

# Results of liver transplantation in patients with acute liver failure due to *Amanita phalloides* and paracetamol (acetaminophen) intoxication

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## Abstract

**Introduction:** *Amanita phalloides* and paracetamol intoxications are responsible for the majority of acute liver failures.

**Aim:** To assess survival outcomes and to analyse risk factors affecting survival in the studied group.

**Material and methods:** Of 1369 liver transplantations performed in the Department of General, Transplant, and Liver Surgery, Medical University of Warsaw before December 2013, 20 (1.46%) patients with *Amanita phalloides* ( $n = 13$ , 0.95%) and paracetamol ( $n = 7$ , 0.51%) intoxication were selected for this retrospective study. Overall and graft survival at 5 years were set as primary outcome measures.

**Results:** Five-year overall survival after liver transplantation in the studied group was 53.57% and 53.85% in patients with paracetamol and *Amanita phalloides* poisoning, respectively ( $p = 0.816$ ). Five-year graft survival was 26.79% for patients with paracetamol and 38.46% with *Amanita phalloides* intoxication ( $p = 0.737$ ). Risk factors affecting patient survival were: pre-transplant bilirubin concentration ( $p = 0.023$ ) and higher number of red blood cells ( $p = 0.013$ ) and fresh frozen plasma ( $p = 0.004$ ) transfused intraoperatively. Likewise, higher number of red blood cells ( $p = 0.012$ ) and fresh frozen plasma ( $p = 0.007$ ) transfused were risk factors affecting 5-year graft survival. Surprisingly, donor and recipient blood type incompatibility was neither the risk factor for 5-year overall survival ( $p = 0.939$ ) nor the risk factor for 5-year graft survival ( $p = 0.189$ ).

**Conclusions:** In selected intoxicated patients urgent liver transplantation is the only successful modality of treatment. Risk factors affecting survival are in correspondence with the patient's pre-transplant status (bilirubin level in serum) and intraoperative status (number of red blood cells and fresh frozen plasma transfused).

## Introduction

Acute liver failure is a condition in which all its functions cease to continue. There are many causes of this rare condition, with the most common being drug-induced hepatic injury (e.g. paracetamol-induced), infections with hepatitis A, B, or E viruses, *Amanita phalloides* intoxication, and narcotic use-related liver damage [1–4]. The existing O'Grady, Japanese, and Bernau classifications divide acute liver failure based on the time period between jaundice and the onset of encephalopathy. In these classifications, terms such as “acute”, “hyperacute”, or “fulminant” liver failure are used [5–7]. The mortality of untreated patients reaches 90% [8]. Initial treatment depends on the causes of hepatocel-

lular injury and patients' general condition. In patients suspected of paracetamol-induced liver injury, prompt administration of N-acetylcysteine (NAC) limits further hepatocellular injury, thus improving the patient's condition [9]. The choice of subsequent treatment has to be made as soon as acute liver failure is diagnosed. This decision may eventually lead to an urgent qualification for liver transplantation. Various criteria can be used in the decision-making process. The most commonly accepted and most widely used criteria are those presented by King's College authors [10]. However, their use in patients with acute paracetamol-induced liver failure is controversial [11]. Due to the usually severe condition of the patients on qualification and on-going doubts, it is vital that survival risk factors for both

patient and transplanted organ (*graft*) are determined and examined.

## Aim

The aim of this study was to analyse the results of treatment and to determine risk factors affecting outcomes of patients with acute liver failure following paracetamol or *Amanita phalloides* poisoning, treated with urgent liver transplantation.

## Material and methods

There have been 1369 liver transplantations carried out during the period between 1994 and 2013 in the Department of General, Transplant, and Liver Surgery (Medical University of Warsaw). For retrospective analysis, 20 patients (1.46%) who underwent urgent liver transplantation due to *Amanita phalloides* ( $n = 13$ , 0.95%) or paracetamol ( $n = 7$ , 0.51%) poisoning were chosen. The end points for this study were 5-year patient and graft survival rates.

