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Original article

Survival in Patients with Cirrhosis According to Etiology. Retrospective Cohort

Jhon Edison Prieto-Ortiz[1*], Nathaly Garzón-Orjuela[2], Santiago Sánchez-Pardo[3], Robin German Prieto-Ortiz[4], Javier Eslava-Schmalbach[5]

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[1] Surgeon, specialist in Internal Medicine, Gastroenterology and Gastrointestinal Endoscopy, Hepatology, and liver transplant. Center for Liver and Digestive Diseases (CEHYD). Bogotá, Colombia.
[2] Master's in Clinical Epidemiology, Universidad Nacional, and member of the Equity and Health research group. Universidad Nacional de Colombia. Bogotá, Colombia.
[3] Surgeon, specialist in Internal Medicine, Universidad Industrial de Santander. Bucaramanga, Santander.
[4] Gastroenterologist, specialist in General Surgery, Gastroenterology and Gastrointestinal Endoscopy, Center for Liver and Digestive Diseases (CEHYD), Hospital Central de la Policía (HOCEN). Bogotá, Colombia.
[5] Physician, Professor of the Surgery Department, Universidad Nacional de Colombia. Bogotá, Colombia.

***Correspondence:** Jhon Edison Prieto-Ortiz. prieto.jhon@gmail.com

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Abstract

Introduction: Cirrhosis is the final stage of chronically progressive liver diseases of various etiologies. It is a common disease, with a variable prevalence in each country. Its peak incidence occurs between 40 and 50 years of age, predominantly in men. **Aims:** To compare a cohort of patients diagnosed with cirrhosis, evaluate their complications and survival according to etiology, describe clinical and laboratory aspects, and determine the role of a fatty liver. **Materials and methods:** A retrospective cohort study was carried out with patients who held a specialized hepatology consultation in the center of liver and digestive diseases (CEHYD) in Bogotá, Colombia, between January 2010 and June 2019. **Results:** We reviewed a total of 1,200 medical records (56.8 % women). There were no statistically significant differences in median survival between groups by etiology, sex, presence or absence of complications, or Child. We noted that the older the age at the diagnosis of cirrhosis, the higher the risk of death; HR 1.04 (95 % CI 1.02-1.075). For each month that follow-up increases, the risk of death decreases by 90 %; HR 0.1 (95 % CI 0.03-0.29). For each month that the follow-up of complications increases, the risk of death is reduced by 2 %; HR 0.98 (95 % CI 0.97-0.99). **Conclusions:** Survival by etiology was similar in the different groups. Nonalcoholic steatohepatitis (NASH) was the leading cause of cirrhosis in this cohort. Efforts should focus on its diagnosis and management in the early stages.

Keywords

Liver cirrhosis, survival, fatty liver, nonalcoholic fatty liver disease.

INTRODUCTION

Cirrhosis is the final phase of progressive and long-term liver disease[1,2]. The prevalence varies in each country, with a maximum incidence between 40 and 50 years, affecting more men[2]. In Western countries, 90% of cases are due to alcohol abuse, non-alcoholic fatty liver disease (NAFLD), and chronic viral hepatitis, including hepatitis B (HBV) and hepatitis C (HCV). About 10% of the etiology of this entity is unknown[1-3].

Cirrhosis is the consequence of the continuous death of hepatocytes, with loss of parenchyma, inflammation, fibrogenesis, changes in cell regeneration, and alterations in macro- and microcirculation[4-6]. It is a dynamic and reversible process at some point[7-9], which has motivated studies in the search for adequate management by identifying and monitoring asymptomatic patients and preventing the entity's complications. Four of them are classic decompensations: Ascites, variceal bleeding, encephalopathy, and jaundice[10-12].

