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ORIGINAL ARTICLE

Liver histology as predictor of outcome in patients with acute liver failure

Ashish Singhal,[1] Saraschand Vadlamudi,[1] Kenneth Stokes,[2] Francis P. Cassidy,[2] Ayumi Corn,[3] Stan S. Shrago,[3] Harlan I. Wright[1] and Vivek Kohli[1]

1 Nazih Zuhdi Transplant Institute, INTEGRIS Baptist Medical Center, Oklahoma City, OK, USA
2 Department of Interventional Radiology, INTEGRIS Baptist Medical Center, Oklahoma City, OK, USA
3 Department of Pathology, INTEGRIS Baptist Medical Center, Oklahoma City, OK, USA

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Correspondence
Vivek Kohli, Nazih Zuhdi Transplant Institute, INTEGRIS Baptist Medical Center, 3300 NW Expressway, Oklahoma City, OK 73112, USA.
Tel.: 001-405-949-3349;
fax: 001-405-945-5844;
e-mail: vivek.kohli@gmail.com

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Summary

Acute liver failure (ALF) is a clinical syndrome associated with significant morbidity and mortality with a highly unpredictable outcome. We retrospectively analyzed 71 ALF patients (53 males; mean age = 27.5 ± 15.6 years) that underwent transjugular liver biopsy (TJLB) at our institution. The aims of this study are (i) to report our experience with TJLB in these patients, and (ii) to examine the role of liver histology in predicting their outcome. We also compared the histopathological findings between TJLB and explanted liver specimens in 31 patients who underwent liver transplantation (LT). Biopsy specimens were satisfactory for histopathological analyses in 69 (97.1%) patients, confirmed the clinical diagnosis in 56 (81.2%) patients, and altered the diagnosis in 13 (18.8%) patients. Minor complications were encountered in four (5.6%) patients. Percentage of hepatocyte necrosis was the only histological parameter that has significant discriminatory prognostic value, with no survivors having >75% necrosis without LT. In conclusions, TJLB is a safe technique for obtaining liver tissue in both adult and pediatric patients with ALF. Histological characteristics, mainly etiological diagnosis and degree of hepatocyte necrosis may assist in clinical decision-making for need of LT in these patients.

Introduction

Acute liver failure (ALF) is a clinical syndrome characterized by the recent onset (<6 months) of jaundice, coagulopathy, and encephalopathy in an otherwise healthy person with no prior history of underlying liver disease [1,2]. It is associated with significant morbidity and mortality in 65–85% of patients with a highly unpredictable outcome [3,4]. The chances of spontaneous recovery depends on the underlying etiology, age of the patient, duration over which the disease develops, the extent of liver damage, and early inception of the supportive care [4–6].

Liver transplantation (LT) remains the only definitive treatment for those who do not recover rapidly or fail supportive care management. But, the overall mortality in ALF is nearly 40% even in the era of LT, as at least 25% of listed patients die while waiting for organ [3]. This is partly because despite of various prognostic scoring systems including the King's College Hospital (KCH) criteria, the Clichy criteria, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and the Model for End stage Liver Disease (MELD) score; none of these scores identify the need and ideal timing for LT definitely [3]. Additionally, to date, liver support devices have not proven to be of value in this condition. If they are helpful

at all it may be as a bridge to LT [7,8]. Developing effective methods of liver support or other alternatives to transplantation and better prognostic scoring systems remain the key goals to further improve the overall survival rates for this condition.

With the exception of viruses and diverse drug and toxic reactions, the cause of ALF in many patients remains unknown. Liver histology can establish a diagnosis and estimate the extent of hepatocellular necrosis and regenerative activity. The most frequently described pathological correlate of ALF is massive hepatic necrosis or, in the older literature, acute yellow atrophy [9]. However, it is clear that ALF can also develop in patients who retain ample liver parenchyma (submassive hepatic necrosis) [10,11], or as a manifestation of previously unrecognized chronic liver disease, such as Wilson's disease [12,13]. Considering the severe coagulopathy of ALF, transjugular liver biopsy (TJLB) is a valid option [14–16]; however, there are no defined guidelines and its potential role has been investigated in limited number of studies [17–19]. This is possibly because centers remained reluctant to perform an invasive procedure in these critically ill patients. In addition, there is high possibility of sampling error due to regional heterogeneity of hepatocyte necrosis. However, given the wide spectrum of pathology and histopathologic changes encountered in ALF, the potential prognostic value of liver biopsy merit its assessment.

