Original Article

Survival rates of early-stage HCV-related liver cirrhosis patients without hepatocellular carcinoma are decreased by alcohol

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Although alcohol abuse is the most common cause of liver cirrhosis in the United States, the enhancing effects of alcohol on the long-term prognosis of hepatitis C virus (HCV) related liver cirrhosis has not been clarified. To investigate how alcohol abuse influences the prognosis of hepatitis virus related liver cirrhosis, we studied 716 Japanese patients. Cumulative survival and hepatocellular carcinoma (HCC) development rates were analyzed in alcohol abusive, cirrhotic patients with or without hepatitis virus infection. Patients who abused alcohol were younger ($p<0.0001$) than HCV infected, non-abusive patients. The overall survival rate among patients with alcoholic cirrhosis (Al group), HCV related cirrhosis (HCV group), and HCV infected + alcoholic cirrhosis (HCV + Al group), showed no significant differences, although the 10-year cumulative survival rate of Al group was the highest of the three groups. The HCC development rate of Al group was the lowest. In addition, alcohol abuse decreased the survival rates of HCV group in the early stage with no HCC ($p = 0.0028$). In conclusion, alcohol abuse might affect the progression of liver damage in HCV infected patients with liver cirrhosis in the early stage, although the influence of alcohol abuse on the long term prognosis seems to be rather small.

Key Words: **prognosis of liver cirrhosis, alcoholic liver disease, hepatitis C virus, hepatocellular carcinoma**

Alcohol abuse is a serious problem, in the United States and Europe, which causes liver cirrhosis.[1,2] Alcohol liver disease (ALD) is the cause of 40% of all liver cirrhosis in the United States.[3] The relative risk for development of hepatocellular carcinoma (HCC) between ALD and hepatitis C viruses (HCV) infection has already been reported.[4] We previously reported that alcohol and HCV infection together accelerate the development of HCC.[5] Alcohol abuse may also affect the prognosis of HCV infected patients with liver cirrhosis. However, the influence of alcohol abuse on the long-term prognosis of HCV infected patients with liver cirrhosis has not been clearly demonstrated.

In this study, we analyzed 716 Japanese cirrhotic patients and determined differences in prognosis.

Materials and Methods

Patients. We retrospectively analyzed the clinical data of a total of 716 patients with liver cirrhosis who were admitted to Kanazawa Medical University Hospital (Ishikawa, Japan) from 1972 to 2007. The diagnosis of liver cirrhosis was mainly made by histological evaluation of liver biopsy specimens and in 232 cases it was confirmed by computed tomographic (CT) scans, ultrasonography, blood chemistry, and/or physical examinations. HCC was diagnosed by histological examination, celiac angiography, CT scans (enhanced arterial and portal venous phases) or ultrasonography.

Three etiological groups were made and 525 of the 716 cirrhotic patients were placed in one of the following groups: alcohol (Al), HCV infected (HCV) or HCV with Al (HCV + Al). The other 191 patients had etiology of liver cirrhosis unlike Al and HCV. Diagnosis of ALD was based on criteria of Takada *et al.*[6] That is, the alcoholic patients have liver dysfunction with 80 g ethanol intake per day for more than 5 years and the other causes of their liver damage could be excluded. HCV infection status was diagnosed when serum anti-HCV antibody and HCV RNA polymerase chain reaction were positive.

We treated cirrhotic patients with ursodeoxycholic acid, if, serum aspartate aminotransferase or alanine aminotransferase levels were increased. When elevation of aminotransferase over 150 U/l was observed, we treated them with glycine intravenously. If serum albumin levels were decreased under 3.5 g/dl, we treated them with branched-chain amino acid orally. When the patient had a hepatic encephalopathy, we treated them with lactulose and cathartics and/or kanamycin orally and/or branched-chain amino acid intravenously. When the patients had an ascites, we treated them with furosemide and spironolactone. If these patients had a decreased level of serum albumin level under 2.5 g/dl, we treated them with albumin preparations intravenously. There were no HCV related cirrhotic patients who were treated with interferon based antiviral treatment.

Clinical characteristics of the patients. In each group, we retrieved their sex, age at diagnosis and the occurrence rate of HCC from medical records, and prepared summary statistics.

Long-term prognosis and HCC development. The cumulative survival rate of each group was calculated. Furthermore, the cumulative rate of HCC development was calculated for 413 (out of 525) non-HCC patients at diagnosis.

Statistical analysis. Data were expressed as means ± standard deviation (SD). The Mann-Whitney U test was used for statistical analysis for the age at diagnosis in each group. Cumulative survival rates and the rates of HCC development were calculated with the Kaplan-Meier method. The statistical analysis for the cumulative 10-year and overall survival rates including both HCC and non-HCC patients were evaluated with the Log-rank method. The statistical analysis for the cumulative 5-year and overall survival rates in non-HCC patients and cumulative rates of HCC develop-

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ment were also evaluated with the Log-rank method. A p value <0.05 was considered significant.

