

# Analysis on Clinical Features and Risk Factors of Death in Yunnan with Acute Mushroom Poisoning

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## Abstract

**Introduction:** Mushroom poisoning has become a global public health problem. However, effective treatment of toadstool poisoning and risk factors evaluation are a trouble for clinicians.

**Objective:** This study aimed to analyze the clinical features and associated risk factors among mushroom poisoning.

**Methods:** This was designed as a retrospective study. Analyzed 137 medical records of mushroom poisoning cases over 5 years in the first people's hospital in Yunnan province.

**Results:** A total of 137 mushroom poisoning cases were reported, of which 70 (52%) were female. Mortality was 13.1% (18). A latency of  $\geq 6$  h was seen in 87 cases (63.50%), with a mortality of 89% (16). Direct bilirubin (DB)  $\geq 34.2$   $\mu\text{mol/L}$  was seen in 16 patients, and 124 cases (90.0%) occurred from June to August (summer).

**Conclusion:** Final regression models indicated that risk factors were associated with latency, DB, and PT. Individuals and health care providers should be educated about the risk of mushroom poisoning, especially in the summer. A latency of  $\geq 6$  h and DB of  $\geq 34.2$   $\mu\text{mol/L}$  are independent risk factors for death in patients with mushroom poisoning.

**Keywords:** Mushroom Poisoning; Epidemiology; Mortality; Risk Factors

## Introduction

Nearly 10,000 kinds of mushrooms have been identified throughout the world, 3,800 of which are found in China, and 421 of these are considered poisonous [1]. Eating wild mushrooms is a common tradition in China, as it is elsewhere in the world. However, it is often difficult to distinguish between edible and poisonous species. In around 95% cases of poisonous mushroom exposure, the species could not be identified [2]. Industrially grown mushrooms are considered relatively safe, whereas eating wild-foraged mushrooms or accidentally ingesting wild mushrooms may result in serious illness or death, especially if they contain amatoxin. Statistical data from the Chinese Centre for Disease Control and Prevention (CDC) shows there were 3,701 cases of mushroom poisoning from 2004 to 2014, with 786 deaths, a mortality rate of 21.24% [3]. Yunnan Province, located in the southwest of China, has a mild, humid, subtropical climate, which is ideal for mushrooms [4]. The local residents consume a large volume of mushrooms and, thus, cases of mushroom poisoning in Yunnan Province account for nearly 40% of the total number in China. There are no specific antidotes, and a systematic analysis of the risk factors for death is currently lacking.

## Materials and Methods

### Study Participants and Diagnostic Criteria

This was a retrospective single centre study of patients presenting at the first people's hospital of Yunnan province with signs/symptoms related to mushroom exposure or intoxication during a 5 years period (from 1 January 2015 to 31 October 2019). The hospital was a tertiary referral centre for other hospitals in the region and provides a catchment area for approximately two million people—with about 2,223,000 (2019) emergencies admissions a year ( $\geq 18$  years of age). These databases were used to identify all patients presenting with (suspected) mushroom poisoning. Cases were retrieved using a comprehensive full-text search algorithm with mushroom poisoning, related terms and a large number of specific mushroom names, as search terms. Each identified case was reviewed by one of the authors of the study. We included each patient requiring medical evaluation for mushroom poisoning, regardless of the circumstances of exposure (i.e., accidental or intentional) and the severity of the complaints. We excluded patients with no history of mushroom consumption and cases where the complaints could be clearly attributed to a cause other than mushroom poisoning based on the available final diagnosis in the medical report and the documented evaluation of the physician assessing the patient.

### Data collection

The following parameters were extracted (if available) from the charts of included patients: age, sex, date of admission and discharge, mushroom species and how they were obtained (e.g., self-harvest, purchased from commercial sources), circumstances of exposure (e.g., accidental, recreational, suicide), symptoms, interval from ingestion to onset of symptoms, treatment provided, length of hospital stay, and outcome (e.g., complications, death). And the laboratory findings: white blood cell count (WBC), neutrophil count (NEU), hemoglobin (HB), platelets, aspartate aminotransferase (AST), alanine amino transferase (ALT), albumin, total bilirubin (TB), direct bilirubin (DB), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), serum creatinine (SCr), blood urea nitrogen (BUN), myoglobin (MB), Creatine kinase-MB (CK-MB), and cardiac troponin I (cTnI) were recorded on the day of admission.

