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Patient Sex in the Setting of Liver Transplant in Alcoholic Liver Disease

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Abstract

Objectives: **The aim of this study was to analyze alcoholic cirrhosis in women who were to undergo liver transplant, including their biochemical and clinical characteristics, main complications, survival rates, and main causes of death compared with men with alcoholic cirrhosis.**

Materials and Methods: **Our study included 400 patients with alcoholic cirrhosis, which we divided according to sex and viral infections. Biochemical parameters and the presence and degree of ascites and encephalopathy, liver function status, and liver rejection and survival rates were analyzed from 1 to 10 years and the main cause of death at 10 years.**

Results: **Patients with nonviral alcoholic cirrhosis and liver transplant had significantly better survival rates (84.1%) at 1 year versus those with viral alcoholic cirrhosis (74.5%; *P* = .036). Men with nonviral alcoholic cirrhosis (14%) and women with hepatitis C virus (29%) had the lowest short-term survival rates. In long-term survival analysis, the lowest rate was observed in women with nonviral alcoholic cirrhosis (26.1%), and the highest rate was observed in women with hepatitis C virus (42.9%). Liver graft failure was one of the main causes of death in male patients (19.5%).**

Conclusions: **Women with alcoholic cirrhosis showed a higher rate of ascites and encephalopathy but lower liver graft rejection than men with alcoholic cirrhosis. Survival rates were similar between men and women, although slightly lower in women who had hepatitis C virus.**

Key words: *Alcohol, Alcoholic cirrhosis, Human clinical toxicology, Liver transplant, Posttransplant survival*

Introduction

With adequate control and health monitoring, alcoholic cirrhosis (AC) is a predictable and reversible disease in its early stages in at-risk populations. However, it is can be neglected because of widespread perceptions that alcohol is integral for entertainment and during meals.[1-3] In recent years, the survival rate of transplanted patients with AC as primary disease has significantly improved, making this liver disease one of the best indications for liver transplant.[4-7] Nevertheless, patients should undergo careful posttransplant risk assessment for rejection development, viral recurrence, and alcoholic relapse.[8,9]

Increased consumption patterns, accompanied by an increase in alcohol consumption by women at very early ages, have been observed over recent years, suggesting that liver diseases will increase in the future.[10-13] Women are more vulnerable to the toxic effects of alcohol abuse because they manifest the harmful effects more quickly, resulting in more rapid neurologic damage and the development of cirrhosis and depression, as well as an increased risk of breast cancer.[14-16]

Despite the strong social and economic effects that AC has in our society, prevention and care interventions have increased in recent years but are still somewhat limited. In this sense, interventions to reduce alcohol consumption in young people and

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exercising appropriate control mechanisms are difficult in most cases.[17-19]

Because alcohol consumption has not previously been the main cause of primary liver disease in women, there are very few studies on AC in the female population. Hence, the aim of this study was to analyze women with AC undergoing liver transplant, including analysis of their clinical and biochemical characteristics, main pre- and posttransplant complications, causes of death, and posttransplant survival rates. Our goal is for this knowledge to be adopted into appropriate preventive measures for women with high alcohol consumption.

Materials and Methods

Patient enrollment and diagnostic criteria of alcohol cirrhosis, viral infection, major complications, and rejection

The medical records of 400 consecutive patients with AC who underwent liver transplant were retrospectively reviewed. Biochemical and clinical characteristics and major pretransplant and posttransplant complications were analyzed in 32 women. Posttransplant survival rates and main causes of death of patients with AC at 10 years posttransplant were studied and classified by sex in 368 men and 32 women. All patients gave informed consent at time of inclusion into our hospital database, including allowing for follow-up. The study protocol was approved by the institutional ethics committee and was in accordance with the 2000 Declaration of Helsinki.

