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Predictors of poor outcome in mushroom poisoning: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the ethics committee of Ondokuz Mayis University (Decision no: B.30.2.ODM.0.20.08).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Mushroom poisoning (MP) can result in a wide range of clinical presentations from mild gastrointestinal complaints to hepatic necrosis or acute liver failure (ALF) requiring liver transplantation (LT). Although several predictive parameters were studied, a guideline based on a consensus is still lacking. This study aimed to investigate the parameters associated with LT-free survival in patients admitted to the emergency department with MP.
Methods: This retrospective cohort study was conducted on 420 adult patients admitted to the emergency department with symptoms of MP after ingestion of mushrooms. Patients with viral hepatitis, autoimmune liver disease, acetaminophen or salicylate toxicity, or other chronic liver diseases were excluded. Favorable outcome was defined as LT-free survival while adverse outcome was defined as death or LT. Liver transaminase levels, treatment modalities, and outcomes were analyzed.
Results: The median age of the patients was 46.9 (31-60) years and 59.8% were female. The season with the most MP admissions was autumn (57.6%). The latent periods of 337 (80.3%) patients were between 0-6 hours, and of 83 (19.8%), longer than 6 hours. Among them, 227 (54.0%) patients were treated with gastric lavage, 272 (64.8%), with activated charcoal, 27 (6.4%) with conventional therapy (CT) and 2 (0.5%) with hemodialysis. All 420 patients received supportive therapy (ST). Patients who received CT had higher mean AST and ALT levels than patients who received only decontamination or ST (P<0.001). One hundred and sixty-two (38.6%) patients refused further treatment while under observation. Among patients who received CT+ST, patients with adverse outcomes (liver transplant or death) had higher transaminase levels (AST: P=0.009, and ALT: P=0.008) and higher coagulation parameters (PTT: P=0.016, INR: P=0.009).
Conclusion: The duration of the latent period, AST, ALT, PTT, and INR may be used as predictors of poor outcome.

Keywords: Mushroom poisoning, Emergency department, Amanita Phalloides, Prognosis

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Introduction

Most cases of poisonous mushroom exposures result in mild gastrointestinal complaints, while some can lead to hepatic necrosis or acute liver failure (ALF) requiring liver transplantation (LT) [1]. Amanita phalloides (AP) is responsible for over 90% of deaths from mushroom poisoning. Initial symptoms are similar to gastroenteritis which makes an early diagnosis difficult in patients who do not report the ingestion of mushrooms [2]. The main pathophysiology in AP-associated poisoning is ALF with elevated transaminases and bilirubin.