### Statistical analysis

All data were processed using SPSS 22.0 software, tested for normal distribution, and reported as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). A comparison of the mean of two samples was used when the variance was uneven, which was expressed as the median (quartile), and the  $\chi^2$  test was used for comparisons between groups. Logistic regression was used to identify the risk factors for death, with the results summarized as odds ratios (ORs) and 95% confidence intervals (CIs). A statistically significant difference was noted when  $P < 0.05$ .

## Results

### Participant characteristics

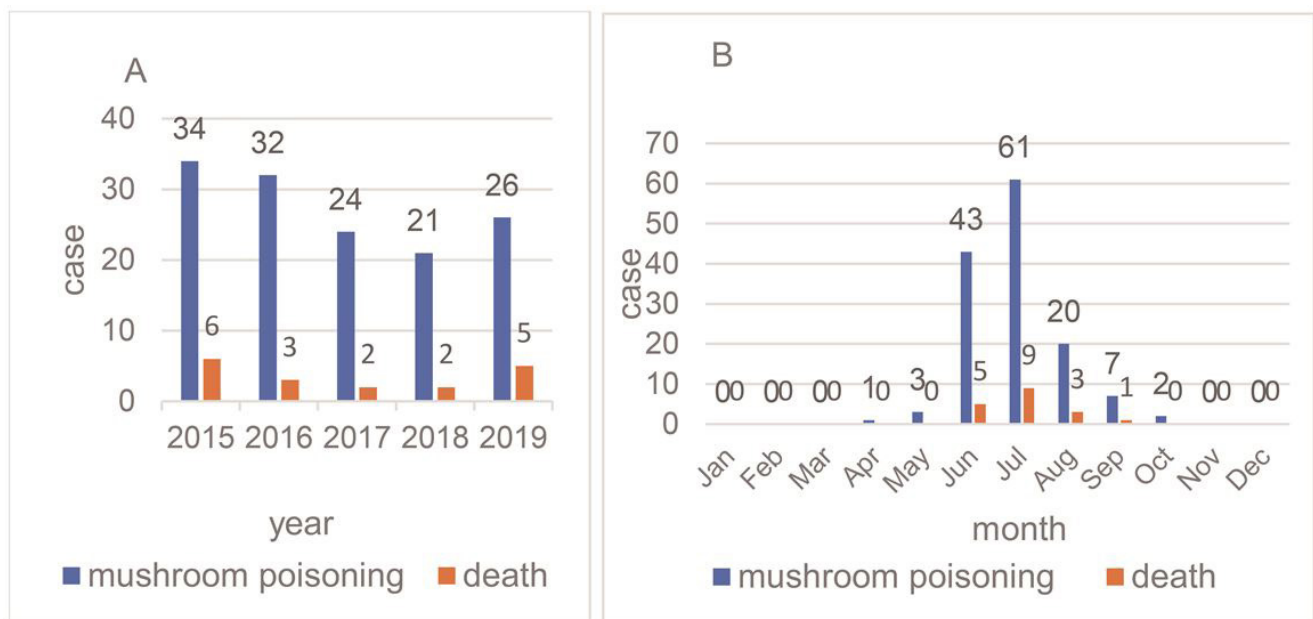
From the year of 2015 to 2019, in a total of 137 patients were provided by the first people's hospital of Yunnan province, of those, 52% were females, and the mean age of the patients was  $42.6 \pm 20.7$  years. The mean duration of hospital-stay was  $8.0 \pm 6.6$  days. Most cases (87, 63.50%) presented  $\geq 6$  h after ingesting the mushrooms (Table 1).