Diagnostic criteria of alcoholic cirrhosis

Alcoholic cirrhosis was diagnosed using clinical, radiologic, and biochemical parameters.[20] In the case of a negative self-report of alcohol consumption, the opinions of relatives were taken into consideration. Data on alcoholic beverage type and average intake were not found in the available patient records. In most cases, there were no symptoms of the first stage of cirrhosis; therefore, the diagnosis was made after a casual scan, ultrasonography examination, or clinical examination. In other cases, the disease remained undetected until the second stage of decompensated cirrhosis, when complications such as ascites, upper gastrointestinal bleeding, and encephalopathy appeared. Cases of suspected cirrhosis were confirmed using specific analysis and imaging techniques. The degree of hepatic fibrosis of all patients included in this study was grade F4 (METAVIR score) at the time of inclusion on the wait list for liver transplant.

Major complications in transplant recipients with alcoholic cirrhosis

Ascites and encephalopathy were the main pretransplant complications shown in our study group of women with AC. Ascites was diagnosed by clinical history, physical examination, and imaging tests, including abdominal ultrasonography, tomography, or magnetic resonance imaging; ascites was graded according to 3 grades of development (from low to high).[21,22] Alcoholic encephalopathy was diagnosed by clinical history, physical examination, and blood ammonia levels. The severity of hepatic encephalopathy was based on the West Haven criteria, which classifies encephalopathy into 4 grades from low (grade 1) to high (grade 4) based on personality changes and the impairment of attention, to their family or themselves, states of disorientation, asterixis, mental confusion, drowsiness, bradypsychia, or coma.[23]

Analyzed biochemical parameters in female transplant recipients with alcoholic cirrhosis

We analyzed 9 biochemical parameters (shown with normal values): creatinine (0.7-1.2 mg/dL), albumin (3.5-5.2 g/dL), total bilirubin (0.3-1.9 mg/dL), alkaline phosphatase (40-130 U/L), glutamic oxaloacetic transaminase (5-40 U/L), glutamic pyruvic transaminase (5-41 U/L), gamma-glutamyltransferase (10-71 U/L), prothrombin activity (70%-100%), and international normalized ratio (INR; 0.9-1.2). Prothrombin activity was measured as percentage of an internal reference standard (Normotest; Nycomed Pharma, Asker, Norway) and INR using standard formulas that considered 3 INR groups for calculating the Model for End-Stage Liver Disease (MELD) score.[24]

Scores in predicting survival rates and main causes of death in transplant recipients with alcoholic cirrhosis

Liver function status in patients with AC was evaluated by the Child-Pugh and MELD scores. For both scoring systems, all analytical values of patients on wait lists for liver transplant were obtained.

The main causes of death in study patients were recorded at 10 years posttransplant. Causes of death

were analyzed and classified according to their relationship with liver disease and sex.

Viral infection diagnosis

Hepatitis C virus (HCV) infection was determined using a qualitative immunoassay (AxSYM HCV v3.0; Abbott, Wiesbaden Delkenheim, Germany) to detect the presence of anti-HCV antibodies, and the results were confirmed by immunoblotting technology (recombinant immunoblot assay) or reverse transcription polymerase chain reaction (REAL; Durviz, Valencia, Spain), following the manufacturer's instructions. Hepatitis B virus (HBV) infection was determined by measuring HBV surface antigen using a radioimmunologic method (Sorin Biomedica, Perugia, Italy). To determine cytomegalovirus (CMV) infection, anti-CMV immunoglobulin G antibodies were tested by immunoassay (Liason test; DiaSorin, Saluggia, Italy); CMV infection was diagnosed with immunoglobulin G antibody levels ≥ 0.6 U/mL. Positive tests were confirmed using real-time polymerase chain reaction (LightCycler CMV Quant kit; Roche, Indianapolis, IN, USA).

Liver rejection diagnosis

The diagnosis of acute or chronic liver rejection was based on a combination of clinical/radiologic/laboratory and histopathologic findings. The treatment of both diseases was based on the intensification of immunosuppression. Retransplants were also considered in this study.

