Outcome and Prognostic Factors of Liver Transplantation in Cryptogenic Liver Cirrhosis

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ABSTRACT

Background: Cryptogenic cirrhosis (CC) is defined as cirrhosis arising without an obvious etiology of chronic liver disease, making it a complex entity to describe and investigate. It is clear from prior epidemiologic and histologic studies that various conditions can lead to a state in which clinical and histologic diagnostic features of the original disease are not uniformly evident.

Objective: Studies on CC in post-liver transplantation (LT) clinical course are scarce. Hence, this study aimed to evaluate the clinical course of CC in LT subjects.

Methods: This prospective cohort study maintained a database with accrued information on all patients who underwent LT at Shiraz University of Medical Sciences, Abu Ali Sina organ transplant center, and was reviewed. All patients aged more than 18 years at the time of transplantation and with a presumptive pre-transplant diagnosis of CC were included in the study. All cases were followed prospectively for one year after LT. A total of 162 cases were entered into the study.

Results: During 1-year follow-up (mean of 308.4 ± 122.06 days), 28 (17.4%), 6 (3.7%), 5 (3.3%), and 35 (21.6%) subjects were rejected, their liver disease recurred, re-transplanted, and deceased, respectively. One year, the patient survival rate was 78.4%. The survival distributions for rejection were not statistically significantly different ($\chi 2$= 0.998, P= 0.318), but it was significant for corticosteroid dose ($\chi 2$= 40.446, P< 0.0001). Those who survived received lower doses of corticosteroids (P< 0.0001), had a higher proportion of receiving mycophenolic acid (P= 0.003), had lower serum levels of WBC (P= 0.006), and had a higher proportion of being positive for HBc Ab (P= 0.002). Subjects who developed rejection had lower serum levels of albumin (P= 0.001) and albumin/protein ratio (P= 0.026), a shorter diagnosis-LT interval (P= 0.028), a higher proportion in receiving MTP pulse (P= 0.019), and a higher proportion in receiving mycophenolic acid (P= 0.044). However, Cox regression multivariate analysis showed no independent variable predicting patients or graft survival.

Conclusion: The prevalence of rejection, recurrence, and survival during the first year of LT amongst CC recipients was near the in-line studies. In addition, owing to the presence of metabolic syndrome components in our cases, it would be plausible that a proportion of our cohort might have NAFLD and NASH. However, correlation with histopathologic and liver function biomarkers was not performed.

KEYWORDS: Cryptogenic cirrhosis; Liver transplantation; Metabolic syndrome; Survival; Liver cirrhosis

INTRODUCTION

Cryptogenic cirrhosis (CC) is defined as cirrhosis arising in the absence of an obvious etiology of chronic liver disease, which makes it a problematic entity to describe and investigate, given this broad definition and the fact that the estimates mainly include CC as an "others" category in diagnoses, accurate prevalence estimation is a challenge. Nevertheless, the prevalence of CC is estimated to be almost 10% by the transplant databases and 5-30% amongst cirrhotic patients. In addition, its prevalence is presumably decreasing as emerging liver diseases like non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are better described [1-4]. That is, the prevalence rate of CC has reduced to an estimated 5% with improvements in the treatment and early detection fields and the improvement of viral hepatitis testing [5].

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Although much of this data has been collected retrospectively and derived from single-center studies and therefore subject to diverse biases, this could reflect the subsequent referral for liver transplantation (LT) and clarify the outcome of cryptogenic cases compared to cases with a known etiology of their cirrhosis. The management of liver diseases is a matter of debate based on various pathologies and entities, such as infection, genetics, environmental factors, etc. [6-9]. Among the management methods is transplantation, which has achieved satisfactory results [10, 11]. Many researchers have stated that transplantation is necessary for cases of CC. The results of LT in cases with CC were also reported by various studies [12-14]. Contos *et al.* reported post-transplantation steatosis approached 100% by five years in patients with CC compared with 25% in a control group with primary biliary cirrhosis (PBC), primary sclerosing cholangitis, or alcohol-related liver disease [13].