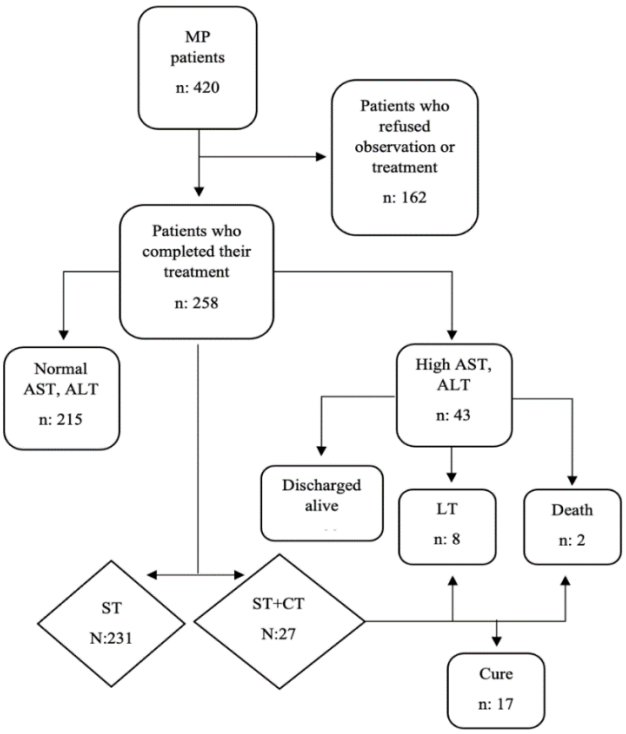
The severity of poisoning depends on the amount of toxin (the lethal dose of α-amanitin for humans is 0.1 mg/kg) and the latent period between ingestion and the initiation of treatment [2, 3]. Several parameters were identified for prognosis; however, none are suggested for deciding the safety of treatment in a local hospital instead of referral to a transplant center [1, 4–6]. An important issue is the lack of a consensus on optimal management despite advancements in the treatment of patients exposed to amatoxin [7]. After oral intake of AP, amatoxins are quickly absorbed in the gastrointestinal system. Therefore, gastric lavage and active charcoal are recommended in the early stages (within 1 hour) of AP ingestion to effectively decrease the absorption of amatoxin [3, 7]. Because of the enterohepatic recirculation of amatoxins, repeated doses of active charcoal are recommended [8]. The therapeutic effects of extracorporeal treatments with hemodialysis, hemoperfusion, or hemofiltration are negligible as the toxins are short-lived in blood plasma [7]. Urgent LT is indicated when decontamination, elimination, or conventional treatments fail to cure the patients. It is critical to make a timely decision for LT as ALF progresses rapidly with only 50-85% of patients surviving until a transplant [9]. The decision to refer to LT may be futile in the presence of multiorgan failure, cerebral edema, or renal failure. Despite several existing criteria for the timing of LT (King's College criteria [10], Escudie's criteria [5], Clichy criteria [11], Ganzert's criteria [12], CLIF-OF [13]), a guideline based on a consensus on this issue is lacking [7, 12].

This study aimed to investigate parameters associated with LT or death free survival in patients admitted to the department (ED) for MP.

Materials and methods

The data of 420 patients aged 18 years or above admitted to the ED with symptoms of poisoning after mushroom ingestion between January 2008 and December 2012 who had laboratory studies (blood count, liver and renal function tests, coagulation parameters) performed were retrospectively analyzed. The diagnosis of MP was made with symptoms following recent ingestion of mushrooms and the exclusion of other diagnoses that could cause similar symptoms or acute liver failure as serum, urine, or stool analysis for fungal toxins cannot be performed in our clinic. Patients with viral hepatitis, autoimmune liver disease, acetaminophen or salicylate toxicity, or other chronic liver diseases were excluded. Age, gender, symptoms at admission, the time between exposure and symptoms (latent period), daily laboratory results, treatments, and outcomes were recorded. Two hundred and fifty-eight (61.4%) patients completed their treatment while 162 (38.6%) refused further treatment while under observation (Figure 1).

Figure 1: Flowchart



The conventional therapy (CT) group consisted of patients with a two-fold or more increase in transaminase levels who received CT. Favorable outcome was defined as LT-free survival while adverse outcome was defined as death or LT. Patients who received an LT after referral were included in the adverse outcome group. Liver transaminase levels, treatment modalities, and outcomes were analyzed. Approval was obtained from the Ondokuz Mayıs University Clinical Studies Ethics Committee (Decision No. B.30.2.ODM.0.20.08). This manuscript is derived from the thesis study "Retrospective analysis of patients admitted to the emergency department with mushroom poisoning."

Statistical analysis

IBM SPSS v23 was used for statistical analysis. Kolmogorov-Smirnov test was used to assess normality. Parameters without normal distribution were compared with the Mann Whitney U test and categorical variables were compared with the Chi-Squared test. Descriptive statistics were presented as median (interquartile range) and frequency (%). Significance was set at $P<0.05$.

Results

This retrospective cohort study was performed on 420 adult patients admitted to the ED between January 2008 – December 2012 after symptoms of poisoning following ingestion of mushrooms. Within the study period, 13.3% (420/3154) of adult poisoning cases were due to mushroom poisoning. There were 251 (59.8%) females, and 169 (40.2%) males, with a median age of 46 (31-40) years. The season with highest number of admissions was autumn (57.6%) and the month with the most admissions was October (31.2%). Two hundred and twenty-seven (80.2%) patients had a latent period of 0-6 hours, while 83 (19.8%) had a latent period of longer than 6 hours. Patient

distribution according to the monthly trend of admissions and the duration of latent period is presented in Table 1.

