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Serum amylase as a novel prognostic marker of organophosphorus poisoning: a retrospective study

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Abstract

Background: This study aims to explore the significance of serum amylase levels in patients with organophosphorus pesticide (OP) poisoning and to provide a new perspective for evaluating the severity and prognosis of OP poisoning.

Methods: The clinical data of 67 patients with acute OP poisoning, who had been treated in the emergency department of the General Hospital of Ningxia Medical University between September 2020 and August 2022, were retrospectively analyzed. Using Spearman rank correlation, serum amylase levels during admission and severity of poisoning correlated with discharge outcomes. Based on serum amylase levels, receiver operating characteristic curves were plotted to predict the severity and mortality of patients who experience organophosphate poisoning. The optimal threshold serum amylase level at admission was determined based on the maximum Youden index.

Results: Using Spearman rank correlation analysis, serum amylase levels at admission positively correlated with the severity of poisoning and discharge outcomes, but the degree of correlation was weak (r_S: 0.344; 0.264; $P < 0.05$). The patients' serum amylase levels at admission had receiver operating characteristic area under the curve values of 0.726 and 0.735 to predict the degree of severe poisoning and death, respectively. Based on the maximum Youden index, the optimal threshold of serum amylase were 97.8 and 194.1 U/L when the degree of poisoning was severe and the discharge outcome of patients was died. In comparison to patients with serum amylase levels ≤194.1 U/L at admission, the OR values of death in patients with serum amylase levels >194.1 U/L at admission was 15.944 (95% CI: 1.825–139.274).

Conclusion: Serum amylase levels in patients with organophosphate poisoning correlate with the degree of poisoning and discharge outcomes. Higher serum amylase level was a risk factor for organophosphorus poisoning death.

Key words: Amylase, Emergency department, Organophosphorus pesticide poisoning, Prognosis

Introduction

According to the latest estimate in the "Suicide worldwide in 2019" report released by the World Health Organization,[1] more than 700,000 persons die by suicide every year globally. Suicide remains the leading cause of death worldwide. Approximately 20% of suicides worldwide are caused by pesticide use, with the majority occurring in rural areas in low- and middle-income countries.[2] Organophosphate poisoning is one of the most common types of poisoning that occurs in developing countries such as China and India.[3] The majority of deaths occur in rural areas; for example, the incidence of pesticide poisoning in rural China is twice as high as in urban China, accounting for more than 60% of suicides. Similarly, in some rural areas of Sri Lanka,[4] the suicide rate due to pesticide use is as high as 71%, and pesticide poisoning is the most common cause of death in hospitals. Suicide, especially using pesticide, is not just to end life, but for various reasons—to get attention, to express pain, or to get revenge; most deaths occur because of the toxicity of the poison ingested.[5] Halving the mortality rate of people ingesting pesticides would save more than 50,000 lives annually and reduce the overall suicide rate by 18%.[6,7]

With the increasing use of organophosphorus pesticides (OPs) and the pressure on people's work and life, the incidence of oral OP poisoning is increasing. Annually, many patients with organophosphate poisoning are treated in the emergency room. Organophosphorus pesticide poisoning is often treated as an emergency or critical illness. Some patients experience severe damage to important tissues and organs after poisoning, often requiring hospitalization in the intensive care unit. Although treatment has gradually improved, the mortality rate remains high. Cholinesterase is often used clinically as a graded indicator of the severity of organophosphate poisoning and for assessing the prognosis of patients.[8] However, the degree of cholinesterase decline is not related to the disease severity and prognosis of the disease.[9] Additional effective indicators are needed to evaluate patients. Many studies have reported on the detection of serum cholinesterase activity in the past but few systematic reports on the detection of serum amylase levels. In this article, we aim to highlight the importance of serum amylase in the prognosis of organophosphate poisoning.

Methods

This study was approved and written informed consent was waived by the Medical Ethics Committee of Ningxia Medical University

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

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General Hospital (Ethics Number: KYLL-2022-1243), owing to the anonymized retrospective nature of the analysis. A 23-month (from September 2020 to August 2022) retrospective study was conducted in 67 patients who had been reported and clinically diagnosed with acute OP poisoning (AOPP) in the emergency room of a general hospital.