The one-year trend of increased mortality in cases with NASH undergoing LT demonstrated that older age, high body mass index, diabetes, and hypertension in NASH cases were probably these reasons [15]. In contrast, in another study, CC cases were compared to cirrhosis due to alcohol or hepatitis C virus (HCV), demonstrating no differences in survival after LT [16]. The findings of cases with CC to that of those transplanted for liver cirrhosis with mixed aetiologies were compared by some studies. Survival after LT was detected to be comparable both in short and long-term follow-ups, but a control group was missing [17].

Therefore, data associated with survival after LT for CC are different. Hence, in this study, we aimed to evaluate the clinical course of patients afflicted with cryptogenic liver cirrhosis after LT and to determine the first-year patient and graft survivals, the early recurrence rate of CC, and its associated risk factors after LT in a significant referral transplant center.

MATERIALS AND METHODS

Study population

This prospective cohort reviewed a study-maintained database with accrued information on all patients who underwent LT at Abu Ali Sina Organ Transplant Center, the referral and most prominent center for organ transplantation in the Middle East, affiliated with Shiraz University of Medical Sciences. All patients aged more than 18 years at the time of transplantation and with a presumptive pre-transplant diagnosis of CC were included in the study. All cases were followed prospectively for one year after LT.

Using post-transplant follow-up charts, all needed data, including age at transplantation, gender, duration of LT, type of drugs, rate of rejections, rate of survival, cause of death, re-transplantation indication, virology tests (such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV), laboratory data at routine follow up periods, need for re-transplantation, grade of inflammation in explant pathology before and after LT, rate of metabolic syndrome before and after transplantation, and patient, and graft survivals were collected.

Ethical Considerations

Written informed consent was obtained from the patients in our study. The purpose of this research was completely explained to the patients, and they were assured that their information would be kept confidential by the researcher. The present study was approved by the Medical Ethics Committee of the Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.405).

Statistical Analysis

Data analysis was carried out using the statistical package for social sciences (SPSS) (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Qualitative and quantitative variables were described using frequency (percent) and mean (standard deviation). Differences among the patient groups in terms of survival and rejection were assessed by Fisher's exact tests

and independent t-test or its nonparametric alternative if indicated by the Kolmogorov-Smirnov test. Survival analysis regarding rejection and corticosteroids was conducted using the log-rank test and Kaplan-Meier curves. A P-value of less than 0.05 was considered significant.

RESULTS

Among a total of 200 patients, after excluding incomplete hospital records and information, a total of 162 subjects with a mean age of 53.48 ± 10.27 years were entered into the analysis. The mean diagnosis-transplantation interval was 1.91 ± 1.45 years. During 1-year follow-up (mean of 308.4 ± 122.06 days), 28 (17.4%), 6 (3.7%), 5 (3.3%), and 35 (21.6%) subjects were rejected, their liver disease recurred, re-transplanted, and deceased, respectively (Table 1). One year, the patient survival rate was 78.4%. Table 1 demonstrates the subjects' demographic and prognosis variables with LT due to CC.

Regarding the association of demographic, clinical, and laboratory variables with survival and rejection in subjects with LT due to CC, comparing survived subjects with deceased subjects, those who survived received the lower doses of corticosteroids (P < 0.001), had a higher proportion in receiving mycophenolic acid (P= 0.003), had lower serum levels of WBC (P= 0.006), and had a higher proportion in being positive for HBc Ab (P= 0.002) (Table 1). However, Cox regression multivariate analysis showed no independent variable predicting patients or graft survival.

Comparing LT rejection subjects with those without LT rejection, subjects who developed rejection had lower serum levels of albumin (P= 0.001), albumin to protein ratio (P= 0.026), shorter diagnosis-LT interval (P= 0.028), a higher proportion in receiving methyl prednisone (MTP) pulse therapy (P= 0.019). It should be noted that the rejection group was marginally different from the non-rejection group regarding the proportion of receiving mycophenolic acid (P= 0.044) (Table 1).

