EJMA

DOI: 10.14744/ejma.267167
EJMA 2025;5(4):167–173

Research Article

Etiological Investigation of Cryptogenic Cirrhosis Patients Undergoing Liver Transplantation

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Abstract

Objectives: This study aimed to investigate hidden etiologies in patients with cryptogenic cirrhosis by evaluating post-liver transplantation explant pathology findings.

Methods: Between 2010 and 2018, 324 patients with cryptogenic cirrhosis from a total cohort of 2,400 were analyzed retrospectively. Pretransplant clinical scores, including FIB-4, APRI, Child, and MELD scores, and posttransplant pathology results were recorded. Patients diagnosed with NASH were further evaluated for body mass index (BMI) and diabetes mellitus (DM). Ascites and hepatocellular carcinoma (HCC) conversion rates were also analyzed.

Results: The mean age of the patients was 47.5±14.6 years. Posttransplant pathology identified specific etiologies in 58.3% of cases: NASH/NAFLD (24.7%), HCC (7.7%), veno-occlusive disease (6.8%), biliary pathology (5.2%), autoimmune hepatitis (4.3%), and Wilson's disease (3%). Etiology remained undetermined in 135 patients (41.7%). Ascites was detected in 71.5% (n=232) of patients, and HCC was found in 17.3% (n=57). Among patients with NASH, 66.15% had DM/insulin resistance, and 72.5% had a BMI >25. The pretransplant mean Child and MELD scores were 12.1±1.4 and 28.5±5.3, respectively.

Conclusion: Explant pathology reveals that various diseases, particularly NASH/NAFLD, often underlie cryptogenic cirrhosis. NASH should be investigated thoroughly in cases of metabolic syndrome. Additionally, occult HBV and veno-occlusive disease should be considered in unexplained cirrhosis, even when standard serology and imaging are negative.

Keywords: Cryptogenic cirrhosis, liver transplantation, non-alcoholic fatty liver disease

Cite This Article: *Kara H, Yılmaz Ürün Y, Yıldırım O. Etiological Investigation of Cryptogenic Cirrhosis Patients Undergoing Liver Transplantation. EJMA 2025;5(4):167–173.*

Liver cirrhosis is a chronic liver disease characterized by progressive fibrosis and regenerative nodules, which can develop due to various causes, such as viral hepatitis, chronic alcohol use, autoimmune diseases, vascular causes, and metabolic and toxic conditions.[1] As the disease progresses, serious complications, such as ascites, portal hypertension, esophageal varices, hepatorenal syndrome, and hepatocellular carcinoma (HCC), may develop.[2]

In developed countries, the most common causes of cirrhosis are alcohol and non-alcoholic fatty liver disease (NAFLD), whereas in developing countries, viral hepatitis plays a more frequent role in the etiology. However, cases in which the etiology cannot be determined despite detailed clinical, laboratory, and imaging evaluations are referred to as "cryptogenic cirrhosis."[3] While up to 30% of cirrhosis cases were classified as cryptogenic in the past, this rate has decreased to around 10% today due to advancements in diagnostic methods.[4]

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Submitted Date: May 15, 2026 **Accepted Date:** June 20, 2026

Recent studies suggest that in a significant proportion of patients diagnosed with cryptogenic cirrhosis, the underlying cause may be silently progressing non-alcoholic steatohepatitis (NASH), and that latent viral infections or autoimmune hepatitis may also play a role in the etiology.[5] In particular, obesity, type 2 diabetes mellitus, insulin resistance, hyperlipidemia, and the presence of metabolic syndrome are considered significant risk factors for the development of cryptogenic cirrhosis. In addition, occult HBV infection that cannot be detected serologically, vascular diseases, autoimmune hepatitis, and rare metabolic disorders may also play a role in the etiology of cryptogenic cirrhosis.[6]

Liver tissue obtained from explants following liver transplantation offers a significant opportunity to identify etiological causes that could not be detected before transplantation. In particular, the ability to reevaluate histopathological findings that are lost in advanced-stage cirrhosis through detailed posttransplant pathological examination may contribute to determining the true etiology in patients classified as having cryptogenic cirrhosis.