Inclusion criteria

The research participants were patients with organophosphorus poisoning (diagnosed by themselves or their companions, based on medical history and related clinical characteristics). The poisoning route was oral administration.

Exclusion criteria

Patients with (1) mixed pesticide poisoning; (2) diabetes, serious heart and lung diseases, and chronic heart, liver, and renal insufficiency; (3) history of severe hypertriglyceridemia, biliary tract diseases, amylase-producing tumor, gastrointestinal diseases, mumps, and pancreatic diseases; (4) long-term drug and alcohol usage; and (5) insufficient data were excluded. Organophosphorus poisoning is related to alcohol, long-term alcoholism, and drug use (such as azathioprine, thiazides, or furosemide), which may affect serum amylase levels.[10]

Diagnostic grading criteria

The diagnostic criteria for AOPP were obtained by referring to the diagnostic criteria of the acute organic phosphorus insecticide poisoning (AOPIP) in the ninth edition of *Internal Medicine*.[8] The AOPIP refers to the fact that OPs enter the body to inhibit acetylcholinesterase activity, causing a massive accumulation of acetylcholine (Ach) at physiologically active sites in the body, accompanied by poisoning symptoms, and signs in the muscarinic, nicotinoid, and central nervous systems. Patients often die because of respiratory failure. According to the "Expert Group of Chinese Emergency Medicine Expert Consensus on diagnosis and treatment of acute organophosphorus pesticide poisoning" (2016),[11] clinical manifestations and cholinesterase activity were used as the basis for classification, and the patients were divided into mild, moderate, and severe poisoning groups (Table 1). Based on the outcomes of the hospitalized patients, they were divided into those who survived and those who died (those who died during hospitalization or within 24 hours after abandoning treatment).

Observation indexes

The clinical case materials of the patients were retrospectively analyzed, including sex, age, hospitalization time, serum amylase levels at admission, poisoning severity, discharge outcomes, and national early warning score (NEWS).[12,13] In this study, 3 mL of venous blood was collected immediately after admission, and serum amylase was detected using the serum amylase and Somogyi method; the normal reference value of serum amylase is 30–110 U/L.

Table 1

Chinese Society of Emergency Medicine Classification of AOPP Severity[11]

Severity	Definitions
Mild	Muscarinic symptoms were the main symptoms, and the whole blood cholinesterase activity was 50%–70% of the normal value.
Moderate	The mentioned symptoms are aggravated, and nicotinic symptoms appear. The whole blood cholinesterase activity is 30%–50% of the normal value.
Severe	In addition to muscarinic symptoms and nicotinic symptoms, there are clinical manifestations of pulmonary edema, respiratory failure, coma, brain edema, and other important organ failure, and the whole blood cholinesterase activity is below 30% of the normal value.

If the clinical manifestations are inconsistent with the results of cholinesterase activity, we should weaken the significance of cholinesterase activity and pay more attention to the comprehensive judgment of clinical situation.

AOPP, acute organophosphorus pesticide poisoning.

Statistical analysis method

SPSS (version 26.0; IBM SPSS Inc., Chicago, IL, USA) was used to analyze the data. For continuous variables, the mean and standard deviation (SD) were used as representations. The number of cases and the rate were used to express categorical variables. Quantitative data with a non-normal distribution were expressed as *M* (P25–P75) after determining normality and variance homogeneity with the Shapiro-Wilk test and Levene's test. Wilcoxon rank-sum test was used to compare the serum amylase levels in patients with different discharge outcomes, and Kruskal-Wallis H test was use to compare the serum amylase levels in patients with different severity of poisoning. Then, the Spearman's correlation coefficient for ranked data was used to evaluate the relationship between serum amylase levels and the severity of poisoning and discharge outcomes. Additionally, the receiver operating characteristic (ROC) curve was used to establish the cut-off values for the serum amylase to predict the severity of poisoning and discharge outcomes of patients. The optimal cut-off serum amylase value was obtained based on a maximized Youden's index, and the sensitivity, specificity and area under the ROC curve (AUC) were also examined. Following patients division was founded on the cut-off serum amylase value, the univariate Logistic regression was utilized to determine whether serum amylase levels correlated with discharge outcomes in patients with OP poisoning. Bilateral tests were used for all statistical tests, and differences were considered statistically significant at $P < 0.05$.