The manifestation of any of them markedly decreases the survival of cirrhotic patients, being worse with hepatocarcinoma (HCC)[12-15], which has an approximate annual incidence of 7%[1,12,15] and is associated with the same causes of cirrhosis, HCV, alcohol, and NAFLD[1,16-20]. Fatty liver is a cause of cirrhosis on the rise[21,22], directly correlated with elements of the metabolic syndrome. For example, type 2 diabetes *mellitus*, obesity, and high blood pressure, all with increased cardiovascular risk[23]. Therefore, this study aims to compare a cohort of patients diagnosed with cirrhosis, evaluate their complications and survival according to their etiology, describe clinical and laboratory aspects, and determine the role of fatty liver.

MATERIALS AND METHODS

We carried out a retrospective cohort study. It included patients who attended a specialized Hepatology consultation at the Center for Liver and Digestive Diseases (CEHYD) in Bogotá between January 2010 and June 2019. Confirmed diagnosis of cirrhosis by the clinic, radiology or liver biopsy, and available medical records were the only inclusion criteria.

Based on the Child-Pugh (CP)[24] cirrhosis severity scale, we defined:

- *Compensated cirrhosis:* A Child A stage, without any additional decompensation
- *Decompensated cirrhosis:* A Child B or C stage, or a Child A cirrhosis with ascites, variceal bleeding, encephalopathy, or jaundice

Additionally, ascites, variceal bleeding, encephalopathy, jaundice, HCC, hepatorenal syndrome, or coagulopathy were defined as complications of cirrhosis.

The information collected was summarized using means and standard deviations for a normal distribution (Shapiro-Wilks test); otherwise, it was summarized with medians and interquartile ranges. We performed the analysis with non-parametric statistics and summarized categorical variables as proportions. Survival was assessed based on medians and interquartile ranges. We used the Kaplan Meier estimator of the survival function and the log-rank test. A Cox hazard model was made for the analysis adjusted by the effect of confounding covariates. STATA v15.1 and R were employed for statistical analysis.

ETHICAL CONSIDERATIONS

As a retrospective study, no intentional intervention or modification of the individuals' biological, physiological, psychological, or social variables was carried out. It was conducted under the principles declared at the 18th WMA General Assembly (Helsinki, 1964) as a world reference for research on human beings. As set forth in Article 11(a), Title II (about research on human beings), Chapter I (about the ethical aspects of research on human beings) of Resolution 008430 dated October 4, 1993, issued by the Ministry of Health of the Republic of Colombia, this study constitutes research without risk. It uses retrospective documentary research techniques and methods, including medical records, interviews, questionnaires, and others, in which sensitive data on illnesses are not identified or processed.

Since it has no risk and only uses documentary research techniques and methods, this study is understood to follow the fundamental principles of ethics: Beneficence, autonomy, justice, and non-maleficence.

RESULTS

We reviewed a total of 1,200 medical records, of which 681 (56.8%) were women. The mean age at diagnosis of cirrhosis was 63 years (interquartile range [*IQR*] 56–71). The death occurred in 51 patients, with a median age of 75 years (*IQR* 65–80). The patients were monitored over time, measured in months, with a median of 17.4 (*IQR* 5.5–45.3). The first complication of cirrhosis occurred in 545 patients (45.4%) 0.7 months after diagnosis (*IQR* 0–18.1). Complications were, in order of importance, ascites (33.8%), variceal bleeding (22.2%), HCC (17.4%), jaundice (14.3%), encephalopathy (7.3%), ascites plus encephalopathy (2.6%), coagulopathy (2%), and hepatorenal syndrome (0.4%). The clinical and demographic characteristics are shown in **Table 1**.

According to the cirrhosis etiology, the patients were classified into five groups (**Table 2**). The lowest median age at diagnosis of cirrhosis was for the cholestatic group. Furthermore, the alcohol group had a lower median age at death, 64 years. The etiological group with the highest percentage of complications was again alcohol (63.5%), and the lowest was the non-alcoholic steatohepatitis (NASH) group, with 31.6%.

Regarding the severity of cirrhosis at admission, 69.6% had Child A (higher in the NASH group), 21.3% Child B, and 3.9% Child C (higher in the alcohol group).

