

## Acute liver failure in Lithuania

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**Key words:** acute liver failure; etiology; survival; liver transplantation; prognostic criteria.

**Summary.** *Objectives.* Acute liver failure (ALF) is a life-threatening condition that can rapidly progress into coma and death due to the cerebral edema and multi-organ dysfunction. The ALF etiology and risk factors have been investigated in West Europe, North America, and Asia; however, there are still no published data about the causes and prognosis of ALF in Central and East European countries. The aim of our study was to analyze the causes, outcomes, and prognostic factors of ALF in patients referred to tertiary care center in Lithuania.

*Material and methods.* A total of 28 consecutive patients admitted to the tertiary care center (one of two university-level medical centers in Lithuania) over the period of January 1996 and December 2004 and who fulfilled the entry criteria of ALF (presence of hepatic encephalopathy (HE) and prothrombin international normalized ratio (INR) >1.5) were included into a prospective study.

*Results.* In our study the most frequent causes of ALF were acute viral hepatitis B (21.4 %), drug-induced hepatitis (21.4%), and indeterminate hepatitis (17.9%); other etiologies included Budd-Chiari syndrome (10.7%), ischemic hepatitis (10.7%), Wilson's disease (7.1%), *Amanita phalloides*-induced liver damage (3.6%), acute fatty liver of pregnancy (3.6%), and malignant infiltration of the liver (3.6%). Among patients with drug-induced liver injury, only one case of acetaminophen poisoning was diagnosed. Clinical status of 9 persons in all patients with ALF corresponded to criteria for liver transplantation (LT) (one liver transplantation was performed), 6 of them had contraindications, and 13 patients did not fulfill requirements for urgent LT. The patients' survival rate in these groups was 11.1%, 16.7% and 69.2%, respectively. In 27 non-transplanted patients univariate analysis revealed the grade of HE on the day of enrolment, total serum bilirubin, pH, and prothrombin INR as risk factors for death from ALF. Multivariate logistic regressive analysis determined only prothrombin INR >3.24 and serum pH £7.29 as independent predictors of lethal outcome in ALF.

*Conclusions.* Acute viral hepatitis B, drug-induced liver injury, and indeterminate hepatitis are the main ALF causes in Lithuania. In non-transplanted patients, the main predictors of lethal outcome were severe coagulopathy and metabolic acidosis. Improvement of liver donation system for urgent liver transplantation is essential requirement for amelioration of ALF patient's survival.

### Introduction

Acute liver failure (ALF) is a rare clinical syndrome characterized by severe and sudden dysfunction of liver cells leading to coagulopathy and hepatic encephalopathy in previously healthy persons without obvious underlying liver disease (1). This severe illness can rapidly progress into coma and death due to the cerebral edema and multi-organ dysfunction (2, 3). The mortality of ALF patients in early pretransplantation period studies reached almost 85–100%;

however, after implementation of liver transplantation, an overall survival rate of 60 to 70% has been achieved (2, 4). The etiologies of acute hepatic failure differ geographically (5–9). Despite a number of studies conducted in West Europe, North America, and Asia to assess etiology and outcomes of ALF (6–9), there are still no published data about the causes and prognosis of ALF in Central and East European countries. Therefore, we conducted a prospective study to analyze the etiology, outcomes, and prognostic factors of

ALF in patients referred to tertiary care center in Lithuania.

### Materials and methods

A total of 28 consecutive patients (16 women and 12 men) admitted to the tertiary care center of Hospital of Kaunas University of Medicine (HKUM) over the period of January 1996 and December 2004 and who fulfilled the entry criteria of ALF (2, 4, 10) – hepatic encephalopathy, coagulopathy (INR >1.5), and no obvious liver disease at least 24 weeks before the enrollment – were included into the study. The average age of patients was about 44 years (range, 19–82 years).