Statistical analyses

Demographic data and results were collected in a database (Microsoft Access 2.0; Microsoft Corporation, Seattle, WA, USA), with analyses performed using SPSS version 20.0 software (SPSS Software Inc., Chicago, IL, USA). All results are expressed as means ± SEM or as a percentage. Pearson chi-square and two-tailed Fisher exact tests were used to compare categorized variables between groups. *P* values < .05 were considered significant. Odds ratio and 95% confidence interval were also calculated. The Kaplan-Meier method and log-rank tests were used to compare differences in short-term patient survival at 1, 3, 5, 7, and 9 months and long-term survival at 1, 3, 5, and 10 years. The total death rate was analyzed at 9 months and at 10 years.

Results

Patient enrollment

Mean age immediately before transplant was similar (53.02 ± 0.43 years) and not significantly different between the sexes (*P* = .675).

Most liver transplant recipients with AC (75.5%) did not present with any type of viral infection, with no significant differences shown between men and women (Table 1). Regarding AC recipients who presented with viral infections (24.5% of total recipients), 65.6% had HCV infection, 4.3% had HCV associated with HBV infection, 2.2% had HCV associated with CMV infection, 21.5% had HBV infection, and 6.5% had CMV infection. The percentage of male recipients with AC and HCV infection was 88.5% (n = 54), whereas in women the percentage was 11.5% (n = 7).

Biochemical characteristics of female patients with alcoholic cirrhosis included on wait list for transplant

We analyzed 9 biochemical parameters in the female AC recipients with and without associated viral infections (Table 1). Creatinine values were within normal limits at 0.9 ± 0.1 mg/dL; similar values were obtained for both subgroups. Similarly, albumin

Table 1. Biochemical Characteristics of Female Patients With Alcoholic Cirrhosis Included on Wait Lists for Liver Transplant

Biochemical Parameter	Normal Value	Number of Women Tested (N = 32) and Mean Result ± SEM	Number of Women Tested and Mean Result ± SEM	
			Nonviral Group (n = 22)	Viral Group* (n = 10)
Creatinine, mg/dL	0.7-1.2	17 (0.9 ± 0.1)	14 (0.9 ± 0.1)	3 (0.8 ± 0.1)
Albumin, g/dL	3.5-5.2	13 (3.4 ± 0.2)	11 (3.5 ± 0.2)	2 (3.2 ± 0.4)
Total bilirubin, mg/dL	0.05-1.2	13 (3.5 ± 1.2)	11 (3.8 ± 1.4)	2 (1.9 ± 1.5)[a]
GOT, U/L	5-40	15 (78 ± 23)	13 (84 ± 26)	2 (35 ± 5)[b]
GPT, U/L	5-41	15 (46 ± 14)	13 (50 ± 16)	2 (22 ± 6)[c]
GGT, U/L	10-71	13 (66 ± 14)	11 (72 ± 16)	2 (32 ± 10)
ALP, U/L	40-130	16 (60 ± 3)	13 (61 ± 4)	3 (59 ± 3)
Prothrombin activity, %	70-100	12 (160 ± 26)	10 (157 ± 31)	2 (170 ± 61)
INR	0.9-1.2	16 (1.4 ± 0.1)	13 (1.4 ± 0.1)	3 (1.4 ± 0.1)

Abbreviations: AC, alcoholic cirrhosis; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; INR, international normalized ratio; SEM, standard error of the mean

*Recipients with viral infection included those with hepatitis C and B viruses and cytomegalovirus.

[a]Total bilirubin values in nonviral AC recipients were compared with viral group (*P* = .007).

[b]GOT values in nonviral AC recipients were compared with viral group (*P* = .022).

[c]GGT values of nonviral AC recipients were compared with viral group *P* = .033).

levels were within normal limits (3.4 ± 0.2 g/dL), and similar values were also obtained for both subgroups. In contrast, high values of total bilirubin (3.5 ± 1.2 mg/dL) were found in all patients analyzed. Statistically significant differences were observed in total bilirubin values between female AC patients with and without viral infections (P = .007). Significantly higher values of glutamic oxaloacetic transaminase were obtained in AC women without viral infections (84 ± 26 mg/dL) versus AC women with viral infections (35 ± 5 mg/dL) (P = .022). Significantly higher values of glutamic pyruvic transaminase were obtained in the AC women without viral infections (50 ± 16 mg/dL), with normal values shown in AC women with viral infections (P = .033). Normal values of gamma-glutamyltransferase and alkaline phosphatase were observed in both groups of patients. Prothrombin activity (%) was also calculated and showed elevated values in both viral and nonviral groups in AC women. Mean values of INR were 1.4 ± 0.1, which were similar in both subgroups.

