 μg/dL). Histopathological examination showed complete lipid depletion, hemorrhage, and necrosis. In contrast, Farnaghi et al. [14] reported that the mean blood cortisol level of ALP-poisoned patients was

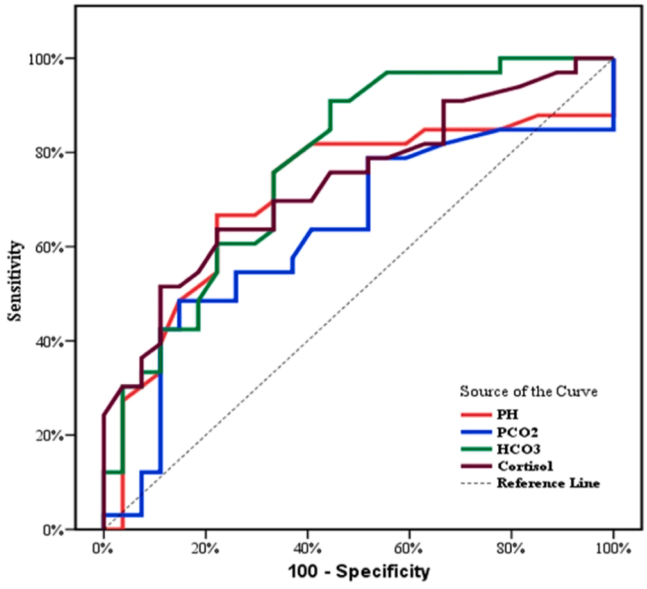

Fig. 2. Receiver operating characteristic (ROC) curve for arterial blood gases (ABG) and serum cortisol level at the time of hospital admission to predict mortality among patients with acute aluminum phosphide poisoning.

Table 5
Receiver operating characteristic (ROC) curve for arterial blood gases and serum cortisol levels at the time of hospital admission to predict mortality among patients with acute ALP poisoning (n = 60 patients).

On admission	**AUC**	**p**	**95 % CI**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
pH	0.712	0.005*	0.575 – 0.849	≤ 7.34	75.76	66.67	73.5	69.2
$PaCO_2$	0.629	0.087	0.484 – 0.774	≤ 25	63.64	59.26	65.6	57.1
HCO_3	0.777	< 0.001*	0.657 – 0.896	≤ 13.5	75.76	66.67	73.5	69.2
Cortisol	0.737	0.002*	0.612 – 0.862	> 45.4	69.70	66.67	71.9	64.3

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; n: number; $PaCO_2$: partial pressure of carbon dioxide; HCO_3: bicarbonate level;
* : p- value significant < 0.05.

24 ± 0.16 μg/dL and did not increase to the expected levels associated with the patient's state of shock and stress. Only 10 % of the patients had a high blood cortisol concentration. The discrepancies between our findings may be attributed to either the timing of sampling or the evaluation of patients in the advanced stages of poisoning when the entire adrenal cortex is likely to have been affected.

However, several studies agreed with our findings. Shadnia et al. [21] found statistically higher cortisol levels in their deceased patients than in the survivors. Also, Masoud et al. [38] reported a higher serum cortisol level of 47.2 μg/dL among a group of thirty ALP-poisoned patients. Furthermore, Saad et al. [28] found high median cortisol levels among ALP deaths compared to survivors (57.6 vs. 35.3 μg/dL) among 40 ALP-poisoned patients.

The changes in the adrenal cortex caused by ALP poisoning can be attributed to either shock or the direct cytotoxic impact of phosphine on adrenal cortex cells [39]. The initial rise in cortisol levels can be explained as an adequate adrenal response to stress on corticotrophin-releasing hormone and ACTH. However, individuals can experience critical illness-related corticosteroid insufficiency even when their cortisol levels are sufficient due to tissue resistance. This resistance can result from anomalies in the glucocorticoid receptor or an elevated conversion of cortisol to cortisone within the tissues [40].