A study protocol and questionnaire included ALF etiology, course and outcome of illness, categorical variables (grade of HE on the day of enrolment into the study and maximal grade of HE, hypoglycemia, metabolic acidosis, thrombocytopenia, markers of viral hepatitis), and continuous variables (period from jaundice occurrence to appearance of HE, total serum bilirubin, serum albumin, liver enzymes (alanine and aspartate aminotransferases), prothrombin INR, serum creatinine, pH). HE was graded as follows: the 1st grade – depression, disordered sleep, and cognitive dysfunction, the 2nd grade – asterixis, confusion, disorientation, and lethargy, the 3rd grade – barely responsive patient, with confused speech and profound somnolence, and the 4th grade – coma. All patients received standard supportive care with monitoring of the clinical, hematological, and biochemical parameters. In addition, patients received causative therapy: lamivudine (for hepatitis B), penicillamine (for Wilson's disease); thrombolysis and stenting (for Budd-Chiari syndrome); penicillin and silymarin (for *Amanita* poisoning). Blood samples were collected from the ALF patients on the day of the enrolment into the study and subsequently every day in purpose to monitor the hematological and biochemical indices. Immunoglobulin M (IgM) antibodies to hepatitis A virus (anti-HAV), hepatitis B (HB) surface antigen (HBsAg), IgM and IgG antibodies to HB core antigen (anti-HBc), and antibodies to hepatitis C virus (anti-HCV) were measured using an enzyme-linked immunosorbent assay (ELISA). HBV DNA and HCV RNA were detected by the polymerase chain reaction. Type B hepatitis caused by acute HBV infection was confirmed by a positive result of HBsAg, IgM anti-HBc or HBV DNA. Exposure to the drug and mushroom (*Amanita*) was systemically assessed by inquiring the patients and their relatives. Ischemic hepatitis was defined as an acute elevation in the serum aminotransferase level of at least 20 folds the upper limit of

normal following the cardio-surgery with cardiopulmonary bypass during a 72-hour period with a hypotensive episode postoperatively, after excluding other possible causes of acute hepatitis or hepatocellular injury. For diagnosis of Wilson's disease, the level of plasma copper and urine copper concentration, serum ceruloplasmin and urine hemoglobin levels were measured; also, histopathological examination of liver post-mortem was performed. Hepatic, caval, and portal vein permeability was assessed by ultrasonography, computer tomography, and angiography in cases of Budd-Chiari syndrome. Neoplastic disease of liver was assessed by ultrasonography, computed tomography, and liver biopsy. Indeterminate hepatitis was considered when the extensive clinical, radiographic, and laboratory evaluation (including toxicological screens, serologic markers for viral hepatitis A, B, and C, antinuclear and anti-smooth-muscle antibodies) was inconclusive.

The approval No. 36/2003 of the Ethical Committee of Hospital of Kaunas University of Medicine was given for the study, which has met the Helsinki Declaration criteria (11). The informed consent was obtained from the relatives of the patients before the enrolment into the study.

The descriptive and inferential analysis was applied for the statistical analysis of the data. The comparison of categorical variables was analyzed using chi-square ( $\chi^2$ ) test. The comparisons of continuous variables were analyzed using Student's *t* test. All continuous variables, which were found to be significant by univariate analysis, were evaluated by the construction of receiver-operator curves for better discrimination of the cut-off values between survivors and non-survivors. The logistic regression analysis was used to identify the variables that independently predict prognosis in patients with ALF. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. A stepwise approach was used to include variables into the logistic model. The level of significance was set at  $P < 0.05$ .

### Results

**Causes of acute liver failure.** In our study, the most frequent etiologies of ALF were viral hepatitis B (21.4%), drug-induced hepatitis (21.4 %), and indeterminate hepatitis (17.9%); other causes included Budd-Chiari syndrome, ischemic hepatitis, Wilson's disease, *Amanita phalloides*-induced liver damage, acute fatty liver of pregnancy, and malignant infiltration of the liver (Table 1). Hepatotoxicity to antimicrobial drugs (isoniazid together with rifampicin) was noted in two cases, and respectively only case

each due the drugs as follows: acetaminophen, halothane, trifluoperazine, lamisil.

**Outcomes.** In our study, the survival rate of ALF was 39.3%. Clinical status of 9 persons in all patients with ALF corresponded to King's College Hospital criteria (12) for LT (transplantation was performed for 1 patient); 6 of all patients had contraindications, and 13 patients did not fulfill requirements for urgent LT. The survival rate in these patients groups was 11.1%, 16.7%, and 69.2%, respectively. Liver transplantation was implemented in Lithuania in 2000 (13). Since 2000, six patients from our study were put on the list for urgent LT, but due to lack of liver donation, the LT was performed only for one patient with acetaminophen poisoning.

