JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.24633
J Inonu Liver Transpl Inst 2024;2(1):11–15

Original Research

Liver Transplantation for Cryptogenic Cirrhosis: Where we are

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Abstract

Objectives: This study aimed to compare clinical and immunological features between patients undergoing liver transplantation with cryptogenic cirrhosis and those with determined etiologies.

Methods: Patients who underwent liver transplantation at our institute between March 2019 and March 2020 were retrospectively analyzed. Data including demographics, laboratory results, and post-transplant outcomes were collected from a prospectively maintained database. Immunoglobulin levels, autoantibodies, and pathological findings were evaluated.

Results: Of 201 patients, 24.4% had cryptogenic cirrhosis. These patients were older (mean age 54.8 years) and had higher BMI (mean 27.3) compared to those with determined etiologies. Immunological biomarkers did not significantly differ between groups. Autoimmune hepatitis was the most common diagnosis upon pathological examination of cryptogenic cases.

Conclusion: Immunological biomarkers did not differentiate cryptogenic cirrhosis from other etiologies in liver transplant patients. Higher BMI was associated with cryptogenic cirrhosis. Pathological examination frequently revealed autoimmune hepatitis in cryptogenic cases.

Keywords: Autoimmune hepatitis, cryptogenic cirrhosis, liver transplantation

Please cite this article as "Baskiran A, Kement M, Ogut MZ, Baskiran DY, Ince V, Yilmaz S. Liver Transplantation for Cryptogenic Cirrhosis: Where we are. J Inonu Liver Transpl Inst 2024;2(1):11–15".

Liver transplantation (LT) represents a critical therapeutic intervention for individuals suffering from end-stage liver diseases, offering a chance of survival and improved quality of life. Among the diverse etiologies leading to irreversible liver damage, cryptogenic cirrhosis (CryC) has long been recognized as a significant indication for LT. CryC delineates a perplexing scenario where liver cirrhosis manifests without a clear underlying cause, despite exhaustive diagnostic endeavors. This diagnostic ambiguity poses challenges in both understanding the disease's pathophysiology and devising optimal treatment strategies. However, recent advancements in diagnostic modalities have heralded a notable decline in CryC prevalence, concurrent with the burgeoning recognition of nonalcoholic steatohepatitis (NASH) as a major etiological factor necessitating LT. This paradigmatic shift in disease landscape underscores the need for a comprehensive reevaluation of the clinical and immunological characteristics exhibited by LT recipients, particularly comparing those with CryC to individuals with identifiable etiologies.[1]

While CryC has historically accounted for a substantial proportion of LT cases, its declining prevalence raises intriguing questions regarding its underlying pathogenesis, clinical course, and outcomes post-transplantation. Under-

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Submitted Date: 04.04.2024 **Revised Date:** 29.05.2024 **Accepted Date:** 29.05.2024 **Available Online Date:** 13.06.2024

standing these nuances is imperative not only for enhancing diagnostic accuracy but also for refining therapeutic interventions tailored to the specific needs of CryC patients. Moreover, the emergence of NASH as a prevalent indication for LT underscores the dynamic nature of liver disease epidemiology and necessitates a recalibration of clinical approaches to optimize patient care.[2-5]

Against this backdrop, this study endeavors to delve into the comparative analysis of clinical and immunological features exhibited by LT recipients with CryC versus those with determined etiologies. By scrutinizing demographic characteristics, comorbidities, liver function tests, and immunological markers, we aim to elucidate the distinct phenotypic profiles of these patient cohorts. Such insights hold immense potential for guiding clinical decision-making, prognostication, and therapeutic interventions in the context of LT for CryC. Moreover, a deeper understanding of the immunological underpinnings of CryC may pave the way for the development of targeted immunomodulatory therapies aimed at ameliorating disease progression and enhancing transplant outcomes.[2-5]

Through this comprehensive investigation, we aspire to contribute to the burgeoning body of knowledge surrounding CryC and its implications for LT, thereby advancing the frontiers of liver disease management and transplantation medicine. Ultimately, our overarching goal is to improve patient outcomes and enhance the efficacy of LT in addressing the diverse spectrum of liver pathologies encountered in clinical practice.

Methods

Study Population

All patients who underwent liver transplantation (LT) at our Liver transplantation Institute between March 2019 and March 2020 were considered for inclusion in this retrospective study. Patients were retrospectively identified from a prospectively maintained database. The diagnosis of cryptogenic cirrhosis (CryC) was established based on the exclusion of all other potential causes of liver disease according to standard criteria.

Exclusion Criteria

Patients were excluded from the study if they were under the age of 18 years or if they were lost to follow-up during the study period.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Inonu University, and informed consent was obtained from all participants.no 2021/2571.

