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MAFLD and NAFLD as underlying etiologies of hepatopathies

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is closely related to metabolic risk factors and is a highly prevalent disorder. NAFLD concept has evolved into metabolic-associated fatty liver disease (MAFLD), reflecting a more inclusive diagnostic approach related to those metabolic factors. Although the rate of liver transplantation (LT) for NAFLD/MAFLD patients has risen in Western countries, in our midst, it remains a relatively uncommon indication for LT recipients. Simultaneously, cryptogenic cirrhosis (CC) continues to be a prevalent cause of LT in our patient population.

Material and methods: A cross-sectional observational study was conducted on 387 adult patients who underwent their first LT for liver cirrhosis (LC) at a Brazilian referral center between 2008 and 2018. The prevalence of clinical and histopathological characteristics of patients with CC and LC of known etiology were analyzed and compared. The diagnosis of MAFLD was reassessed according to established criteria for both groups.

Results: Seventy-nine (20.4%) patients had CC, and 308 (79.6%) had LC with a defined etiology; among these, only one had NAFLD. Type 2 diabetes mellitus (T2DM) presented independent association with the CC group (32.5% vs. 21.3%; odds ratio 2.45, 95% confidence interval 1.34-4.46; p=0.003). The other characteristics showed no association with the groups. Fifteen patients (22.7%) previously diagnosed with CC were found to have MAFLD, along with 37 (15.6%), who underwent LT for cirrhosis with a defined etiology. **Conclusion:** NAFLD/MAFLD were frequent in patients undergoing LT in both groups, and T2DM was more prevalent in the CC group. These findings suggest that NAFLD is probably an unidentified etiology in patients with CC.

Keywords: cryptogenic cirrhosis, non-alcoholic fatty liver disease, liver cirrhosis, liver transplantation, metabolic fatty liver disease

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is classically defined as the accumulation of triglycerides in the liver, affecting ≥5% of the hepatocytes, according to either imaging or histological exams, considering the absence of any concurrent chronic liver ailment or alternative causes of hepatic steatosis.[1,2,3] Histologically, NAFLD can be classified into two main categories: non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH). The latter is characterized by liver inflammation and evidence of hepatocellular injury, such as ballooning of hepatocytes that may progress to fibrosis and cirrhosis. NAFLD is currently the most common liver disease, affecting approximately a quarter of the global population.[1,2] The surging prevalence of NAFLD over recent decades can be attributed to the escalating rates of its primary risk factors, such as type 2 diabetes mellitus (T2DM), excess body weight, obesity, and dyslipidemia. Consequently, NAFLD is often recognized as the hepatic component of the metabolic syndrome. The concept of NAFLD has evolved into metabolic-associated fatty liver disease (MAFLD), reflecting a more inclusive diagnostic approach related to those metabolic disorders, aiming to encompass a broader spectrum of diagnostic criteria and avoid the exclusion of concurrent liver conditions.[4] NAFLD/MAFLD holds significant prominence as an etiology for liver cirrhosis and currently ranks as the second most common indication for liver transplantation (LT) in the United States of America (USA).[5] In Brazil, the available data on its prevalence are limited. Several studies employing ultrasonography as a diagnostic tool have yielded different results, indicating a spanning from 10% to 35% for liver steatosis.[6–9]

In the state of Minas Gerais, Brazil, NAFLD remains an uncommon diagnosis in patients undergoing LT, despite the increased knowledge about the disease, the high prevalence of the risk factors associated with its development, and the increased tendency to indicate LT for NASH in Western countries.[10,11] In parallel, cryptogenic cirrhosis (CC), the terminology used when the etiology of cirrhosis remains unknown despite appropriate clinical, laboratory, and pathological evaluations,[12] continues to be a prevalent cause of LT.[10] There is a scarcity of data in Brazil regarding epidemiological and etiological evaluation of patients with CC, as well as the prevalence of MAFLD in patients with cirrhosis of known etiology. NAFLD has been indicated in several studies as a possible cause of CC;[13,14] thus, it is in this context that the present study is inserted, as its principal objective was to investigate the possibility of NAFLD or MAFLD as a cause of CC, as well as the coexistence of MAFLD and cirrhosis due to other etiologies in patients submitted to LT.

Material and methods

Study design

This is an observational, cross-sectional, descriptive and analytical study, conducted at the Faculdade de Medicina and Hospital das Clínicas, Universidade Federal de Minas Gerais (HC-UFMG), Belo Horizonte, Brazil, in 2019-2021.