Table 1: Monthly trend of admissions and durations of latent period

Trend of admission		n (%)
Autumn	September	27 (6.4)
	October	131 (31.2)
	November	84 (20.0)
Total		242 (57.6)
Summer	June	43 (10.2)
	July	58 (13.8)
	August	20 (4.8)
Total		121 (28.8)
Spring	March	7 (1.7)
	April	6 (1.4)
	May	30 (7.1)
Total		43 (10.2)
Winter	December	6 (1.4)
	January	7 (1.7)
	February	1 (0.2)
Total		14 (3.3)
Latent Period	0-6 hours	337 (80.2)
	≥ 6 hours	83 (19.8)

The most frequent complaint at admission was nausea, present in 394 (93.8%) patients, followed by vomiting in 366 (87.1%) patients, and diarrhea in 83 (19.8%) patients. Patients with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (n=43) had a median latent period of 6 (4-10) hours, while patients with normal AST and ALT levels (n=215) had a median latent period of 2 (1-4) hours (P<0.001). There were 215 (51.2%) patients with normal transaminase levels throughout the treatment and 43 patients (10.2%) with elevated enzymes at admission or during treatment. One hundred and sixty-two (38.7%) refused observation or further treatment. The distribution of patients according to transaminase levels is given in Table 2.

Table 2: The distribution of patients according to transaminase levels

	n (%)	AST (U/L) Median (IQR)	ALT (U/L) Median (IQR)
Normal throughout treatment	215 (51.2)	21.0 (17.8-25.9)	18.0 (13.4 – 24.3)
Normal at admission, high during treatment	9 (2.1)	26.1 (23.4-31.0)	19.8 (14.8 -30.1)
High at admission, Lower during treatment	26 (6.2)	136.0 (61.4-411.3)	142.0 (80.6- 327.9)
Referred for transplant	8 (1.9)	967.7 (322.2-2358.7)	1217.0 (356.3 – 3053.2)
Refused observation or treatment	162 (38.6)	21.3 (17.9-26.8)	18.2 (13.5 -25.1)
Total	420 (100)	21.9 (18.1-28.9)	19.3 (14.1-27.9)

AST: Aspartate aminotransferase (U/L), (Reference range; 8-46), ALT: Alanine Aminotransferase (U/L), (Reference range; 0-35), IQR: Interquartile range

All 258 (61.4%) patients who accepted observation and treatment received repeated doses of activated charcoal along with supportive therapy (ST) (fluids + symptomatic treatment). Twenty-seven (6.4%) patients with a two-fold or more elevation in transaminase levels received CT (treatment with penicillin, silibinin, N-Acetylcysteine (NAC)) along with ST. Patients who received ST+CT had higher transaminase levels than patients who received only ST (P<0.001). Peak laboratory values with different therapies received by the 258 patients who accepted observation and treatment are given in Table 3.

Patients with adverse outcomes (LT + Death) had higher transaminase levels (AST: P= 0.009, ALT: P=0.008), and higher coagulation parameters (PTT: P=0.016, INR: P=0.009) than patients with favorable outcomes (cure). Other laboratory values (T. Bil: P=1.000, D. Bil: P=0.980, BUN: P=0.414, Cre: P=0.407) were not significantly different between the groups (Table 4).

Table 3: Peak laboratory values and patient treatment

	Treatment		
	ST+CT (n=27) Median (IQR)	ST (n=231) Median (IQR)	*P*-value
AST (U/L)	1924.9 655.8-5019.8	21.8 18.3-28.7	<0.001
ALT (U/L)	1987.9 550.0-5148.4	18.3 14.1-26.4	<0.001
T. Bil (mg/dL)	2.0 1.3-4.6	0.6 0.5-1.0	<0.001
D. Bil (mg/dL)	0.6 0.2-2.9	0.1 0.1-0.1	<0.001
BUN (mg/dL)	21.1 15.4-32.3	14.8 11.6-18.6	0.002
Cre (mg/dL)	1.0 0.7-1.6	0.7 0.6-0.9	0.001
PTT (sec)	14.0 11.7- 22.7	11.6 11.0- 12.1	<0.001
INR	1.2 1.1-2.1	1.0 1.0-1.1	<0.001