We aimed to evaluate the survival of subjects with LT due to CC based on rejection and corticosteroid dose. The survival analysis was performed using the Kaplan-Meier method. A log-rank test was run to determine if there were differences in the survival distribution between the rejection and rejection-free groups. The survival distributions for the two groups were not statistically significantly different ($\chi 2$: 0.998, P= 0.318). The survival curves are depicted in Fig. 1.

Furthermore, the survival curves of different corticosteroid doses were statistically significantly different ($\chi 2$: 40.446, P< 0.001); subjects who were required to receive MTP pulse therapy had lower survival during 1-year follow-up. On the other hand, no significant difference in survival was shown in terms of low doses (less than 7.5 mg per day) versus higher doses (more than 7.5 mg per day). The survival curves are depicted in Fig. 2.

DISCUSSION

In our study, the 1-year patient survival and graft rejections were 78.4% and 82.6%, respectively. Considering the previously published evidence, one can express that LT's peri-transplantation and long-term survival vary between studies and aetiologies. That is, while liver transplanted cirrhosis due to AIH, PBC [16-18], or HCV infection [16, 19] has a good 5- and 10-year patient survival (>70%), patients with CC treated with LT have lower survival rates. Regarding LT due to CC, Alamo et al. [20] reported a very high perioperative mortality rate (up to 20%), which accounted for the main reason for worse transplantation outcomes and a rejection rate of 25%. A study on the UNOS database for graft and patient survival according to the underlying disease found that CC had a worse outcome than NASH cirrhosis or other conditions after LT [19]. In Masior *et al.* [21] study, the 1-year patient and graft survivals were 85.2% and 83.3%, respectively. Moreover, Yalamanchili *et al.* [22] and Charlton *et al.* [2] reported that 1-year patient survival was 86% and 72%, respectively. In conclusion, our survival rate was similar to that of the in-line studies.

Table 1: Association between demographic, clinical, and laboratory variables and survival in subjects with liver transplantation due to cryptogenic cirrhosis during one-year evaluation.