This study aimed to evaluate the explant pathology results of patients with cryptogenic cirrhosis who underwent liver transplantation and to investigate underlying occult etiologies. Furthermore, degrees of fibrosis were assessed using pretransplant APRI and FIB-4 scores, and MELD and Child-Pugh scores were calculated. Metabolic risk factors, such as obesity, diabetes mellitus, and insulin resistance, were examined in patients diagnosed with NASH. Additionally, the presence of HCC, the development of ascites, and the distribution of blood groups were evaluated to reveal the clinical characteristics of cryptogenic cirrhosis in more detail.

Methods

Study Design and Patient Selection

In our study, the medical records of patients who presented to the Hepatology Outpatient Clinic at İnönü University Turgut Özal Medical Center between 2010 and 2018 and underwent liver transplantation were retrospectively reviewed. Despite comprehensive pretransplant clinical, biochemical, serological, microbiological, radiological (ultrasonography, portal vein Doppler, elastography, etc.), and histopathological (liver biopsy) examinations, the etiology remained unclear; a total of 324 patients diagnosed with "cryptogenic cirrhosis" who underwent liver transplantation were included in the study.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the study were determined as follows:

Inclusion Criteria: (1) Being 18 years of age or older, (2) having received a diagnosis of "cryptogenic cirrhosis" despite detailed pretransplant investigations that failed to identify the etiology, and (3) having undergone liver transplantation at İnönü University Turgut Özal Medical Center and having access to posttransplant explant liver pathology results.

Exclusion Criteria: (1) Patients whose cirrhosis etiology was determined before transplantation, including viral hepatitis such as HBV, HCV, HDV, HAV, or HEV; autoimmune or biliary pathologies confirmed by ASMA, LKM-1, ANA, or AMA positivity; ischemic hepatitis; known history of alcoholism; Wilson's disease; hemochromatosis; or drug-induced toxic hepatitis, etc.; (2) patients who had not undergone liver transplantation or for whom explant pathology data were unavailable; and (3) patients with missing pretransplant laboratory or clinical data required for the scoring systems to be used in the study.

Data Collection and Analysis

The post-liver-transplant explant liver pathology results of the 324 patients included in the study were retrospectively analyzed to determine the actual etiologies. Using the patients' pretransplant laboratory data, APRI and FIB-4 scores were calculated to predict the degree of liver fibrosis; Child and MELD scores were calculated to determine the severity of liver failure and the urgency of transplantation.

For patients whose explant pathology was consistent with non-alcoholic steatohepatitis (NASH), body mass index (BMI) and the presence of diabetes mellitus (DM) were examined to calculate NAFLD scores. Additionally, the radiological, endoscopic, and pathological data of all patients were reviewed to document the presence of major complications of cirrhosis, including hepatocellular carcinoma (HCC), ascites, and esophageal varices. Pretransplant tumor marker levels, primarily alpha-fetoprotein (AFP), were also included in the analysis.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean±standard deviation for continuous variables and as number (n) and percentage (%) for categorical variables. Only descriptive statistics were used in the study.

AI-Assisted Technology Statement: In the production of this work, the authors utilized Gemini 3 Flash (Google, May 2026 version) as an AI-assisted tool. The technology was employed to restructure the manuscript into a blinded format by separating the title page and main text, ensure that the

statistical reporting met the journal's specific requirements, such as adding location data for the software, and improve English language flow. The prompts used primarily focused on "reformatting existing clinical data and text according to specific submission guidelines." All AI-generated structural and linguistic suggestions were critically appraised by the authors to ensure scientific accuracy and integrity.

Ethical Approval

Approval for this study was obtained from the İnönü University Non-Interventional Clinical Research Ethics Committee (Date: 30.07.2019 and Decision/Protocol Number: 2019/310), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

The study included a total of 324 patients (126 female [38.9%] and 198 male [61.1%]) who were followed up with a preliminary diagnosis of cryptogenic cirrhosis and underwent liver transplantation. The mean age of the patients was 47.5±14.6 years. When pretransplant clinical scores were examined, the mean Child score was 12.1±1.4, and the mean MELD score was 28.5±5.3. Based on imaging methods, ascites was observed in 71.5% of patients (n=232), while hepatocellular carcinoma (HCC) was detected in 17.3% of patients (n=57) based on clinical, radiological, and pathological data (Table 1).