In view of an increasingly prominent role of LT in the management of ALF, limited organ availability, lack of good alternatives to transplantation, and potential complications of lifelong immunosuppression, the accurate assessment of the cause, prognosis, and eligibility for LT must be quickly established. The aims of this study are (i) to report our experience with TJLB procedures in patients with ALF, (ii) to examine the role of liver histology in determination of etiology and clinical outcome (survival vs. death or progression to LT), and (iii) to compare the histopathological findings (diagnosis and percentage of liver necrosis) between TJLB and explanted liver specimens in 31 patients who underwent LT.

Patients and methods

A retrospective analysis of 71 consecutive patients that were admitted with clinical diagnosis of ALF at our institution between 1998 and 2008. The study was approved by the institutional review board.

Patients

The study group includes 53 males and 18 females with a mean age of 27.5 ± 15.6 years (range: 1 month–59 years). Sixteen (22.5%) patients were <16 years of age. At admission, 36 (50.7%) patients had grade 3–4 encephalopathy [20]. The mean platelet count was 190 ± 112 (range: 24–480) $\times 10^3/mm^3$, international normalized ratio (INR) 2.9 ± 1.7 (range: 1.3–8.8), aspartate transaminase (AST) 3046 ± 3930 (range: 127–17 196) IU/l, alanine transaminase (ALT) 2583 ± 3328 (range: 75–18 318) IU/l, and serum bilirubin 12.3 ± 9.6 (range: 2.4–35.2) mg/dl. All patients underwent TJLB after correction of coagulopathy, if needed, with a goal INR <2.

Transjugular liver biopsy technique

All TJLBs were performed under conscious sedation using 50–100 μg of fentanyl (Fentanyl; Hospira, IL, USA) and 1–2 mg of midazolam (Fulset; Hospira, IL, USA) intravenously with continuous non-invasive monitoring. Local anesthesia was performed with 1% lidocaine and the right internal jugular vein was accessed under the ultrasound guidance. A 19G Quick-Core® needle biopsy system (Cook Incorporated, Bloomington, IN, USA) with a 20 mm throw length was used, which was introduced via the guide wire. Correct positioning of the biopsy set was verified by fluoroscopy. Two to four passes were performed in case of unfragmented samples and more in case of fragmented specimens. We tried to obtain at least two biopsy specimens more than half of the cutting length of the biopsy needle. The procedure was terminated when the adequate samples has been obtained as judged by the performing interventional radiologist. A post TJLB check venogram was performed to rule out any bleeding, fistulas, or capsule perforation. Major and minor complications were classified according to the Society of Interventional Radiology criteria [21]. All samples were sent to histopathology in formalin.

Results

The TJLB procedure was considered a technical success when visually adequate specimens were obtained, which was true in all patients (100%; Table 1). The median time to perform TJLB was 20 min (range: 14–35 min). All patients underwent only one biopsy. There were no major hemorrhagic complications after TJLB. Minor complications were encountered in four patients (5.6%) including

Table 1. Outcomes of TJLB performed in 71 patients with ALF.

Technical success	100% (71/71)
Complication rate	5.6% (4/71)
Mean procedure time (range)	20 (14–35) min
Adequacy of specimen	97.1% (69/71)
Mean number of cores (range)	3 (2–5)
Mean core tissue length (range)	1.9 (1.7–2.2) cm

minor bleeding from the cervical puncture site in two, intrabdominal hemorrhage in one, and self-limited subcapsular extravasation was noted in one. All complications were managed conservatively, and required no surgical intervention or blood transfusions. Histological evaluation was done by two pathologists (SS and AC). Liver tissue was adequate for histological diagnosis in 69 (97.1%) patients. The mean number of cores was three (range: 2–5); the mean core tissue length was 1.9 cm (range: 1.7–2.2 cm), and on average, five complete portal tracts (range: 0–10) were identified.

A presumptive etiological diagnosis was established clinically before TJLB in all cases. Histological diagnoses based on TJLB findings confirmed this clinical diagnosis in 56 (81.2%) of 69 patients. In four of the remaining 13 patients with clinical diagnosis of ALF other than acetaminophen toxicity or viral hepatitis (A and B); an unexpected diagnosis was made histologically. These included giant cell hepatitis in one, Reye's syndrome in one, mitochondrial disorder in one, and malignant hemangioendothelioma in one. In other three patients with a presumptive clinical diagnosis of cryptogenic ALF, a diagnosis of autoimmune hepatic failure; and in one patient with a clinical diagnosis of acetaminophen induced ALF, a diagnosis of idiosyncratic drug reaction was established histologically. Clinically, the coexistence of chronic liver disease was suspected in two cases; however, histological analyses demonstrated associated fibrosis in five patients.