Table 3 shows, in all patients, a median survival of 34 months (95% *CI* 29–52). There were no statistically significant differences in median survival between the groups of etiology, sex, presence or absence of complications, or Child. However, higher survival was identified in the cholestatic group (**Figure 1**), being a woman (**Figure 2**), not having a complication (**Figure 3**), and Child C (**Figure 4**), the median survival being 54, 43, 52, and 37 months, respectively.

Considering the variables and the follow-up time illustrated in **Table 4**, the univariate analysis found that as the

Table 1. Clinical and laboratory variables in patients with cirrhosis

Variable	Number	Median (*IQR*)*
BMI kg/m^2	1139	27 (24 to 30)
White cells (cell/mL)	1154	5500 (4400 to 6890)
Hemoglobin (g/dL)	1153	14 (13 to 16)
Hematocrit %	1153	43 (38 to 47)
Platelets (cell/mm^3)	1155	158 000 (111 650 to 224 500)
Glycemia mg/dL	1087	98 (88 to 115)
AST IU/dL	1158	54 (34 to 90)
ALT IU/dL	1161	50 (31 to 87)
GGT IU/dL	1049	120 (56 to 259)
Alkaline phosphatase IU/dL	1125	132 (95 to 211)
Total bilirubin (mg/dL)	1143	1 (0,6 to 1,7)
Direct bilirubin (mg/dL)	1139	0,4 (0,2 to 0,8)
Indirect bilirubin (mg/dL)	1137	0,5 (0,3 to 0,9)
Total protein (g/dL)	1044	7,3 (6,9 to 7,8)
Albumin (g/dL)	1100	4 (3,4 to 4,3)
INR	1117	1,1 (1 to 1,2)

BMI: Body mass index; INR: International normalized ratio; *IQR*: Interquartile range tested for normality (Shapiro-Wilk test).

age at diagnosis of cirrhosis increases, the risk of death is higher; *HR* 1.04 (95% *CI* 1.02-1.075; $p = 0.000633$). For each month that the follow-up of cirrhotic patients increases, the risk of death is reduced by 90%; *HR* 0.1 (95% *CI* 0.03-0.29; $p < 0.00$). Similarly, a longer follow-up of complications reduces the risk of death by 2%; *HR* 0.98 (95% *CI* 0.97-0.99; $p = 0.000695$). Finally, the group of other causes of cirrhosis presents a risk of death 3.87 times compared to the cause of cirrhosis due to cholestatic disease (p = 0.0386), statistically significant estimates.

DISCUSSION

Studies in the United States showed that in 2010, chronic liver diseases and cirrhosis were the cause of 31,903 deaths, with age-adjusted mortality of 9.4 per 100,000 individuals, and decompensated cirrhosis accounted for more than 150,000 hospitalizations, with a cost close to 4 billion US dollars[25,26]. These data highlight the importance of monitoring the cirrhotic patient.

When reviewing this cohort, the average age of cirrhosis was 63 years, as reported in the Swedish population study by Nilsson *et al*[26], with a follow-up of more than 1,000 patients. The highest incidence of the disease occurred in the group of 60–64 years, with a predominance in the female sex, as in our series. In other international series, the male gender predominates, probably due to etiological differences[27,28].

D'Amico emphasizes a different prognosis in terms of mortality according to the presence or absence of decompensations[12,28,29]. In our cohort, the analysis focused on the presence or absence of complications. Classic ascites, variceal bleeding, jaundice, and encephalopathy[12] were added to HCC, hepatorenal syndrome, and coagulopathy. In this series, complications occurred in 45.9% of all patients shortly after the diagnosis of cirrhosis (0.7 months) (*IQR* 0-18.1) and with a total follow-up of 17.4 months (*IQR* 5.5-45.3). European series show follow-up periods of up to 10 years or more[27,28]. These two pieces of data alert us to the lateness of our diagnoses since, in most cases, the complication leads to the diagnosis of cirrhosis, and advanced disease does not allow for further follow-up.

