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CLIF-OF >9 predicts poor outcome in patients with Amanita phalloides poisoning

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ABSTRACT

Purpose: Amanita phalloides poisoning with high mortality is rare but serious. The aim of this study is to identify the risk indicators of death in patients with Amanita phalloides poisoning and a good score tool to predict prognosis.

Methods: In this respective study (1/2009–12/2018), the patients (n = 105) with Amanita phalloides poisoning from two hospitals of China Medical University who met the inclusion/exclusion criteria were included. The laboratory markers and the clinical scoring systems including Child–Turcotte–Pugh (CTP), Sequential organ failure assessment (SOFA), Liver injury and Failure evaluation (LiFe), Chronic liver failure-organ failure score system (CLIF-OF), King's College criteria (KCH criteria), Model for end-stage liver disease (MELD) and Platelet-bilirubin-albumin (PALBI) within 24 h of admission to the two hospitals were analyzed and area under the curve (AUC) analyses were also performed regarding the prediction of death.

Results: The data analysis indicated that high international normalized ratio (INR) (>3.6, AUC = 0.941) and plasma ammonia (>95.1 μmol/L, AUC = 0.805) were closely associated with mortality after multivariate logistic regression. CLIF-OF (>9) within 24 h with really good diagnostic accuracy (>90%) significantly outperformed the other scores in predicting mortality.

Conclusion: CLIF-OF (>9) within 24 h of admission is considered as a satisfactory and practical tool to predict a poor outcome of Amanita phalloides poisoning.

1. Introduction

Wild mushroom poisoning with high mortality is a serious problem worldwide [1]. Amanita phalloides, as one of the lethal mushrooms, is responsible for the majority of the fatalities caused by toxic mushroom poisoning [2]. Most of the patients orally ingested the Amanita phalloides by mistake, because it was difficult for some of the mushroom harvesters to distinguish Amanita species from edible mushrooms.

The typical clinical manifestations of Amanita phalloides poisoning are characterized by an asymptomatic latency period within the 5–6 h after oral ingestion, followed by gastrointestinal disorders and severe hepatitis [3]. Since the initial clinical manifestation was similar to gastroenteritis, most of the patients were not sent to hospital in time. Sometimes, the patients suffered from digestive symptoms including nausea, vomiting and diarrhea were mistaken as benign gastroenteritis by the clinicians in local clinics or hospitals. The clinicians paid much more attention to these patients until the potentially life-threatening illness occurred. These unfavorable factors contribute to the delayed diagnosis and treatment of Amanita phalloides poisoning.

Amatoxins are absorbed from digestive tract but also rapidly eliminated from the blood, and then distributed to liver and kidneys within 48 h [4]. Amanita phalloides poisoning may progress into acute liver failure (ALF) and eventually death if liver transplantation is not performed. Moreover, ALF is responsible for the majority of deaths. Although much treatments including potential antidotes, detoxification procedures, and supportive therapies are performed, it still has a high mortality of up to 10%–30% [5,6].

Statistically speaking, there were only about ten cases of occasional Amanita phalloides poisoning in our city every year. Hence, it is difficult to conduct a randomized controlled trial. In this study, we respectively

Abbreviations: ALF, acute liver failure; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC, area under the curve; BILD, conjugated bilirubin; BILT, total bilirubin; BUN, blood urea nitrogen; CI, confidence interval; CLIF-OF, Chronic Liver Failure-Organ Failure; CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy; INR, international normalized ratio; KCH, King's College Hospital criteria; LiFe, Liver injury and Failure evaluation; MELD, Model of End Stage Liver Disease; NLR, neutrophil-lymphocyte ratio; NPV, negative predictive value; PA, predictive accuracy; PALBI, Platelet-albumin-bilirubin; PPV, positive predictive value; ROC curve, receiver operating characteristic curve; SOFA, Sequential Organ Failure Assessment; UNBIL, unconjugated bilirubin; WBC, white blood cell.

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Table 1
The formulas of the utilized scores.