AST: Aspartate aminotransferase (U/L), ALT: Alanine aminotransferase (U/L), T. Bil: Total Bilirubin (mg/dL), PTZ: Prothrombin Time (sec), INR: International Normalized Ratio, BUN: Blood Urea Nitrogen (mg/dL), Cre: Creatinine (mg/dL), ST: Supportive Treatment, CT: Conventional Treatment, IQR: Interquartile range

Table 4: Peak laboratory values according to outcomes in patients who received conventional therapy

Outcomes in patients who received conventional therapy			
	Cure (n=17) Median (IQR)	LT+Death (n=10) Median (IQR)	*P*-value
AST (U/L)	1147.7 428.4-2315.1	4856.4 1633.6-7993.6	0.009
ALT (U/L)	671.9 436.0-2571.2	4801.6 2244.3-5661.0	0.008
T. Bil (mg/dL)	2.0 1.6-3.2	2.3 1.2-4.7	1.000
D. Bil (mg/dL)	0.6 0.4-2.4	0.4 0.2-3.2	0.980
BUN (mg/dL)	17.2 11.0-33.3	21.2 17.8-30.8	0.414
Cre (mg/dL)	0.9 0.7-1.3	1.2 0.8-2.3	0.407
PTT (sn)	12.3 11.6- 18.0	24.2 13.7- 71.3	0.016
INR	1.1 1.1-1.3	2.2 1.2-7.4	0.009

AST: Aspartate aminotransferase (U/L), ALT: Alanine aminotransferase (U/L), T. Bil: Total Bilirubin (mg/dL), PTT: Prothrombin Time (sec), INR: International Normalized Ratio, BUN: Blood Urea Nitrogen (mg/dL), Cre: Creatinine (mg/dL), LT: Liver Transplantation, IQR: Interquartile range

Of the patients referred for transplant, 8 (1.9%) received an LT. The peak laboratory value of patients referred for LT are given in Table 5. In our clinic, 2 (0.47%) patients aged 78 and 80 years died on the 6th and 8th days of their treatment due to liver failure despite conventional therapy and hemodialysis for acute renal failure. Among 27 patients who received ST + CT due to two-fold or more elevation of transaminases, the death rate was 7.40%.

Table 5: Peak laboratory values of patients referred for liver transplantation

	Reference Range	Median (IQR)
AST (U/L)	8-46	4367 (1541-6657)
ALT (U/L)	0-35	4442 (2110-5429)
T. Bil (mg/dL)	0.1-1.5	1.40 (1.17-3.50)
D. Bil (mg/dL)	0.0-0.4	0.22 (0.20-0.79)
PTT (sec)	10-14	20.75 (13.65-29.35)
INR	0.85-1.15	1.71 (1.24-2.65)
BUN (mg/dL)	5-24	21.98 (17.82-32.21)
Cre (mg/dL)	0.4-1.4	1.08 (0.72-1.40)

AST: Aspartate aminotransferase (U/L), ALT: Alanine aminotransferase (U/L), T. Bil: Total Bilirubin (mg/dL), D. Bil: Direct Bilirubin (mg/dL), PTT: Prothrombin Time (sec), INR: International Normalized Ratio, BUN: Blood Urea Nitrogen (mg/dL), Cre: Creatinine (mg/dL), IQR: Interquartile range

Discussion

The outcomes after mushroom poisoning depend on the type of ingested mushroom, the toxin amount, laboratory values, clinical findings, treatment received, need for hemodialysis, and the need for liver transplantation. Despite a good amount of accumulated knowledge of fungal toxins, there are discrepancies in diagnosis and treatment.