Major complications in female transplant recipients with alcoholic cirrhosis

Ascites and encephalopathy were the main complications in female recipients with AC. Ascites presence was observed in 43.8% of these patients, although most patients with ascites did not have concomitant viral infections. The patients were classified according to their degree of ascites: 85% of women had grade 2 ascites and 15% had grade 3, with none having grade 1. Similar data were obtained in both viral and nonviral AC patient groups, although grade 2 ascites was more frequently observed in nonviral AC patients (91% vs 50%), although these differences were not statistically significant (P = .295).

The presence or absence of encephalopathy was also considered. In total, 64% of women presented with encephalopathy, regardless of presence of viral infection. Patients presented with grade 1 encephalopathy (60%) or grade 2 (40%), with none having grade 3.

Posttransplant evolution and outcomes of female patients with alcoholic cirrhosis

We observed an overall acute rejection rate of 12.5% in female AC recipients, which was slightly lower than in total liver recipients. Only 9.45% of female AC recipients had chronic rejection (Table 2). Of note was the observation that the liver retransplant frequency in female AC patients was lower (3.1%) than in total liver transplant recipients (11.6%), although not statistically significant. Finally, HCV recurrence was slightly lower in AC recipients than in total liver recipients (28.6% and 37.5%, respectively).

Table 2. Posttransplant Liver Evolution of Female Patients With Alcoholic Cirrhosis

	Women With Liver Transplant[a] (n = 368), No. (%)	Women With Alcoholic Cirrhosis (n = 32), No. (%)
Acute liver rejection	227 (22.8)	4 (12.5)
Chronic liver rejection	74 (7.4)	3 (9.45)
Retransplant	116 (11.6)	1 (3.1)
Hepatitis C virus recurrence	113 (37.8)	2 (28.6)

[a]Includes all transplanted patients except female patients with alcoholic cirrhosis.

Analysis of Child-Pugh and MELD scores in female patients with alcoholic cirrhosis

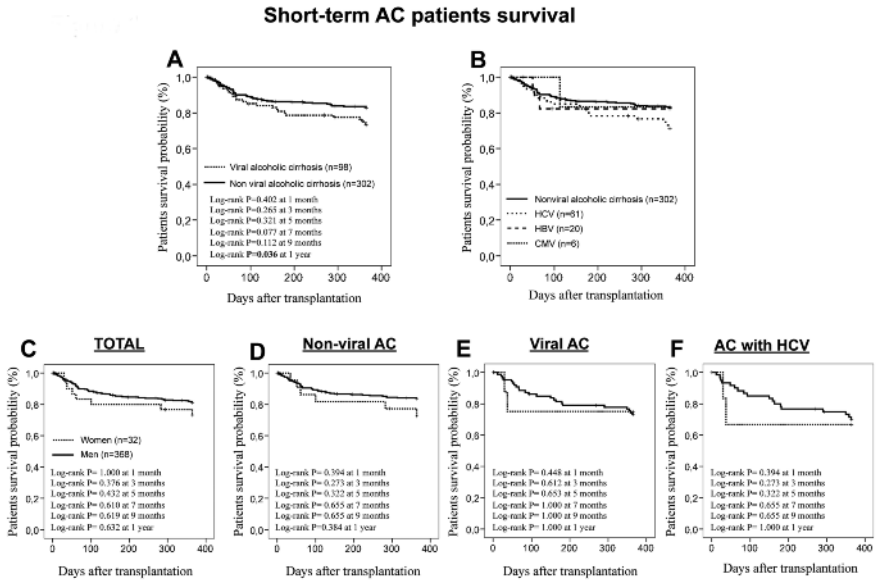
Most female AC patients were classified as Child-Pugh B (63.6%) or Child-Pugh C (36.4%). No differences were observed in patients with different concomitant viral infections. On the other hand, most female AC patients had MELD values ranging from 10 to 19 (61.5%), with 7.7% having MELD values higher than 19 and 30.8% having MELD values lower than 9. Results were similar among female AC recipients with and without viral infections.