Scores	Formulas
CTP	Calculated by five variables, including: bilirubin, INR, albumin, ascites and hepatic encephalopathy [10].
SOFA	Calculated by six variables, including: PaO_2/FiO_2 ratio, Glasgow score, hypotension (mean arterial pressure, vasopressor use), total bilirubin, platelet and serum creatinine or urine volume [11].
LiFe	Calculated by three variables, including arterial lactate, total bilirubin and INR [12].
CLIF-OF	Calculated by six variables, including total bilirubin, creatinine, HE, INR, hypotension (mean arterial pressure, vasopressor use) and PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio [13].
KCH	Included: prothrombin time >100 s or age >10 or <40 years; jaundice >7 days before onset of encephalopathy, prothrombin time >50 s and bilirubin >300 μmol/L [14].
MELD	$9.6 \times \ln[\text{creatinine(mg/dl)}] + 3.8 \times \ln[\text{bilirubin(mg/dl)}] + 11.2 \times \ln[\text{INR}] + 6.4$ The values of creatinine and bilirubin were set to 1.0 mg/dL if they were below 1.0 mg/dL [15].
PALBI	$(2.02 \times \log_{10}\text{bilirubin}) + (-0.37 \times [\log10\ \text{bilirubin}]^2) + (-0.04 \times \text{albumin}) + (-3.48 \times \log_{10}\text{platelets}) + (1.01 \times [\log_{10}\text{platelets}]^2)$ [16].

Abbreviation: CTP, Child-Turcotte-Pugh score; SOFA, Sequential Organ Failure Assessment score; LiFe, Liver injury and Failure evaluation score; CLIF-OF, Chronic Liver Failure-Organ Failure score; KCH, King's College Hospital criteria; MELD, Model of End Stage Liver Disease score; PALBI, Platelet-albumin-bilirubin score.

analyzed and identified the laboratory markers which may predict mortality of Amanita phalloides poisoning. We also evaluated the potential predictive abilities of Child–Turcotte–Pugh (CTP), Sequential organ failure assessment (SOFA), Liver injury and Failure evaluation (LiFe), Chronic liver failure-organ failure score system (CLIF-OF), King's College criteria (KCH criteria), Model for end-stage liver disease (MELD) and Platelet-bilirubin-albumin (PALBI) in Amanita phalloides poisoning. The purpose of this study is to identify the risk indicators of Amanita phalloides poisoning and investigate a good score tool to predict prognosis.

2. Materials and methods

2.1. Ethics statement

This retrospective observational study was approved by the Medical Ethics Committee of Shengjing Hospital and the First Hospital of China Medical University and complied with the guidelines of the Declaration of Helsinki.

2.2. Study design

This study was conducted at Shengjing Hospital of China Medical University and the First Hospital of China Medical University which are defined as the referral centers for critically-ill patients in Liaoning Province, China. All the patients (>16 years old) with Amanita phalloides poisoning admitted to the Emergency Departments (EDs) of the two hospitals between January 2009 and December 2018 were reviewed retrospectively and systematically. Since amatoxin analysis in serum, urine and feces is unavailable in the two hospitals, the diagnosis of Amanita phalloides intoxication was mainly based on the clinical manifestations and patients' descriptions of the ingested wild mushroom. With reference to the two classical books [7,8], written by a mycologist Zhu-Liang Yang, a picture album containing different types of wild toxic mushrooms had been previously established for further diagnosis of Amanita phalloides poisoning. The patients or their relatives figured out the type of wild mushrooms by comparing the pictures in the picture album. The patients who met the following criteria were enrolled in this study: (1) a history of recent Amanita phalloides oral ingestion; (2) vomiting or/and diarrhea within 24 h after ingestion; (3) clinical chemistry criteria for drug-induced liver injury (DILI) [9]. Patients were excluded if they had: (1) chronic liver/kidney disease; (2) viral hepatitis; (3) heavy oral alcohol ingestion.