Data Collection

Clinical, demographic, and laboratory data were collected from patient records. This included age, gender, body mass index (BMI), graft source (living donor transplants), Model for End-Stage Liver Disease (MELD) scores, liver function tests, and immunological markers such as immunoglobulin levels (IgG1, IgG2, IgG3, Anti-gliadin IgA) and levels of autoantibodies (ANA, ASMA, anti-dsDNA). Additionally, post-transplant pathological findings and early survival data were investigated.

Statistical Analysis

Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Student's t-test was used to compare continuous variables, while Chi-square or Fisher's exact test was employed for dichotomous variables. All statistical analyses were conducted using SPSS version 20 software. p-values < 0.05 were considered statistically significant (IBM Corp. 1989, 2013. U.S. Government Users Restricted Rights - Use, duplication or disclosure restricted by GSA ADP Schedule Contract with IBM Corp.)

Results

During the study period, a total of 341 patients underwent LT. Among them, 140 patients were excluded from the study due to predefined exclusion criteria. Therefore, the final study cohort consisted of 201 patients, among whom 67% (n=132) were male, and the mean age was 49.9±13 years.

Preoperatively, 63 patients (31.3%) were initially diagnosed with cryptogenic cirrhosis (CryC). However, pathological examination revealed the etiology of cirrhosis in 14 of these cases. Consequently, a total of 49 patients (24.4%) were classified into the cryptogenic group (Table 1). The distribution of underlying diagnoses among the 201 patients who underwent LT is presented in Table 2.

Table 1. Pathological findings of the patients who were initially diagnosed as CryC

Findings	n (%)
No specific feature	42 (66.7)
HCC(incidental)	7 (11.1)
Autoimmune Hepatitis	5 (7.9)
NASH	3 (4.8)
Veno-occlusive Disease	3 (4.8)
Wilson Disease	2 (3.2)
Viral Hepatitis	1 (1.6)

CryC: Cryptogenic Cirrhosis; HCC: Hepatocelluler Carcinoma; NASH: Non Alcholic Steato Hepatitis.

Table 2. The frequencies of underlying diagnoses in 201 patients underwent LT.

Diagnosis	n (%)
Cryptogenic Cirrhosis	49 (24.4)
HBV	38 (18.9)
HCC	27 (13.4)
Autoimmune Hepatitis	17 (8.5)
Veno-occlusive disease	13 (6.5)
Alcoholic Cirrhosis	11 (5.5)
Wilson Disease	8 (4)
HBV+HDV	7 (3.5)
NASH	7 (3.5)
HCV	5 (2.5)
Primary Biliary Cirrhosis	5 (2.5)
Primary Sclerosing Cholangitis	5 (2.5)
Cystic Liver Disease (Ech. alveolaris)	4 (2)
Hemochromatosis	2 (1)
Epitel Hemanjioendotelioma	1 (0.5)
Toxic Hepatitis	1 (0.5)

CryC: Cryptogenic Cirrhosis; HCC: Hepatocelluler Carcinoma; NASH: Non-Alcoholic Steato Hepatitis; HBV: Hepatitis B; HCV Hepatitis C; HDV: Hepatitis D.

Comparison of demographic, clinical, and biochemical characteristics between the groups is summarized in Table 3. Patients with cryptogenic cirrhosis were found to be significantly older than those with other etiologies (54.8±10.2 vs. 48.3±13.5, p=0.002) and had a higher body mass index (BMI) (27.3±4.4 vs. 25.7±4.7, p=0.045). However, other parameters such as gender distribution, liver function tests, and immunological markers were similar between the groups.

Discussion

Cryptogenic cirrhosis (CryC) remains a significant indication for liver transplantation (LT) worldwide, albeit with varying prevalence rates across different regions. Our study adds to the growing body of literature on CryC by providing insights into its clinical, pathological, and prognostic characteristics within our patient cohort. Despite efforts to ascertain the etiology of liver cirrhosis, a considerable proportion of patients are diagnosed with CryC, highlighting the complexity of liver disease diagnosis and management.

The prevalence of CryC among LT recipients in our study cohort was notably higher (24.4%) than previously reported rates in Western countries (4–10%). This discrepancy may be attributed to several factors, including referral patterns, diagnostic practices, and regional variations in the epidemiology of liver diseases. Notably, our center serves as a tertiary referral center for complicated liver diseases in our region, receiving referrals from both within the country and neighboring countries. Consequently, we often encounter patients with advanced decompensated liver