Results

Clinical characteristics of patients with liver cirrhosis. The characteristics in each group are shown in Table 1. There were a total of 525 patients and the male to female ratio was 2.3:1, indicating that the male gender has a predisposition to liver cirrhosis. Approximately 91% of patients in Al group were male subjects. The male to female ratio was 1:1 in HCV group. Almost all cirrhotic patients with HCC had HCV infection. The patients in Al and HCV + Al groups were significantly younger than those in HCV group (p<0.0001).

Prognosis of liver cirrhosis caused by alcohol abuse with or without virus-related liver cirrhosis. The 3-year survival rates of Al group, HCV group and HCV + Al group were 77.8%, 71.6% and 66.8%, respectively. The 5-year survival rates were 66.3%, 55.6% and 57.4%, respectively. The 10-year survival rates were 50.7%, 30.7% and 35.3%, respectively. The cumulative survival rate of Al group was higher than that of HCV group (p = 0.013) or HCV + Al group (p = 0.075) during the 10 years from the diagnosis of cirrhosis. The 20-year survival rates were 0% in all groups. The cumulative overall survival rate in Al group was higher than that of HCV + Al group0000 (p = 0.093) or HCV group (p = 0.071).

In the total 413 non-HCC patients at the diagnosis of liver cirrhosis, 9 of 157 patients in Al (5.7%), 11 of 51 patients in HCV + Al (21.6%) and 39 of 205 patients in HCV (19.0%) had HCC for 20 years. The cumulative HCC development in Al, HCV and HCV + Al groups are shown in Fig. 1. The 10-year rates of HCC development in Al, HCV and HCV + Al were 13.4%, 46.9% and 39.3%, respectively. The cumulative rate of HCC development in Al group was significantly lower than that in HCV group (p = 0.0065), and lower than that in HCV + Al group, but not significantly (p = 0.063).

The cumulative survival rates of patients who did not develop HCC, 148 patients in Al group, 40 patients in HCV + Al group and 166 patients in HCV group, were monitored. Those of Al, HCV and HCV + Al groups are shown in Fig. 2. The 5-year survival rates of Al, HCV and HCV + Al were 73.2%, 74.5% and 66.7%, respectively. The 10-year survival rates were 57.5%, 46.5% and 50.5%, respectively. Regarding the overall survival rate, there were no significant differences among the HCV + Al, HCV and Al groups. The 5-year cumulative survival rate of HCV + Al group was lower than that of HCV group (p = 0.0028) or Al group (p = 0.089). In addition, HCV + Al group had the worst survival rate among the 3 groups, at 8.2 years.

The survival rate of patients who did not develop HCC was higher than that of patients who developed HCC over the estimated period.

Discussion

In this study, no significant differences of the 20-year cumulative survival rate among the Al, HCV and HCV + Al groups were seen, although the 10-year cumulative survival rate of Al group was higher than that of HCV or HCV + Al group. In addition, alcohol abuse decreased the cumulative survival rates in early-stage of HCV-related liver cirrhotic patients with no HCC at the diagnosis of liver cirrhosis.

HCC development is considered to be an important factor of mortality in patients with liver cirrhosis [7]. In our study, the rate of HCC development in Al group was lower than that in HCV or HCV + Al group. Therefore, the 10-year survival rate of Al group might be higher than that of HCV or HCV + Al group. However, no significant difference of the 20-year cumulative survival rate was seen among HCV, Al and HCV + Al groups, because the failure of liver function as well as HCC development might influence the more long-term survival.

At the diagnosis of cirrhosis, the patients in HCV + Al group were significantly younger than those in HCV group. Therefore, alcohol is considered to quicken the progression of HCV-related liver cirrhosis. However, the influence of alcohol on the long-term prognosis of HCV-related liver cirrhosis is considered to be negligible. We could not analyze the reason for this, because the number of patients in the late stage of liver cirrhosis decreased over time.

Our previous and the other studies have found that chronic alcoholic patients with HCV infection have more impaired liver function than without HCV infection.[8,9] However, the mechanism for

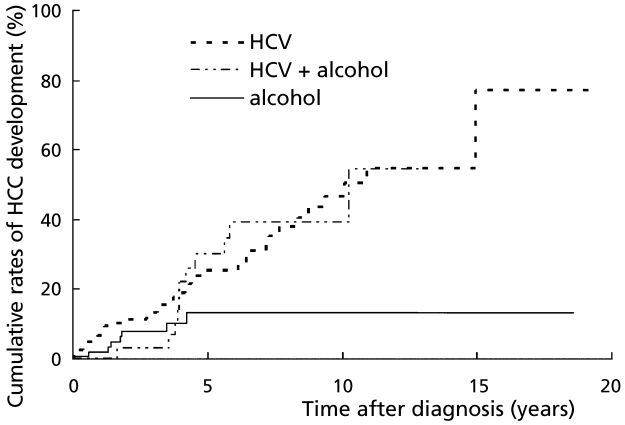

Fig. 1. Cumulative rates of HCC development in patients with liver cirrhosis. Al group had a lower cumulative rate of HCC development than HCV + Al or HCV group (p = 0.06 or 0.006, respectively).