Participants

All patients aged ≥18 years old undergoing their first LT for liver cirrhosis (LC) due to any etiology at HC-UFMG in the period from 2008 to 2018 were included, except for those transplanted for hepatocellular carcinoma without established LC, acute hepatits, or metastases from other sites, which corresponds to a total of 16 patients. A total of 387 participants were eligible. They were separated into two groups: those classified as having CC and those with LC with a defined etiology. Alcoholic-related liver disease was considered when there was a history of significant alcohol intake (>20g/day or 140g/week for women; >30g/day or 210g/week for men). Patients were considered as having CC if they had no defined etiology based on histopathological analysis of pre-transplant liver biopsies or examination of the explanted liver and if they did not meet the laboratory and clinical criteria for a recognized hepatopathy before the LT. Furthermore, autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) were collectively grouped under the term "autoimmune hepatopathy."

Clinical data

Clinical-epidemiological and laboratory data were collected from electronic medical records of the first appointment at the Liver Transplantation Outpatient Clinic. Obesity and overweight were defined as body mass index (BMI) ≥30kg/m^2 and BMI ≥25kg/m^2 and <30kg/m^2, respectively.[15]

Histological data

Biopsy slides from the explanted liver were reviewed by a single pathologist experienced in liver histopathology in a blinded fashion. The analysis was individual and standardized, by filling out a form with previously established parameters, based on the scheme proposed by Kleiner et al.[3] There was no standardization in relation to the size of the biopsy, because the slides from the explanted liver were previously prepared at the time of the LT of each patient. No slide was considered insufficient for analysis. The number of slides analyzed per patient varied from one to eight, depending on availability. Based on this analysis, the NAFLD activity score (NAS) was calculated and the fibrosis stage was evaluated and then compared between the two study groups (CC vs. non-cryptogenic). It was considered in the present study, as possible NASH when NAS values were ≥3, and unlikelihood of NASH if NAS ≤2. Concerning the grade of fibrosis, advanced fibrosis suggestive of cirrhosis (4-a, 4-b, 4-c) and fibrosis not suggestive of cirrhosis (1-a, 1-b, 1-c, 2, 3) were defined according to histological evaluation. There were available slides of biopsies from the explanted liver from 303 patients.

Diagnostic review

MAFLD was evaluated as a possible etiology in the patients of the CC group and in those with LC due to a defined etiology (in this case, as a concomitant etiology), based on the recent established criteria.[4] We considered MAFLD patients, those who had ≥5% steatosis (evidenced in pre-LT imaging exams or in the histological analysis of the pre-LT or explanted liver biopsies), associated with T2DM and/or obesity/overweight, and/or association of two of the following three parameters: abnormal HDL, hypertriglyceridemia, pre-T2DM. Obesity and overweight were defined based on BMI values recorded during the initial medical appointments at the Liver Transplantation Outpatient Clinic. In this analysis, only patients with no ascites in their first clinical record were included.

Patients with ≥5% steatosis in the histological analysis of the pre-LT or explanted liver biopsies without a specific etiology defined by classical clinical, laboratory, and histological criteria were considered as having NAFLD in this study. For the analyses regarding the etiological definition (MAFLD or NAFLD), only patients whose slides of the explanted liver were reviewed were included. Among the patients in the group with cirrhosis due to defined etiologies, those with hepatopathies that may lead to steatosis – hepatitis C genotype 3 and Wilson's disease – were excluded. We also excluded patients with hepatitis C for whom there was no information about the viral genotype. Patients with cirrhosis due to ethanol, who presented steatosis only in a histological or imaging exam performed before LT were not included in the analysis due to the possibility of alcohol consumption when these exams were performed.

Statistical analysis

The statistical analyses of the clinical data were performed using the software IBM SPSS, version 23.0 (SPSS Inc., Chicago, Illinois). In addition to the traditional tests used for comparing nominal and continuous variables, logistic regression models, which included variables that presented a p-value <0.20 in the univariate analysis, were developed to assess independent associations between the explanatory variables and the outcomes. The analyses regarding the comparison of histological data and the diagnosis of MAFLD and NAFLD were performed using the software RStudio, version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). The variables were compared using the chi-square test with Yates continuity correction. Values of p <0.05 were considered statistically significant for all analyses.