In the etiological analysis based on posttransplant explanted liver pathology results, the etiology of 135 patients (41.7%) could not be determined despite all investigations and was classified as "cryptogenic cirrhosis." The most common etiological factor identified was hepatic steatosis (NASH/NAFLD) in 80 patients (24.7%). The etiological distribution of the remaining patients was as follows: primary HCC (n=25, 7.7%), veno-occlusive disease (n=22, 6.8%), biliary pathologies (PSC, PBC; n=17, 5.2%), autoimmune hepatitis (n=14, 4.3%), and Wilson's disease (n=10, 3%). In the remaining 21 patients (6.4%), rarer causes, such as HBV, HCV, hemochromatosis, ischemic hepatitis, hemophagocytic syndrome, glycogen storage disease, and amyloidosis, were identified (Table 2).

In our study, subgroup analysis of 80 patients with findings consistent with NASH revealed that 66.15% of these patients (n=53) had diabetes mellitus (DM) or insulin resistance. When the body mass index (BMI) of the NASH group was evaluated, 40% (n=32) were found to be obese (BMI >30), while 32.5% (n=26) were overweight (BMI 25–30).

While the APRI and FIB-4 scores of the patients were consistent with advanced fibrosis in all cases, the NAFLD score supported advanced fibrosis in 91% of the NASH group.

Table 1. Clinical characteristics of the patients

Variables	n=324
Mean Age	47.5 (±14.6)
Sex	
Male	198 (%61.1)
Female	126 (%38.9)
MELD	28.5 (±5.3)
CHILD	12.1(±1.4)
Ascites	
Yes	232 (71.5%)
No	92 (28.5%)
HCC	
Yes	57 (17.3%)
No	267 (82.7%)

MELD: Model for end-stage liver disease; CHILD: Child–pugh classification/score; HCC: Hepatocellular carcinoma

Discussion

In our study, examination of the pathology of explanted livers from patients with cryptogenic cirrhosis who underwent liver transplantation revealed that the underlying etiology could be reclassified in a significant proportion of

Table 2. Etiological distribution according to explant liver pathology

Variables	n=324 (%)
Veno-occlusive disease	22 (6.8%)
NASH/NAFLD	80 (24.7%)
HCC	25 (7.7%)
Cryptogenic	135 (41.7%)
Alpha-1 antitrypsin deficiency	1 (0.3%)
Hemochromatosis	4 (1.2%)
Hepatitis B virus related hepatitis	7 (2.1%)
Biliary pathology-related cirrhosis	17 (5.2%)
Ischemic hepatitis	2 (0.6%)
Autoimmune hepatitis	14 (4.3%)
Wilson disease	10 (3.0%)
Glycogen storage disease	1 (0.3%)
Amyloidosis	2 (0.6%)
Hepatitis C virus related hepatitis	2 (0.6%)
Hemophagocytic syndrome	2 (0.6%)

NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; HCC: Hepatocellular carcinoma

cases. The fact that NASH/NAFLD was the most frequently identified cause supports the role of metabolic liver diseases in the development of cryptogenic cirrhosis.

In a study conducted by Charlton and colleagues, the authors reported a high prevalence of obesity, diabetes mellitus, and dyslipidemia among patients with cryptogenic cirrhosis who underwent liver transplantation. They suggested that a significant proportion of these patients may have NASH. The study evaluated patients with cryptogenic cirrhosis who underwent liver transplantation and reported that, despite advanced investigations, the exact etiology could not be determined in some cases, and that this situation might be related to the blurring of histopathological features, particularly in advanced-stage liver disease.[4] In our study as well, the finding that the NASH/NAFLD rate in explant pathology was 24.7% supports this view. Furthermore, the fact that 66.15% of patients diagnosed with NASH had diabetes mellitus or insulin resistance and 72.5% were overweight or obese clearly demonstrates the decisive role of metabolic syndrome components in the etiology of cryptogenic cirrhosis. These results highlight the need for careful evaluation of metabolic risk factors, even if steatosis findings have resolved before transplantation.