Variables; frequency (%) or mean standard deviation (SD) [range]		Total; n= 162	Mortality			Rejection		
			Alive; n= 127	Deceased; n= 35	P*	Not-rejected; n= 133	Rejected; n= 28	P*
Gender	Male	113 (70.6)	91 (71.7)	22 (66.7)	0.668	92 (70.2)	21 (75)	0.819
	Female	47 (29.4%)	36 (28.3)	11 (33.4)		39 (29.8)	7 (25)	
Age, years		53.48±10.27 [18-74]	53.23 ± 10.45	54.37 ± 9.68	0.562	53.00 ± 10.53	55.85 ± 8.90	0.184
Body mass index		27.77±4.44 [17.5-40]	27.73 ± 3.93	27.95 ± 5.97	0.791	27.61 ± 3.64	28.49 ± 7.17	0.534
Diagnosis to liver transplant interval, years		1.91 ± 1.45 [0.08-7]	1.95 ± 1.5	1.79 ± 1.26	0.583	2.05 ± 1.51	1.38 ± 1.07	0.028
Diabetes		60 (37.3)	44 (34.6)	16 (47.1)	0.231	52 (39.4)	8 (28.6)	0.390
Hypercholesterolemia (>250 mg/dL)		17 (10.5)	14 (11)	3 (8.6)	1	15 (11.3)	2 (7.1)	0.739
Hypertriglyceridemia (>150 mg/dL)		3 (1.9)	1 (0.8)	2 (5.7)	0.118	1 (0.8)	2 (7.1)	0.078
Hepatitis B	surface antigen	8 (4.9)	8 (6.3)	0 (0%)	0.203	8 (6.0)	0 (0%)	0.353
	surface antibody	116 (71.6)	89 (70.1)	27 (77.1)	0.527	94 (70.7)	21 (75)	0.819
	core antibodies	24 (14.8)	24 (18.9)	0 (0)	0.002	21 (15.8)	3 (10.7)	0.770
Model for End-Stage Liver Disease (MELD) score		19.36 ± 3.58 [10-38]	19.29 ± 3.66	19.6 ± 3.29	0.655	19.26 ± 3.68	19.89	3.08
Atorvastatin		42 (26.9)	34 (27.6)	8 (24.2)	0.826	38 (29.5)	4 (15.4)	0.225
Everolimus		39 (24.1)	35 (27.6)	4 (11.4)	0.072	27 (20.3)	12 (42.9)	0.016
Cortico-steroid	>7.5mg	92 (64.3)	80 (67.2)	12 (50)		74 (60.7)	17 (85)	
	>7.5mg or increased dose	44 (30.8)	37 (31.1)	7 (29.2)	<0.001	43 (35.2)	1 (5)	0.019
	MTP pulse	7 (4.9)	2 (1.7)	5 (20.8)		5 (4.1)	2 (10)	
Tacrolimus		136 (84)	107 (84.3)	29 (82.9)	0.8	111 (83.5)	24 (85.7)	1.000
Mycophenolic acid		143 (89.4)	117 (93.6)	26 (74.3)	0.003	114 (87)	28 (100)	0.044
Cyclosporine		3 (1.9)	2 (1.6)	1 (2.9)	0.521	0 (0)	3 (10.7)	0.005
Sirolimus		3 (1.9)	3 (2.4)	0 (0)	1.000	3 (2.3)	0 (0)	1.000
Triple Therapy		2 (1.2)	2 (1.6)	0 (0)	1.000	1 (0.8)	1 (3.6)	0.318
Cellcept		143 (89.4)	117 (93.6)	26 (74.3)	0.003	114 (87.0)	28 (100)	0.044
White blood cell count		6.28±3.27 [1.5-25.6]	5.91 ± 2.67	7.63 ± 4.71	0.006	6.29 ± 3.35	6.33 ± 2.98	0.949
Protein		5.66±0.97 [3.2-8.2]	5.69 ± 0.99	5.54 ± 0.91	0.45	5.68 ± 0.96	5.54 ± 1.05	0.510
Albumin		2.95±0.56 [1.8-4.9]	2.97 ± 0.56	2.91 ± 0.6	0.599	3.02 ± 0.57	2.62 ± 0.40	0.001
Albumin/Protein		0.53±0.11 [0.29-0.83]	0.54 ± 0.11	0.53 ± 0.12	0.894	0.54 ± 0.11	0.49 ± 0.10	0.027
Antinuclear antibody		4 (2.5)	3 (2.4)	1 (2.9)	1.000	4 (3)	0 (0)	1.000
Anti-Smooth Muscle Antibody		1 (0.6)	1 (0.8)	0 (0)	1.000	1 (0.8)	0 (0)	1.000
Recurrence		6 (3.7)	4 (3.1)	2 (5.7)	0.611	4 (3.0)	2 (7.1)	0.280

* Fisher's exact/Chi-square test or independent t-test; bold values indicate significant association at a 0.05 level