**Prognostic criteria.** In 27 nontransplanted patients, univariate analysis revealed the grade of HE on the day of enrolment, total serum bilirubin, pH, and prothrombin INR as risk factors for death from ALF (Table 2). Multivariate logistic regressive analysis determined only  $\text{INR} > 3.24$  ( $\text{OR} = 8.5$ ; 95%  $\text{CI} = 1.7\text{--}28.5$ ;  $P < 0.01$ ) and serum  $\text{pH} \leq 7.29$  ( $\text{OR} = 12.3$ ; 95%  $\text{CI} = 1.5\text{--}101.5$ ;  $P < 0.002$ ) as independent predictors of lethal outcome.

## Discussion

The etiologies of acute hepatic failure differ geographically (5–9). The most often cause of liver damage by drug is noticed in United Kingdom (75%), Australia (42%), and USA (32%). Moreover, the acetaminophen overdosage predominates in these studies and constitutes the biggest share of all drug-induced liver damages, 73%, 36%, and 20%, respectively (4, 14–18). Liver injury caused by acetaminophen toxicity in our study was very rare (3.6%), about the same as it is reported in France (2%) (19). The first patient with suicidal overdosage of acetaminophen (7.5 g) was admitted at the HKUM in 2000. The lethal outcome of this case was related with initial management at the other hospital, where N-acetylcysteine was not administered 20 hours after ingestion of the drug. The urgent orthotopic LT performed 7 days after the drug ingestion was unsuccessful due to progressive cerebral edema because of prolonged search of the donor. During the period of 2000–2004, additional eight cases of acetaminophen overdosage were recorded, but the early usage of antidote has limited liver injury to mild dysfunction, so patients did not match the inclusion criteria into our study. It

**Table 1. Causes and outcomes of acute liver failure during the period of 1996–2004**

Causes	Number of patients (%)	Number of survivors
Viral hepatitis B	6 (21.4)	3
Drug-induced hepatitis	6 (21.4)	3
Indeterminate hepatitis	5 (17.9)	1
Budd-Chiari syndrome	3 (10.7)	2
Ischemic hepatitis	3 (10.7)	0
Wilson's disease	2 (7.1)	0
Mushroom ( <i>Amanita</i> )-induced	1 (3.6)	1
Acute fatty liver of pregnancy	1 (3.6)	1
Malignant liver infiltration	1 (3.6)	0
Total	28 (100)	11

**Table 2. Prognostic indices of the informative parameters for the lethal outcome in nontransplanted patients with acute liver failure**

Criterion	Cut-off value	Odds ratio	95% CI	P value
HE on the day of enrolment into the study	>1st grade	5.1	1.2–22.2	0.041
Prothrombin INR	>3.24	11.5	1.3–104.6	0.022
Total serum bilirubin ( $\mu\text{mol/L}$ )	>102.5	6	1.4–26.2	0.019
pH	$\leq 7.29$	2.8	1.3–6	0.003

HE – hepatic encephalopathy; INR – international normalized ratio; CI – confidential interval.

is notable that all cases of acetaminophen overdose in Lithuania as in the United Kingdom were of suicidal origin (4, 18, 20).

In the Asia as the most common cause of ALF, the viral hepatitis (A, B, E) was noticed (95–100%), while in the Western countries (USA, Denmark, France), viral damage of liver with ALF takes place in about one-third of the cases (7–10, 21, 22). In our study, all six cases (21.4%) of ALF due to the viral hepatitis were related to HBV infection.

The survival rate in our study was as high as 39.3%, and it was similar to survival of ALF patients without LT reported by Ostapowicz *et al.* in USA (16). The recent data on ALF showed the increased survival rate as compared to the pretransplantation period (2, 4, 16). It was related not only to implementation of LT, but also to application of more advanced therapies in case of viral hepatitis B, Budd-Chiari syndrome, Wilson's disease, acetaminophen overdose. Liver damage might change into more benign course, and rate of better ALF outcome can be increased if the appropriate treatment would be used (2, 17, 23). However, in our study, the survival rate of patients corresponding to standard criteria for LT (12) was low (11.1%) due to lack of liver donation in Lithuania (24); so only one patient underwent transplantation procedure. These data correspond to the results of a recent

study from Spain (25), where survival rate of ALF patients who were not transplanted due to contraindications of LT was only 7.8%.