Normal serum cortisol levels differ by diurnal variation. Serum cortisol levels are slightly high in the morning (10–20 μg/dL), while gradually decreasing to 3–10 μg/dL at 4 p.m., and reduced to 5 μg/dL or less at night [21]. In the present study, an initial serum cortisol level of > 45.4 μg/dL had a negative predictive value of 71.9 % and a positive predictive value of 64.3 % for mortality. Masoud et al. [38] found that serum cortisol measurement had an AUC of 0.8, which is considered good, for predicting mortality in phosphide-poisoned patients six hours after admission. At a cut-off value of $>$ 73 μg/dL, the test had a sensitivity of 80 % and specificity of 85.7 %.

Contrary, Masoud and Barghash [41] reported that the threshold for cortisol was less than 29.1 μg/dL, with a sensitivity of 88.89 % and specificity of 100 %. They observed a decrease in cortisol levels with increasing severity, which they attributed to severe adrenocortical insufficiency. Saad et al. [28] conducted a study that found blood cortisol levels of $\geq$ 28.3 μg/dL accurately predict death in patients poisoned with ALP. The predictor had a sensitivity of 100 %, correctly identifying all patients who died. However, its specificity was 45.4 %, also placing a significant number of patients who did not die as being at risk. The differences in threshold values can be attributed to the varying time elapsed between exposure and arrival at the hospital. The study included patients exposed to ALP within a maximum of 48 hours. Our study excluded patients who were exposed for more than 6 hours.

During a severe illness, the cortisol response may be hindered in some individuals due to various factors that affect the hypothalamic-pituitary-adrenal axis or its receptors. These factors include head injury, central nervous system depressants, pituitary infarction, structural damage to the adrenal gland from hemorrhage, infarction, or infection, and septic shock. In patients with sepsis, high levels of inflammatory cytokines can hinder the synthesis of adrenal cortisol, inhibiting its production [42,43]. Therefore, Bhatnagar and Pal [44] and Katwal et al. [45] found in their case reports that the administration of steroids was effective in the treatment of ALP-poisoned patients.

Anticipating which patients in the ICU can help physicians allocate resources effectively and improve patient care [46]. It is important to look for key diagnostic indicators to identify adrenal insufficiency in patients admitted to the ICU. Moreover, considering a patient's cortisol levels can aid in determining patients with rapid deterioration and the appropriate therapeutic approach. Aluminum phosphide patients usually suffer from hemodynamic instability despite receiving sufficient fluid resuscitation, primarily caused by reduced systemic vascular resistance, as well as signs of inflammation without a clear source that does not improve with empirical treatment [47].

5. Strength and limitations

Mortality due to ALP poisoning is a common health problem, especially in developing countries. Our main findings showed that non-survivors had significantly low pH, $PaCO_2$, and HCO_3. In addition, serum cortisol levels were significantly elevated and increased with time. Serial arterial blood gases and cortisol levels may be predictors of mortality in acute ALP poisoning. These laboratory parameters are simple, measurable, and convenient predictors that are available in all healthcare facilities in developing countries.

The limitation of the current study is the relatively small sample size and no measurement of confirmatory ACTH stimulation test due to the urgent critical state of ALP patients. Therefore, future studies with a large number of patients from different poison control centers are recommended. Furthermore, a comprehensive hormonal assay is needed.

6. Conclusion

Acute ALP poisoning is a major health problem with a relatively high mortality rate. Predicting mortality in patients with acute ALP poisoning could help physicians and health administrators in decision-making. Furthermore, we found that serial ABG and cortisol levels are early and relevant blood biomarkers that could predict mortality and give an idea about the dynamic change of ALP-poisoned patients. The reduced blood pH $\leq$ 7.34, serum bicarbonate $\leq$ 13.5 mEq/L, and elevated cortisol level > 45.4 μg/dL may serve as predictors of mortality. Clinicians can effectively identify patients at high risk of mortality, leading to timely interventions and improved outcomes.

Authors' contributions

Heba K. Khalifa, Wafaa M. Masoud and Alshaimma Mahmoud Elmansy contributed to the study's conception, design, performed material preparation, data collection, and analysis. All authors wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript. Alshaimma Mahmoud Elmansy is responsible for communication during and after the manuscript submission.

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CRediT authorship contribution statement

Wafaa M. Masoud: Writing – original draft, Methodology, Data curation. **Alshaimma Mahmoud Elmansy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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.

Data availability

Data will be made available on request.

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