During the study period, 13.3% (420/3154) of adult poisoning cases were due to MP. In a different study from the same region, this rate was 9.3% [14]. In previous reports, MP

was most common in patients aged 35-55 years and women were more frequently affected than men [14–17]. In our study, the median age was 46.9 (31-60) years and 59.8% of the patients were female. The seasons with the highest amount of MP admissions are spring and autumn, which can vary with region and climate [14–17]. In this study, 57.6% of MP admissions were in autumn, and the month with the highest number of admissions was October (32.1%). Mushrooms grow primarily in spring and autumn when they are also most harvested and ingested. This seasonality in mushroom growth explains the trend in hospital admissions. MP seen in other seasons occur after ingestion of dried or frozen mushrooms collected in the spring or autumn [16, 17]. Symptoms depend on the type of ingested mushroom, ranging from mild gastrointestinal symptoms to organ failure and death.

Several classifications were proposed to differentiate MP according to the presentation symptoms. Gastrointestinal symptoms are shared across many MP syndromes [17, 18]. In this study, the chief complaint was nausea in 93.8% of the patients followed by vomiting present in 87.1% of the patients. Other complaints included headache, dizziness, malaise, dry mouth, aphasia, dysarthria, diaphoresis, and hypersalivation, which made up 12.8% of all complaints. Mushrooms with slow-acting toxins (most prominent being A. phalloides) cause cellular damage and symptoms of poisoning become eminent within 6-24 hours of ingestion. In A. phalloides poisoning, symptoms include vomiting of increasing severity, abdominal pain, and diarrhea. Liver enzymes are elevated in liver damage. The prognosis depends on the amount of ingested toxins [5, 16]. In our hospital, toxins could not be identified in MP cases, therefore, it was not possible to identify the ingested species in our patients. Patients with elevated transferase levels (n=43) had a median latent period of 6 (4-10) hours, while patients with normal levels (n=215) had a median latent period of 2 (1-4) hours, similar to previous reports in the literature [4, 7, 8, 12]. Although the type of toxins in MP patients could not be determined, poisoning with a latent period of 6-24 hours is caused by slow acting fungal toxins. Amatoxin is responsible for the majority of MP cases with slow acting toxins where liver enzymes are elevated in the early phase due to liver toxicity [8, 9].

Medical treatment strategies against AP poisoning are all nonspecific. There are no randomized trials on the results of CT in MP, and such trials are indeed difficult due to the low number of cases and the ethical challenges of denying an effective treatment. Drugs most used alone or in combination against MP are penicillin G, N-Acetylcysteine, and silibinin [6–8]. Penicillin G and silibinin act by inhibiting amatoxin uptake by the hepatocytes. NAC has antioxidant and glutathione recycling properties. These drugs can be used alone or in combinations [2, 8].

In the poisoning severity score, cases with mild signs or symptoms and a two-fold or more rise in transaminases are classified as minor poisoning [19]. In this study, 27 (%6.4) patients with at least a two-fold increase in transaminases and signs of poisoning received CT (penicillin, silibinin, NAC) in addition to ST. Among patients who received CT + ST, the worse outcome group had higher transaminase levels and higher coagulation parameters than the favorable outcome group (Table 2). After ST + CT, transaminase levels and coagulation parameters returned to normal in 18 (62.9%) patients, while 8 (29.6%) were referred to LT. Patients with late emerging symptoms of gastrointestinal toxicity, failure to respond to CT+ST, and ALF should be referred to centers that can offer an LT [7]. The critical issue with LT is the timing of its decision, however, a consensus is lacking [9]. Our study shows that transaminase levels and coagulation parameters may be used as prognostic markers. Although studies have reported death rates with MP ranging from 2.3% to 3.8%, MP cases who do not receive LT for ALF due to amatoxin have death rates of 10-30% [16,20]. In this study, the death rate among 27 patients who were given CT + ST was 7.40%.

A limitation of this study is that the mushroom species were not identified with measurement of toxin levels. Other limitations are its retrospective design and the low number of severe poisoning cases.

Conclusion

Duration of the latent period, AST, ALT, PTT, and INR may be used as predictors of adverse outcome. Studies with larger number of cases are necessary to further investigate the predictors of outcome in MP.

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