World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i34.11935

World J Gastroenterol 2014 September 14; 20(34): 11935-11938
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Outcomes after liver transplantation for combined alcohol and hepatitis C virus infection

Rashid Khan, Ashwani K Singal, Bhupinderjit S Anand

Rashid Khan, Division of Gastroenterology and Hepatology, University of Texas Medical Branch, Galveston, TX 77555, United States
Ashwani K Singal, Division of Gastroenterology and Hepatology, University of Alabama Birmingham, Birmingham, AL 35294-0012, United States
Bhupinderjit S Anand, Department of Gastroenterology and Hepatology, Michael DeBakey VA Center, Baylor College of Medicine, Houston, TX 77030, United States
Author contributions: Khan R performed literature search, analyzed data and wrote the manuscript; Singal AK oversight writing of the initial draft and provided additional literature to write the paper; Anand BS reviewed the final draft.
Correspondence to: Ashwani K Singal, MD, MS, Division of Gastroenterology and Hepatology, University of Alabama Birmingham, 1808 7th Ave South, BDB 351, Birmingham, AL 35294-0012, United States. ashwanisingal.com@gmail.com
Telephone: +1-205-9759698 Fax: +1-205-9750961
Received: January 28, 2014 Revised: March 28, 2014
Accepted: May 28, 2014
Published online: September 14, 2014

Abstract

Alcohol abuse and chronic hepatitis C virus (HCV) infection are two major causes of chronic liver disease in the United States. About 10%-15% of liver transplants performed in the United States are for patients with cirrhosis due to combined alcohol and HCV infection. Data on outcomes on graft and patient survival, HCV recurrence, and relapse of alcohol use comparing transplants in hepatitis C positive drinkers compared to alcohol abuse or hepatitis C alone are conflicting in the literature. Some studies report a slightly better overall outcome in patients who were transplanted for alcoholic cirrhosis *vs* those transplanted for HCV alone or for combined HCV and alcohol related cirrhosis. However, some other studies do not support these observations. However, most studies are limited to a retrospective design or small sample size. Larger prospective multicenter studies are needed to better define the outcomes in hepatitis C drinkers.

Key words: Alcoholic liver disease; Hepatitis C virus; Liver transplantation; Graft survival; Mortality

Core tip: This article deals with prevalence and impact of hepatitis C virus (HCV) on progression and severity of alcoholic cirrhosis. We searched the literature on graft and patient survival among patients receiving liver transplantation for combined alcohol and HCV infection comparing to transplants received for either disease alone.

Khan R, Singal AK, Anand BS. Outcomes after liver transplantation for combined alcohol and hepatitis C virus infection. *World J Gastroenterol* 2014; 20(34): 11935-11938 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i34/11935.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i34.11935

INTRODUCTION

Hepatitis C virus (HCV) infection and alcohol abuse represent the two most common causes of cirrhosis and indications for liver transplantation (LT) in the West[1-3]. The prevalence of HCV infection peaked in 2001 at 3.6 million people infected. Cirrhosis accounted for 20% of all cases of HCV in 2006 and based upon mathematical modeling, the proportion of HCV with cirrhosis is projected to reach 45% by 2030[4]. It is now well recognized that HCV-infected patients have worse patient and graft survival than those transplanted for other etiologies[1,5]. Liver disease in patients with HCV recurrence post-LT takes an aggressive course and cirrhosis can occur within 5 years[6,7]. In contrast, outcomes after LT for alcoholic liver disease (ALD) are as good as for other etiologies[8-10].

Table 1 Patient survival at 1 and 5 years after liver transplantation: Studies comparing patients transplanted for hepatitis C *vs* alcoholic cirrhosis *vs* mixed etiology (combined alcohol and hepatitis C) *n* (%)

	Study design	1 yr survival (sample size)			5 yr survival (sample size)		
		HCV	ALD	ALD-HCV	HCV	ALD	ALD-HCV
Dhar *et al*[24]	Retrospective	31 (80)	24 (90)	11 (72)			
Aguilera *et al*[18]	Retrospective	122 (72)	96 (90)	51 (86)	83 (49)	81 (76)	43 (73)
Burra *et al*[16]	Population	4166 (81)	6301 (84)	714 (84)	1906 (67)	2867 (73)	261 (65)
Singal *et al*[19]	Population	15595 (88)	8559 (89)	6003 (88)	13469 (76)	7597 (79)	5185 (76)

ALD: Alcoholic liver disease; HCV: Hepatitis C virus.