### Statistical analysis

Quantitative and qualitative variations are presented as medians (interquartile range) and numbers (%). Mann-Whitney  $U$  test and Fisher's exact test were used as appropriate. For survival calculations, the Kaplan-Meier method was used. The log-rank test was used for comparisons. Risk factors were determined based on Cox proportional hazards regression. Hazard ratios (HR) are given with 95% confidence intervals (CI). Statistica 10 (StatSoft Inc., Tulsa, USA) was used for analyses. The significance level was set at 0.05.

## Results

Baseline characteristics of patients are presented in Table I. In the direct perioperative period 8 (40%) patients died, and 1 (5%) died during the surgery. Causes of death were as follows: multi-organ failure ( $n = 5$ ), intraoperative bleeding ( $n = 1$ ), septic shock ( $n = 1$ ), and portal vein thrombosis ( $n = 1$ ). Postoperative morbidity was 70% (14 of 20). The most frequent complications were: multi-organ failure (30%) and postoperative hepatic artery thrombosis (15%). Three patients required re-transplantation due to the following causes: hepatic artery thrombosis ( $n = 2$ ) and acute graft rejection ( $n = 1$ ). Five-year survival rates in patients with paracetamol and *Amanita phalloides* poisoning were 53.57% and 53.85% ( $p = 0.816$ ), respectively (Figure 1). Whereas the corresponding 5-year graft survival rates were 26.79% and 38.46%, respectively ( $p = 0.737$ , Figure 2).

Risk factors of overall survival included elevated preoperative serum bilirubin concentration ( $p = 0.023$ ) and

higher number of transfused blood units ( $p = 0.013$ ) and fresh frozen plasma ( $p = 0.004$ ) (Table II). Likewise, the number of transfused blood units ( $p = 0.012$ ) and fresh frozen plasma ( $p = 0.007$ ) were significantly associated with graft survival (Table II). ABO-incompatible liver transplantations, however, did not prove to be a risk factor for either overall patient ( $p = 0.939$ ) or graft ( $p = 0.189$ ) survival.

## Discussion

Intoxication caused by ingestion of mushrooms from *Amanita phalloides* species is responsible for the vast majority of mushroom poisonings. This rare cause of hepatotoxic injury results in mortality reaching 30% in all patients who ingest *Amanita phalloides*, and not only those who develop acute liver failure [12]. The toxicity of *Amanita phalloides* is related to two distinct groups of toxins: phallotoxins and amatoxins. Liver, renal, and enterocellular damage are caused mostly by amatoxins [13]. The onset of intoxication symptoms usually begins 6–12 h after ingestion and is divided into three consecutive phases – gastrointestinal, hepatotoxic, and the last one, with apparent hepato-renal syndrome, in the most severe poisoning, resulting in fulminant liver failure and death. To date, in spite of ongoing attempts and clinical trials, no effective medication has been discovered. In adjunctive therapy, penicillin G, and NAC are used, but with little effectiveness. In cases of fulminant liver failure, liver transplantation remains the only option (Figure 3).

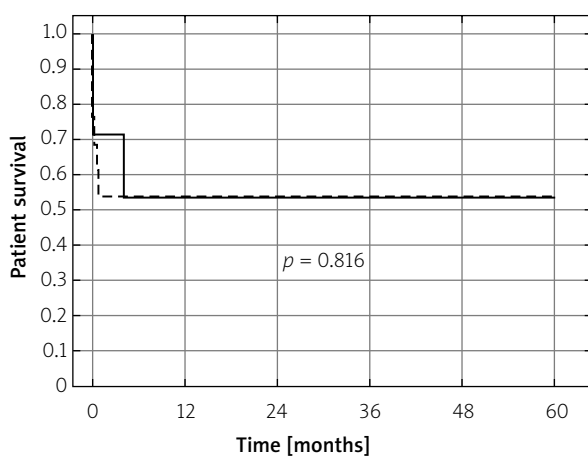
A study from 2002, including 20-year data analysis from facilities in the United States and in Europe regarding *Amanita phalloides* poisonings, shows that only 32 out of 2108 hospitalised patients underwent liver transplantation [14]. Therefore, the number of patients in the Department of General, Transplant, and Liver Surgery at the Medical University of Warsaw seems even more interesting (it is a result of common harvesting and eating mushrooms in Poland, as well as the reference level of our facility regarding treatment with liver transplant). The small percentage of patients who underwent transplantation, and on the other hand, the high mortality reaching as much as 30%, indicates that *Amanita phalloides* poisoning is a condition in which only collaboration with highly specialised facilities and making prompt decisions might save those patients.

