Original Article

Significance and Outcome of Living-donor Liver Transplantation in Acute Mushroom Intoxication

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Abstract

Introduction: Mushroom intoxication (MT) can lead to acute liver injury which may result in Mushroom intoxication-related liver failure (M-ALF) requiring liver transplantation (LT). In the present study, we want to share the experience of our institute regarding living-donor LT (LDLT) due to mushroom poisoning. **Aim:** The aim of this study is to identify the predictors of poor prognosis in patients with ALF secondary to mushroom intoxication requiring LDLT. **Materials and Methods:** All patients with MT between 2008 and 2016 were evaluated. Demographics, symptoms, interval between symptoms and admission to our institute, laboratory data, model for end-stage liver disease (MELD)/pediatric end-stage liver disease (PELD) scores, clinical course, and outcomes of supportive therapy and LT were evaluated. There were two groups in the study: Group A = responsive to supportive therapy (n = 9) versus Group B = unresponsive to supportive therapy (n = 9). **Results:** During the study, a total of 18 patients were admitted with M-ALF. Twelve (66.7%) of them were female, and the mean age was 39.9 ± 18.2 years. All of the nine patients in Group A fully recovered with supportive therapy. In Group B, one patient died during waiting period for LT and 8 patients received LDLT LDLT. Three of the eight patients who were transplanted died in the postoperative early period within postoperative 5 days. The patients in Group B had significantly higher MELD/PELD scores and encephalopathy rate than in Group A ($P < 0.05$). International normalized ratio (INR), bilirubin, ammonium levels, and platelet count were significantly different between groups ($P < 0.05$). The patients in Group B had significantly longer interval before admission to our institute ($P < 0.05$). **Conclusion:** The presence of encephalopathy, higher MELD/PELD, INR, bilirubin, ammonium levels, and lower platelet count was related to poor prognosis in MT. LDLT provides a good therapeutic option in patients with M-ALF. The time is a crucial factor in successful treatment of MT. Early admission to a tertiary referral center with expertise in LT results in a better prognosis and increased survival following M-ALF.

Keywords: *Acute liver failure, Amanita phalloides, living donor liver transplantation, mushroom intoxication*

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Introduction

Acute liver failure (ALF) is defined as clinical syndrome defined by coagulopathy and hepatic encephalopathy resulting from acute and severe liver damage in patients without preexisting liver disease.[1-3] Mushroom intoxication is a relatively rare cause of ALF. Furthermore, there are more than 2000 types of mushrooms, and 50 of them are poisonous for humans. The true incidence of mushroom

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intoxication is unknown due to undetermined cases, and therefore, mortality rates reported in literature may be significantly underestimated.[4,5]

Amanita phalloides is the most poisonous mushroom type which has three toxins; amatoxin, phallotoxin, and virotoxin. Amatoxins mainly affect tissues with high rates of protein synthesis, including the liver, kidneys, brain, pancreas, and testes because it inhibits ribonucleic acid polymerase II.[4] Amatoxin causes serious hepatotoxicity.[4] Mushroom intoxication-related liver injury (M-ALI) may progress into Mushroom intoxication-related liver failure (M-ALF) and eventually death if liver transplantation (LT) is not performed. M-ALF is frequently characterized by a rapid evolution to coma and death due to increased intracranial pressure, systemic infection, and multiorgan failure.

Supportive treatment and artificial liver support systems have limited therapeutic value in patients with ALF; such measures may be useful as a bridging therapy before LT. Probability of spontaneous recovery is low despite appropriate medical treatment. Time is very crucial, and LT should be employed in patients with progressive clinical course in ALF. Therefore, living-donor LT (LDLT) provides a lifesaving option for allocation of the liver in shorter period of time when compared to deceased donor.[6,7]

Mushrooms are widely consumed in our country. Hence, mushroom intoxication is a common health problem in Turkey with a high mortality rate. We aimed to share our experience regarding LDLT and its results in M-ALF and to investigate the risk factors for poor prognosis in mushroom intoxication.