About 8%-10% of all LT in the United States are performed in patients with cirrhosis due to combined HCV and alcohol or mixed etiology[2]. It has been shown that about 30% of patients with HCV-related cirrhosis, listed for LT have a significant history of alcohol consumption[11]. These conflicting data may be due to physicians not carefully eliciting the drinking patterns in HCV patients. Several studies have shown a synergistic interaction between HCV and alcohol resulting in more severe disease with rapid progression of fibrosis[12-15]. However, little is known about the interaction between HCV and alcohol consumption in the post-transplant setting. In this article, we will review the current literature on the outcome of patients receiving LT for liver disease due to mixed etiology.

BASELINE CHARACTERISTICS

Patients undergoing LT for cirrhosis due to mixed etiology are younger than those transplanted for HCV or alcohol abuse alone, with a median age of 49.5 years *vs* 59 years *vs* 53 years respectively, $P < 0.001$. Similar findings were reported in another study on the mean age of HCV transplants, alcoholic cirrhosis transplants, and patients transplanted for combined alcohol and HCV (53 ± 9 years *vs* 52 ± 8 years *vs* 49 ± 8 years respectively, $P < 0.001$)[16]. In one study, the duration of liver disease before LT was reported to be shorter in patients with mixed etiology by about 10 years as compared to alcohol alone (median 15 and 25 years, respectively)[17]. Even though alcoholic cirrhosis patients were older, they were sicker at the time of transplantation than those with cirrhosis secondary to HCV or mixed etiology; the proportion of patients with Child-Pugh-Turcotte stage C were 47% *vs* 30% *vs* 43% respectively, $P = 0.01$)[18]. In this study, the prevalence of hepatocellular carcinoma (HCC) was higher in patients with HCV-induced cirrhosis and patients with cirrhosis due to mixed etiology as compared to alcoholic cirrhosis (44% *vs* 35% *vs* 18% respectively, alcohol *vs* mixed, $P = 0.01$, HCV *vs* alcohol $P < 0.001$)[18]. Similar findings were observed in another study on the prevalence of HCC in the three groups[19]. Further, the tumors in the mixed group were found to be larger compared to those in patients with alcoholic cirrhosis (mean diameter 4.25 cm *vs* 0.85 cm)[17]. It may be inferred that patients transplanted for mixed etiology tend to have a more aggressive and faster progression to end-stage liver disease requiring transplantation.

WAIT LIST MORTALITY

Patients with cirrhosis due to mixed etiology are more likely to die while they are waiting for LT. Lucey *et al*[20] showed that patients with cirrhosis due to alcohol differed from patients with cirrhosis due to causes other than alcohol for wait list mortality only with respect to HCV positive cases, with 14% higher risk of death in patients with liver disease due to mixed etiology, $P = 0.006$. In this study, the survival benefit from LT was dependent upon the MELD score in patients with HCV, with a transplant benefit seen with a MELD score > 29. However, the survival benefit from LT was independent of MELD score for alcohol-related cirrhosis[20]. This finding is probably due to the apparent low rate of post transplantation heavy drinking. Further, it takes up to 5-10 years of alcohol use to have a negative impact on the graft[21,22].

GRAFT AND PATIENT SURVIVAL

Several studies have reported the outcomes after LT in patients with cirrhosis due to mixed etiology and compared the findings with patients transplanted for HCV and for alcoholic cirrhosis alone (Table 1). However, these studies have provided conflicting results[2,17-20,23,24]. A database looking at the experience of multiple European transplant centers found the survival rates following LT to be lower in patients transplanted for viral or mixed etiology compared to patients transplanted for alcoholic cirrhosis[16]. The authors further found that *de novo* tumors were a major cause of death in patients receiving LT for alcoholic cirrhosis. Patient mortality due to social issues including non-compliance to medications and non-adherence to medical instructions was more frequent in alcoholic cirrhosis and mixed etiology groups compared to HCV cirrhosis. In a more recent study based on the UNOS database, the five year graft and patient survival were similar in patients transplanted for mixed etiology and HCV cirrhosis but were lower compared to those transplanted patients for alcoholic cirrhosis (76% *vs* 76% *vs* 79% respectively; HCV *vs* mixed etiology $P = 0.87$ and HCV *vs* alcohol, $P < 0.0001$)[19]. However, a retrospective study at a single center in Europe obtained different results. In this study, the outcome of 60 patients with LT for cirrhosis due to mixed etiology was compared with

patients with HCV cirrhosis and alcoholic cirrhosis[18]. The authors found that patient survival at 5 years after LT was lower in patients with HCV cirrhosis compared to mixed etiology and alcoholic cirrhosis (49% *vs* 73%, and 76% respectively, HCV *vs* mixed group, $P = 0.0001$, mixed *vs* alcohol $P = 0.74$)[18]. Factors such as variations in the study design, data source, study population, and sample size may account for the differences in the findings among various studies. Further, in the study reported from the single European center showed increased rates of anti-HCV treatment and of re-transplantation in patients with cirrhosis due to mixed etiology as compared to the other two groups which may explain the conflicting results[18]. These data on HCV treatment are not available in studies reporting data using UNOS or European LT databases.