All the patients were transferred from the local hospitals more than two days after Amanita phalloides ingestion, due to the organ function deterioration. Gastric lavage with charcoal was efficient to eliminate toxicants, but it was not available in the study, due to the delayed admission to our hospitals. During the hospitalization, all the patients

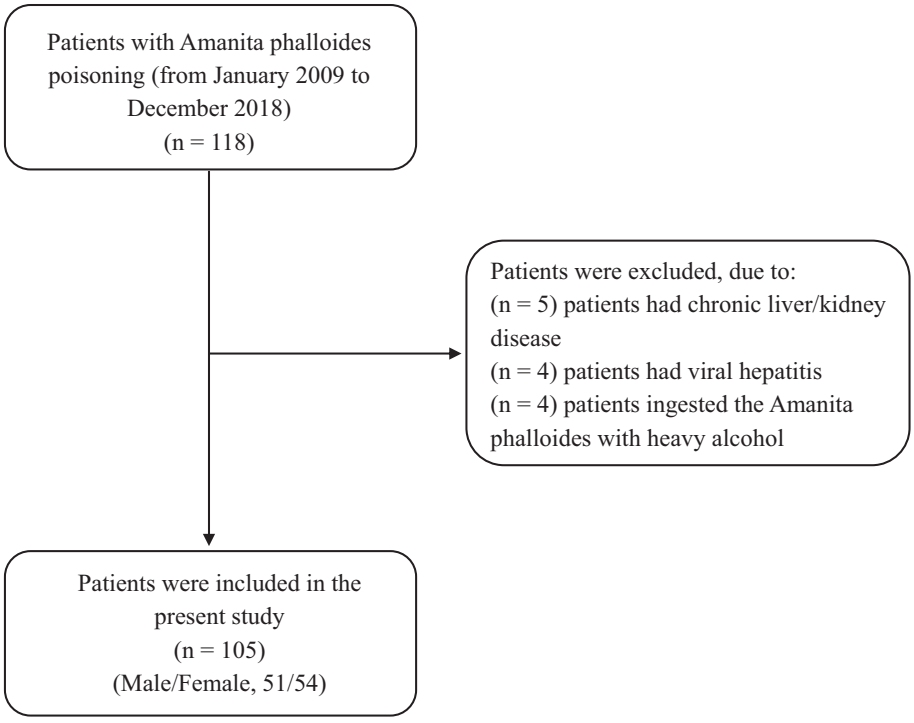

Fig. 1. Flow diagram of the patient selection process.

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Table 2
Comparison of the clinical and laboratory variables in non-survivors and survivors

Variables	Reference range	Non-survivors (n = 24)	Survivors (n = 81)	p-value
Gender (male/female)		11/13	40/41	0.76
Age (years)		59 (52, 64)	57 (50.5, 61)	0.243
Interval from ingestion to admission (day)		3 (3, 4)	3 (2.3, 4.8)	0.786
Hepatic encephalopathy				
Grade 1 or 2 (Y/N)		6/18	7/74	0.074
Grade 3 or 4 (Y/N)		16/8	0/81	<0.001
Laboratory data				
Peak WBC ($\times 10^9$/L)	3.9–9.7	14.2 (9.8, 27.1)	12.3 (9.0, 17.3)	0.085
Nadir hemoglobin (g/L)	130–172	113.5 (94.3, 134.3)	127.5 (117.8, 139.3)	0.228
Nadir platelet ($\times 10^9$/L)	130–350	28.5 (21.8, 47.3)	67.0 (40.5, 118.3)	<0.001
Peak neutrophils ($\times 10^9$/L)	1.9–7.2	11.9 (9.5, 16.2)	9.6 (5.6, 13.1)	0.129
Nadir lymphocyte ($\times 10^9$/L)	1.1–2.7	0.2 (0.2, 0.3)	0.6 (0.4, 0.9)	0.799
Peak NLR		40.3 (31.7, 47.3)	11.4 (5.1, 24.5)	<0.001
Peak ALT (U/L)	5–34	4907.5 (2193, 6180.5)	4601 (3518.5, 6028.3)	0.284
Peak AST (U/L)	0–40	3654.0 (1394.0, 5781.0)	3638.5 (2631.0, 5453.5)	0.213
Peak BILT (μmol/L)	3.4–20.5	149.3 (87.2, 212.5)	50 (29, 116.1)	<0.001
Peak BILD (μmol/L)	0–8.6	83.6 (47.8, 126.1)	28.2 (11.1, 72.6)	<0.001
Peak UNBIL (μmol/L)	3,4–11.9	43.1 (25.2, 95.4)	25.7 (16.5, 34.7)	<0.001
Nadir total protein (g/L)	60–83	49.6 (43.6, 58.9)	49.5 (45.2, 53.4)	0.322
Nadir albumin (g/L)	35–53	30.1 (26.6, 34.5)	29.9 (26.2, 32.9)	0.926
Peak creatinine (μmol/L)	59–104	97.1 (78.0, 145.9)	56.7 (47.4, 81.9)	0.05
Peak BUN (mmol/L)	3–9.2	10.3 (7.9, 20.4)	7.9 (5.7, 10.4)	0.077
Peak APTT (s)	21–37	47.7 (41.8, 57.0)	36.0 (31.0, 40.3)	<0.001
Nadir fibrinogen (g/L)	2–4	0.9 (0.7, 1.0)	1.8 (1.2, 2.0)	<0.001
Peak D-dimer (μg/L)	0–252	3309.5 (2603.8, 7510.3)	933.5 (418.8, 2163.0)	<0.001
Peak INR	0.8–1.5	7.9 (4.5, 12.7)	2.0 (1.4, 3.5)	<0.001
Peak ammonia (μmol/L)	9–33	122.3 (65.5, 160.5)	63.2 (43.9, 81.0)	<0.001