Based on the clinical and biochemical findings, and existing prognostic scores, 50 (70.4%) patients were listed for LT and 21 patients were continued on supportive management. Forty-five (90%) patients were listed as United Network for Organ Sharing (UNOS) status 1 candidates while five patients were listed per their respective MELD scores because of associated chronic liver disease on TJLB.

Nine of 50 patients died while waiting for transplant. Tables 2 and 3 illustrates the outcome based on diagnoses and percentage of hepatocyte necrosis respectively. The diagnoses among non-survivors were acetaminophen overdose in two, cryptogenic in four, autoimmune in one, idiosyncratic drug reaction (sulpha drug) in one, and mitochondrial disease in one. Seven of them demonstrated hepatocellular necrosis >90% on TJLB and four had histological findings suggestive of coexisting chronic liver disease. The median time from listing to adverse outcome was 3.5 days (range: 1–31 days). While on waiting list, ten patients showed improvement with supportive treatment and were taken off from the list subsequently. Among survivors, the biopsy findings demonstrated varying degree of micro- and macro-vesicular steatosis with associated steatohepatitis in six patients, and hepatocellular necrosis ranged from no necrosis in two, necrosis <25% in two, necrosis 25–50% in four, to necrosis up to 75% in two patients. The diagnoses among them were acetaminophen overdose in four, cryptogenic in two, hepatitis A in one, hepatitis B in one, and autoimmune in two.

Thirty-one (68.8%) patients with status 1 underwent LT within a median time of 3 days (range: 1–28 days) from listing and 30 (96.8%) survived. A comparison of TJLB specimen and explanted liver in these 31 patients showed that TJLB underestimated the percentage of hepatocellular necrosis in eight patients and missed the associated fibrosis in four patients (Table 4). Two patients who had hepatocyte necrosis between 25% and 50% on TJLB had 51–75% necrosis on liver explant. Similarly, six

Table 2. Outcome based on percentage of hepatocellular necrosis in 69 patients with ALF.

		Outcome		
Liver necrosis, %	*n*	Recovery	Transplant	Died
<25	10	10	–	–
25–50	13	8	3	2
51–75	27	5	15	7
>75	19	–	13	6

Table 3. Outcome based on diagnoses in 71 patients with ALF.

		Outcome		
Diagnosis	*n*	Recovery	Transplant	Died
Acetaminophen induced	26	14	8	4
Cryptogenic	14	2	7	5
Autoimmune	10	5	4	2*
Hepatitis B	9	2	5	2
Hepatitis A	3	1	2	–
Wilson's disease	2	–	2	–
Fatty liver of pregnancy	1	1	–	–
Reyes syndrome	1	–	1	–
Malignant hemangioendothelioma	1	–	–	1
Parvovirus B-19	1	–	1	–
Idiosyncratic drug reaction	1	–	–	1
Giant cell hepatitis	1	–	1	–
Mitochondrial disease	1	–	–	1

*One patient died after transplantation.

Table 4. Comparison of percentage of hepatocellular necrosis between pretransplant TJLB and liver explant in 31 patients.

		Liver explant, *n*			
Liver necrosis, %	Pretransplant TJLB, *n*	<25%	25–50%	51–75%	>75%
<25	–	–	–	–	–
25–50	3	–	1	2	–
51–75	15	–	–	9	6
>75	13	–	–	–	13

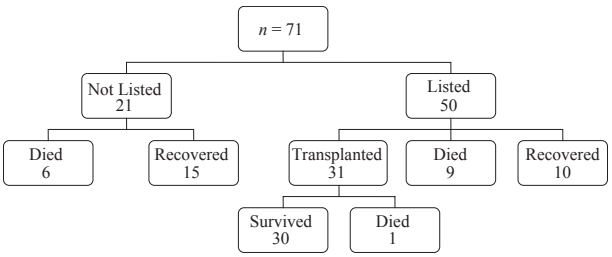

Figure 1 Outcome of all admissions for ALF.

patients who had hepatocyte necrosis between 51% and 75% on TJLB had >75% necrosis on liver explant.

Overall, 21 patients were not listed for LT (Fig. 1). Sixteen patients were not listed due to predictable favorable clinical diagnosis and prognosis – acetaminophen induced ALF in 11, autoimmune hepatitis in three, fatty liver of pregnancy in one, and acute hepatitis B with necrosis <50% in one. Five patients had a contraindication – malignancy in one, lack of social or family support in two, active alcoholism in one, and associated cirrhosis in one. Fifteen (71.4%) non-listed patients recovered with conservative treatment. Among six non-survivors, one had hepatocellular necrosis up to 50% with associated cirrhosis, one had malignant hemangioendothelioma, and four demonstrated hepatocellular necrosis >70%.