Despite explant pathology, the fact that the etiology could not be determined in 41.7% of patients is noteworthy, as it suggests that current diagnostic approaches may be insufficient in a significant proportion of cryptogenic cirrhosis cases. Therefore, our study indicates that routine serological tests, imaging methods, and classical histopathological examinations are not always sufficient for etiological differentiation in advanced cirrhosis. In particular, genetic analyses, advanced immunophenotyping, viral nucleic acid testing, and metagenomic sequencing are recognized as important methods for identifying underlying hidden etiologies in cases of cryptogenic cirrhosis.

In a study by Wong and colleagues, it was noted that a significant proportion of patients awaiting liver transplantation have NASH.[5] Similarly, a study by Huang and colleagues indicated that metabolic dysfunction-associated fatty liver disease is one of the fastest-growing causes of cirrhosis.[6] In our study, the fact that NASH/NAFLD was the most frequently identified cause in the posttransplant pathological examination of patients with unknown pretransplant etiology suggests that this global trend is also evident in our country. In particular, the increase in the prevalence of obesity and type 2 diabetes mellitus necessitates a more systematic investigation of metabolic-origin diseases in patients diagnosed with cryptogenic cirrhosis.

DeLeve and colleagues noted that sinusoidal obstruction syndrome is characterized by perisinusoidal fibrosis and lobular congestion and that the primary mechanism underlying its pathogenesis is damage to sinusoidal endothelial cells. The study demonstrated that vascular liver diseases are often diagnosed late due to nonspecific laboratory and imaging findings and that some cases can only be diagnosed through liver biopsy or posttransplant pathology.[7] In our study as well, the fact that the diagnosis was established posttransplant via pathology in 6.8% of patients initially classified as cryptogenic is consistent with these literature findings. In this context, the findings of our study support the necessity of considering vascular causes in patients with unexplained cirrhosis through Doppler ultrasound, cross-sectional imaging, and histopathological evaluation when indicated.

The presence of cases of autoimmune hepatitis in which autoantibodies, such as ANA, ASMA, and LKM-1, may be negative can lead to delayed diagnosis and result in patients being managed as having cryptogenic cirrhosis. Czaja reported that seronegative autoimmune hepatitis poses diagnostic challenges, particularly in the advanced stages of fibrosis or cirrhosis, due to the blurring of typical histological and immunological findings. It is emphasized that the absence of autoantibodies does not rule out the diagnosis of autoimmune hepatitis, and this diagnosis must always be considered in cases of unexplained chronic hepatitis or cirrhosis.[8] Similarly, in cholestatic diseases, such as primary biliary cholangitis and primary sclerosing cholangitis, serological, biochemical, and imaging findings may be absent, making diagnosis challenging. The American Association for the Study of Liver Diseases guidelines recommend systematically investigating autoimmune and cholestatic causes in cases of unexplained cirrhosis.[9] In our study, autoimmune hepatitis was observed in 4.3% of cases, while biliary pathologies, including primary biliary cholangitis and primary sclerosing cholangitis, were detected in 5.2% of cases. These findings indicate that autoimmune and cholestatic liver diseases represent significant yet frequently overlooked causes among cases classified as cryptogenic cirrhosis.

Ferenci et al.[10] reported that Wilson's disease can present with highly variable clinical manifestations and that some patients may present directly with decompensated cirrhosis; however, when diagnosed early, the progression of liver damage can be halted with chelation therapy. Pietrangelo demonstrated that hereditary hemochromatosis can remain asymptomatic for many years and that untreated patients may progress to cirrhosis; however, if detected early through serum ferritin and transferrin saturation levels, the development of cirrhosis and hepatocellular carcinoma can be largely prevented with regular phlebotomy.[11]

Eriksson and colleagues, on the other hand, reported that alpha-1 antitrypsin deficiency, particularly in the PiZZ genotype, increases the risk of progressive fibrosis, cirrhosis, and primary liver cancer.[12]