Abbreviation: WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; ALT, alanine transaminase; AST, aspartate aminotransferase; BILT, total bilirubin; BILD, conjugated bilirubin; UNBIL, unconjugated bilirubin; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time; INR, international normalized ratio.

were treated with adequate intravenous hydration which was beneficial to improve severe dehydration. Potential antidotes including benzylpenicillin (1 MU/kg/day), silibinin (loading dose of 5 mg/kg over one hour, followed by a continuous dose of 20 mg/kg/day) and *N*-acetylcysteine (loading dose of 150 mg/kg intravenously over 15 min, followed by 50 mg/kg over 4 h, followed by 100 mg/kg over 16 h) were used in our study. Unfortunately, liver transplantation was not performed in these patients due to the shortage of donor liver.

2.3. Data collection

Data from all patients were collected using a standard data collection form, which included these following: (1) demographic characteristics such as gender and age; (2) the time interval between oral ingestion and admission to the referral centers; (3) the numbers of patients with hepatic encephalopathy; (4) laboratory data monitored every 12–24 h in this study including white blood cell (WBC), hemoglobin, platelet, neutrophils, lymphocyte, neutrophil-lymphocyte ratio (NLR), alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (BILT), conjugated bilirubin (BILD), unconjugated bilirubin (UNBIL), total protein, albumin, creatinine, blood urea nitrogen (BUN), activated partial thromboplastin time (APTT), fibrinogen, D-dimer, international normalized ratio (INR), ammonia; (5) Clinical scoring systems including CTP [10], SOFA [11], LiFe [12], CLIF-OF [13], KCH criteria [14], MELD [15] and PALBI [16].The formulas of the utilized scoring systems are shown in Table 1.

2.4. Statistical analysis

Continuous variables with normal distribution were presented as mean ± standard deviation (SD) and non-normal variables were presented as median and interquartile [M (QL, QU)]. The two groups were compared by using Student's *t*-test or Mann-Whitney *U* test based on the different types of variables. Categorical data of the two groups were estimated by using Chi-squared test or Fisher's exact test. Multivariable logistic regression analysis was used to identify independent risk factors. ROC curve analysis was used to evaluate the discriminative abilities of CTP, SOFA, LiFe, CLIF-OF, KCH criteria, MELD and PALBI in predicting the mortality. All the data were analyzed by the SPSS software (Version 19.0; SPSS, Chicago, IL, USA). The p-value here was adjusted for multiple testing via the Benjamini-Hochberg procedure. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

A total of 105 poisoned patients (Male/Female, 51/54) were finally evaluated in our study according to the inclusion criteria (Fig. 1). As

Table 3
Multivariable logistic regression analysis and ROC analysis of prognostic factors in Amanita phalloides poisoning

Risk factors	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	+LR	−LR	OR (95% CI)	p-value
Peak INR	3.6	0.941	95.8	77.3	93.3	6.25	0.098	1.465 (0.875–0.979)	<0.001
Peak ammonia (μmol/L)	95.1	0.805	66.7	91.1	87.0	7.47	0.37	1.036 (0.701–0.885)	<0.001

Abbreviation: INR = international normalized ratio; AUC = area under the curve; +LR = positive likelihood ratio; −LR = negative likelihood ratio; OR = odds ratio; CI = confidence interval.