ALCOHOL RELAPSE

Recidivism (relapse of alcohol consumption) rates after LT vary widely, ranging from 7% to 95%[25,26]. These variations are due to differences in the definitions used for recidivism, methods used for diagnosing alcohol abuse, the follow-up period, and the study population across different studies[3]. In a pooled analysis of 50 studies evaluating recidivism after LT, the rates of any alcohol use after LT were 5.7% per 100 person years, and 2.5% per 100 person years risk for harmful drinking[27]. The data on the negative impact of recidivism on the graft are conflicting[28-31]. Conjeevaram *et al*[28] observed that the incidence of heavy drinking post OLT was uncommon, but fatal in terms mortality and graft loss. They further observed that the presence of steatosis and Mallory bodies in the explanted liver predicted recidivism[28]. In one study, the recidivism rates were similar in transplants performed for alcoholic cirrhosis and for mixed etiology (5 out of 56 *vs* 3 out of 32 patients). Further, the return to excessive drinking was not common[17]. All the five patients in the ALD group were alive at 5 to 8.8 years after LT. Of the three patients that returned to drinking in patients transplanted for mixed etiology, one patient died of continued alcohol abuse[17]. Another study examined the impact of recidivism on the liver graft in patients transplanted for alcoholic cirrhosis with or without concomitant HCV. No significant differences in the graft histology were observed between HCV positive heavy drinkers (> 200 g/wk), occasional drinkers (< 200 g/wk), and abstainers[23]. Aguilera *et al*[18] noted that patients undergoing transplantation for ALD had a higher rate of relapse compared to patients receiving LT for HCV cirrhosis and for cirrhosis due to mixed HCV and alcohol (18%, 3%, and 8% respectively, HCV *vs* alcohol $P < 0.001$). However, the duration of alcohol consumption was shorter, with a relatively small quantity of alcohol use. Further, no significant differences were noted in the liver tests in the three groups[18]. Based upon the current literature, recidivism after LT in patients with cirrhosis due to both alcohol and HCV does not seem to affect the liver function adversely. However, long-term outcome of patients with recidivism is less favorable compared to occasional drinkers and abstainers[32]. Hence, these patients should be advised to maintain complete abstinence after LT.

HCV RECURRENCE

Perhaps, one of the major concerns in patients transplanted for HCV cirrhosis is the risk for HCV recurrence and its impact on the liver graft. Alcohol may potentiate this damage by transiently increasing the circulating levels of HCV RNA[19]. However, the current literature does not provide convincing evidence that HCV recurrence in patients transplanted for liver disease secondary to mixed etiology is more aggressive than that in patients with HCV cirrhosis alone[17,18]. The results of a study from a single center on patients transplanted for alcoholic cirrhosis, HCV cirrhosis, or cirrhosis secondary to mixed etiology showed that the only variable associated with a better outcome after LT was the use of anti-HCV therapy after LT[18]. There was no difference after one year in patients transplanted for HCV-related cirrhosis compared to LT in patients with mixed etiology with respect to the development of severe recurrent HCV infection (45% *vs* 45%, $P = 0.66$), acute hepatitis (26% *vs* 28%, $P = 0.85$), or fibrosis stage > 1 (34% *vs* 35%, $P = 0.88$)[18]. Patients transplanted for mixed etiology received anti-HCV treatment more often compared to patients transplanted for HCV cirrhosis. With regard to alcohol relapse, the data was limited by the small sample size, and needs further validation.

CONCLUSION

The current literature supports the notion that cirrhosis secondary to mixed etiology (combined alcohol and HCV) is an acceptable indication for LT, with graft and patient survival comparable to patients receiving LT for HCV cirrhosis or for ALD. The synergistic interaction between alcohol and HCV leads to more aggressive disease prior to LT including higher wait-list mortality. However, the impact of mixed disease after LT remains unclear, with conflicting findings, suggesting the need for more prospective multicenter studies on a larger sample size to better examine this question and devise strategies to improve the management of these patients.