In our study, when the transplant pathology of patients with cryptogenic cirrhosis was examined, Wilson's disease was detected in 3%, hereditary hemochromatosis in 1.2%, and alpha-1 antitrypsin deficiency in 0.3% of cases. Although the overall prevalence of these diseases appears low, our findings indicate that hereditary and metabolic liver diseases constitute a clinically significant proportion of cases classified as cryptogenic cirrhosis. It is important to investigate these conditions, particularly in cases of cirrhosis that develop at a young age, have a family history, or cannot be explained by common etiological factors, such as viral hepatitis, alcohol use, and metabolic syndrome. Our study demonstrates that these conditions may easily be overlooked in subsequent pathology, as clinical and laboratory findings lose their specificity in advanced-stage cirrhosis. However, the availability of effective disease-modifying treatment options for all these conditions strongly supports the necessity of evaluating Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency in the differential diagnosis of unexplained cirrhosis cases.

In our study, HBV-associated hepatitis was detected in 2.1% of cases and HCV-associated hepatitis in 0.6%. In these patients, who had negative serological test results before transplantation and were diagnosed with cryptogenic cirrhosis, the identification of viral etiology through explant pathology supports the importance of occult viral hepatitis in the etiology of cryptogenic cirrhosis. Similarly, Raimondo et al.[13] noted that in cases of occult HBV infection, particularly where HBV DNA persists at low levels, viral persistence may continue in the liver despite HBsAg negativity, and this could lead to the development of cirrhosis and hepatocellular carcinoma. Studies by Im et al.[14] also emphasized that while these serological markers may become negative during the low-replicative phase of HBV infection, HBV DNA can still be detected, particularly in liver tissue, and therefore serology alone is insufficient. Regarding HCV, Pawlotsky et al.[15] reported that HCV RNA is the only reliable diagnostic method in cases with negative or low-titer anti-HCV and that molecular tests are of critical importance, particularly in patients with advanced fibrosis. The findings of our study support the need to avoid overlooking occult viral hepatitis, particularly in seronegative or atypically presenting patients, and underscore the significant role of molecular tests in the diagnostic algorithm.

The incidence of hepatocellular carcinoma (HCC) was found to be 17.3% in our study. This rate supports the notion that cryptogenic cirrhosis carries a significant risk of malignancy, particularly in patients with advanced-stage disease. Previous studies have also shown that a significant proportion of cryptogenic cirrhosis is associated with underlying NASH/NAFLD and that the development of HCC is not uncommon in this patient group. A study by Bugianesi and colleagues emphasized that, given the global increase in the prevalence of NAFLD, NASH-related cirrhosis constitutes a significant risk group for the development of hepatocellular carcinoma. Furthermore, it has been shown that many cases classified as cryptogenic cirrhosis are actually of NASH origin and that inflammation, oxidative stress, and insulin resistance are the key mechanisms triggering carcinogenesis in these patients.[16]

These mechanisms accelerate HCC development, particularly through the effects of chronic low-grade inflammation and metabolic dysfunction on DNA damage and hepatic cell proliferation. The high HCC rate identified in our study underscores the need for close monitoring of patients with cryptogenic cirrhosis not only for liver failure but also for the development of malignancy. In this context, ensuring early diagnosis through regular ultrasound and alpha-fetoprotein (AFP) monitoring is of critical clinical importance.

The fact that the patients' mean MELD score was 28.5 and their Child-Pugh score was 12.1 indicates that the cases included in the study belonged to the advanced-stage decompensated cirrhosis group. At this stage of liver failure, initial etiological clues diminish because advanced fibrosis and nodular regeneration become predominant in the hepatic parenchyma. In evaluations of the MELD score by Kamath and colleagues, it was demonstrated that as the MELD score increases, decompensation worsens during the pretransplant period, and the diagnostic power of clinical and biochemical parameters for etiological differentiation decreases. The Child-Pugh classification, on the other hand, has revealed that in advanced cirrhosis, liver functional reserve is significantly reduced, and at this stage, complications take precedence over the etiology of the disease.[17] In this context, the literature also reports that histopathological specificity decreases in advanced cirrhosis and that many cases classified as cryptogenic can only be reclassified through posttransplant explant examination.