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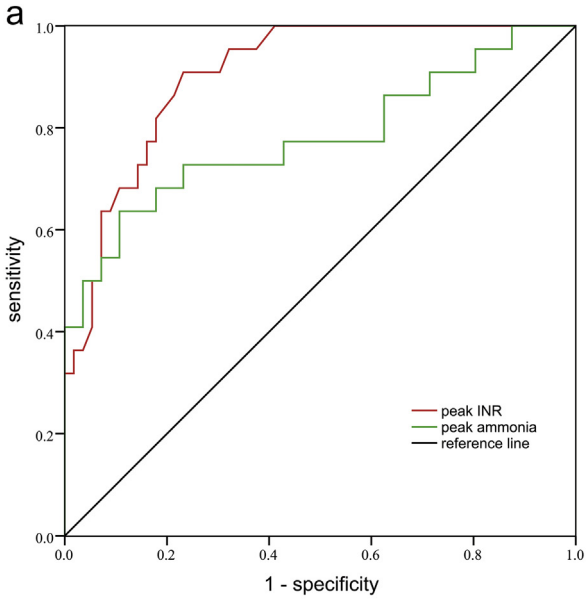

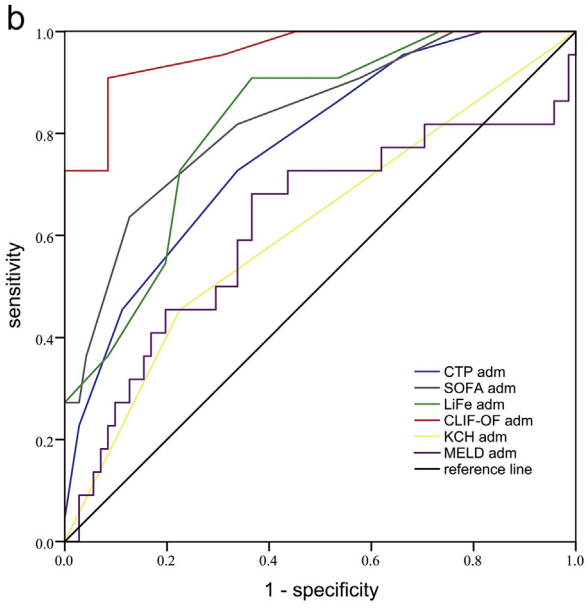

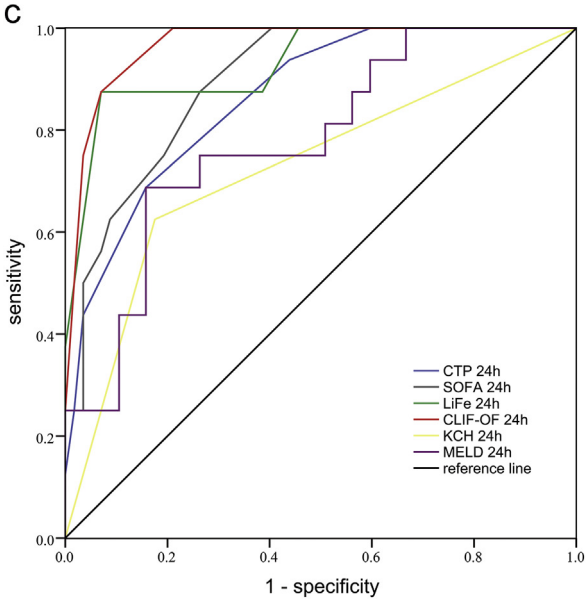

Table 4
Analysis of CTP, SOFA, LiFe, CLIF-OF, KCH, MELD and PALBI score of two groups