Materials And Methods

All patients admitted or referred to our institute with suspicion of mushroom intoxication between November 2008, and June 2016 were evaluated. Data were obtained from patient database. Autoimmune liver disease, viral hepatitis, toxicity of salicylate, or acetaminophen were ruled out in all patients on admission using serology and toxicology screening. All patients initially received supportive therapy including a combination of gastric lavage, volume resuscitation, activated charcoal, penicillin G, N-acetyl cysteine, artificial liver support systems, and hemofiltration. The following data were evaluated: demographics, presenting symptoms, laboratory values, model for end-stage liver disease (MELD) or pediatric end-stage liver disease (PELD) scores, clinical course, and outcomes of supportive therapy and LT. The patients were divided into two groups according to their clinical course. Group A (therapy responsive group) consisted of patients who had low-MELD/PELD scores and mild encephalopathy on admission who fully recovered with supportive therapy. Group B consisted (therapy unresponsive group) of patients who had high-MELD/PELD scores and severe encephalopathy who died or underwent LT. The median MELD score, the encephalopathy, and the laboratory data in the postoperative period scale of the patients who died after LDLT were analyzed. We compared the groups to identify the predictors for poor prognosis in mushroom intoxication.

Eight patients who underwent LDLT in accordance with the standard technique defined in detail previously.[8] Five patients received right lobe donation LT and the three patients received left lateral lobe donation LT. Donor evaluation was done according to our evaluation protocol described previously.[9]

Statistical analyses

Categorical variables were compared using the Pearson Chi-square or Fisher's exact test. Continuous variables were compared using the 2-tailed Student's *t*-test, or the Wilcoxon signed-rank. Any $P < 0.05$ was considered statistically significant. All statistical analysis was performed using statistic program for social sciences software version 15 (SPSS v. 15, IBM, USA).

Results

During the study period, a total of 18 patients were admitted with symptoms attributable to mushroom intoxication. Twelve (66.7%) of them were female, and the mean age was 39.9 ± 18.2 years. Nine (60%) of the patients were in pediatric age group who were under 16-year-old. All patients presented with nausea and vomiting within 3–9 h after ingesting mushrooms. In addition, all of them had abdominal pain and diarrhea

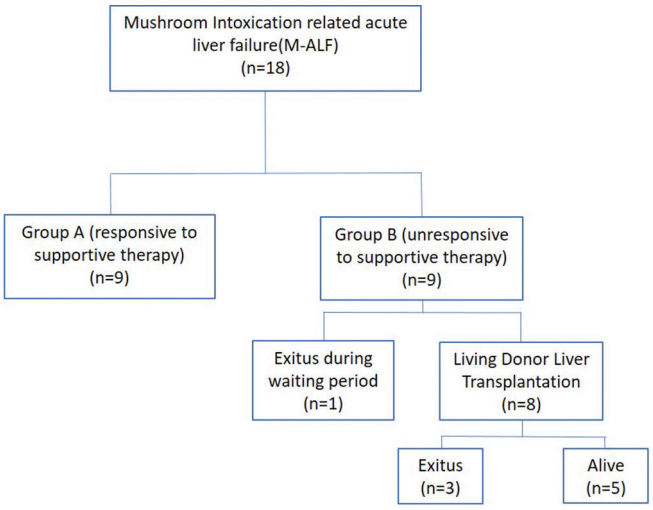

Figure 1: The flow chart of the outcomes of mushroom intoxication-related liver failure. M-ALF = Mushroom Intoxication-related acute liver failure