Variable	Total (n=137)	Survivor (n=119)	Death (n=18)	X <sup>2</sup> /t	P
Gender				0.066	0.798
Male [case(%)]	67(48%)	53(45%)	14(78%)	-	-
Female [case(%)]	70(52%)	66(55%)	4(22%)	-	-
Age (years)	42.60 $\pm$ 20.75	41.62 $\pm$ 21.46	48.78 $\pm$ 13.40	-0.947	0.344
Duration of hospital-stay (d)	7.95 $\pm$ 6.53	7.35 $\pm$ 4.27	12.17 $\pm$ 3.80	-1.624	0.104
Symptom onset time				3.219	0.073
Early-onset (<6h, %)	50(36.50%)	48(40.34%)	2(11.11%)	-	-
Late-onset ( $\geq 6$ h, %)	87(63.50%)	71(59.66%)	16(88.89%)	-	-

**Table 1:** The demographic characteristics of mushroom poisoning

### The epidemiologic of mushroom poisoning

Mushroom poisoning had a regional distribution, mainly occurring in Chuxiong and Qujing in Yunnan Province. Annual presentations, peaked in 2015 and ranged from 21 to 34 patients (Figure 1A). Most cases (104, 75.9%) presented in the summer months (June and July) (Figure 1B).



**Figure 1:** The epidemiologic of mushroom poisoning (A) Annual distribution of presentations due to mushroom poisoning; (B) Monthly distribution of mushroom poisoning

## Symptoms and signs

Table 2 shows the frequencies of the patients' signs and symptoms at the time of admission. The most common clinical presentations were gastrointestinal symptoms, including vomiting, nausea, abdominal pain, and diarrhea. Neurological symptoms (headache, confusion, auditory, and visual hallucination) were also commonly reported (70, 51.1%), and coma occurred in severe cases (2, 1.4%). The classification of mushroom poisoning is based on four principle sets of symptoms [5] : (1) Gastrointestinal (74, 54.0%) with vomiting, nausea, abdominal pain, and diarrhea; (2) Neuropsychiatric (43, 31.4%) with headaches, confusion, auditory and visual hallucinations, and coma; (3) Multiple organ failure(18, 13.1%) with hepatic and renal dysfunction, cardiac enzyme and myocardial injury marker abnormalities, oliguria, and anuria; (4) Hemolysis(2, 1.5%) with fatigue, jaundice, and hepatic dysfunction.

Presenting symptom/sign	No. (%) of cases
<b>Gastrointestinal symptoms</b>	
Vomiting/Nausea	71(51.8%)
Diarrhea	46(33.6%)
Abdominal pain	26(19.0%)
<b>Neurological symptoms</b>	
Dizziness / lethargy	18(13.1%)
Headache	26(19.0%)
Auditory / visual hallucination	70(51.1%)
Confusion	18(13.1%)
Amyasthenia	22(16.1%)
Dystaxia	26(19.0%)
Sweating	23(16.8%)
Disturbance of consciousness	25(18.2%)
Coma	2(1.5%)
<b>Other symptoms and signs</b>	
Fever (>38°C)	4(2.9%)
Jaundice	5(3.6%)
Dyspnea	6(4.2%)
Thoracic pain	5(3.6%)
Tachycardia	26(19.0%)
Hypotension	4(2.9%)

**Table 2:** Presenting symptoms and signs

## Associated risk factors of mushroom poisoning

The mean values of the laboratory measurements at admission are provided in Table 3. We performed a comparison of the laboratory indexes between the two groups with different prognoses. Furthermore, the laboratory results with statistically significant differences were selected for univariable logistic regression (Table 4). The results show that the incidences of latency  $\geq 6$  h, WBC  $\geq 12 \times 10^9/L$ , NEU  $\geq 10 \times 10^9/L$ , ALT  $\geq 200$  U/L, AST  $\geq 200$  U/L, PT  $\geq 20$  s, INR  $\geq 1.5$ , TB  $\geq 34.2$   $\mu\text{mol/L}$ , and DB  $\geq 34.2$   $\mu\text{mol/L}$  were signifi-

cantly higher in the death group than the survival group (OR >1). We concluded that the above indexes are risk factors for death from mushroom poisoning (all  $P < 0.01$ ). Multivariable logistic regression analysis showed that DB of  $\geq 34.2 \mu\text{mol/L}$  (OR = 55.077, 95%CI = 2.003-1785.159) and a latency of  $\geq 6$  h (OR = 25.638, 95%CI = 1.320-498.062) were risk factors for death. DB  $\geq 34.2 \mu\text{mol/L}$  was the strongest risk factor (Table 5).