Discussion

In the clinical setting of ALF, the decision making for the eligibility and the timing of liver transplantation is of major importance, as there is a distinct possibility of full recovery without transplantation to poor outcome with transplantation. Currently, various prognostic scoring systems are being used, while useful; they leave much to be desired in terms of predicting the outcome accurately for ALF.

The decision to proceed for transplantation can be greatly enhanced by establishing the diagnosis in patients with ALF. The Acute Liver Failure Study Group (ALFSG) has found that etiology is among the most significant predictor of outcome; patients with ALF due to acetaminophen, hepatitis A, ischemic insult, and pregnancy related disease have >50% transplant-free survival; while all other etiologies have survival rates of <25% without liver transplantation [3]. In the present study, TJLB confirmed the pre-biopsy etiological diagnoses in 81.2% patients and changed the diagnoses in 13 patients. Among the 13 patients, four patients with histological diagnosis of giant cell hepatitis, Reye's syndrome, mitochondrial disorder, and idiosyncratic drug reaction were listed as status 1. Two of them underwent LT successfully whereas two died while waiting for an organ. Five patients were listed per their respective MELD scores due to associated fibrosis and other features of chronic liver disease on TJLB. The remaining four patients were not listed considering the favorable prognosis in three patients with autoimmune hepatitis (all recovered) and poor prognosis in one patient with malignant hemangioendothelioma (died). These observations are comparable with the rates for alteration of clinical diagnoses after TJLB in earlier studies [17,18]. In future, it is possible that the more accurate prognostic scores may be developed separately for each of the major etiologies of ALF.

Transjugular liver biopsy also estimates the percentage of hepatocyte necrosis. Percentage of necrosis appeared to have significant discriminatory prognostic value. In the present study, all 10 patients with hepatocellular necrosis <25% and eight (61.5%) patients with necrosis 25–50% recovered with conservative treatment. Among the remaining five patients with necrosis 25–50%, three required an LT and two died without LT. None of the 19 patients with necrosis >75% recovered without LT, 13 underwent LT and six died without LT. Furthermore, all five patients with necrosis >50% and associated fibrosis suggestive of chronic liver disease died without LT. In a study of 61 patients with ALF, Donaldson *et al.* reported that the TJLB is both safe and effective as an adjuvant to the KCH criteria in the diagnosis and prognosis of patients with non-acetaminophen induced fulminant liver failure [17]. They reported a similar correlation between degree of hepatocellular necrosis and survival, a necrosis rate of greater than 70% was associated with a poor outcome. Similarly, in a prospective study of 17 patients with ALF who underwent TJLB, Miraglia *et al.* found that submassive or massive (>85%) liver necrosis and cirrhosis are predictors of poor prognosis [18]. They concluded that TLJB is a quick and effective tool in clinical decision-making, especially in deciding patient selection and the best timing for LT. Therefore, in accordance with earlier studies, our study suggests a direct correlation between the percentage of hepatocellular necrosis and probability for death and/or LT.

The possibility of sampling error because of regional heterogeneity in the distribution of necrosis in ALF is a major limitation of biopsy [22]. In contrast, we observed that there was a tendency for underestimation of hepatocellular necrosis on the TJLB when compared with the explanted liver. This could be explained by the chronological difference of the procedures with TJLB being performed several days prior to the liver transplant. On going hepatocyte injury during this time may add to an increased necrosis noted on the explanted liver.

Being a retrospective analysis, our study has several limitations. The study lacks the data to compare the prognosis based on various prognostic scoring systems and degree of hepatocellular necrosis on TJLB. The study lacks the details of the treatment for patients who

improved with supportive care. We lack the data on non-survivors who underwent the autopsy and their respective findings. But study such as this remains important as the livers from patients presenting with ALF show a spectrum of pathologies, including minimal change, mild-to-severe confluent necrosis, and even established cirrhosis. The broad range of pathological features underscores the concept of ALF as an entity that should remain defined strictly by clinical criteria. Therefore, the approach to the patient with ALF should be guided principally on clinical grounds, and further classification should be based on pathological and etiologic considerations.

In conclusion, TJLB is a safe technique for obtaining liver tissue in both adult and pediatric patients with ALF. It is associated with a low incidence of complications Histological characteristics, mainly etiological diagnosis and degree of hepatocyte necrosis may assist in clinical decision-making for need of LT in these patients.

Authorship

AS and VK: research design, performance of research, data analysis, writing of paper. SV: performance of research, data analysis. KS, FPC, AC, SSS and HIW: performance of research.

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