Table 1: Summary of the data of the patients

Gender	Age	Treatment	Interval (days)	Prognosis	INR	Creatinine	Total bilirubin	MELD/ PELD	Encephalopathy (stage)	Ammonia	Lactate	AST	ALT
Female	63	Supportive	2	Alive	2.2	0.9	2.4	18	No	170	22	10,689	11,189
Male	6	Supportive	2	Alive	1.5	0.4	1.1	9	No	119	10	1739	1639
Female	15	Supportive	2	Alive	1.4	0.5	0.7	8	No	74	13	235	198
Male	11	Supportive	2	Alive	1.3	0.56	0.8	8	No	105	11	1414	1699
Female	13	Supportive	2	Alive	8.8	0.5	2.1	33	No	174	23	4088	3885
Male	8	Supportive	1	Alive	2.5	0.4	1.1	9	No	190	12	6222	6571
Female	54	Supportive	1	Alive	2.5	0.7	2.39	20	Yes (2)	381	16.1	4202	8639
Male	49	Supportive	3	Alive	2.3	4.1	1.9	31	Yes (3)	332	18.3	803	1777
Female	19	Supportive	3	Alive	9.4	0.4	5.08	38	Yes (2)	351	29	6110	6985
Female	5	Supportive	3	Exitus	9.3	0.4	2.4	36	Yes (2)	288	27	7886	5311
Male	29	LDLT	5	Alive	4.1	0.7	8.2	30	Yes (2)	463	57	3712	6767
Female	3	LDLT	5	Alive	4.02	0.45	2.4	31	Yes (4)	894	NA	1326	1163
Male	9	LDLT	5	Alive	3.3	0.6	5.9	21	Yes (3)	1186	NA	12532	10611
Female	16	LDLT	4	Alive	8.4	0.78	19.85	40	Yes (3)	512	45	1471	4096
Female	67	LDLT	5	Alive	3.9	1	5.62	29	Yes (2)	183	50	1669	1656
Female	20	LDLT	5	Exitus	15	0.4	4.26	40	Yes (4)	643	36	12,051	10,153
Female	50	LDLT	5	Exitus	9.3	1.6	5.7	42	Yes (3)	1085	178	3394	3994
Female	46	LDLT	5	Exitus	1.06	0.56	14.3	17	Yes (3)	541	NA	1187	4022

The units are as follows creatinine (mg/dl), bilirubin (mg/dl), albumin (g/dl), Na (mEq/L), ammonia (ug/dl), AST (UI/L), ALT (UI/L), Lactate (mmol/L). BMI=Body mass index; INR=International normalized ratio (%); MELD=Model for end-stage liver disease; PELD=Pediatric end-stage liver disease; LDLT=Living-donor liver transplantation; AST=Aspartate transaminase; ALT=Alanine aminotransferase; NA=Not available