Nevertheless, paracetamol intoxication is the most frequent cause of hepatotoxic damage [1] (Figure 3). Early NAC administration, i.e. up to 8 h from poisoning, results in significant reduction of hepatotoxicity risk and improvement of the patient's general condition [15]. In those whose condition was not improved after N-acetyl cysteine administration and implemented conservative

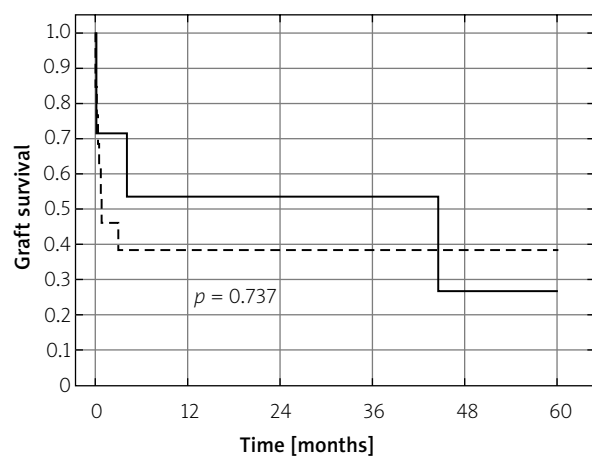
**Table I.** Comparison of baseline characteristics between patients with paracetamol and *Amanita phalloides* intoxication

Parameter	Paracetamol intoxication	<i>Amanita phalloides</i> intoxication	Value of <i>p</i>
Number of patients	7	13	–
Sex (male)	5 (71.4%)	6 (46.2%)	0.279
Age [years]	21 (19–26)	48 (45–50)	< 0.001
Red blood cell count [mln/mm <sup>3</sup> ]	3.52 (3.35–4.81)	3.72 (3.21–4.13)	0.601
Haemoglobin value [g/dl]	11.17 (9.3–12.5)	11.75 (8.6–13.0)	0.740
White blood cell count [10 <sup>3</sup> /mm <sup>3</sup> ]	10.01 (7.4–14.6)	7 (5.1–14.51)	0.270
Platelet count [10 <sup>3</sup> /mm <sup>3</sup> ]	122 (45–156)	75.5 (44–119)	0.417
Bilirubin value [mg/dl]	5.4 (4.12–8.4)	5.82 (3.62–7.97)	0.860
Creatinine level [mg/dl]	1.27 (0.71–5.08)	1.51 (0.95–3.22)	0.758
Albumin level [mg/ml]	2.4 (2.2–3.5)	2.7 (2.5–3.4)	0.475
Blood urea level [mg/dl]	60 (17–90)	40.31 (21.2–97.7)	1.000
AST [IU/l]	2207 (95–5074)	1134 (68–1766)	0.470
ALT [IU/l]	2685 (681–5581)	950 (309–3612)	0.299
GGTP [IU/l]	100 (48–402)	78 (53–223)	0.669
ALP [IU/l]	148 (83–173)	114 (89–141)	0.299
LDH [IU/l]	2309 (695–12719)	2106 (1112–12161)	0.710
INR	2.27 (2.06–5.13)	3.43 (2.77–4.89)	0.417
MELD score	31 (21–40)	29 (27–34)	0.962
Red blood cell transfusions	4 (3–4)	6 (5–8)	0.060
Fresh frozen plasma transfusions	9 (8–10)	9 (7–14)	1.000
Cold ischaemic time [h]	8.5 (7.8–9)	9 (7.3–9)	0.837
Donor age [years]	40 (33–49)	50 (44–56)	0.115
Blood group match	6 (85.71%)	9 (69.23%)	0.417

Qualitative and quantitative data are shown as the number (%) and median (interquartile range), AST – aspartate transaminase, ALT – alanine transaminase, GGTP –  $\gamma$ -glutamyl transferase, ALP – alkaline phosphatase, LDH – lactate dehydrogenase, INR – international normalised ratio, MELD – Model of End-Stage Liver Disease.