Scores	Time	Non-survival group	Survival group	p-value
CTP [M (QL, QU)]	Admission	9.5 (9, 10)	8 (6, 9)	<0.001
	24 h	10 (9, 11)	8 (6, 9)	<0.001
SOFA [M (QL, QU)]	Admission	5 (4, 7)	3 (2, 4)	<0.001
	24 h	6 (5, 9)	3 (2, 4)	<0.001
LiFe [M (QL, QU)]	Admission	5 (3, 6)	1 (0, 3)	<0.001
	24 h	5 (5, 6)	1 (0, 3)	<0.001
CLIF-OF [M (QL, QU)]	Admission	11 (10, 12)	7 (6, 8)	<0.001
	24 h	12 (11, 13)	7 (6, 8)	<0.001
KCH (Y/N)	Admission	8/14	14/68	0.02
	24 h	14/8	8/72	<0.001
MELD	Admission	25.9 ± 11.6	17.2 ± 7.6	<0.001
	24 h	28.3 ± 7.1	16.4 ± 7.5	<0.001
PALBI	Admission	−1.95 ± 0.57	−2.09 ± 0.33	0.138
	24 h	−1.79 ± 0.32	−1.95 ± 0.32	0.068

Abbreviation: CTP, Child-Turcotte-Pugh score; SOFA, Sequential Organ Failure Assessment score; LiFe, Liver injury and Failure evaluation score; CLIF-OF, Chronic Liver Failure-Organ Failure score; KCH, King's College Hospital criteria; MELD, Model of End Stage Liver Disease score; PALBI, Platelet-albumin-bilirubin score.

shown in Table 2, the mean age of enrolled patients was 54.2 ± 11.6 years old (range 18–80 years old). The interval from oral ingestion to admission to the EDs of the two hospitals was 3.3 ± 1.5 days (range 1–10 days). The main clinical symptoms were vomiting (102 cases, 97.1%) and diarrhea (100 cases, 95.2%), followed by abdominal pain (93 cases, 88.6%), and jaundice (24 cases, 22.9%). 16 patients had jaundice at the time of referral and eight patients developed jaundice within seven days of admission. Six patients suffered from hepatic encephalopathy at the time of referral and 23 patients had late-onset hepatic encephalopathy. Finally, 24 patients (24/105, 22.9%) died of acute liver failure with or without the other organ dysfunction. The patients with grade 3 or 4 of hepatic encephalopathy had poor outcomes (p-value <0.05).

3.2. Laboratory data analysis

As shown in Table 2, there were no statistically significant differences between the two groups with respect to gender, age and time interval from oral ingestion to admission to the EDs of the two hospitals. Univariable analysis results showed the peak values of the following markers: NLR, BILT, BILD, UNBIL, APTT, INR, D-dimer and plasma ammonia in non-survivors were significantly higher than survivors (p-value <0.05). Besides, the nadir platelet and fibrinogen in non-survivors were significantly lower than survivors (p-value <.05).

Multivariable logistic regression analysis results (Table 3) showed that peak INR (OR = 1.465) and peak plasma ammonia (OR = 1.036) were independent risk factors of Amanita phalloides poisoning. As shown in Table 3 and Fig. 2a, the peak INR had good AUC (0.941) and when the cut-off value was 3.6, the sensitivity was 95.8% and the specificity was 77.3% (95% CI: 0.875–0.979; +LR: 6.25, −LR: 0.098). The peak plasma ammonia also had good AUC (0.805) and when the cut-off value was 95.1, the sensitivity was 66.7% and the specificity was 91.1% (95% CI: 0.701–0.885; +LR: 7.47, −LR: 0.37). Herein, the risk indicators including peak INR > 3.6 and peak ammonia >95.1 μmol/L can be considered as the risk indictors of death in Amanita phalloides poisoning.