Results

Clinical characteristics of patients

In the present study, we evaluated 387 patients; among them, 79 (20.4%) were diagnosed with CC, while 308 (79.6%) were identified as having LC with a recognized underlying cause. The most prevalent etiology for LC was alcoholic cirrhosis (125 cases; 32.3%), followed by cirrhosis due to chronic C hepatitis (76 cases; 19.6%) and autoimmune hepatic disorder (69 cases; 17.8%). Only one patient (0.3%) was diagnosed with NAFLD. CC represented the second most common diagnosis, comprising 20.4% (79) of the patients. Additional frequency details are provided in Table 1. The frequencies of NAFLD-associated metabolic risk factors in the CC and defined etiology cirrhosis groups are outlined in Tables 2 and 3. The occurrence of T2DM was higher in the CC group (32.5% vs. 21.3%; p=0.040), remaining associated with the CC group after adjustment for the other variables (odds ratio 2.45; 95% confidence interval 1.34-4.46; p=0.003). On the other hand, systemic arterial hypertension, BMI, and lipid profile displayed no significant differences between the two groups. Statistical analysis of the additional characteristics revealed no associations with etiology (Tables 2 and 3).

Histological characteristics

The analysis of the histopathological characteristics of the explanted liver from 303 participants showed no significant differences between the CC and cirrhosis with a defined etiology groups regarding NAS and fibrosis, as shown in Table 4.

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Review of diagnoses NAFLD and MAFLD

This analysis and the one related to the review of the diagnoses according to traditional NAFLD criteria are described in Table 5. The frequency of MAFLD was similar in the two groups (CC 22.7% vs. cirrhosis with a defined etiology 15.6%; p=0.242). Nineteen additional cases of NAFLD were identified within the CC group.

Table 1 Etiology of liver cirrhosis in the 387 participants included in the study.

Etiology	N (%)
Cryptogenic Cirrhosis	79 (20.4)
Other Etiologies	
Alcohol cirrhosis	125 (32.3)
Hepatitis C vírus	76 (19.6)
Autoimmune hepatopathy	69 (17.8)
Hepatitis B vírus	19 (4.9)
Budd-Chiari syndrome	7 (1.8)
Caroli disease	4 (1.0)
Alpha-1-antitrypsin deficiency	2 (0.5)
Bile ducts atresia	1 (0.3)
Secondary biliary cirrhosis	1 (0.3)
Wilson's disease	1 (0.3)
Haemochromatosis	1 (0.3)
NAFLD	1 (0.3)
Oxalosis	1 (0.3)
Total	387 (100.0)

NAFLD: non-alcoholic fatty liver disease, N: absolute number; %: percentage in reference to the total number of cases.

Table 2 Clinical and laboratory characteristics of the patients stratified according to the etiology of cirrhosis

Variables	Cryptogenic cirrhosis N=79	Other etiologies N=308	p-value
Sex[1]			0.284
Male	51/79 (64.6)	218/308 (70.8)	
Female	28/79 (35.5)	90/308 (29.2)	
T2DM	25/77 (32.5)	64/300 (21.3)	0.04
Arterial hypertension	18/79 (22.8)	59/299 (19.7)	0.549
Obesity	19/79 (24.1)	51/307 (16.6)	0.126
Age (years)	61.0 [51.1/69.1]	59.2 [50.1/65.0]	0.101
BMI	26.3 [23.6-29.9]	25.7 [22.8-29.1]	0.194
BMI			0.685
<25	29/79 (36.7)	127/307 (41.4)	
25-29.9	32/79 (40.5)	121/307 (39.4)	
≥ 30	18/79 (18.8)	59/307 (19.2)	
LDL	90.0 [64.1-118.0]	84.0 [65.0-111.9]	0.63
HDL	45.0 [33.0-57.0]	44.0 [33.0-56.0]	0.563
VLDL	16.0 [12.5-23.0]	16.0 [12.0-23.0]	0.771
Total cholesterol	154.0 [122.0-180.0]	151.0 [125.0-181.0]	0.991
Triglycerides	100.0 [68.8-153.0]	87.0 [66.0-131.0]	0.144
Blood glucose	90.5 [82.3-114.5]	91.0 [82.0-107.3]	0.907
A1C	5.8 [5.2-6.8]	5.4 [4.9-6.7]	0.336

1: sex assigned at birth. n/N: number of occurrences/total number for which data were available. Values expressed as median [interquartile range] or absolute and relative numbers. HDL: high-density lipoprotein; BMI: body mass index; LDL: low-density lipoprotein; A1C: glycated hemoglobin; T2DM: type 2 diabetes mellitus; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein. RV: reference value.