**Figure 1.** Five-year survival rates in patients with paracetamol (solid line) or *Amanita phalloides* (dotted line) treated with liver transplantation

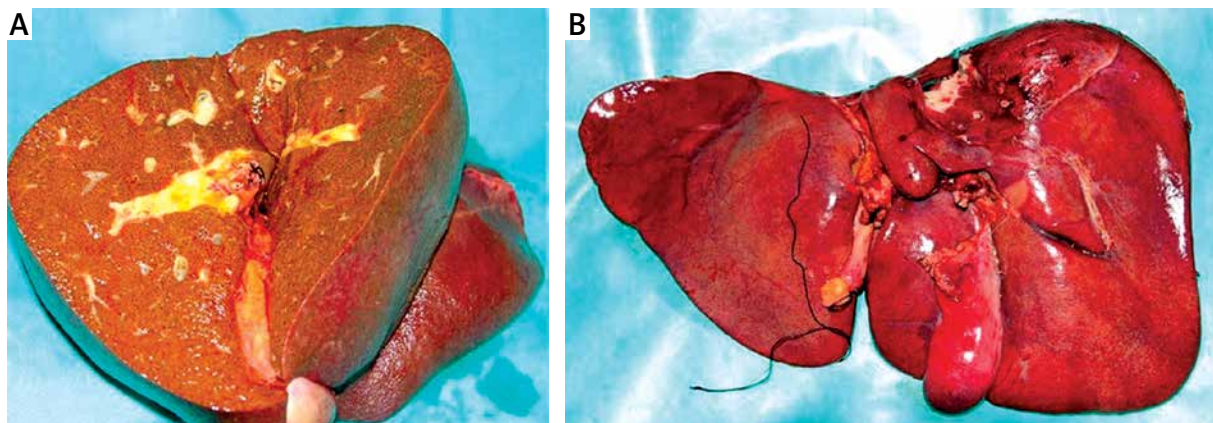


**Figure 2.** Five-year graft survival rates in patients with paracetamol (solid line) or *Amanita phalloides* (dotted line)

**Table II.** Risk factors of overall survival and graft survival

Parameter	Overall survival		Graft survival	
	HR (95% CI)	Value of <i>p</i>	HR (95% CI)	Value of <i>p</i>
<i>Amanita phalloides</i> intoxication*	1.171 (0.293–4.689)	0.823	1.217 (0.365–4.050)	0.749
Sex (male)	1.594 (0.422–6.026)	0.491	1.401 (0.443–4.425)	0.566
Age [years]	1.010 (0.964–1.049)	0.811	1.005 (0.969–1.042)	0.792
Blood group mismatch between donor and recipient	0.940 (0.195–4.535)	0.939	2.294 (0.665–7.914)	0.189
Haemoglobin value [g/dl]	0.841 (0.652–13.0)	0.184	0.901 (0.704–1.521)	0.406
Bilirubin value [mg/dl]	1.179 (1.023–1.358)	0.023	1.146 (1.000–1.314)	0.051
Creatinine level [mg/dl]	1.161 (0.958–1.407)	0.127	1.120 (0.931–1.348)	0.229
AST [IU/l]	0.998 (0.970–1.027)	0.896	0.994 (0.965–1.023)	0.676
ALT [IU/l]	0.991 (0.963–1.020)	0.538	0.988 (0.961–1.016)	0.386
INR	1.163 (0.761–1.776)	0.486	1.239 (0.858–1.790)	0.252
MELD score	1.081 (0.997–1.173)	0.058	1.057 (0.987–1.131)	0.113
Red blood cell transfusions	1.250 (1.048–1.491)	0.013	1.245 (1.049–1.479)	0.012
Fresh frozen plasma transfusions	1.287 (1.080–1.535)	0.004	1.249 (1.062–1.470)	0.007
Cold ischaemic time [h]	0.986 (0.604–1.611)	0.956	0.902 (0.574–1.418)	0.655
Donor age [ears]	0.967 (0.909–1.029)	0.296	0.988 (0.936–1.044)	0.672