Results

General clinical information

A total of 74 patients were admitted to the General Hospital of Ningxia Medical University for organophosphorus poisoning. Seven patients were excluded, including 3 patients younger than 18 years and 4 patients with incomplete or lost medical information. Finally, 67 patients with organophosphorus poisoning who met all the inclusion criteria of our study were included (Fig. 1). The general clinical information of the 67 patients with organophosphorus poisoning is shown in Table 2. There were 27 men and 40 women, aged from 18 to 82 years, with the median age is 40 (30–52) years old. Organophosphorus pesticide exposure was definite in all cases. The types of pesticide poisoning were omethoate in 3 cases, dichlorvos in 43 cases, trichlorfon in 9 cases, chlorpyrifos in 6 cases, malathion in 1 case, phoxim in 3 cases, phorate in 1 case, and chloramine phosphate in 1 case. The amount of oral pesticide administered was about 5–500 mL. All 67 patients ingested through the digestive tract. The mean time from poisoning to hospitalization was 8.4 ± 4.4 hours (mean ± standard deviation). Increased amylase levels in patients with mild, moderate, and severe poisoning were 37.5% (3 of 8), 23.5% (4 of 17), and 71.4% (30 of 42), respectively. The mortality rate in patients with severe disease was 19.0% (8 of 42).

Comparison of serum amylase levels in patients with poisoning in different stages of disease and different discharge outcomes

The serum amylase levels of 67 patients with different severities of poisoning and outcomes were compared (Table 3). The differences in serum amylase levels among patients with mild, moderate, and

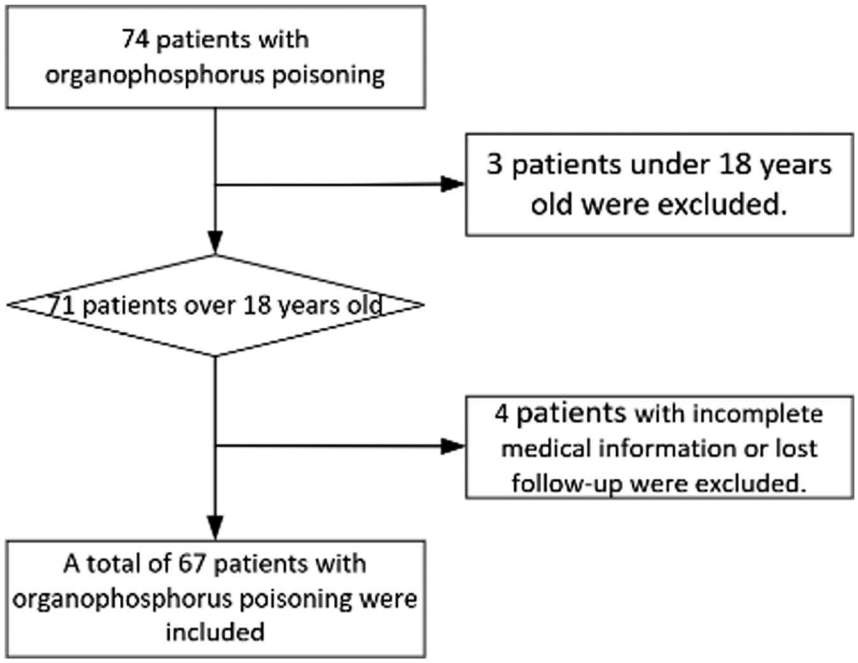

Figure 1. Study flow chart.

severe disease at admission were statistically significant ($P < 0.05$). Dead patients admitted to the hospital had significantly higher median serum amylase levels than did survivors ($P < 0.05$). As shown in Table 3, according to the 2 groups of samples discharged from the hospital, the overall difference represented by the 2 samples was statistically significant (Z: –2.146; $P = 0.032$).

Analyzing the relationship between serum amylase levels at admission and poisoning severity and discharge outcomes in patients with organophosphorus poisoning

The Shapiro-Wilk test results showed a non-normal distribution of serum amylase levels at admission. Spearman's correlation coefficient for ranked data revealed that the serum amylase levels at admission positively correlated with the severity of poisoning and discharge outcomes, but the degree of correlation was weak (r_s: 0.344; 0.264; $P < 0.05$). A positive correlation was identified between the NEWS and the severity of poisoning, as well as the discharge outcomes (r_s: 0.766; 0.353; $P < 0.05$).