3.3. Clinical scoring systems for mortality risk assessment

All the clinical scoring systems of non-survivors were significantly different from survivors ($p < 0.05$), except PALBI score (Table 4). As

Fig. 2. a ROC curves of peak INR and peak ammonia in Amanita phalloides poisoning; b ROC curves of CTP, SOFA, LiFe, CLIF-OF, KCH criteria, and MELD scores in Amanita phalloides poisoning at admission; c ROC curves of CTP, SOFA, LiFe, CLIF-OF, KCH criteria, and MELD scores in Amanita phalloides poisoning at 24 h of admission.

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Table 5
Comparison of CTP, SOFA, LiFe, CLIF-OF, KCH, and MELD score within 24 h of admission to the emergency departments

	Score	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)	Cut-off value	95% CI
Admission	CTP	0.857	79.2	75.0	51.4	91.9	76.8	8	0.722–0.919
	SOFA	0.889	81.8	76.9	50.0	93.8	78.0	3	0.810–0.943
	LiFe	0.859	90.9	69.5	52.6	95.3	75.3	3	0.764–0.926
	CLIF-OF	0.981	90.9	97.4	90.9	97.4	95.9	9	0.930–0.998
	KCH	0.663	45.5	87.2	50.0	85.0	78.0	N/A	0.562–0.755
	MELD	0.723	70.8	75.0	47.2	89.1	74.0	20.5	0.624–0.807
24 h	CTP	0.909	85.0	69.1	47.5	90.9	75.0	8	0.828–0.960
	SOFA	0.959	82.8	76.8	55.6	94.0	82.0	3	0.895–0.990
	LiFe	0.952	90.0	92.6	81.8	95.8	86.5	3	0.875–0.988
	CLIF-OF	0.962	90.0	91.7	90.5	97.1	91.3	9	0.901–0.991
	KCH	0.676	50.0	85.3	50.0	85.3	77.3	N/A	0.568–0.772
	MELD	0.772	80.0	82.5	59.3	92.9	81.9	24.1	0.781–0.935

Abbreviation: CTP, Child-Turcotte-Pugh score; SOFA, Sequential Organ Failure Assessment score; LiFe, Liver injury and Failure evaluation score; CLIF-OF, Chronic Liver Failure-Organ Failure score; KCH, King's College Hospital criteria; MELD, Model of End Stage Liver Disease score; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

shown in Table 5 and Fig. 2b and c, ROC curves analysis indicated that MELD and KCH criteria (AUC < 0.8) failed to show good ability to predict a fatal outcome. Although the AUC values of CTP, SOFA, and LiFe scores at admission to the EDs were 0.85–0.90, the diagnostic accuracy was <80%. Interestingly, the AUC values of SOFA and LiFe scores at 24 h of admission were 0.959 and 0.952, respectively. Although both of the AUC values are close to CLIF-OF (AUC = 0.962) with no significance (adjusted p-value = 0.061, adjusted p-value = 0.171) shown in the Supplementary Table 1, the diagnostic accuracy values of SOFA and LiFe scores (82.0%, 86.5%) were clearly inferior to CLIF-OF (91.3%).

It is worth noting that the AUC value of CLIF-OF at admission to the EDs (AUC = 0.981) and at 24 h of admission (AUC = 0.962) were significantly superior to other clinical scoring systems. As shown in Table 5, when the cut-off value of CLIF-OF at admission to the EDs or 24 h of admission was set to 9, all the values of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were >90%. Furthermore, CLIF-OF performed best in predicting outcome in Amanita phalloides poisoning.

4. Discussion

It is known that Amanita phalloides accounted for the majority of wild mushroom poisonings [2]. Unfortunately, Amanita phalloides were not identified by the pickers who were mostly villagers living in mountainous areas. In this study, almost all the patients did not identify the toxic Amanita phalloides and orally ingested them by chance. The initial symptoms including vomiting and diarrhea accounted for >90% of poisoning cases. Due to the delayed admission to our hospitals, the laboratory markers and clinical manifestation of the patients greatly deteriorated.