Variable	Total (n=137)	Survival (n=119)	Death (n=18)	Z/t	P
<b>Blood routine</b>					
WBC( $\times 10^9/\text{L}$ )	8.93 $\pm$ 4.29	8.40 $\pm$ 3.67	12.51 $\pm$ 6.04	-2.851	0.004
(NEU( $\times 10^9/\text{L}$ )	(3.80,8.33)5.26	(3.61,7.32)5.01	(5.98,14.50)9.95	-3.479	0.001
Hb(g/L)	138.09 $\pm$ 25.19	137.43 $\pm$ 24.12	141.72 $\pm$ 31.46	-0.908	0.364
PLT( $\times 10^9/\text{L}$ )	212.37 $\pm$ 77.17	215.74 $\pm$ 74.32	203.78 $\pm$ 108.92	0,470	0.639
<b>Liver function</b>					
ALT(U/L)	22.50(13.00,65.25)	20.00(12.50,49.0)	2941.25(897.50,5097.40)	-4.718	< 0.001
AST(U/L)	25.00(19.00,83.50)	24.00(18.50,184.60)	1019.00(137.00,2536.00)	-4.814	< 0.001
ALB (mmol/L)	40.32 $\pm$ 6.90	40.71 $\pm$ 6.48	38.25 $\pm$ 9.21	-1.171	0.242
TB (( $\mu\text{mol/L}$ )	9.50(4.15,15.10)	8.80(4.00,13.30)	53.90(17.50,74.40)	-4.836	< 0.001
DB (( $\mu\text{mol/L}$ )	6.70(3.95,13.70)	6.10(3.80,11.40)	42.95(11.58,62.63)	-4.607	< 0.001
<b>Coagulation</b>					
PT(s)	13.50(1.29,14.60)	13.30(12.80,14.10)	16.90(14.30,62.65)	-4.301	< 0.001
INR(s)	1.01(0.96,1.12)	1.01(0.96,1.07)	1.24(1.08,5.51)	-1,400	< 0.001
APTT(s)	38.0(34.65,42.55)	37.9(34.20,41.30)	39.8(35.10,53.90)	-1.899	0.058
<b>Renal function</b>					
SCr ( $\mu\text{mol/L}$ )	63.00(48.75,81.00)	61.00(48.00,76,00)	93.50(61.75,134.25)	-3.196	0.001
BUN (mmol/L)	4.60(3.50,6.95)	4.30(3.50,6.30)	10.70(4.50,14.80)	-3.693	< 0.001
<b>Electrolyte</b>					
K+(mmol/L)	4.17 $\pm$ 0.48	4.12 $\pm$ 0.41	4.53 $\pm$ 0.75	-3.007	< 0.001
Na+(mmol/L)	136.59 $\pm$ 17.93	136.82 $\pm$ 19.13	135.33 $\pm$ 4.21	-2.327	0.020
Myocardial injury	(n=79)	(n=71)	(n=6)	-	-
CK-MB( $\mu\text{g/L}$ )	1.7(0.8,4.3)	1.5(0.7,3.3)	4.0(1.7,12.1)	-2.345	0.019
MB( $\mu\text{g/L}$ )	67.1(32.8,145.5)	59.9(28.4,127.4)	145.5 (56.5,984.2)	-2.488	0.013
cTnI ( $\mu\text{g/L}$ )	0.03(0.005,0.140)	0.015(0,0.002)	0.007(0.003,0.021)	-2.050	0.040