In different studies, the survival of patients with compensated cirrhosis is relatively good, with a median of 12 +/- 2 years on average[30-32]. Our data in patients without complications show a median survival of four years and four months (52 months), well below international data. Although it is higher than the group with complications, it does not present statistically significant differences and could be explained by the number of events analyzed. Moreover, the mortality rate (*HR*) in patients with complications was 1.22 (*CI* 0.58–2.53; *p* not significant), similar to Nilson's study after the first year (*HR* 1 .44, *CI* 1.23-1.68) [26]. Again, these results suggest that our population probably requires more medical follow-up for their cirrhosis.

According to Child (**Table 3**), the results are similar when analyzing survival between 34 and 37 months for the three groups. Although it seemed to be longer for Child C, it favored Child B in the survival curve (**Figure 4**). No statistically significant differences were found in any case. These findings are explained by the low number of events ($n = 51$); however, it is expected that this cohort of patients will be monitored to clarify these results.

Although the survival data by cirrhosis etiology (**Table 3** and **Figure 1**) did not present statistically significant differences, they seemed to favor cholestatic disease (*HR* reference pattern in **Table 4**). Apparently, it is an etiological cause of cirrhosis with a better prognosis, probably due to its onset in childhood or younger populations, with earlier diagnosis, better follow-up, and, in theory, less liver damage[31]. In a study with 9,261 patients, the cholestatic

Table 2. Differences between groups by etiology

Etiology of cirrhosis	NASH *n* = 399 (33.2%)	Cholestatic *n* = 245 (20.4%)	Alcohol *n* = 230 (19.2%)	Other *n* = 191 (15.9%)	HCV *n* = 135 (11.2%)	Total *n* = 1,200 (100%)
Sex*						
- Woman	257 (64.4)	208 (84.9)	27 (11.7)	91 (47.9)	98 (72.6)	681 (56.8)
- Man	142 (35.6)	37 (15.1)	203 (88.3)	100 (52.1)	37 (27.4)	519 (43.2)
Age at first consultation (years) Median (*IQR*)**	64 (57.8 to 71)	59 (48.7 to 69)	64 (56 to 70)	62 (55 to 70.8)	64 (58.5 to 71)	63 (55 to 70) n = 1200
Age at diagnosis of cirrhosis (years) Median (*IQR*)**	65 (59 to 72)	60 (48 to 69)	63 (55 to 71)	63 (54.3 to 70.8)	64 (60 to 70)	63 (56 to 71) n = 1200
Age at death (years) Median (*IQR*)	70 (67.5 to 78.5)	77.5 (72.3 to 80.8)	64 (60 to 78)	74.5 (64.3 to 79.8)	78 (71 to 81.3)	75 (65 to 80) n = 51
Complication*						
- Yes	126 (31.6)	121 (49.4)	146 (63.5)	94 (49.2)	58 (43)	545 (45.4)
- No	273 (68.4)	124 (50.6)	84 (36.5)	97 (50.8)	77 (57)	655 (54.6)
Follow-up of cirrhosis from its diagnosis in months Median (*IQR*)**	15 (6.3 to 31.3)	28.4 (9.7 to 59.2)	17.3 (3.7 to 47.1)	12.9 (4 to 35)	23 (4.5 to 48.3)	17.4 (5.5 to 45.3) n = 1186
- Follow-up of complications from the diagnosis of cirrhosis in months	0	3.8	0	0.02	5.3	0.7
- Median (*IQR*)**	(0 to 12)	(0 to 30.6)	(0 to 12)	(0 to 33.13)	(0 to 33.13)	(0 to 18.1) n = 545
Child*						
- A	326 (84.2)	170 (70.8)	125 (58.4)	116 (69.1)	98 (76)	835 (69.6)
- B	50 (12.9)	64 (26.7)	69 (32.2)	47 (28)	26 (20.2)	256 (21.3)
- C	11 (2.9)	6 (2.5)	20 (9.3)	5 (2.9)	5 (3.8)	47 (3.9)
Other: HBV, HCV, and B coinfection, medications, or toxic substances, three or more mixed, HBV plus alcohol						