Table 3 Logistic regression model for analysis of the association of variables with cryptogenic cirrhosis

Characteristics	Univariate analysis		Multivariate analysis	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
T2DM	1.77 (1.02- 3.08)	0.04	2.45 (1.34-4.46)	0.003
Obesity	1.59 (0.88-2.89)	0.126	-	-
Age	-	0.101	-	-
BMI	0.04 (0.00-3.31)	0.194	-	-
Triglycerides	1.00 (1.00-1.00)	0.144	-	-

T2DM: type 2 diabetes mellitus; BMI: body mass index; CI: confidence interval OR: odds ratio.

Table 4 Comparison of histological characteristics between groups

Variables	Cryptogenic (N=66)	Other etiologies (N=237)	p-value
NAS ≥3	16 (24.2)	53 (22.4)	0.683
NAS ≤2	50 (75.8)	184 (77.6)	
Fibrosis ≥4	62 (93.9)	228 (96.2)	0.348
Fibrosis ≤3 or absent	4 (6.0)	9 (3.8)	

Values are expressed in absolute and relative numbers. NAS: *Nonalcoholic fatty liver disease Activity Score*.

Table 5 Analysis of NAFLD or MAFLD among cryptogenic cirrhosis and cirrhosis with a defined etiology groups

	Cryptogenic cirrhosis	Cirrhosis of defined etiology
Absence of NAFLD/MAFLD	47 (71.2%)	200 (84.4%)
NAFLD	19 (28.8%)	-
MAFLD	15 (22.7%)	37 (15.6%)
Total of cases	66 (100%)	237 (100%)

Values are expressed in absolute and relative numbers. All patients with MAFLD met criteria for NAFLD. MAFLD: metabolic fatty liver disease; NAFLD: nonalcoholic fatty liver disease.

Discussion

In this study, we compared the clinical, laboratory, and histopathological characteristics of two patient groups who underwent LT: those diagnosed with CC and those with cirrhosis of a known etiology. Our investigation focused on exploring the possibility of NAFLD and MAFLD as causes of CC, as well as also the occurrence of MAFLD as an associated etiology alongside other hepatopathies. The independent association of T2DM with the CC group found in the current study reinforces the hypothesis that some patients diagnosed with CC could have an unidentified advanced metabolic hepatic disease (MAFLD or NAFLD). On the other hand, the lack of association between NAS and other variables that constitute risk factors for NASH does not favor the hypothesis of NAFLD as a possible etiology of CC.

However, the identification of MAFLD or NAFLD in 56 out of the 303 (18.5%) patients whose slides were reviewed, with 19 patients belonging to the CC group, strongly supports the notion that these etiologies could have been previously undiagnosed causes of the CC. Furthermore, MAFLD was observed in 37 (15.6%) patients from the second group, indicating a frequent coexistence of this condition alongside other hepatopathies.

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Several previous studies have pointed to the tendency of the disappearance of the histological characteristics of NASH in individuals who progress to advanced fibrosis.[16,17] Although less commonly, these patients, even in advanced stages of the disease, may present some residual features, such as steatosis and ballooning.[18] No significant difference was found in the NAS analysis between the two groups. However, according to the histological and clinical analyses, a significant number of patients fulfilled the criteria for NAFLD and MAFLD in both groups.

The results regarding the NAS analysis may reflect the fact that the analyzed biopsy slides were from patients with advanced hepatopathy, thereby limiting the detection of other features associated with active disease. Another possible explanation for the comparable findings between the two groups is the presence of nearly 16% of patients in the known etiology group who met MAFLD criteria. This implies that a significant number of patients exhibited at least steatosis in their end-stage liver, which could not be attributed to any other etiology, including alcohol-related causes, as the examination was conducted after a minimum of six months of abstinence.[19] The accuracy of NAS analyses and clinical differentiation between the two groups could have been improved if liver biopsies from active liver disease had been performed – it constitutes the main limitation of this study. However, this analysis was not possible due to the unavailability of pre-LT liver biopsy for most participants: 67 (84.8%) patients in the CC group had no biopsy before transplantation; among 12 patients submitted to pre-LT biopsy, all had moderate fibrosis to cirrhosis, without findings compatible with any specific etiology (data not shown).