Short-term posttransplant survival of patients with alcoholic cirrhosis

Survival and death rates of AC patients classified according to the presence or absence of concomitant viral infections and sex were analyzed over a posttransplant period of 12 months (Figure 1). In the total AC patients analyzed (n = 400), survival rate was 95.5% at 1 month, 89% at 3 months, 85.8% at 5 months, 84.5% at 7 months, 84% at 9 months, and 81.8 at 1 year. Rate of death was 18.8% in total AC patients at 1 year.

The greatest significant difference was observed at 1-year posttransplant, when survival in nonviral AC patients was 84.1% versus 74.5% in viral AC patients (P = .036) (Figure 1A). At 7 months posttransplant, nonviral AC patients also had a higher survival rate (86.4%) than viral AC patients (78.6%), although the difference was not statistically significant (P = .077). No differences in survival and death rates were observed among AC patients with different concomitant viral infections (Figure 1B).

Figure 1. Kaplan-Meier Patient Survival Curves of Alcoholic Cirrhosis Patients: Short-Term Analysis



Abbreviations: CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus
(A, B) Kaplan-Meier patient survival curves of total patients with alcoholic cirrhosis with and without associated viral infections and different associated viral infections, respectively. **(C-F)** Kaplan-Meier patient survival curves according to sex, without viral infection, with viral infection, and with HCV infection, respectively.

Short-term survival and death rates were similar and not significantly different between men and women (15.8% vs 18.7%; $P = 0.619$) (Figure 1C). No statistically significant differences were shown between male and female AC patients with and without viral infections (Figure 1, D and E).

At 9 months posttransplant, we observed an increased death rate in patients with HCV (22.9%) versus those without viral infections (14.2%). At 9 months, death rate was also lower in male AC patients without viral infections (14.0%) than in female AC patients with HCV infection (29.0%). At 1-year posttransplant, the highest death rate was observed in viral AC patients (27.8%), with women being the most affected group (28.5%) (Figure 1F).

In short-term analysis, the lowest death rate was observed in male AC patients without viral infection (14%) and the highest in AC women with HCV (29%) (Figure 1, D and F).

Long-term posttransplant survival of patients with alcoholic cirrhosis

Survival and death rates of AC patients classified according to presence or absence of concomitant viral infections in men versus women were analyzed over a 10-year period posttransplant (Figure 2). At 10 years, the death rate for total AC recipients (n = 400) was 30.5%, with survival rate of 74.5% at 3 years, 71.8% at 5 years, and 69.5% at 10 years.

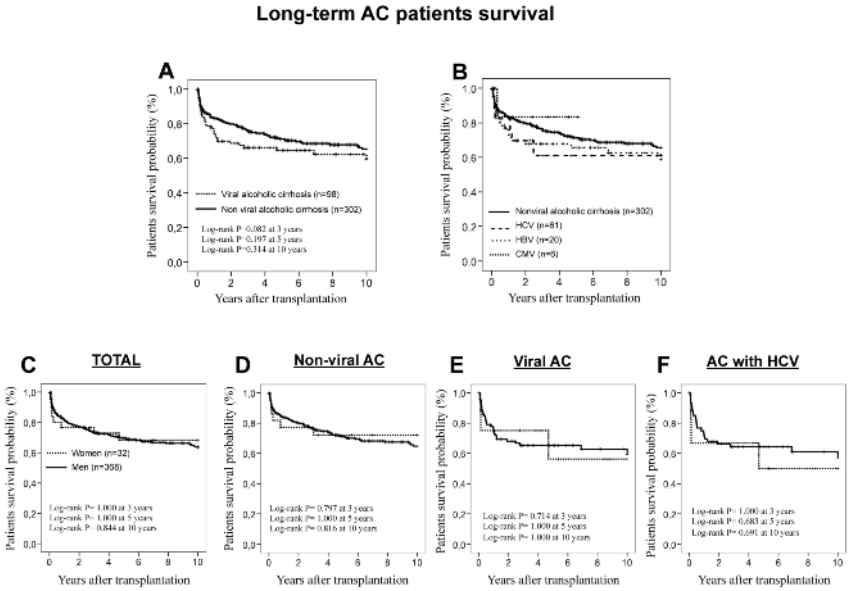
At 3 years posttransplant, patients without viral infections had a slightly higher survival rate (76.8%) than those with viral infections (67.3%), although the difference was not significant ($P = .082$). In the other analyzed years, no differences in survival rates were observed between the groups. The death rate of AC recipients with viral infections (34.7%) was higher than those without viral infections (29.1%) at 10 years, but the difference was not statistically significant ($P = .314$) (Figure 2A).