*Significant differences ($p < 0.005$) between etiological groups of cirrhosis, Fisher's exact test.
**Significant differences ($p < 0.005$) between etiological groups of cirrhosis, Kruskal-Wallis test.
IQR: Interquartile range.

disease had a mortality rate per 100 patients/year of 6.3 (3.1-12.5) below alcohol, virus, and NASH, this being the highest at 15.2 (12.9-17.8)[32]. These trends are similar to our study, with *HR* for alcohol, HCV, and NASH of 1.56, 1.62, and 2.36, respectively (**Table 4**).

Having other causes of cirrhosis increases the risk of death 3.87 times (**Table 4**). This group comprises etiological combinations that result in more progressive liver damage. European HCV studies[21-23] mention that having multiple risk factors, such as viral factors, fatty liver, and alcohol, increases the likelihood of death, as suggested in other studies[12,15,27].

Our data show NASH as the primary etiology of cirrhosis (33.2%). The importance of fatty liver as a cause of liver disease and cirrhosis is corroborated by local and international series, where it is shown to displace other etiologies[11,19,33-37]. It must be remembered that worldwide, between 20% and 40% of the population suffers from it. A meta-analysis involving 8,515,431 estimated this global prevalence at 25%, with prevalence rates in South America

Table 3. Survival by group and difference comparison

	Number of events	Median survival (95% *CI*) (months)	Log-rank test
Total	51	34 (29 to 52)	
Etiology of cirrhosis (**Figure 1**)			
- HCV	9	38 (25 to NC)	
- Alcohol	10	31.5 (14 to NC)	
- Cholestatic	8	54 (43 to NC)	$p = 0.099$
- NASH	15	34 (26 to 57)	
- Other	9	25 (21 to NC)	
Gender (**Figure 2**)			
- Woman	31	43 (31 to 60)	$p = 0.15$
- Man	20	29 (16 to 50)	
Complications (**Figure 3**)			
- Yes	42	33 (27 to 50)	$p = 0.58$
- No	9	52 (34 to NC)	
Child* (**Figure 4**)			
- A	31	34 (25 to 54)	
- B	13	34 (29 to NC)	$p = 0.066$
- C	5	37 (11 to NC)	

NC: Not calculated.
*In two patients, it was not calculated due to a lack of data

Table 4. Differences between cirrhosis groups and follow-up

Follow-up variables	*HR* (95% *CI*) (univariate)	
Age at first consultation in years	1.02 (0.99 to 1.04)	$p = 0.096$
Age of diagnosis of cirrhosis in years	1.04 (1.02 to 1.075)	$p = 0.000633$
Follow-up of cirrhosis from its diagnosis in months	0.1 (0.03 to 0.29)	$p < 0.00$
Follow-up of complications after the diagnosis of cirrhosis in months	0.98 (0.97 to 0.99)	$p = 0.000695$
Etiology of cirrhosis		
- Cholestatic	1	
- Alcohol	1.56 (0.59 to 4.12)	$p = 0.3681$
- HCV	1.62 (0.58 to 4.44)	$p = 0.3498$
- NASH	2.36 (0.93 to 5.99)	$p = 0.0695$
- Other	3.87 (1.36 to 11)	$p = 0.0110$
Sex		$p = 0.156$
- Woman	1	
- Man	1.51 (0.85 to 2.68)	
Complications		$p = 0.591$
- No	1	
- Yes	1.22 (0.58 to 2.53)	
Child		
- A	1	
- B	0.48 (0.23 to 1.01)	$p = 0.0556$
- C	1.59 (0.60 to 4.18)	$p = 0.3462$