REFERENCES

1 **Forman LM**, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; **122**: 889-896 [PMID: 11910340]

2 **Singal AK**, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755-760 [PMID: 23370710 DOI: 10.1097/TP.0b013e31827afb3a]

3 **Singal AK**, Chaha KS, Rasheed K, Anand BS. Liver transplantation in alcoholic liver disease current status and con-

troversies. *World J Gastroenterol* 2013; **19**: 5953-5963 [PMID: 24106395 DOI: 10.3748/wjg.v19.i36.5953]
4 **Davis GL**, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513-21, 521.e1-6 [PMID: 19861128 DOI: 10.1053/j.gastro.2009.09.067]
5 **Gane EJ**, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, Maertens G, Williams R. Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; **334**: 815-820 [PMID: 8596547 DOI: 10.1056/NEJM199603283341302]
6 **Prieto M**, Berenguer M, Rayón JM, Córdoba J, Argüello L, Carrasco D, García-Herola A, Olaso V, De Juan M, Gobernado M, Mir J, Berenguer J. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. *Hepatology* 1999; **29**: 250-256 [PMID: 9862874 DOI: 10.1002/hep.510290122]
7 **Berenguer M**, Prieto M, San Juan F, Rayón JM, Martinez F, Carrasco D, Moya A, Orbis F, Mir J, Berenguer J. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology* 2002; **36**: 202-210 [PMID: 12085366 DOI: 10.1053/jhep.2002.33993]
8 **Starzl TE**, Van Thiel D, Tzakis AG, Iwatsuki S, Todo S, Marsh JW, Koneru B, Staschak S, Stieber A, Gordon RD. Orthotopic liver transplantation for alcoholic cirrhosis. *JAMA* 1988; **260**: 2542-2544 [PMID: 3050180]
9 **Pereira SP**, Williams R. Liver transplantation for alcoholic liver disease at King's College Hospital: survival and quality of life. *Liver Transpl Surg* 1997; **3**: 245-250 [PMID: 9346747]
10 **Belle SH**, Beringer KC, Detre KM. Liver transplantation for alcoholic liver disease in the United States: 1988 to 1995. *Liver Transpl Surg* 1997; **3**: 212-219 [PMID: 9346742]
11 **Schiff ER**. Hepatitis C and alcohol. *Hepatology* 1997; **26**: 39S-42S [PMID: 9305662 DOI: 10.1002/hep.510260707]
12 **Oshita M**, Hayashi N, Kasahara A, Hagiwara H, Mita E, Naito M, Katayama K, Fusamoto H, Kamada T. Increased serum hepatitis C virus RNA levels among alcoholic patients with chronic hepatitis C. *Hepatology* 1994; **20**: 1115-1120 [PMID: 7523270]
13 **Nishiguchi S**, Kuroki T, Yabusako T, Seki S, Kobayashi K, Monna T, Otani S, Sakurai M, Shikata T, Yamamoto S. Detection of hepatitis C virus antibodies and hepatitis C virus RNA in patients with alcoholic liver disease. *Hepatology* 1991; **14**: 985-989 [PMID: 1660025]
14 **Zignego AL**, Foschi M, Laffi G, Monti M, Careccia G, Romanelli RG, De Majo E, Mazzanti R, Buzzelli G, La Villa G. "Inapparent" hepatitis B virus infection and hepatitis C virus replication in alcoholic subjects with and without liver disease. *Hepatology* 1994; **19**: 577-582 [PMID: 8119681]
15 **Brechot C**, Nalpas B, Feitelson MA. Interactions between alcohol and hepatitis viruses in the liver. *Clin Lab Med* 1996; **16**: 273-287 [PMID: 8792072]
16 **Burra P**, Senzolo M, Adam R, Delvart V, Karam V, Germani G, Neuberger J. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant* 2010; **10**: 138-148 [PMID: 19951276 DOI: 10.1111/j.1600-6143.2009.02869.x]
17 **Goldar-Najafi A**, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, Khettry U. Liver transplantation for alcoholic liver disease with or without hepatitis C. *Int J Surg Pathol* 2002; **10**: 115-122 [PMID: 12075404]
18 **Aguilera V**, Berenguer M, Rubín A, San-Juan F, Rayón JM, Prieto M, Mir J. Cirrhosis of mixed etiology (hepatitis C virus and alcohol): Posttransplantation outcome-Comparison with hepatitis C virus-related cirrhosis and alcoholic-related cirrhosis. *Liver Transpl* 2009; **15**: 79-87 [PMID: 19109849 DOI: 10.1002/lt.21626]