Survival rates were also analyzed according to type of viral infection, with lower survival rates observed in the AC patients with HCV infection (survival rate of 36% at 10 years) (Figure 2B).

Analysis of posttransplant survival in terms of sex showed no differences over the entire study period, with similar death rates at 10 years for both men and women (30.5%) (Figure 2C). Similar results were found for survival and death rates of nonviral AC patients (Figure 2D) and viral AC patients (Figure 2E).

We observed the highest death rate at 10 years in AC women with HCV infection (42.9%), although the rate was not significantly different versus AC men (35.2%; $P = .695$) (Figure 2F). In long-term analysis, the lowest death rate was shown in female AC patients

Figure 2. Kaplan-Meier Patient Survival Curves of Total Patients With Alcoholic Cirrhosis: Long-Term Analysis



Abbreviations: CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus
(A, B) Kaplan-Meier patient survival curves of total patients with alcoholic cirrhosis with and without associated viral infections and different associated viral infections, respectively. **(C-F)** Kaplan-Meier patient survival curves according to sex, without viral infections, with viral infection, and with HCV infection, respectively.

without viral infection (26.1%) and the highest in AC women with HCV (42.9%) (Figure 2, D and F).

Main causes of death in patients with alcoholic cirrhosis

During the 10 years after transplant, 122 patients with AC died, with similar death rates in both sexes (30.7% in men vs 28.1% in women) (Table 3). We found that 23% of deaths were related to liver disease, although most causes of death were unrelated to liver transplant (58.2%).

Liver graft failure was one of the main causes of death in male recipients (19.5%), followed by bacterial sepsis (16.8%) and multiple organ failure (15.9%), but not related to liver transplant. In female recipients, the main cause of death was not related to liver transplant (77.7%).

Table 3. Main Causes of Death in Patients With Alcoholic Cirrhosis and Liver Transplant Recorded at 10 Years Posttransplant

Cause of Death	Total Patients* (N = 122), No. (%)	Patients With AC	
		Men (n = 113), No. (%)	Women (n = 9), No. (%)
Liver related	28 (23.0)	27 (23.9)	1 (11.1)
Chronic rejection	2 (1.6)	2 (1.8)	
Graft failure	23 (19.0)	22 (19.5)	1 (11.1)
Primary dysfunction	2 (1.6)	2 (1.8)	
Viral relapse (HCV)	1 (0.8)	1 (0.9)	
Nonliver related	71 (58.2)	64 (56.6)	7 (77.7)
Cardiac arrest	6 (4.9)	4 (3.5)	2 (22.2)
Digestive bleeding	7 (5.7)	7 (6.2)	
Edema lung	2 (1.6)	2 (1.8)	
Metastasis	6 (4.9)	6 (5.3)	
Multiorgan failure	19 (15.7)	18 (15.9)	1(11.1)
Neoplasia pharynx	1 (0.8)	1 (0.9)	
Pancreatitis	1 (0.8)	1 (0.9)	
Pneumonia	3 (2.5)	3 (2.6)	
Sepsis	22 (18.0)	19 (16.8)	3 (33.3)
Shock	4 (3.3)	3 (2.6)	1 (11.1)
Unknown	15 (12.3)	14 (12.3)	1 (11.1)
Other	8 (6.5)	8 (7.1)	

Abbreviations: AC, alcoholic cirrhosis; HCV, hepatitis C virus
*Total individuals who died at 10 years posttransplant.