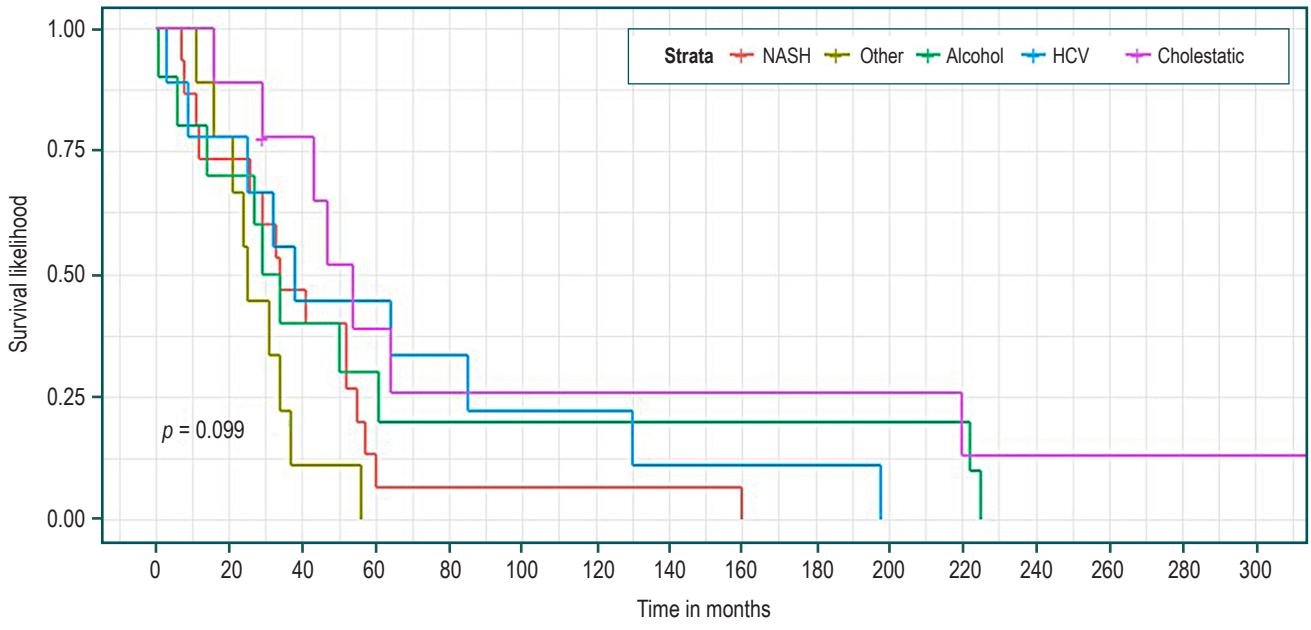

Figure 1. Survival curves by cirrhosis etiology - Kaplan Meier.