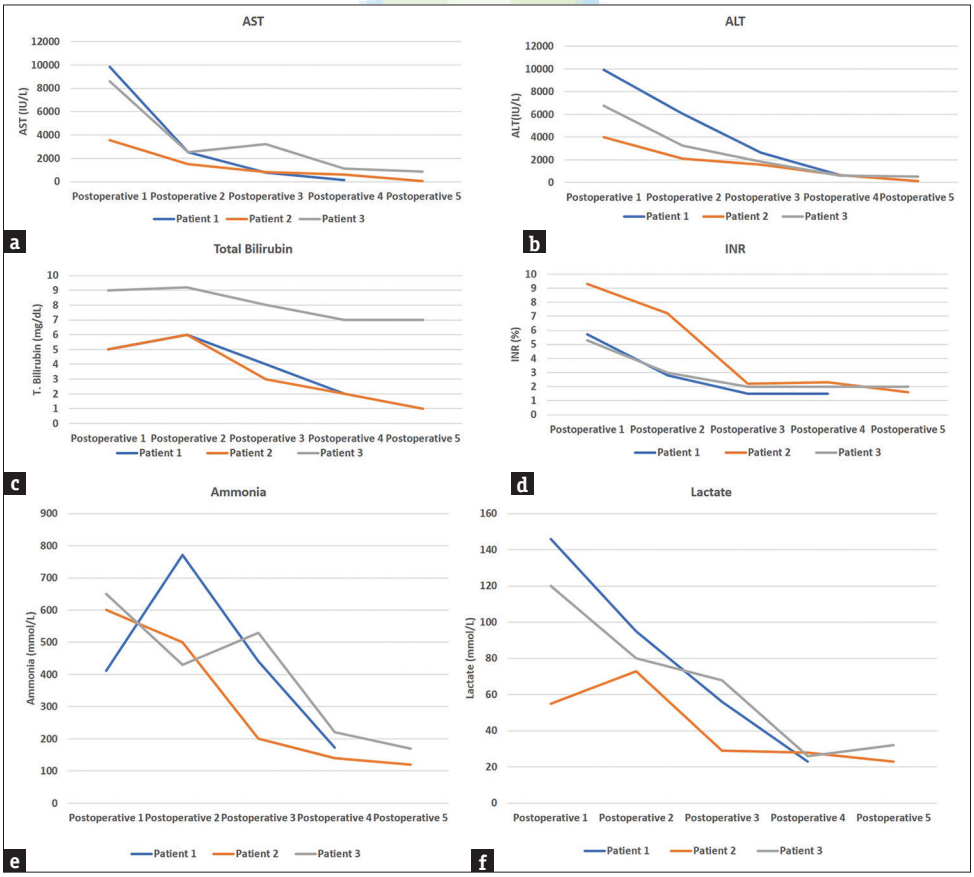

Figure 2: The summary of the laboratory data of the patients with postoperative mortality. (a) The course of postoperative aspartate transaminase. (b) The course of postoperative alanine aminotransferase. (c) The course of postoperative total bilirubin. (d) The course of postoperative international normalized ratio. (e) The course of postoperative ammonia levels. (f) The course of postoperative lactate levels

Table 2: Comparisons of study groups in terms of prognostic factors

	Group A (*n*=9)	Group B (*n*=9)	*P*
Gender (female, *n* (%)	3 (50)	3 (33)	0.26
Age (years)	19.3±21.6	20±18.1	0.95
BMI (kg/m^2; mean±SD)	22.9±5.6	21.7±5.3	0.76
Interval to admission (days mean±SD)	2.20±0.87	4.63±0.70	0.001
INR (%)	2.95±2.91	7.15±3.94	0.04
Creatinine (mg/dl; mean±SD)	0.54±0.19	0.65±0.38	0.52
Bilirubin (mg/dl; mean±SD)	1.36±0.71	7.43±5.92	0.03
Albumin (g/dl; mean±SD)	3.78±0.26	3.81±0.43	0.89
Na (mEq/L; mean±SD)	134.8±0.4	135.9±4.7	0.6
Platelet (cells/mm^3; mean±SD)	298.5±131.4	163.7±88.9	0.03
MELD/PELD scores (mean±SD)	14.2±9.9	33.6±8.2	0.01
Encephalopathy (absent/present)	6/3	0/9	0.002
Ammonia (ug/dl; mean±SD)	137.2±44.8	653.1±331.7	0.02
AST (UI/L; mean±SD)	3889±1587	4502±1500	0.62
ALT (UI/L; mean±SD)	4084±1667	3316±1105	0.56

BMI=Body mass index; INR=International normalized ratio; MELD=Model for end-stage liver disease; PELD=Pediatric end-stage liver disease; AST=Aspartate transaminase; SD=Standard deviation; ALT=Alanine aminotransferase

with various severities. The data regarding the patient laboratory values are summarized in Table 1.

In our study, nine patients recovered with supportive therapy and they were added to Group A. Nine patients were added to Group B because they were unresponsive to supportive therapy and needed transplantation (n = 8) or died (n = 1) [Figure 1]. Three of the eight patients who were transplanted died in the postoperative period. The aspartate transaminase, alanine aminotransferase, bilirubin, international normalized ratio (INR), ammonia and lactate levels steadily decreased; however, the course resulted in mortality [Figure 2]. These did not show any improvement of the encephalopathy scale after LDLT.

The 5-year-survival of the 8 patients that received LDLT was 62.5%. All the postoperative deaths were in the early period within the first 5 days following LDLT. The patients in the Group B had significantly higher MELD/PELD scores and encephalopathy rate than those in the Group A. INR, bilirubin, ammonium levels, and platelet count were significantly different among the groups. The interval before admission to our institute in group A was significantly lower than Group B (2.20 vs. 4.63 days, P = 0.001). All the data regarding the study groups are summarized in Table 2.