Evaluation of prognostic factors of 27 nontransplanted patients revealed the main predictors of lethal outcome to be severe coagulopathy and metabolic acidosis. The most popular prognostic system in use for ALF is so called the Criteria of King's College Hospital (KCH). Despite relatively small number of cases analyzed, prognostic factors revealed in our study were found to be in accordance with widely accepted KCH criteria (12).

### Conclusions

Acute viral hepatitis B, drug-induced liver injury, and indeterminate hepatitis are the main ALF causes in Lithuania. In nontransplanted patients, the main predictors of lethal outcome were severe coagulopathy and metabolic acidosis. Improvement of liver donation system for urgent liver transplantation is essential condition for amelioration of ALF patient's survival.

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## Ūminis kepenų funkcijos nepakankamumas Lietuvoje

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**Raktažodžiai:** ūminis kepenų nepakankamumas, etiologija, išgyvenamumas, kepenų persodinimas, prognostiniai kriterijai.

**Santrauka.** Darbo tikslas. Ūminis kepenų nepakankamumas yra gyvybei pavojinga būklė, kuri gali greitai progresuoti iki komos ir baigtis mirtimi dėl smegenų edemos ir dauginės organų disfunkcijos. Ūminio kepenų nepakankamumo etiologija ir rizikos veiksniai Vakarų Europoje, Šiaurės Amerikoje ir Azijoje yra gerai ištirtinėti, tačiau apie jo priežastis ir prognozę Centrinės ir Rytų Europos šalyse publikuotų duomenų stinga. Šio darbo tikslas – išanalizuoti priežastis, baigtis ir prognostinius veiksnius pacientų, sirgusių ūminiu kepenų nepakankamumu ir gydytų tretinio lygio universitetinėje Lietuvos ligoninėje.

**Medžiaga ir metodai.** Nuo 1996 m. sausio iki 2004 m. gruodžio mėn. imtinai į tretinio lygio vieną iš dviejų Lietuvos universitetinių ligoninių priimti 28 pacientai, kurie atitiko ūminio kepenų nepakankamumo perspektyviosios studijos įtraukimo kriterijus (hepatinė encefalopatija ir protrombino tarptautinis normalizuotas santykis (TNS) >1,5).

**Rezultatai.** Mūsų tyrime dažniausia ūminio kepenų nepakankamumo priežastis buvo B hepatitas (21,4 proc.), vaistų sukeltas hepatitas (21,4 proc.) ir nenustatytos priežasties hepatitas (17,9 proc.), kitos priežastys – tai Budd-Chiari sindromas (10,7 proc.), išeminis hepatitas (10,7 proc.), Wilson'o liga (7,1 proc.), *Amanita*

*phalloides* sukeltas kepenų pažeidimas (3,6 proc.), ūminė nėščiąjų hepatozė (3,6 proc.) ir maligninė kepenų infiltracija (3,6 proc.). Apsinuodijimas acetaminofenu diagnozuotas tik vienam pacientui tarp vaistų sukeltų hepatitų. Devynių pacientų klinikinė būklė atitiko neatidėliotino kepenų persodinimo kriterijus (vienam ji buvo atlikta), šešiams buvo kontraindikacijų, 13 – indikacijų nenustatyta. Pacientų išgyvenamumas šiose grupėse buvo atitinkamai – 11,1 proc., 16,7 proc. ir 69,2 proc. 27 pacientams, kuriems kepenų persodinimo operacija nedaryta, vienveiksmės analizės metu nustatyti letalios baigties rizikos veiksniai: hepatinės encefalopatijos laipsnis įtraukimo į tyrimą dieną, bendrasis serumo bilirubinas, pH ir protrombino TNS. Daugiaveiksmė logistinė regresinė analizė, kaip nepriklausomus letalios baigties nuo ūminio kepenų nepakankamumo kriterijus nustatė tik protrombino TNS > 3,24 ir pH ≤ 7,29.

**Išvados.** Ūminis B virusinis hepatitas, vaistų sukeltas ir nenustatytos priežasties hepatitai dažniausiai sukelia ūminį kepenų nepakankamumą Lietuvoje. Nepersodinus kepenų, pagrindiniai letalios baigties kriterijai buvo ryški koagulopatija ir metabolinė acidozė. Kepenų donorų skubiam kepenų persodinimui sistemos tobulinimas yra būtinas gerinant pacientų, sergančių ūminiu kepenų nepakankamumu, baigtis.

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