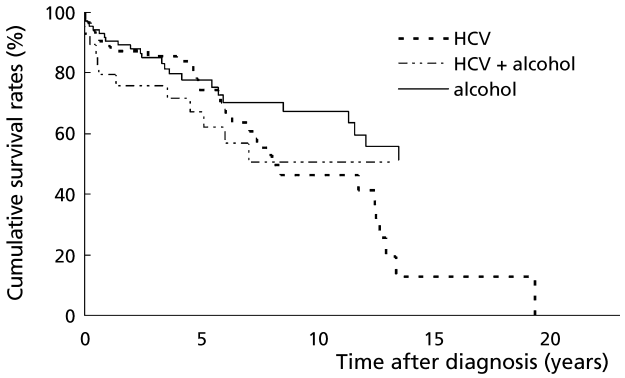

Fig. 2. Cumulative survival rates of cirrhotic patients who did not develop HCC. HCV + Al group had the worst survival rate at 8.2 years. The 10-year cumulative survival rate of HCV + Al group is 16.7% lower, and of HCV group is 20.8% lower than that of Al group.

Table 1. Clinical characteristics of the patients with liver cirrhosis

Cause	Cases (%)	Sex		Age at onset (mean ± *SD)	HCC (%)
		Male	Female		
Al	172 (24.0)	157	15	56.0 ± 10.5	24 (14.0)
HCV + Al	67 (9.4)	62	5	58.0 ± 10.0	27 (40.3)
HCV	286 (39.9)	145	141	65.0 ± 11.1	120 (42.0)
Total	525	364	161	61.0 ± 11.4	171 (32.6)

1972–2007 years. *: standard deviation, #: p<0.0001, HCC: hepatocellular carcinoma, Al: alcohol, HCV: hepatitis C virus.

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the enhancing effects of alcohol on the prognosis of HCV-related liver cirrhosis is still not clear. We previously reported in 39 patients with alcoholic liver damage that HCV infected patients had a higher cumulative rate of HCC development and a lower cumulative survival rate than non-HCV infected patients.[9] The present study also showed similar results based on a larger number of patients than the previous study.

We have reported that the development of HCV related-HCC may be enhanced by alcohol abuse.[5] However, in the present study, there was no significant difference of the cumulative rate of HCC development between HCV and HCV + Al groups. The previous study was a multiple logistic-regression analysis conducted with a larger number of patients in five different hospitals.[5] These differences may be related to the differences in statistical significance.

In this study, alcohol abuse might affect the decreased survival rates in early-stage of HCV-infected liver cirrhotic patients with no HCC at the diagnosis of liver cirrhosis, although this effect on the overall prognosis of HCV infected cirrhotic patients seems to be rather small. The peroxidation of lipids and production of reactive oxygen species (ROS) are major factors in alcoholic liver damage.[10] Recently, it was clarified that they are also related to the pathogenesis of chronic type C hepatitis. Moriya *et al.*[11,12] reported that the HCV core protein induced hepatic steatosis and HCC in transgenic mice. Otani *et al.*[13] reported that mitochondrial ROS production in Huh-7 cell was up-regulated by expressing HCV core protein and the more production was seen by ethanol-load. In addition, it was also reported that alcohol depleted the mitochondrial reduced glutathione, which exacerbates depolarization and cell death. Consequently, the degradation of lipids and production of ROS are considered to be involved in the damage of hepatocytes in HCV infected patients with alcohol abuse. In fact, Ye *et al.*[14] reported in cultured hepatoma cells that HCV RNA replication was disrupted by treatment with lovastatin, an inhibitor of 3-hydroxy-3-methyglutaryl CoA reductase. Furthermore, Emerit *et al.*[15] reported that Cu/Zn superoxide dismutase reduced the expression of transforming growth factor-beta1 (TGF-β1) in transgenic mice over-expressed the HCV core protein. Further studies are required to evaluate the effects of antidyslipidemic and/or antioxidant therapy in HCV-related liver cirrhosis.

In the United States, alcohol is the most common cause of liver disease.[3] Armstrong *et al.*[16] reported that the prevalence of HCV infection has remained broadly constant, with 3.2 million people infected with HCV, and the number of patients with infection for over 20 years is expected to peak in 2015. Therefore, treatment for alcoholic patients with HCV infection will become a major problem.

Conclusions

We concluded that alcohol abuse might affect the progression of liver damage in early stage cirrhotic patients with HCV infection, although the influence of alcohol abuse on the long term prognosis of cirrhotic patients with HCV infection seems to be rather small. Therefore, cirrhotic patients with HCV infection should strictly abstain from alcohol.

Abbreviations

ALD	alcohol liver disease
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
CT	computed tomographic
Al	alcohol
SD	standard deviation
TGF-β1	transforming growth factor-beta1

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