Results of ROC curve analysis of serum amylase level at hospital admission in predicting poisoning severity and death

Based on the ROC curve analysis, the ROC-AUC values of serum amylase levels at hospital admission for the prediction of mild, moderate, severe, and death were 0.430 (95% confidence interval [CI]: 0.243–0.617; $P = 0.523$), 0.260 (95% CI: 0.142–0.378; $P = 0.003$), 0.726 (95% CI: 0.603–0.849; $P = 0.002$), and 0.735 (95% CI: 0.613–0.836; $P = 0.028$), respectively, as shown in Fig. 2. This indicates that serum amylase levels were poor at predicting mild and moderate outcomes but was able to predict severe outcomes. According to the principle of maximum Youden index, the optimal critical values for predicting severe and death were 97.8 and 194.1 U/L, respectively. The sensitivities for predicting severe poisoning and death were 76.2% and 87.5%, with specificities of 72.0% and 69.5%, respectively, as shown in Table 4.

Table 2

General Clinical Data of 67 Patients with OP Poisoning

Characteristics	Category	Number
Sex, n (%)	Male	27 (40.3)
	Female	40 (59.7)
Inpatient days, d, *M* (P25–P75)		4 (3–8)
Classification of toxic drugs, n (%)	Omethoate	3 (4.4)
	Dichlorvos	43 (64.2)
	Dipterex	9 (13.5)
	Dursban	6 (9.0)
	Malathion	1 (1.5)
	Phoxim	3 (4.4)
	Phorate	1 (1.5)
	Chloramine phosphorus	1 (1.5)
Time from taking poison to emergency, h, *M* (P25–P75)		7 (5–11)
Age, y, *M* (P25–P75)		40 (30–52)
Amylase level, n (%)	Normal	30 (44.8)
	Abnormal	37 (55.2)
Pesticide consumption, mL, *M* (P25–P75)		100 (60–200)
NEWS, n (%)	0–4 points	21 (32.8)
	5–6 points	13 (19.4)
	≥7 points	33 (47.8)
Poisoning grade, n (%)	Mild poisoning	8 (11.9)
	Moderate poisoning	17 (25.4)
	Severe poisoning	42 (62.7)
Discharge outcome, n (%)	Survive	59 (88.1)
	Die	8 (11.9)

OP, organophosphorus pesticide.

Table 3

Comparison of Serum Amylase Levels at Admission in 67 Patients with Poisoning Severity and Different Discharge Outcomes

Parameter	Category	n (%)	Admission Serum Amylase Level, U/L, *M* (P25–P75)	*H*/*Z*	*P*
Severity of poisoning	Mild poisoning	8 (11.9)	88.6 (64.8–384.6)	$H = 10.330$	0.006
	Moderate poisoning	17 (25.4)	78.5 (57.7–108.3)		
	Serious poisoning	42 (62.7)	195.0 (92.3–621.4)		
Discharge outcome	Survive	59 (88.1)	119.0 (65.9–329.6)	$Z = -2.146$	0.032
	Die	8 (11.9)	390.5 (230.6–694.125)		

$P < 0.05$ shows a significant difference in the index of serum amylase between different groups.

Effects of organophosphate poisoning on serum amylase levels and postdischarge prognosis determined via univariate logistic regression

According to the principle of the maximum Youden index, the optimal critical value of serum amylase levels in the hospital for predicting death was 194.1 U/L, and the optimal critical value (194.1 U/L) was selected as the classification limit. Single-factor logistic regression showed that comparing to patients with serum amylase levels ≤194.1 U/L at admission, the OR values of death in patients with serum amylase levels >194.1 U/L at admission was 15.944 (95% CI: 1.825–139.274; $P = 0.012$). Single-factor logistic regression analysis of serum amylase levels in patients with organophosphate poisoning at admission and at discharge is shown in Table 5.