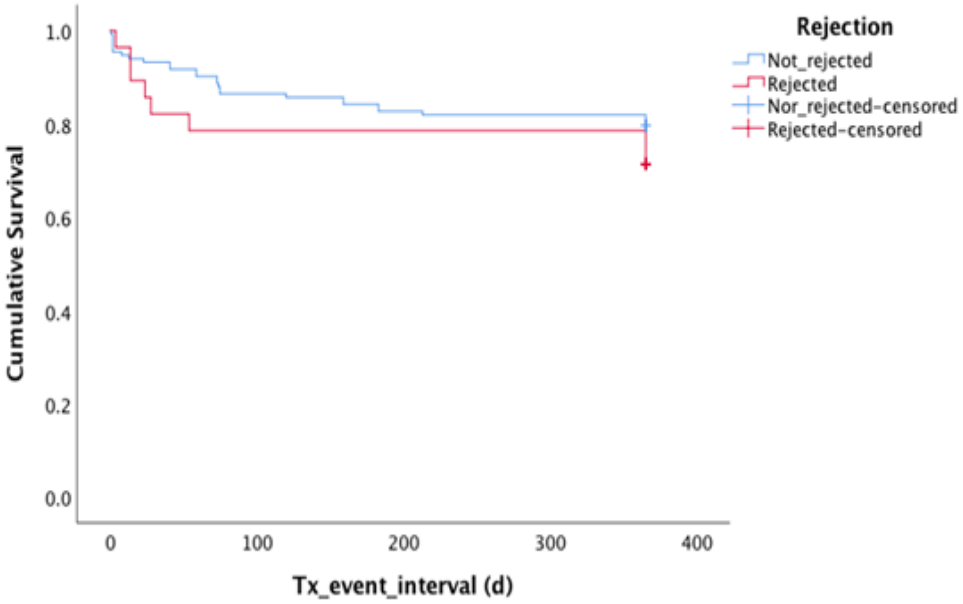

Figure 1: The survival curves of liver transplantation by the Kaplan-Meier method grouped by rejection.

A great heterogeneity exists regarding laboratory parameters predicting post-LT survival or rejection. For instance, in Masior *et al.* [21] study, patient and graft survival was significantly correlated with aspartate aminotransferase, alanine aminotransferase, bilirubin, and international normalized ratio levels. Regarding laboratory data, although we did not evaluate liver function biomarkers, we found that patient and graft survival was directly linked to HBV antibody positivity and lower levels of WBC and higher levels of albumin and albumin/protein ratio, respectively, in univariate analysis. Lower levels of WBC may indirectly imply more aggressive immunosuppressive regimens, including potent antimetabolites such as mycophenolate mofetil.

In our study, the mean age of LT recipients, with male predominance, was 53.48 ± 10.27 years., which was similar to other studies [21-23]. Yalamanchili *et al.* [22] reported that the only survival-predicting parameter was a younger age at the time of transplantation. However, gender distribution varies between studies. Rinaldi *et al.* [24] showed that the independent predictors of death in LT recipients were age and Child-Pugh class at diagnosis.

In this study, survival was correlated with MTP pulse therapy, mycophenolic acid, levels of WBC, and HBc Ab results. Furthermore, rejection was correlated with albumin and albumin to protein ratio, diagnosis to LT interval, MTP pulse, and mycophenolic acid.

In the post-LT period, the potential etiology of liver disease can be speculated based on transplantation course, clinical and biochemical data, and histopathological assessment, as previous reports have shown that it could lead to the correct diagnosis of up to 70% [25, 26]. Initially, Caldwell et al. [27] suggested that NASH is the primary cause of CC as these groups share many characteristics, like older age and a higher prevalence of obesity and diabetes compared to patients with other forms of cirrhosis. Recent studies have confirmed NAFLD and NASH as the underlying liver disease in a vast majority of subjects with CC. For example, in Marmur *et al.* [28] study, 44% of the cryptogenic patients had NAFLD in a previous liver biopsy or clinical features of the metabolic syndrome. These conditions are linked to the metabolic syndrome components, mainly obesity and diabetes mellitus type 2 [15, 29]. In addition, patients' characteristics in these conditions are similar, except for older