HR – hazard ratios, 95% CI – 95% confidence intervals, AST – aspartate transaminase, ALT – alanine transaminase, GGTP –  $\gamma$ -glutamyl transferase, ALP – alkaline phosphatase, LDH – lactate dehydrogenase, INR – international normalized ratio, MELD – model of end-stage liver disease, \*vs. paracetamol intoxication. Hazard ratios for quantitative variables were given per: 1 year for donor and recipient age 1 g/dl for haemoglobin concentration; per 1 mg/dl for serum bilirubin and creatinine concentrations; 1000 U/l for AST and ALT; 1 for INR; 1 point for MELD; 1 unit for transfusions; 1 h for cold ischaemic time.

**Figure 3.** Liver damage due to *Amanita phalloides* intoxication (A) and paracetamol overdose (B)

therapy, liver transplantation remains the only treatment. Unlike *Amanita phalloides* poisoning, ingestion of which is usually accidental, paracetamol intoxication is often intentional (44% of cases) [16], raising ethical concerns. One of the most important risk factors for successful suicidal attempt is a history of such in the past [17]. Thus, it is questionable if such patients should have equal access to liver transplants as do patients af-

ter accidental poisoning [18]. The limited availability of organs accounts for a very thorough and just process of qualification for liver transplantation. The greatest problem and qualification limitation for urgent liver transplantation is clearly the passing of time. It is not always possible to determine the patient's intentions, especially when his/her condition deteriorates and even basic amnesia is hard to obtain. Thus, it is crucial to access

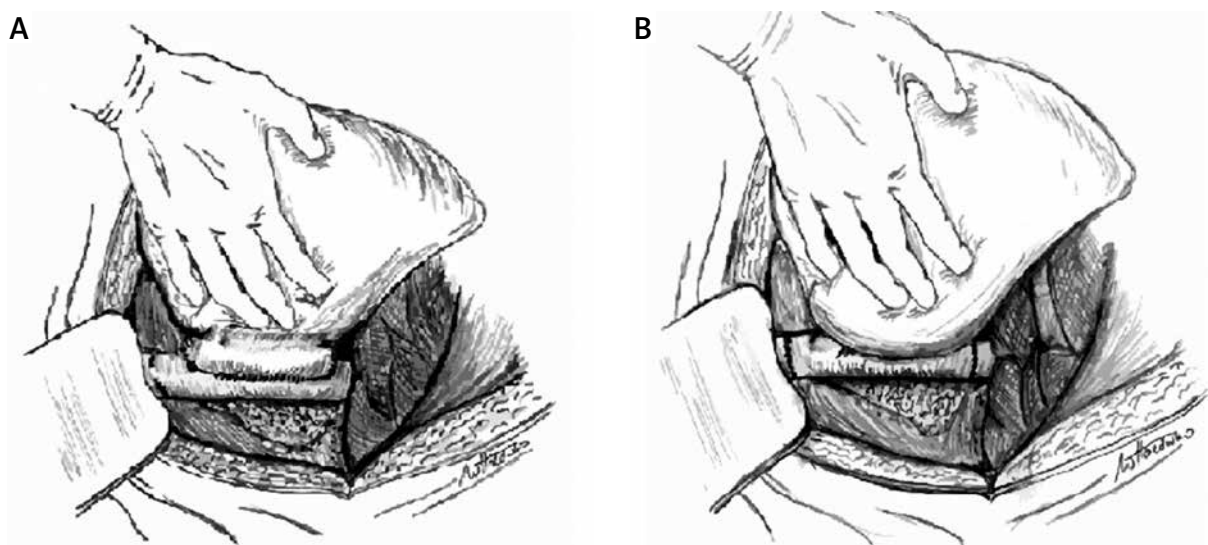
the patient thoroughly, regarding his/her medical condition and the environment around the patient after the transplantation, and, in cases where a suicide attempt is suspected, prompt psychiatric care should be provided.