\*:WBC: White Blood Cell Count; NEU: Neutrophil Count; HB: Hemoglobin; PLT: Platelet; AST: Aspartate Aminotransferase; ALT: Alanine Amino Transferase; ALB: Albumin; TB: Total Bilirubin; DB: Direct Bilirubin; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; INR: International Normalized Ratio; SCr: Serum Creatinine; BUN: Blood Urea Nitrogen; MB: Myoglobin; CK-MB: Creatine kinase -MB; cTnI: cardiac troponin I

**Table 3:** Comparison of laboratory data of mushroom poisoning patients between two groups with different prognosis

Risk factor	Survivor (n=119)	Death (n=18)	OR (95%CI)	P
latent phase $\geq$ 6h	87(73.1%)	16(88.89%)	5.600(1.231~25.467)	0.026
WBC $\geq$ 12 $\times$ 10 <sup>9</sup> /L	18(15.1%)	8(44.4%)	4.480(1.560~12.910)	0.005
NEU $\geq$ 10 $\times$ 10 <sup>9</sup> /L	11(9.2%)	9(50.0%)	8.150(2.750~24.220)	< 0.001
AST $\geq$ 200U/L	12(10.1%)	11(61.1%)	19.650(6.160~62.630)	< 0.001
ALT $\geq$ 200U/L	12(10.1%)	11(61.1%)	10.190(3.410~30.430)	< 0.001
TB $\geq$ 34.2 $\mu$ mol/L	3(2.5%)	10(55.6%)	23.540(6.810~81.380)	< 0.001
DB $\geq$ 34.2 $\mu$ mol/L	6(5.0%)	10(55.6%)	48.330(11.050~211.430)	< 0.001
PT $\geq$ 20s	1(0.8%)	8(44.4%)	37.220(6.880~201.480)	< 0.001
APTT $\geq$ 40S	35(29.7%)	11(61.1%)	2.220 (0.810~6.040)	0.120
INR $\geq$ 1.5	3(2.5%)	9 (50.0%)	14.510 (3.940~55.440)	< 0.001

**Table 4:** Univariable logistic regression analysis of death risk factors of mushroom poisoning patients

Risk factor	Sx	X <sup>2</sup>	p	OR (95%CI)
latent phase $\geq$ 6h	1.514	4.594	0.032	25.638(1.320~498.062)
WBC $\geq$ 12 $\times$ 10 <sup>9</sup> /L	1.461	1.196	0.303	4.410(0.282~86.635)
NEU $\geq$ 10 $\times$ 10 <sup>9</sup> /L	1.439	1.063	0.608	1.956(0.263~74.044)
AST $\geq$ 200U/L	1.627	1.184	0.277	5.872(0.242~142.385)
ALT $\geq$ 200U/L	1.761	0.422	0.516	0.319(0.010~10.061)
TB $\geq$ 34.2 $\mu$ mol /L	1.216	3.764	0.052	10.593 (0.976~114.945)
DB $\geq$ 34.2 $\mu$ mol /L	1.775	5.102	0.024	55.077 (2.003~1785.159)
PT $\geq$ 20s	1.737	1.161	0.281	6.498(0.216~195.658)
APTT $\geq$ 40S	1.564	3.684	0.055	0.050(0.002~1.065)
INR $\geq$ 1.5	2.228	0.351	0.554	3.744(0.048~295.014)

**Table 5:** Multivariable logistic regression analysis of death risk factors of mushroom poisoning patients

## Mushroom-induced myocardial toxicity

In some poisoned patients, myocardial toxicity was very prominent and mainly manifested as an increase in myocardial enzymes (Table 3) and electrocardiogram (ECG) changes [6]. Some cases had one or more ECG abnormalities; there were ST-T changes in 20 patients, sinus bradycardia in one, sinus tachycardia in two, atrioventricular block in five, and atrial premature beat in one case. Myocardial injury marker was documented in 79 cases, six of whom died (7.6%), and the difference was statistically significant (all  $P < 0.05$ ). Changes in ECG, serum CK-MB, cTnI, and MB may indicate myocardial injury.