Regarding the comparison of clinical data between the groups (first analysis), the independent association of T2DM with the CC group suggests that part of the patients with CC may have progressed from NAFLD, since T2DM is one of the main risk factors for the disease. On the other hand, no difference was found between the two groups when the variables obesity and overweight and data of the lipid profile (LDL, HDL, VLDL, total cholesterol, triglycerides) were evaluated. The fact that the data were collected in the first appointment at the Liver Transplantation Outpatient Clinic, may have contributed to underestimation of these parameters (lipid profile, obesity, and overweight), because the patients were already in the terminal stage of liver disease and often in a state of consumption. Additionally, the relatively high number of missing data possibly influenced the statistical inferences of the variables related to metabolic dysfunction - LDL, HDL, VLDL, total cholesterol, triglycerides, and glycated hemoglobin.

The prevalence of NAFLD/MAFLD has increased worldwide, as well as the indication of LT for LC due to this disease.[11,12,20–22] Specifically, in the state of MG, the second most populous state in Brazil, CC remains a prevalent cause of LT and, simultaneously, NAFLD is an uncommon diagnosis among patients queuing for LT, despite the increased knowledge about this condition and the high prevalence of risk factors associated with its development. According to data available in the Informatized System of the Brazilian Ministry of Health updated up to November 5, 2021, 1,846 patients were enrolled in the LT waiting list in MG from 2008 to 2021. Of these, 298 (16.1%) were enrolled as having CC and 87 (4%) as having "cirrhosis due to NAFLD" or "metabolic diseases with indication for transplantation". The first patient enrolment with this diagnosis in the state of MG occurred in 2010 and more than half of these patients (44 patients) were enrolled between 2020 and 2021 (data provided by MG Transplants in November 2021).

The transition from NAFLD to MAFLD concepts entails a shift towards an affirmative diagnosis rather than an exclusionary one, focusing on criteria associated with metabolic disorders, which prevalence is increasing. The identification of newly diagnosed MAFLD patients in both groups in this study carries paramount significance and emphasizes the need for prompt clinical management of the metabolic disorders, particularly given their status as transplant recipients. The synergism between MAFLD and other liver diseases has been much discussed,[23,24] and possibly patients with MAFLD associated with another liver disease are more prone to develop fibrosing hepatopathy. This occurrence did not fit the concept of NAFLD, which considers the exclusion of other hepatopathies for its diagnosis. It is not possible to retrospectively infer how much MAFLD interfered in the natural course of liver disease in patients with other associated liver disorders, but the identification of these patients, as well as those previously classified as having CC, is of prognostic importance since it is known that MAFLD may recur in liver grafts.[25,26] Moreover, patients with this condition are at higher risk of cardiovascular events,[27–29] as this is the hepatic manifestation of a systemic metabolic dysfunction and, therefore, requires non-drug and, in some cases, drug intervention in the post-LT period. Our results and the epidemiology of patients in the transplant queue in MG State point to some misdiagnosis of MAFLD in both CC and definied etiology groups. Late diagnosis of NAFLD/MAFLD may also be related to the fact that it is a hepatopathy with indolent and asymptomatic evolution, in addition to having as risk factors comorbidities often neglected. Identifying a significant number of patients with previously undiagnosed NAFLD in the CC group and MAFLD in both groups is compatible with the trend towards increased NAFLD diagnosis in Western countries associated with an increased prevalence of metabolic syndrome. Indeed, MAFLD is an underdiagnosed LC etiology in Brazil in both the CC and cirrhosis with defined etiology patients.

Conclusion

NAFLD and MAFLD were frequent diagnoses in patients undergoing LT for CC and cirrhosis due to a hepatopathy of known etiology. The review of diagnoses led to identifying19 (28.8%) patients with steatosis due to this condition in the CC group, and 37 (15.6%) patients with MAFLD who also presented LC of known etiologies. The independent association of T2DM and the CC group suggests that NAFLD may be an etiology not previously diagnosed in these patients. It is also possible that NAFLD frequence is underestimated because the analysis was performed in patients with end-stage liver disease. Clinical and biopsy evaluation at an earlier moment in the course of the hepatopathy would possibly increase the identification of new cases. The change of paradigms regarding the concept of the disease reflects the importance of recognizing this diagnosis in the face of persistent metabolic injury.

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Conflicts of interest

The author declares there is no conflict of interest.

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