Discussion

It is estimated that there are over 2,000 types of mushrooms worldwide. Merely 20%–25% of the species have been identified and only 3% of these are poisonous.[10] Kintziger *et al*[11] reported a survey from Florida regarding mushroom exposure calls to the Florida Poison Information Center Network and cases of mushroom poisoning reported in emergency department and hospital inpatient data between 2003 and 2007. They found that mushroom ingestion is frequent in children but results in life-threatening condition in only 1% (13/1346) of the cases.[11]

The genus Amanitais responsible for 90% of fatal mushroom poisonings.[12] The main clinical feature of the amatoxins intoxication is ALF. Massive centrilobular hepatic necrosis is key histopathological findings in liver biopsy specimens.[13] Acute toxic hepatitis may develop rapidly and result in liver insufficiency and ultimately hepatic coma.[14]

In our study, of 18 patients had M-ALF, only 9 (50%) patient survived without transplantation. Eight patients with M-ALF required LT and five of them survived following LT. The Hy's law states that the mortality rate in drug-induced hepatocellular jaundice is between 10% and 50%. The law is based on observations by Hyman (Hy) Zimmerman.[15] In our study, the overall mortality rate was 37.5% which consistent with Hy's law.

The postoperative data regarding the three patients that died following LDLT were analyzed. There were no vascular problems in the imaging studies performed postoperatively, and the liver function tests as well as ammonia and lactate were steadily decreasing in the postoperative period. The patients died due to late admission to our institute, high dose of exposure to the mushroom, and the systemic toxicity of the mushroom intoxication.

The U. S. ALF Study Group (ALFSG) recently reported a cohort study; they evaluated amatoxin-induced acute liver injury (A-ALI) and amatoxin-induced ALF (A-ALF) patients enrolled in the US ALFSG registry between 1998 and 2014. Among the 2224 patients in the registry, 18 (0.8%) had A-ALI (n = 5) or A-ALF (n = 13). Of the 13 patients with ALF, six (46%) survived without transplantation, and two (15%) died without transplantation, and five (39%) survived with transplantation. In five patients with A-ALI, four (80%) recovered with supportive therapy and one (20%) survived with LT.[16]

LT for mushroom intoxication was first reported by Woodle *et al*.[17] in 1985, since then it has been

a well-established option in the treatment of these patients. However, an indication of LT for M-ALF is still uncertain. Various criteria to determine the timing of LT for ALF have been proposed, although none of them are universally accepted. The most frequently used criteria are The King's College Prognostic Model (KCPM), Ganzert's and Clichy's criteria.[18-23] We preferred The KCPM in our study. We found that presence of encephalopathy, higher MELD/PELD scores, INR, bilirubin, ammonium levels, and lower platelet count were related to poor prognosis in our patients with mushroom intoxication.

LT offers improved prognosis and a valid curative therapeutic option to patients with ALF. LDLT is a lifesaving procedure by providing quicker access to the required organ when compared to deceased donor LT. Time is a crucial factor and delay in consideration of LT would cause rapid progression to death.[24] In our study, interval between exposure to admission to our department was significantly longer for patients in Group B when compared to Group A.

In Group B, one patient did not have a living donor and therefore died during the waiting period for deceased donor. Three of the eight patients who died after transplantation in the study were referred to our institute from another center in the later stages of the disease, and therefore, the patients had higher MELD scores and encephalopathy scale on admission. In patients with mushroom intoxication, it should be considered that ALF may progress rapidly, and LT may be required. Therefore, these patients should be evaluated and treated in centers with expertise in LT.

Similar to the majority of published studies on mushroom intoxication, the most important limitation of our study was that the number of patients was too small to obtain appropriate statistical data. Other limitations of the present study are due to the fact that we did not determine the type of mushroom and serum toxin levels. Therefore, there is a need for multicenter prospective studies involving a greater number of patients to confirm our results.