## Discussion

Mushroom poisoning has become a global public health problem, and Yunnan has the highest incidence of mushroom poisoning in China. The reported mortality rate in western countries is 1.02% [7]; while, in Turkey, the mortality rate is 2.1% [8]. There were 1,920 cases of mushroom poisoning in Japan from 2001 to 2010, with a mortality rate of 0.52% [9]. The mortality rate of mushroom

poisoning in the United States was reported to be 0.04% [10]. However, the mortality rate in this study was 13.1%, and the mortality in China is significantly higher than in other countries. Therefore, mushroom poisoning is fairly significant worldwide and has become a major public health problem in China. A study reported a total of 1,404 patients with wild mushroom poisoning in Chuxiong, Yunnan, from 2001 to 2013 [11]. The NPDS reported 133,700 cases of mushroom exposure from 1999 to 2016 (7428/year) [12]. The prognosis of patients with mushroom poisoning is affected by many factors [13]. However, so far, most studies on mushroom poisoning have focused on analyzing the clinical manifestations or have been epidemiological investigations. There has been a lack of large sample studies on the clinical characteristics and risk factors of death from mushroom poisoning.

During the 5-year study period, there were 137 cases related to mushroom poisoning, with a seasonal peak in the summer (104 cases in June and July, 75.9%) (Fig. 1B). Summer has the optimal climate for mushroom growth in Yunnan, China. Mushrooms that grow in different areas contain different toxins. *Amanita phalloides*, *Amanita bisporigera*, and *Amanita virosa* are the main species causing mortality in North America and Europe [14]. In Southern China, a reported 16 species of *Amanita* cause over 70% of Chinese fatalities, whereas, in Yunnan Province, *Boletaceae* sp. are the main culprits.

Mushroom poisoning incidents occur throughout the world each year, but it is difficult to identify the mushroom species responsible. Because mushroom specimens are difficult to collect and store, there is currently a lack of authoritative mushroom toxicology agencies to identify the toxins [15]. In up to 95% of cases, the species of mushroom ingested cannot be identified. The American Association of Poison Control Centre reported 6,600 cases of mushroom poisoning in 2012, but only 17% of the causative mushrooms were identified [16]. In our study, the identification of mushroom poisoning was based on a history of mushroom consumption and the morphology of the mushroom described by patients and family members. However, in three quarters of the cases, the mushrooms were self-harvested. *Boletaceae* was the most commonly identified mushroom family in our study, which indicates that this mushroom is commonly consumed in Yunnan. Among the main symptoms of mushroom toxicity in our study, gastrointestinal symptoms were the most common, followed by neuropsychiatric symptoms. Patients with *Boletaceae* poisoning often presented with hallucinations (auditory and visual hallucinations), and other symptoms and signs were also described (Table 2). These symptoms and signs had no direct correlation with the outcome. We found that the time of symptom occurrence was related to the outcome. Most cases (87, 63.50%) presented  $\geq 6$  h after consuming the mushrooms, which was associated with poor outcomes (Table 1), and this was consistent with a previous study [17]. Patients who showed an early onset of symptoms ( $< 6$  h post-ingestion) often had a positive outcome, while later symptom onset ( $\geq 6$  h post-ingestion) were connected with worse outcomes. There was a significant relationship between the latency and the duration of hospitalization. According to the logistic regression analysis, an incubation period of  $\geq 6$  h is one of the risk factors for death in mushroom poisoning patients. We suspected that this is related to the long-term stimulation of the gastrointestinal tract by the toxins, which leads to serious water-electrolyte imbalance and intestinal mucosal barrier damage, allowing toxins to enter the blood, finally leading to liver and kidney damage. Surprisingly,  $DB \geq 34.2 \mu\text{mol/L}$  was another risk factor for death from mushroom poisoning. Previous studies have shown that the main target organ of many mushroom toxins is the liver [18]: toxins damage the liver cells, leading to hepatocyte jaundice, and they have also been shown to destroy erythrocyte membranes and cause hemolysis. In the early stages of mushroom poisoning, drugs should be provided to protect the liver and stabilize erythrocyte membranes (such as N-acetylcysteine, silybin etc.). Therefore, for mushroom poisoning, clinicians should identify early, and intervene effectively. At present, there are no specific antidotes for toxic mushroom poisoning, and the main treatment methods are emetics, gastric lavage, catharsis, and symptomatic treatments [19]. The gastrointestinal symptoms were early onset ( $< 6$  h post-ingestion) and were not severe in 74 patients, all of who recovered after symptomatic treatment and a short duration of hospital care. Neuropsychiatric symptoms were documented in 54 patients in our study. The neuropsychiatric effects were all slight, the symptoms were often early onset ( $< 6$  h post-ingestion), and most recovered after symptomatic treatment and a short duration of hospital care. However, three patients with late onset neuropsychiatric symptoms ( $\geq 6$  h post-ingestion) died.