In our study, the finding that APRI and FIB-4 scores were consistent with advanced fibrosis in all cases was an expected result and supports the role of these indices in reflecting the severity of fibrosis in patients with advanced cirrhosis. In particular, the fact that the NAFLD score confirmed advanced fibrosis in 91% of the NASH group demonstrates that noninvasive scoring systems are reliable tools for assessing fibrosis in metabolic-related liver diseases. In vali-

dation studies of the FIB-4 index developed by Sterling and Lai,[18] it was demonstrated that this score, based on age, AST, ALT, and platelet counts, has a high negative predictive value for detecting advanced fibrosis. Similarly, Wai et al.[19] reported that the APRI score can be used to predict the stage of fibrosis in patients with chronic hepatitis B and C but that it reflects the degree of fibrosis rather than establishing an etiological diagnosis. In studies conducted by McPherson et al.[20] in a NAFLD population, it was demonstrated that FIB-4 and similar noninvasive scores are particularly valuable in ruling out advanced fibrosis and cirrhosis but may have limited sensitivity in early-stage disease. In this context, the findings of our study indicate that scores such as APRI and FIB-4 reflect the severity of fibrosis, particularly in advanced-stage patients, but are not sufficient on their own to determine the underlying etiology in cryptogenic cirrhosis.

Our study has certain limitations, such as its single-center and retrospective design. Since the study included only advanced-stage patients who underwent liver transplantation, it may not be representative of patients with earlier-stage cryptogenic cirrhosis. Additionally, the inability to perform advanced molecular tests that could identify occult viral infections or genetic causes in some patients may have contributed to the high proportion of cases with unexplained etiology.

The most significant strengths of our study include the large patient sample size, the standardized transplantation and pathology evaluations conducted at a single center, and the detailed examination of explanted liver tissue. Furthermore, the systematic assessment of metabolic risk factors contributes to a better understanding of NASH-associated cryptogenic cirrhosis.

Conclusion

This study, which examined the pathology of explanted livers in patients followed up with a preliminary diagnosis of cryptogenic cirrhosis who underwent transplantation, demonstrated that non-alcoholic fatty liver disease (NASH/NAFLD) underlies a significant proportion of cases in which the etiology was previously considered unclear. In cirrhotic patients with metabolic syndrome components, such as obesity, diabetes, and hypertension, which have become major problems of the modern era, NASH/NAFLD should be considered the primary etiology. The use of noninvasive tests, such as imaging methods and the NAFLD score in the early stages, diagnosis through liver biopsy when necessary, and a focus on lifestyle changes are critical for preventing disease progression. On the other hand, the ability to detect pathologically latent hepatitis B in patients with negative serological tests and the presence of veno-occlusive diseases that may be missed in routine imaging highlight the need for advanced vascular imaging methods in etiological investigations. Our study highlights the importance of accessible, low-cost, and clinically feasible tests, such as Child and MELD. The fact that the proportion of true cryptogenic cirrhosis cases with an unexplained etiology, despite thorough investigations, was found to be higher in our study compared with the literature suggests a need for further genetic and molecular studies to elucidate the underlying mechanisms of this disease.

Disclosures

Ethics Committee Approval: This study was approved by The İnönü University Scientific Research and Publication Ethics Committee (Approval No: 2019/310 -30.07.2019)

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Financial Disclosure: The authors declared that this study received no financial support.

Authorship Contributions:

Concept: M.K.; Design: M.K.; Supervision: Y.Y.Ü., O.Y.; Resource: Y.Y.Ü.; Materials: Y.Y.Ü., O.Y.; Data Collection and/or Processing: O.Y.; Analysis and/or Interpretation: M.K., Y.Y.Ü.; Literature Search: M.K., O.Y.; Writing: M.K.; Critical Reviews: M.K., Y.Y.Ü., O.K.

Peer-review: Externally peer-reviewed.

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