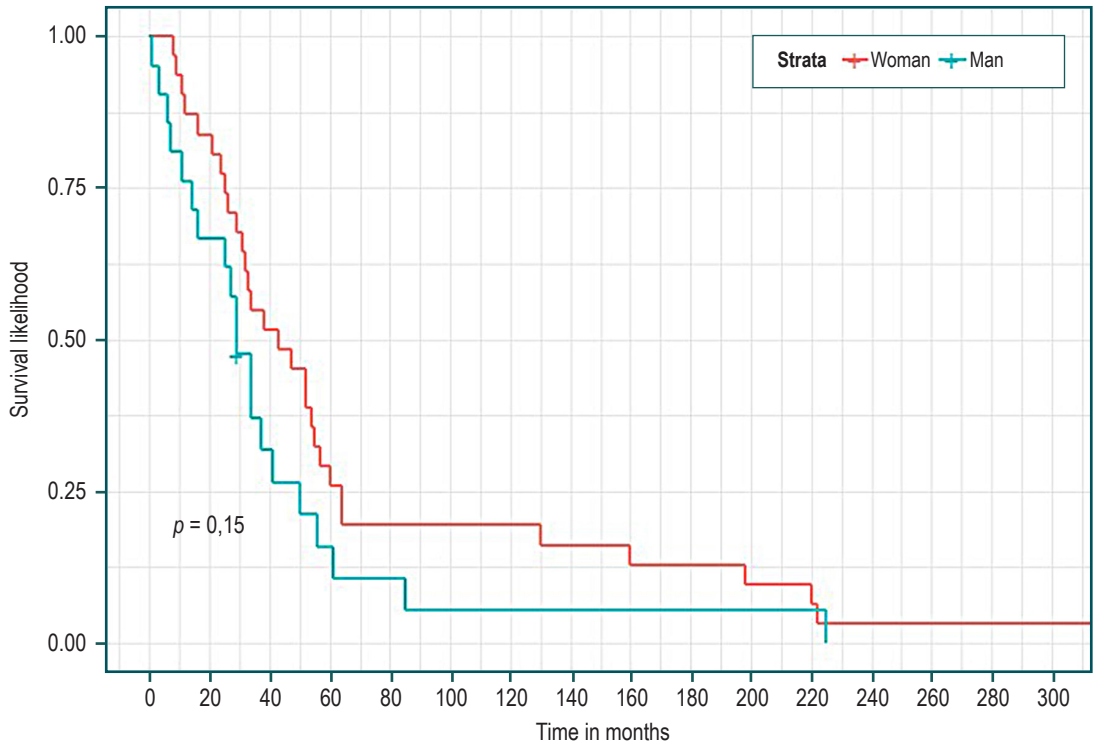

Figure 2. Survival curves by sex - Kaplan-Meier.

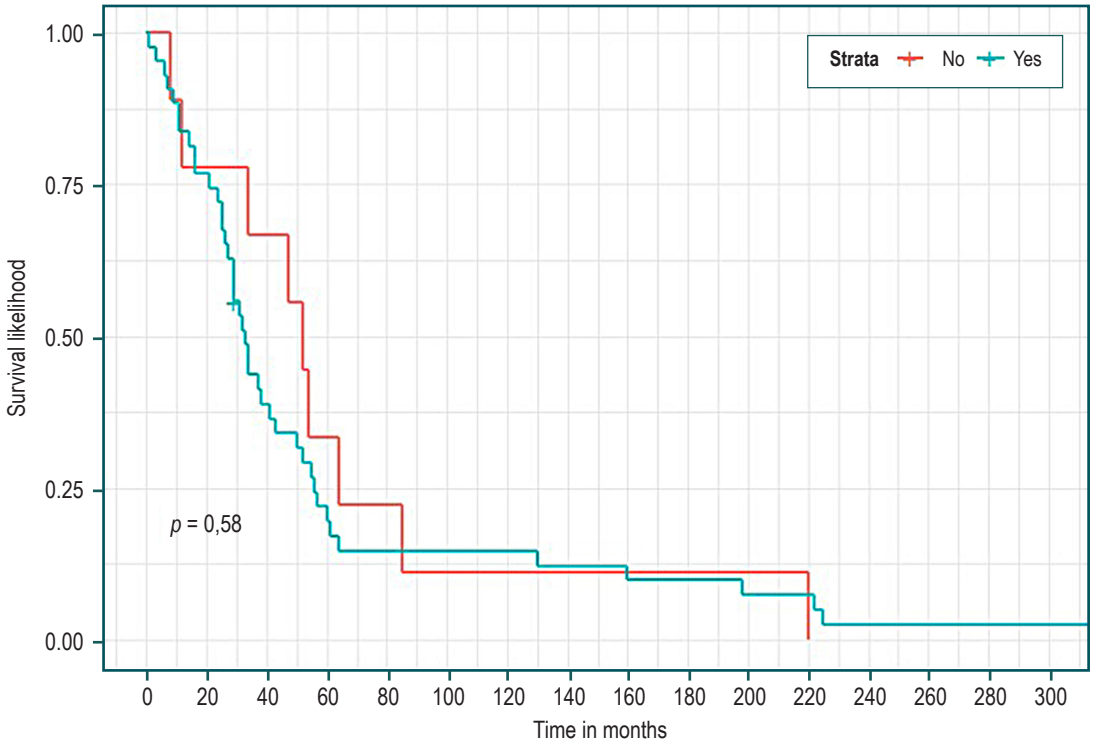

Figure 3. Survival curves by presence or absence of complications - Kaplan Meier.