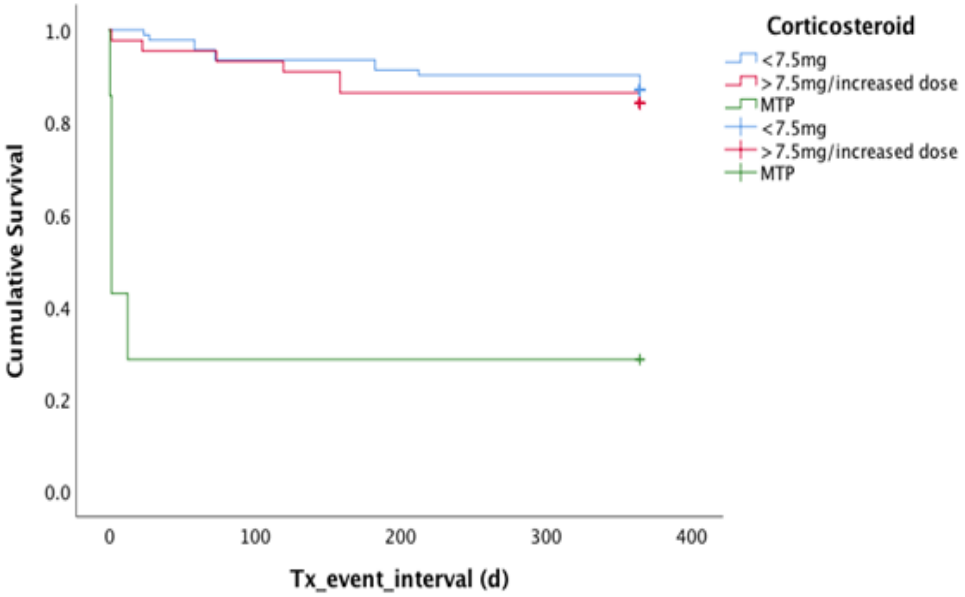

Figure 2: The survival curves of liver transplant patients by the Kaplan-Meier method grouped by corticosteroid dose.

age and a higher BMI in NASH patients. Also, post-LT lipid profile and incidence of hypertension, diabetes, and hyperlipidemia are similar, and fatty liver is common after LT for CC or NASH [22]. Studies have also stated that post-LT survival is similar in NASH and CC [23]. Based on these reports, in our study, the mean BMI was 27.77 ± 4.44, falling into the overweight category; 37% of patients had diabetes, 12.4% of patients had either triglyceride > 200 or cholesterol > 250, and approximately a quarter of patients were on statins. Our figures were relatively higher than in-line retrospective cohorts, i.e., Masior *et al.* [21], and near to that of NASH cohorts, i.e., Lukas *et al.* [23] (mean BMI of 27.72 ± 1.232, DM prevalence of 33.33%). By and large, NAFLD might likely be one of the causes of cryptogenic liver cirrhosis in our study. It should be noticed that the current project was limited as it lacked the liver function biomarkers since the immunological background of liver damage was most frequently suggested to determine the causes of cryptogenic liver cirrhosis [30, 31], as well as a full histopathologic description of samples from all subjects. Moreover, our data regarding donor graft characteristics were limited as patient survival appears to be affected by donor graft characteristics [20].

In our study, the occurrence of rejection was not correlated with survival. One of the explanations might be that with current immunosuppressive regimens, almost all episodes of acute rejections can be resolved successfully, even acute steroid-resistant rejections, through administering anti-thymocyte globulin [32, 33].

Another finding of our study was the deterioration correlation of corticosteroid pulse therapy with survival and allograft rejection. The primary concerns with high doses of corticosteroids are their adverse side effects, notably infections, metabolic derangements, and significant short and long-term morbidity [33, 34]. In this context, we found that higher levels of serum WBC were associated with mortality, which may reflect the increased frequency of infections. [35] Higher doses of steroids during the first months of LT might be related to early and probably transient steatosis [36]. In addition, in LT, due to HCV infection, corticosteroids are preferred to be avoided since the use of steroids was associated with enhanced viral replication and, thus, more aggressive viral recurrence; for example, in a study, prednisone dose at month six was significantly associated with disease-free survival of the liver

graft [37]. Noteworthy, regarding graft rejection, this correlation might be administrated in response to the graft rejection rather than in corresponding to the cause of the rejection, as the risk of organ rejection may increase following early corticosteroid dose reduction or withdrawal.

As we mentioned, higher levels of serum WBC were significantly associated with mortality in CC after LT, which may reflect the increased occurrence of infections. In a study from the MAYO clinic, the authors explained that a considerable proportion of mortalities in CC could be attributed to a high rate of fatal infections despite immunosuppression, similar to other causes of LT [2]. Also, many studies have demonstrated increased concurrent infection due to several prevalent pathogens in our study area. [38-44] Authors further clarified that as the pathogenesis of CC has, by definition, yet to be determined, the predominant etiology that attenuates immunological function and thereby predisposes cryptogenic recipients to severe infections is yet to be known [2, 45, 46].