Some previous studies reported that patients of Amanita phalloides poisoning with the peak levels of AST >4000IU/L [1] or >2000 IU [17] were more likely to have a poor outcome; Conversely, our findings showed that AST and ALT levels at admission were not associated with mortality, consistent with another study [18]. The hepatic enzyme markers cannot reflect hepatocellular necrosis and hepatotoxicity in patients with acute liver failure [19,20]. BILT, PT, INR, and APTT were considered as helpful indicators of hepatic dysfunction. The previous studies showed that BILT >2 mg/dL [1] or 5 mg/dL [18], peak INR >2 [1], serum factor V < 30% [1], PT >50 s [17], prothrombin index <10% [5] or 25% [21], or APTT >50 s [18] may predict poor clinical outcomes in patients with acute liver injury induced by Amanita mushroom intoxication [18]. In reference to the relatively small quantities used in these researches that were mentioned above, the conclusions were slightly different. In this study, although the peak BILT, peak APTT, peak INR, nadir FIB, and peak D-dimer were significantly different in the two groups, only peak INR was the independent risk factor of death by using multivariable logistic regression analysis. Furthermore, the peak INR had good AUC value (0.941) and the peak INR >3.6 had good sensitivity (95.8%) and specificity (77.3%) to predict a fatal outcome.

Ammonia and other waste products which are toxic to the brain could cause hepatic encephalopathy. It is notable that plasma ammonia is a marker for hepatic encephalopathy [19]. The multivariable analysis results showed that peak plasma ammonia >95.1 μmol/L was another independent risk factor of death of Amanita phalloides poisoning. The non-survivors with severe hepatic encephalopathy (grade 3–4) were significantly less than survivors (p-value <0.05). This is consistent with the previous study that hepatic encephalopathy was at serious risk for death in Amanita phalloides poisoning [17],

In accordance to the results mentioned above, it was not just one factor associated with the poor prognosis of Amanita phalloides poisoning. Herein, the clinical scoring systems were calculated and the AUC were performed regarding the prediction of fatal outcome. Although KCH criteria and MELD score had great ability in predicting mortality of acute liver failure [22,23], they did not show the predictive ability in this study. SOFA score presented a better predictive ability of fatal outcome than MELD score and KCH criteria within 24 h of admission [24]. LiFe score showed good diagnostic accuracy for predicting in-ICU mortality of critically ill cirrhosis patients [25]. Nevertheless, the CTP, SOFA, and LiFe scores were not superior to the CLIF-OF score in this study (Supplementary Table 1).

CLIF-OF was calculated by six variables including total bilirubin, creatinine, HE, INR, hypotension and PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio. These markers were used to evaluate hepatic function, renal function, pulmonary function and coagulation function. CLIF-OF was a better prognostic score than MELD, MELD-Na, and CTP in predicting mortality of ACLF and non-ACLF patients [26,27]. In addition, compared with the independent risk factors INR and plasma ammonia, CLIF-OF performed best in predicting outcome in Amanita phalloides poisoning in terms of AUC, sensitivity and specificity. With really good diagnostic accuracy (>90%) and NPV (>97%) within 24 h of admission, CLIF-OF (>9) were prognostic of impending death in this study. It could help identify patients with a better outcome who could be cared for in a lower setting of medical care in the early time. CLIF-OF was considered as a practical tool to evaluate the prognosis of patients. Both clinicians and emergency doctors must pay attention to these patients with high CLIF-OF score (>9) within 24 h of admission to emergency department. A comprehensive treatment regimen may be effective in reducing the mortality in Amanita phalloides intoxication.

This study had some major limitations. First, the sample size of this study was small and all the enrolled patients who ingested wild mushrooms were from two institutions. Second, this study was a retrospective observational design and the undetected bias may have been present.

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5. Conclusion

As Amanita phalloides poisoning is a devastating clinical condition, CLIF-OF score (>9) within 24 h of admission is considered as a satisfactory tool for assessing the severity of Amanita phalloides poisoning. Notably, this study is not a prospective multicenter randomized controlled trial. The conclusion in this study should be considered exploratory or preliminary, that will require confirmation in other studies in the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2020.01.027.

Informed consent

This is a retrospective study that include anonymized patients extracted from hospital database; No informed consent was taken.

Author contributions

ZL designed the study. YY, ZL, and MZ collected and analyzed the data. ZL and YY wrote the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors declared that they have no conflicts of interest in this work.

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