Discussion

Organophosphorus compounds inhibit acetylcholinesterase activity at nerve endings and neuromuscular junctions, resulting in excessive Ach receptor stimulation. Excessive stimulation of the muscarinic, nicotinic, and central nervous system receptors leads to poisoning symptoms.[14] In addition to salivation, lacrimation, urination, defecation, stomach cramps, vomiting, bradycardia, hypotension, and myosis, patients with muscarinic symptoms may experience bronchospasms. Nicotinoid symptoms include tremors, spasms, and paralysis.

Organophosphorus pesticide poisoning can be prognosticated by serum amylase, according to a study by Sumachi et al.[15] The presence of hyperamylasemia in OP poisoning helps predict its severity and symptoms. Serum amylase is mainly found in the pancreas, salivary glands, stomach, gallbladder, jejunum, ileum, ovary, breast, and other organs; when these organs are damaged or inflamed, blood amylase levels rise. As the most important hydrolytic amylase in vivo, the components of amylase include pancreatic isoenzymes and salivary isoenzymes, which are mainly secreted by the salivary glands. Excessive production or removal of obstacles can trigger the occurrence of hyperamylasemia and increase the risk of complications such as acute pancreatitis.[16] Our results showed that comparing to patients with serum amylase levels ≤194.1 U/L at admission, the OR values of death in patients with serum amylase levels >194.1 U/L at admission was 15.944 (95% CI: 1.825–139.274; $P = 0.012$). Therefore, serum amylase levels at hospital admission may serve as a biomarker for predicting the degree of organophosphorus poisoning and assessing patient prognosis.

Approximately 12% of adults injured by OP poisoning experience acute pancreatitis as a result of the poisoning. According to current theories, the etiology of pancreatic alterations after OP poisoning involves pancreatic ductal hypertension and exocrine stimulation of the pancreas. The reason for the increase in amylase in the analysis of AOPP[17] might be as follows: (1) Stimulation of the vagus nerve by a cholinergic mechanism can promote the secretion of pancreatic juice, thus increasing the secretion of trypsin and causing an increase in blood amylase activity. (2) Intestinal smooth muscle spasm occurs after poisoning, and the opening of the pancreatic tube and duodenum is in a spastic state, resulting in pancreatic duct obstruction to varying degrees. In addition, Ach accumulation and vagal nerve excitation cause hypersecretion of pancreatic fluid, and the pressure in the pancreatic duct and its branches increases, leading to rupture of the pancreatic acinus and pancreatic canaliculus, pancreatic enzyme overflow, and occurrence of pancreatitis, resulting in elevated serum amylase levels. (3) The toxicants stimulate the gastric mucosa to increase the production of gastrin, secretion of the pro-pancreatic hormone by the duodenum, secretion of pancreatic enzymes, and serum amylase. (4) Hypoxia and hypotension caused by respiratory and circulatory dysfunction can cause damage to the pancreas and increase serum amylase. Organophosphorus pesticide poisoning can also result in respiratory failure. It is possible that respiratory failure is caused by elevated serum amylase levels derived from the saliva, as

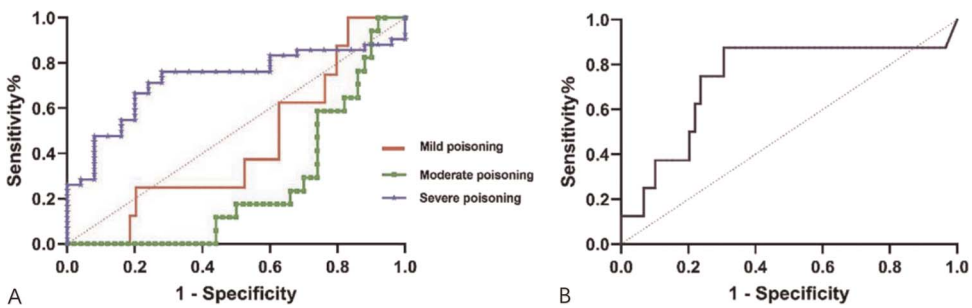

Figure 2. Receiver operating characteristic curve of serum amylase levels of hospitalized patients with organophosphorus poisoning predicting mild, moderate, and severe poisoning and death. (A) The severity of poisoning. (B) Death.