19 **Singal AK**, Hmoud BS, Guturu P, Kuo YF. Outcome after liver transplantation for cirrhosis due to alcohol and hepatitis C: comparison to alcoholic cirrhosis and hepatitis C cirrhosis. *J Clin Gastroenterol* 2013; **47**: 727-733 [PMID: 23751845 DOI: 10.1097/MCG.0b013e318294148d]
20 **Lucey MR**, Schaubel DE, Guidinger MK, Tome S, Merion RM. Effect of alcoholic liver disease and hepatitis C infection on waiting list and posttransplant mortality and transplant survival benefit. *Hepatology* 2009; **50**: 400-406 [PMID: 19472315 DOI: 10.1002/hep.23007]
21 **DiMartini A**, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, Fung JJ, Fontes P. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transpl* 2006; **12**: 813-820 [PMID: 16528710 DOI: 10.1002/lt.20688]
22 **Lucey MR**. Liver transplantation for alcoholic liver disease: past, present, and future. *Liver Transpl* 2007; **13**: 190-192 [PMID: 17256778 DOI: 10.1002/lt.21014]
23 **Burra P**, Mioni D, Cecchetto A, Cillo U, Zanus G, Fagiuoli S, Naccarato R, Martines D. Histological features after liver transplantation in alcoholic cirrhotics. *J Hepatol* 2001; **34**: 716-722 [PMID: 11434618]
24 **Dhar S**, Omran L, Bacon BR, Solomon H, Di Bisceglie AM. Liver transplantation in patients with chronic hepatitis C and alcoholism. *Dig Dis Sci* 1999; **44**: 2003-2007 [PMID: 10548350]
25 **Björnsson E**, Olsson J, Rydell A, Fredriksson K, Eriksson C, Sjöberg C, Olausson M, Bäckman L, Castedal M, Friman S. Long-term follow-up of patients with alcoholic liver disease after liver transplantation in Sweden: impact of structured management on recidivism. *Scand J Gastroenterol* 2005; **40**: 206-216 [PMID: 15764153 DOI: 10.1080/00365520410009591]
26 **Lim JK**, Keeffe EB. Liver transplantation for alcoholic liver disease: current concepts and length of sobriety. *Liver Transpl* 2004; **10**: S31-S38 [PMID: 15382288 DOI: 10.1002/lt.20267]
27 **Dew MA**, DiMartini AF, Steel J, De Vito Dabbs A, Myaskovsky L, Unruh M, Greenhouse J. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl* 2008; **14**: 159-172 [PMID: 18236389 DOI: 10.1002/lt.21278]
28 **Conjeevaram HS**, Hart J, Lissoos TW, Schiano TD, Dasgupta K, Befeler AS, Millis JM, Baker AL. Rapidly progressive liver injury and fatal alcoholic hepatitis occurring after liver transplantation in alcoholic patients. *Transplantation* 1999; **67**: 1562-1568 [PMID: 10401763]
29 **Anand AC**, Ferraz-Neto BH, Nightingale P, Mirza DF, White AC, McMaster P, Neuberger JM. Liver transplantation for alcoholic liver disease: evaluation of a selection protocol. *Hepatology* 1997; **25**: 1478-1484 [PMID: 9185771 DOI: 10.1002/hep.510250628]
30 **Tang H**, Boulton R, Gunson B, Hubscher S, Neuberger J. Patterns of alcohol consumption after liver transplantation. *Gut* 1998; **43**: 140-145 [PMID: 9771419]
31 **Pageaux GP**, Michel J, Coste V, Perney P, Possoz P, Perrigault PF, Navarro F, Fabre JM, Domergue J, Blanc P, Larrey D. Alcoholic cirrhosis is a good indication for liver transplantation, even for cases of recidivism. *Gut* 1999; **45**: 421-426 [PMID: 10446113]
32 **Faure S**, Herrero A, Jung B, Duny Y, Daures JP, Mura T, Assenat E, Bismuth M, Bouyabrine H, Donnadieu-Rigole H, Navarro F, Jaber S, Larrey D, Pageaux GP. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. *J Hepatol* 2012; **57**: 306-312 [PMID: 22521352 DOI: 10.1016/j.jhep.2012.03.014]

P- Reviewer: Antonelli A, Borgia G, Hou WH, Wang K
S- Editor: Gou SX **L- Editor**: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327