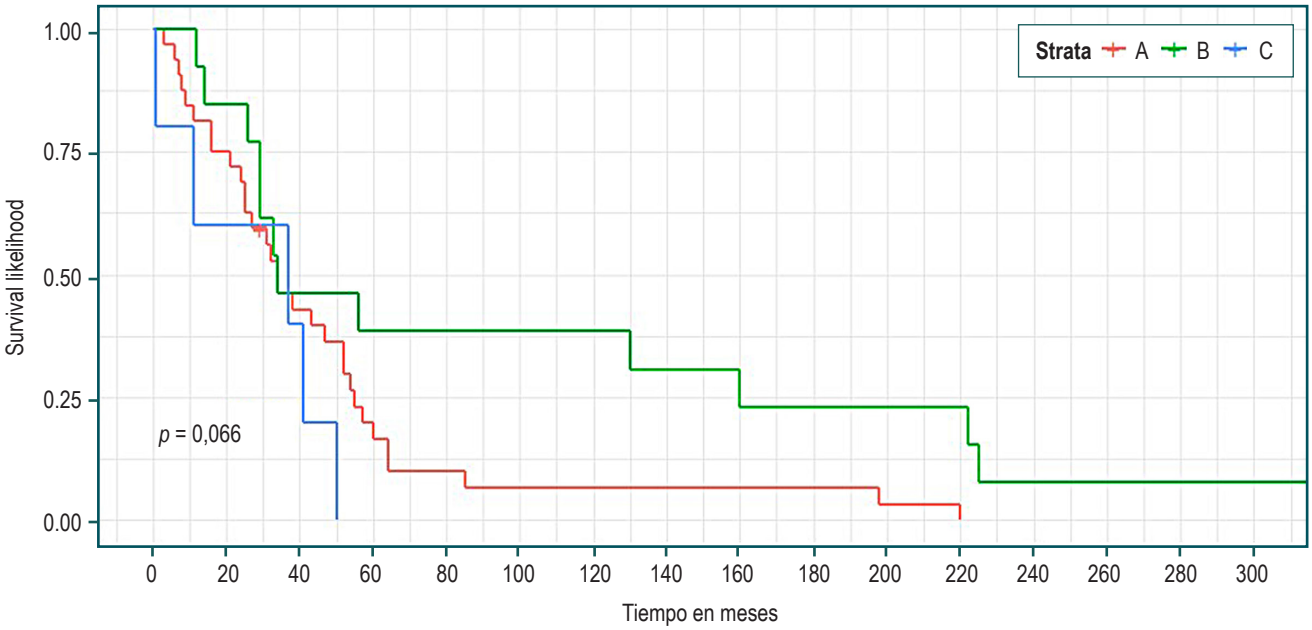

Figure 4. Survival curves by Child - Kaplan Meier.

of 31%[38]. Therefore, NASH as a cause of cirrhosis and its complications could even be underdiagnosed.

Despite being a single-center study, this is a Colombian cohort of patients under follow-up. It provides research options to learn about our reality and evidence of the fatty liver pandemic and its association with cirrhosis.

CONCLUSIONS

In the present cohort of cirrhotic patients, survival by etiology, gender, or presence/absence of complications did not show statistically significant differences; however, these complications manifest very quickly and alert us to late diagnoses. NASH was the leading cause of cirrhosis, and efforts should be directed towards its diagnosis and management in the early stages.

Conflict of interests

The authors declare no conflict of interest in conducting this study.

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