Conclusion

Indication of LT in mushroom intoxication is still uncertain due to lack of high-level evidence. In our study, the presence of encephalopathy, higher MELD/PELD, INR, bilirubin, ammonium levels, and lower platelet count were found related to worse clinical course in mushroom intoxication. The etiology of the ALF has a wide variety of etiologies that show great differences in terms of management protocols. Mushroom intoxication-related ALF can show rapid clinical deterioration. For this reason, for management of such cases, new diagnostic criteria are necessary. Patients with acute mushroom intoxication should be evaluated and treated in centers that have experience in LDLT. There is a need for multicenter prospective studies involving a greater number of patients to confirm our results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Polson J, Lee WM; American Association for the Study of Liver Disease. AASLD position paper: The management of acute liver failure. Hepatology 2005;41:1179-97.
2. Polson J, Lee WM. Etiologies of acute liver failure: Location, location, location! Liver Transpl 2007;13:1362-3.
3. Escorsell A, Mas A, de la Mata M; Spanish Group for the Study of Acute Liver Failure. Acute liver failure in Spain: Analysis of 267 cases. Liver Transpl 2007;13:1389-95.
4. Kantola T, Kantola T, Koivusalo AM, Höckerstedt K, Isoniemi H. Early molecular adsorbents recirculating system treatment of amanita mushroom poisoning. Ther Apher Dial 2009;13:399-403.
5. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, *et al.* Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947-54.
6. Park SJ, Lim YS, Hwang S, Heo NY, Lee HC, Suh DJ, *et al.* Emergency adult-to-adult living-donor liver transplantation for acute liver failure in a hepatitis B virus endemic area. Hepatology 2010;51:903-11.
7. Choi JW, Yoon KT, Park JY, Kim JK, Ahn SH, Paik YH, *et al.* Usefulness and safety of extracorporeal liver support therapy using MARSR for patients with liver failure: A preliminary report. Korean J Gastroenterol 2009;54:28-35.
8. Ozgor D, Dirican A, Ates M, Gönültas F, Ara C, Yilmaz S, *et al.* Donor complications among 500 living donor liver transplantations at a single center. Transplant Proc 2012;44:1604-7.
9. Dirican A, Baskiran A, Dogan M, Ates M, Soyer V, Sarici B, *et al.* Evaluation of potential donors in living donor liver transplantation. Transplant Proc 2015;47:1315-8.
10. Gonmori K, Yoshioka N. The examination of mushroom poisonings at Akita university. Leg Med (Tokyo) 2003;5 Suppl 1:S83-6.
11. Kintziger KW, Mulay P, Watkins S, Schauben J, Weisman R, Lewis-Younger C, *et al.* Wild mushroom exposures in Florida, 2003-2007. Public Health Rep 2011;126:844-52.
12. Mas A. Mushrooms, amatoxins and the liver. J Hepatol 2005;42:166-9.
13. Pond SM, Olson KR, Woo OF, Osterloh JD, Ward RE, Kaufman DA, *et al.* Amatoxin poisoning in Northern California, 1982-1983. West J Med 1986;145:204-9.
14. Mydlík M, Derzsiová K, Frank K. Renal replacement therapy in acute poisonings – One center experience. Przegl Lek 2013;70:381-5.
15. Zimmerman HJ. Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 1999.

16. Karvellas CJ, Tillman H, Leung AA, Lee WM, Schilsky ML, Hameed B, *et al.* Acute liver injury and acute liver failure from mushroom poisoning in North America. Liver Int 2016;36:1043-50.
17. Woodle ES, Moody RR, Cox KL, Cannon RA, Ward RE. Orthotopic liver transplantation in a patient with amanita poisoning. JAMA 1985;253:69-70.
18. O'Grady J. Timing and benefit of liver transplantation in acute liver failure. J Hepatol 2014;60:663-70.
19. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-45.
20. Ganzert M, Felgenhauer N, Zilker T. Indication of liver transplantation following amatoxin intoxication. J Hepatol 2005;42:202-9.
21. Bonacini M, Shetler K, Yu I, Osorio RC, Osorio RW. Features of patients with severe hepatitis due to mushroom poisoning and factors associated with outcome. Clin Gastroenterol Hepatol 2017;15:776-9.
22. Bernuau J. Selection for emergency liver transplantation. J Hepatol 1993;19:486-7.
23. Escudié L, Francoz C, Vinel JP, Moucari R, Cournot M, Paradis V, *et al. Amanita phalloides* poisoning: Reassessment of prognostic factors and indications for emergency liver transplantation. J Hepatol 2007;46:466-73.
24. Ates M, Hatipoglu S, Dirican A, Isik B, Ince V, Yilmaz M, *et al.* Right-lobe living-donor liver transplantation in adult patients with acute liver failure. Transplant Proc 2013;45:1948-52.