Discussion

In this retrospective study, we analyzed a cohort of AC patients who had liver transplant procedures. We investigated the biochemical and main pre- and posttransplant clinical complications in women and the short- and long-term posttransplant survival rates and main causes of death, comparing men versus women in those with and without viral infections.

There were more men with AC than women with AC, in accordance with trends shown in other AC cohort studies,[25-27] probably due to the higher number of heavy drinkers among men.[3] However, the prevalence of young female drinkers is growing,[28] and an increase in the consequent disorders is to be expected[29-31] because women are more susceptible to the hepatotoxic effect of alcohol[11,32,33] due to

differences in body structure and metabolism, meaning that women absorb more alcohol. The immediate effects of alcohol also occur more quickly and last longer in women. A study in the United Kingdom recently observed the tendency of women to lack any recorded notification of alcohol use,[34] which is a major impediment to taking appropriate measures to prevent AC and future liver transplant. However, alcohol intervention programs in young people, including women, are being developed due to the consequences of alcohol consumption during pregnancy. It is hoped that such measures will result in decreased alcohol-related liver disease in future populations.[17]

Regarding biochemical values in female AC patients, alkaline phosphatase values were lower than in male AC patients[4] and prothrombin activity values were slightly higher in women than in men, with statistically significant differences in both cases ($P < .001$); the latter results seemed to have no influence on Child-Pugh scores.

We did observe more pretransplant complications (ascites and encephalopathy) in female AC recipients than mentioned in other studies regarding male AC recipients, although the differences were not significant.[4]

Female AC recipients had a lower incidence of acute graft rejection than male AC recipients, as shown previously[4] (12.5% vs 26.6%), although this difference was not statistically significant ($P = .353$) and could be due to differences in population sizes. Prognostic indicators (Child-Pugh and MELD) were also not notably different between women and men. Our data did not identify significant differences in short- and long-term survival or death rates between women and men, and significant differences were only found when comparing nonviral versus viral patients at 1 year posttransplant. Nevertheless, the survival rates showed significant differences regarding type of viral infection.

Hepatitis C virus infection seemed to affect short-term survival in AC patients regardless of sex, although the rate was slightly increased in women infected with HCV in both the short- and long-term analyses versus men with HCV. This indicates a similarity in survival between male and female patients who underwent liver transplant in our population, although differences in metabolism in women make them more susceptible to long-term health problems due to the toxic effects of alcohol.[5,35-37]

Our data showed that the main causes of death (liver graft failure, multiorgan failure, and sepsis) were unrelated to liver diseases. Another study observed that death was mainly due to alcohol and cancer, especially in the upper aerodigestive tract, although cardiovascular, digestive, and respiratory diseases and violence/accidents were also causes.[10]

Conclusions

In our cohort of patients, AC was more common in men than in women,[4] with similar rates of concomitant viral infections. Women with AC had lower alkaline phosphatase and prothrombin activity levels and higher frequency of ascites and encephalopathy; however, incidence of acute rejection of liver implant was lower than in men with AC. Short- and long-term survival rates were similar in both sexes, although women had a slightly lower survival rate due to the presence of HCV. Graft failure, sepsis, and long-term multiorgan failure were the leading causes of death in our population.

In light of the few studies conducted on AC in women after liver transplant and the recent incorporation of women into the high alcohol consumption culture, as well as the accompanying social and clinical impacts, further research into female AC should be conducted. These studies should include the amount of alcohol in grams per week, age of first alcohol consumption, and alcoholic recidivism and complications before and after transplant to understand and improve long-term female patient survival and design new strategies to prevent, detect, and reduce AC frequency in women.

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