It should be stressed that the results of liver transplantation in patients with acute liver failure, following either *Amanita phalloides* poisoning or paracetamol intoxication, are worse than those performed due to other indications [2, 3]. This comes from the fact that those patients are operated on in general poor condition, on an emergency basis. Failure does not only concern the liver, but often also the kidneys. Some patients develop cerebral oedema symptoms prior to transplantation. In analysed material, the paracetamol intoxication group included younger patients (median age 21 years). The young age of intoxicated patients is usually related to intentional actions and suicide attempts. Apart from that, no significant differences were found between groups. What is interesting, 5-year overall and graft survival rates were similar. Comparable survival rates in both groups suggest that the greatest risk for the patients is time period prior to transplantation. Their further survival, however, after a successful transplant, does not rely greatly on the cause of acute liver failure.

Higher serum bilirubin levels prior to transplantation turned out to be a negative risk factor for 5-year survival rates in these patients. This parameter is directly related to the condition and function of a damaged liver. In patients with acute liver failure following poisoning, not only is serum bilirubin elevated but also aminotransferase levels, and the prothrombin index decreases, cerebral oedema occurs, etc. Nevertheless, out of all biochemical tests only bilirubin elevation proved

statistically significant as a poor prognosis factor. One way of minimising this effect might be either early qualification of a patient for transplantation (often the delay is related to late transfer of patients from other facilities) or prolonged waiting time for an organ. Obviously, the influence of the people involved in the treatment of these patients affects improvement only in the first of the aforementioned situations, i.e. patient's referral to high-reference facilities where medical doctors thoroughly assess and qualify patients for a possible transplantation. Notably, bilirubin level  $> 17.5$  mg/dl is one of the King's College criteria for urgent liver transplantation due to indications other than paracetamol poisoning. This parameter alone should not be a reason for qualification, but in case of exceeding the above-mentioned level it can be taken into consideration.

Other risk factors of poorer survival rates of both patients and grafts included larger number of transfused red blood cell units and fresh frozen plasma. Patients with acute liver failure present significant coagulopathy (INR reaching 7), which, from the beginning of the surgery, causes persistent bleeding requiring the use of volume expanders and haemostatic factors, such as recombinant coagulation factor VII a (*NovoSeven*). Nonetheless, bringing intraoperative bleeding under control is extremely difficult, if not impossible in some cases. These patients also present with a lack of portal hypertension, which results in a need for veno-venous bypass (bio-pump) and implementation of a surgical method involving excision of retrohepatic vena cava (classical surgical technique) (Figure 4). The amount of volume expanders transfused during the operation is influenced not only by the patient's general condition,



**Figure 4.** Side-to-side cavocavostomy technique (A) and classic technique for orthotopic liver transplantation (B)

mainly being coagulopathy issues, but also technical conditions (surgeries in the past, if applicable, necessity of bio-pump use), and the duration and course of the surgery itself (classical surgical technique, operator's experience). For surgeons, the last aspect seems the most important one because it is the only one that depends on their actions, which affects further survival of the patient.

Paracetamol or *Amanita phalloides* poisoning are rare causes of liver transplantation. Patients whose condition deteriorates usually require urgent liver transplantation. It seems that the most crucial risk factor a surgeon has any influence on during the transplantation itself is the amount of transfused red blood cell units and fresh frozen plasma. This means that for this kind of surgery, experienced surgeons would be the most suitable operators. High levels of serum bilirubin prior to the surgery, being at the same time a survival risk factor, may indicate that some patients have been transferred to a reference centre too late.

## Conclusions

Liver transplantation results are similar in patients with acute liver failure following *Amanita phalloides* and paracetamol intoxication. Risk factors affecting poor patient survival regard directly the patient's condition prior to transplantation, which is presented by serum bilirubin level. The second risk factor proved to be the amount of transfused packed red blood cell units and fresh frozen plasma.

## Conflict of interest

The authors declare no conflict of interest.

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