Another finding of our study was that mycophenolic acid was significantly correlated with a higher rejection rate but lower mortality, but these associations were not maintained after multivariate analysis. Studies on these correlations are lacking in the field of LT due to CC. It has been reported that when mycophenolic acid is included in immunosuppression regimens of renal transplantation subjects, it might be accompanied by a protective effect against post-transplant de novo malignancies [47]. Still, this protective role has not been reported in post-LT recurrence of hepatic cell carcinomas [48]. Moreover, Wiesner *et al.* reported that mycophenolic acid was an important factor in improved outcomes in patients on tacrolimus-based immunosuppression after adjusting for confounding variables in a large sample of 11670 patients in the SRTR database [49]. However, using mycophenolic acid monotherapy in LT has shown to be accompanied by a high incidence of acute cell-mediated rejection, severe chronic rejection, and severe steroid-resistant rejection [50, 51]. Also, a recently published meta-analysis showed that mycophenolic acid monotherapy significantly increased the acute rejection rate (risk ratio = 4.50, P = 0.027). Although the target population of these studies was not identical to ours, the results were in line with the present study. It should be noted that because mycophenolic acid is usually used in combination with other immunosuppressant agents, its efficacy is expected to be modulated by different agents. Further studies are needed to obtain the role of medications on outlook amongst LT recipients with cryptogenic liver cirrhosis.

In our study, only 6 (3.7%) subjects experienced liver disease recurrence during the first year of LT. In a survey by Atrache *et al.* [52], liver disease recurred in a higher proportion of subjects (20 out of 83), though their samples were mixed with NASH or CC, and there was a higher presence of metabolic syndrome. Charlton *et al.* [2] reported no recurrence of CC in 39 LT. Alamo *et al.* [20] reported the prevalence of recurrence as 4%. The low rate of recurrent disease in cryptogenic recipients might be suggestive of metabolic, hepatotoxin, or autoimmune-mediated aetiologies of CC in the majority of subjects because all of these aetiologies have low rates of histological recurrence in the allografted LT [28].

Marmur *et al.* [28] showed that CC patients had significantly higher frequencies of recently developed weight loss, partially explained by the fact that CC patients have a more advanced liver disease at the time of referral for LT evaluation. Additionally, since one of the indicators of advanced liver failure is hypoalbuminemia, theoretically, the presence of hypoalbuminemia in CC would be plausible. Moreover, malnutrition is an independent risk factor for poor survival after LT [53]. However, in our study, univariate analysis showed that lower albumin or albumin-to-protein ratio levels were significantly correlated with rejection but not survival. Conversely, higher BMIs are associated with malnutrition. Further studies are warranted to clarify these findings.

Finally, we found that survived LT recipients

had a higher proportion of being positive for HBc Ab after one year. Although in a systematic review by Cholongitas *et al.* [54], liver grafts from anti-HBc positive donors can be safely used, preferentially in HBsAg-positive or anti-HBc/anti-HBs positive recipients without the need for prophylaxis with lamivudine, this finding needs to be further evaluated.

Among the limitations of our study are the limited and single center population and the lack of histopathological evaluation. Also, the applied policies due to the novel coronavirus disease of 2019 limited patient management, evaluations, and follow-ups. [55-59] Further multicentral studies are justified to achieve a more precise conclusion and findings.

In conclusion, the prevalence of rejection, recurrence, and survival during the first year of LT amongst CC recipients was near the inline studies. In addition, similar to the previous studies, owing to the presence of metabolic syndrome components in our cases, it would be plausible that a proportion of our cohort might have NAFLD and NASH. However, correlation with histopathologic and liver function biomarkers was not performed. Moreover, increased WBC count and increased infection prevalence were linked to mortality. Further studies with longer follow-ups and more comprehensive included variables are warranted.

CONFLICT OF INTEREST:

None declared.

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