For hemolysis, glucocorticoids and alkalized urine were administered. In cases of multiple organ failure, supportive treatment was provided first, and additional blood purification, artificial liver therapy, continuous renal replacement therapy, silybin, high-dose



penicillin, and N-acetylcysteine were given in selected cases. Acute liver failure, occurred with a high mortality rate and accounted for 66.7% (12/18) of deaths in this study, which is consistent with the findings of a previous study in which the mortality from acute liver failure was 50-90% [20]. To further explore whether it is a risk factor for death by mushroom poisoning, we used a combination of AST and ALT  $\geq 200$  U/L (more than five times the basic value) in the logistic regression analysis. The results show that ALT or AST  $\geq 200$  U/L may increase the risk of death from mushroom poisoning more than 10 times (Table 4). The symptoms of these patients are usually late onset ( $\geq 6$  h after ingestion). Of note, many studies have reported that liver transplantation can effectively reduce mortality from mushroom-induced liver failure [21].

Furthermore, we also investigated and analyzed the laboratory findings (Table 3). Electrolyte (Na<sup>+</sup>, K<sup>+</sup>) abnormalities are often associated with gastrointestinal symptoms, changes in liver enzymes and coagulation function indicate liver injury, and SCr and BUN are indicators of renal failure. Univariable logistic regression (Table 4) indicated that the above indexes were the risk factors for death from mushroom poisoning (all  $P < 0.01$ ). This conclusion is consistent with a previous study concerning predictors of poor outcomes in patients with wild mushroom-induced acute liver injury in Korea [22] Multivariable logistic regression analysis showed that DB  $\geq 34.2$   $\mu\text{mol/L}$  was the most influential risk factor for death (OR = 55.077, 95%CI = 2.003-1785.159). A latency period of  $\geq 6$  h (OR = 25.638, 95%CI = 1.320-498.062) (Table 5) was also an independent risk factor.

## Conclusion

In summary, individuals and health care providers should be educated about mushroom poisoning. Mushroom poisoning leads to high numbers of fatalities, long hospital stays, and high medical expenses. Moreover, it is difficult to identify the type of mushroom and toxin involved. Therefore, more research is needed to identify the toxins and pathogenesis of mushroom poisoning. The clinical manifestations and laboratory tests showed a lack of specificity, but a latency of  $\geq 6$  h and elevated WBC, NEU, ALT, AST, PT, APTT, INR, TB, DB, K<sup>+</sup>, Na<sup>+</sup>, SCr, and BUN may be early indicators of the prognosis in patients with acute mushroom poisoning. DB of  $\geq 34.2$  and latency  $\geq 6$ h were the risk factors of death by mushroom poisoning. Clinicians should ensure be vigilant of these signs and undertake careful investigations and management to further improve the survival rate of patients with mushroom poisoning. Our study was a retrospective design, which is prone to selection bias. In this retrospective study, we could not identify the species of mushrooms or the toxins. We attempted to mitigate this bias by identifying patients through hospital, administrative, and clinical databases. Given our small sample size, we were unable to statistically adjust for potential confounding factors.

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