Table 4

Results of ROC Curve Analysis for Prediction of Mild, Moderate, and Severe Poisoning and Death by Admission Serum Amylase Levels in Patients with Poisoning

Index	ROC Curve			Optimal Threshold (U/L)	Sensitivity, %	Specificity, %	Youden Index
	AUC	AUC 95% CI	*P*				
Severe poisoning	0.726	0.603–0.849	0.002	97.8	76.2	72.0	0.482
Die	0.735	0.613–0.836	0.028	194.1	87.5	69.5	0.570

AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Table 5

Univariate Logistic Regression Analysis Between Serum Amylase Levels in Patients with Organophosphate Poisoning and Discharge Outcome as Death

Influencing Factor	Coefficient of Regression	Standard Error	Wald Value	*P*	OR	95% CI
Admission serum amylase level*	2.769	1.106	6.271	0.012	15.944	1.825–139.274
Constant term	–3.714	1.012	13.462	<0.001	0.024	–

*Admission serum amylase levels ≤194.1 and >194.1 U/L.

CI, confidence interval. OR, odds ratio.

massive salivation is another precipitating factor in OP poisoning, indicated in previous studies.[18,19] Furthermore, severe OP poisoning increases salivation and amylase secretion by activating the parasympathetic and sympathetic nervous systems. Therefore, it has been speculated that plasma amylase levels may be associated with respiratory failure by stimulating the autonomic nervous system.[20,21]

Several studies have confirmed that the serum amylase levels tend to increase with an increase in the degree of organophosphate poisoning, suggesting that organophosphate pesticides can affect the serum amylase secretion levels, which have guiding significance for the treatment of organophosphate pesticide poisoning. In this study, Spearman rank correlation analysis showed that the serum amylase levels at admission positively correlated with the severity of poisoning and discharge outcomes; however, the degree of correlation was weak (r_s: 0.344; 0.264; $P<0.05$). Based on the ROC curve analysis, the ROC-AUC of the serum amylase levels at admission for predicting the death of patients with organophosphate poisoning was 0.735 (95% CI: 0.613–0.836; $P = 0.028$). Under the principle of the maximum Youden index, the optimal threshold serum amylase level at admission was 194.1 U/L, with a sensitivity of 87.5% and a specificity of 69.5%. In comparison to patients with serum amylase levels ≤194.1 U/L at admission, the OR values of death in patients with serum amylase levels >194.1 U/L at admission was 15.944 (95% CI: 1.825–139.274; $P = 0.012$). Therefore, serum amylase levels at admission have the predictive value as a potential biomarker for predicting the discharge outcomes of patients with organophosphate poisoning. Previous studies have shown that serum amylase levels can predict the prognosis of patients with organophosphate poisoning and the clinical severity of organophosphate poisoning. Compared with previous studies, the poisonous drugs used in this study were broadly classified. Analysis showed that serum amylase levels were poor predictors of mild and moderate disease but could predict severe disease and death. Besides, comparisons showed that serum amylase levels ≥220 U/L were used as a biomarker[22,23] for predicting the discharge outcomes of patients with organophosphorus poisoning.

Limitations

This study had some limitations. First, the small sample size and retrospective single-center design may have led to a selection bias. In addition, some patients with incomplete clinical data did not participate in our study, which may have led to incomplete data analysis. Second, amylase can be used as a prognostic indicator of organophosphorus poisoning, but larger samples and multicenter studies are needed to confirm the additional value of these markers for clinical prediction scores, to provide clinicians with a safer and more effective evaluation tool.

Conclusion

The serum amylase levels of patients with organophosphorus poisoning are associated with the degree of clinical poisoning and the discharge outcomes. Higher serum amylase level was a risk factor for organophosphorus poisoning death.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Guo X performed the statistical analysis and wrote the manuscript; Chen Z provided poisoning-related professional knowledge and proofread the manuscript; Feng K acquired financial support for the project leading to this publication; Zeng S and Zhang J conducted the data collection; Ma Z and Yuan C provided statistical advice. All authors read and approved the final manuscript.

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Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. This study was approved by Ningxia Medical University General Hospital's Ethics Committee (Ethics Number: KYLL-2022-1243). Written informed consent was waived owing to the anonymous nature of the data.

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None.

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