Table 3. Demographic. clinical and biochemical characteristics of the groups

Parameters	Patients with Cryptogenic Cirrhosis (n=49)	Patients with Determined Etiologies (n=152)	p
Age	54.83±10.18	48.28±13.47	0.002
Gender (M/F)	30/19	102/50	0.451
BMI (kg/m2)	27.25±4.38	25.70±4.70	0.045
MELDNa	14.54±5.39	15.67±13.74	0.573
Early Mortality (%)	7 (14.29)	17 (11.18)	0.560
IgG1	13.79±4.40	14.90±7.04	0.319
IgG2	6.24±2.87	5.97±11.58	0.872
IgG3	0.98±0.55	1.14±1.68	0.534
IgG4	1.49±1.48	1.24±1.93	0.411
AntiGliadin IGA	19.51±17.49	22.41±36.15	0.693
AMA(Negative/Positive) (1/100 titer)	2/21	67/8	0.655
ASMA(Negative/Positive) (1/100 titer)	1/10	7/49	0.521
ANA (1/100 titer)	0.75±1.36	0.47±0.29	0.307
dsDNA			
<10	38 (77.55%)	131 (86.18%)	0.350
10-15	4 (8.16%)	7 (4.61%)	
>15	7 (14.28%)	14 (9.21%)	

IgG: Immunglobulin G; ANA: Anti-nükleer antikorlar; ASMA :Anti Smooth Muscle Antikor; AMA: Anti mitokondriyal Antikor; BMI: Body mass Index; MELD: The Model for End-Stage Liver Disease.

disease and high Model for End-Stage Liver Disease (MELD) scores, contributing to the higher prevalence of CryC in our cohort.

Comparisons with other studies from different geographic regions reveal substantial variability in CryC prevalence and clinical characteristics. For instance, Siriwardana et al. reported CryC as the leading indication for LT (58%) in Sri Lanka, with a predominantly male population and a mean age of 51 years. This highlights the diverse epidemiological patterns of liver diseases worldwide, influenced by factors such as environmental exposures, genetic predispositions, and healthcare infrastructure.[6]

In our study, despite extensive pre-transplant workup including viral profiles, immunoglobulin levels, autoantibody profiles, and specific markers for liver diseases, a definitive etiology could not be established in a significant proportion of CryC patients. This underscores the diagnostic challenge posed by CryC and the limitations of current diagnostic modalities in elucidating its underlying cause. Consistent with previous studies, we observed that a subset of patients initially diagnosed with CryC had identifiable etiologies upon pathological examination post-transplantation.[7] Ayata et al. similarly found that detailed clinicopathological correlation revealed specific diagnoses in the majority of cases initially labeled as CryC, including nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, and alcohol-related liver disease.[8]

Interestingly, despite the higher mean BMI observed in CryC patients in our cohort, histological examination revealed features of NASH in only a minority of cases. This suggests that CryC may not always be synonymous with NASH and underscores the importance of histopathological evaluation in establishing the etiology of liver cirrhosis.

Moreover, the presence of incidental hepatocellular carcinoma (HCC) in a subset of CryC patients raises concerns regarding surveillance and management strategies in this population. Thuluvath et al. demonstrated a higher prevalence of HCC in NASH cirrhosis compared to CryC in a large cohort analysis, highlighting the need for vigilant surveillance protocols in patients with CryC, especially considering the rising incidence of NASH-related HCC.[9]

The perioperative outcomes of CryC patients undergoing LT have been a subject of debate, with some studies reporting higher mortality rates compared to patients with other etiologies. Alamo et al. and Masior et al. reported higher perioperative mortality rates in CryC patients, attributing this to the advanced stage of liver disease and associated comorbidities.[10,11] However, in our study, we did not observe a significant difference in perioperative mortality between CryC and other etiologies. This suggests that meticulous patient selection, perioperative management, and advances in surgical techniques may have contributed to improved outcomes in CryC patients undergoing LT at our center.

Nevertheless, several limitations of our study warrant consideration. Regional differences in liver disease epidemiology and referral patterns may limit the generalizability of our findings to other populations. Additionally, the retrospective nature of the study and the relatively small sample size may have introduced selection bias and limited statistical power. Furthermore, the study was conducted during the COVID-19 pandemic, which may have impacted transplant practices and outcomes.

Conclusion

In conclusion, our study provides valuable insights into the clinical characteristics, diagnostic challenges, and outcomes of CryC patients undergoing LT. Despite regional variations in CryC prevalence and etiology, histopathological evaluation remains crucial in elucidating the underlying cause of liver cirrhosis in these patients. Future research endeavors should focus on refining diagnostic algorithms, exploring novel biomarkers, and elucidating the pathophysiological mechanisms underlying CryC to improve patient outcomes and optimize transplant allocation strategies.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of Inonu University, and informed consent was obtained from all participants.no 2021/2571.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.B., M.K., M.Z.O., S.Y.; Design – A.B., M.K., M.Z.O., S.Y., Supervision – A.B., M.K., M.Z.O., V.I., S.Y.,; Materials A.B., M.K., M.Z.O., D.Y.B.; V.I., Data collection &/or processing – A.B., M.K., M.Z.O., D.Y.B.; V.I., Analysis and/or interpretation – A.B., M.K., M.Z.O., V.I., S.Y; Literature search – A.B., M.K., M.Z.O., D.Y.B.; V.I., Writing – A.B., M.K., M.Z.O., Critical review – A.B., M.K., M.Z.O., D.Y.B.; V.I., S.Y.

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