

Retrospective Cohort Study

Significant cohort of non-alcoholic fatty liver disease with portal vein thrombosis in transplant waiting list

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Abstract

AIM: To characterize non-alcoholic fatty liver disease (NAFLD) presentation with esophageal varices.

METHODS: We carried out a retrospective cohort study on 258 patients with esophageal varices at a single tertiary referral center. These patients underwent diagnosis of several liver diseases, including: NAFLD-associated cirrhosis, hepatitis B, hepatitis C, Wilson disease, autoimmune liver diseases, and others.

RESULTS: Of the 258 patients, 39% of patients exhibited esophageal varices due to NAFLD-associated cirrhosis. Of the 38 (14.7%) patients developed hepatocellular carcinoma during follow-up, 52% were due to hepatitis B, 26% due to hepatitis C and 13.2% due to NAFLD. Of the 258 patients, 50.0% with NAFLD, 33.3% with hepatitis B, 26.3% with hepatitis C, and 58.3% with other diseases were alive at the end of the 5-year period with a significant difference according to the Kaplan-Meier log Rank test ($P = 0.040$). Portal vein thrombosis was detected in 47.5% of patients with NAFLD, in 29% of patients with hepatitis B, in 17% of patients with hepatitis C, and in 62% of patients with other related diseases ($P < 0.0001$).

CONCLUSION: Our study showed a proportionally

greater elevation in liver transplant candidacy in patients with NAFLD and portal vein thrombosis. Older patients were more prone to developing cirrhosis, hepatocellular carcinoma and a high mortality rate. However, younger patients exhibited more portal vein thrombosis and gastric varices.

Key words: Hepatocellular carcinoma; Non-alcoholic fatty liver disease; Portal vein thrombosis; Esophageal varices

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Core tip: We aimed to characterize non-alcoholic fatty liver disease (NAFLD) presentation with esophageal varices. We carried out a retrospective cohort study on 258 patients with esophageal varices at a single tertiary referral center. Of the 258 patients, 39% exhibited esophageal varices due to NAFLD-associated cirrhosis. The incidence of portal vein thrombosis was 47.5% in patients with NAFLD, 29% in hepatitis B, 17% in hepatitis C, and 62% in patients with other related diseases ($P < 0.0001$). Our study showed a proportionally greater elevation in liver transplant candidacy in patients with NAFLD and portal vein thrombosis.

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INTRODUCTION

Excessive accumulation of fat in hepatocytes in the absence of significant alcohol consumption occurs in up to 30% of adults^[1,2]. This condition, termed non-alcoholic fatty liver disease (NAFLD), predisposes to non-alcoholic steatohepatitis (NASH), which progresses to cirrhosis and its complications, including hepatocellular carcinoma (HCC)^[2-4]. Several studies have also reported that in some patients, NAFLD can lead to HCC without transitioning through cirrhosis^[4,5-10]. Currently, it is estimated that NAFLD is the third leading cause of HCC after hepatitis C and B. Although earlier studies suggested that NAFLD may be less severe and progress slowly in Asian populations, the progression of fibrosis and cirrhosis in patients with NAFLD is no longer believed to differ significantly by ethnicity^[11-13].

The prevalence of NASH as a precursor of NAFLD-associated cirrhosis is 3% and 20% in non-obese and obese subjects, respectively^[14]. The global obesity epidemic has been associated with the increasing burden of NAFLD. It has been estimated that the rising prevalence

of NAFLD will soon lead to large cohorts of patients with decompensated cirrhosis. In this respect, NAFLD is expected to become the leading indication for liver transplantation in the Western world, particularly in the United States. Longitudinal follow-up studies showed an increase in the mortality rate among patients with NAFLD due to hepatic decompensation^[15-19]. These studies usually included a limited number of patients with short follow-up period and with selected patients such as compensated cirrhosis.

It is possible that risk factors for NAFLD-associated cirrhosis and HCC in Eastern countries differ from those in the West. Thus, we aimed to document the characteristics of patients with NAFLD-associated cirrhosis from Turkey, a European country sharing 97% of its borders with Asia. Relative to other Europeans, the Turkish population exhibits a higher rate of obesity that is comparable to that in the United States. In Turkey, 47.7% of all deaths have been attributed to cardiovascular diseases (most likely cerebrovascular and ischemic heart diseases), which are highly correlated with obesity^[20]. Overall, 56% of the Turkish population is overweight, especially preobese (body-mass index: 25-29.9 kg/m²). This has been attributed in part, to the predominance of non-working women who manifest a higher incidence rate of obesity than their working counterparts (33% vs 14%).

In light of the epidemic spread of obesity in Turkey, and the association of this disease with NAFLD, the current follow-up study evaluated patients with esophageal varices from 2003 at a single tertiary referral liver center, with the aim to investigate the relationship between esophageal varices and NAFLD. The results were compared in terms of the development of portal vein thrombosis (PVT), HCC, survival and mortality. The association between esophageal varices and hepatitis B and hepatitis C was also examined, as these etiologies are also of importance to esophageal varices. According to the World Health Organization, Turkey is one of the countries with intermediate (2%-8%) endemic rate for hepatitis B and less than 2% (1.0%-1.9%) for hepatitis C^[21,22].

MATERIALS AND METHODS

Retrospective cohort study design

We have kept the records of patients with hepatitis B or C who have been followed prospectively at our hepatology unit and affiliated liver center. Confidentiality of records was maintained according to the guidelines issued by Türkiye Yüksek İhtisas Hospital Institutional Ethics Committee. Data were collected for esophageal varices only at the advanced endoscopy unit. A cohort of patients with esophageal varices from 2003 to 2014 was reviewed. All patients were of Turkish origin and were informed and consented about the investigation and treatment. Eligible patients were ≥ 18 years of age and have had esophageal varices diagnosed by upper

gastrointestinal endoscopy examination. They had regular clinical follow-up and endoscopic examinations at our clinic. Efficacy data were based on the last evaluation. Transplanted cases were excluded. The main inclusion criterion was the presence of esophageal varices with or without gastric varices.

Only 258 patients with endoscopically defined high risk varices had reliable data and were included in this study. Each patient was evaluated for fundal varices, PVT, cirrhosis, HCC, and mortality. After the first evaluation, patients were divided into 4 groups: Those with hepatitis B, hepatitis C, NAFLD and others related to autoimmune hepatitis, Wilson Disease, primary biliary cirrhosis, *etc.*

Alcohol history was determined through self-reporting and/or from information provided by family members. History of drug abuse, chronic hepatitis, hypertension, and diabetes was also recorded. Ultrasonographic evaluation of the hepatobiliary system was performed in each patient. Fatty liver was diagnosed by increased echogenicity or increased liver-kidney contrast. NAFLD was diagnosed according to standard criteria^[19]. Serum serology of hepatitis B surface antigen, anti-hepatitis B surface, anti-hepatitis B core-total and anti-hepatitis C virus (anti-HCV) were measured by enzyme-linked immunosorbent assay. If necessary, liver biopsies were re-evaluated by an experienced pathologist according to established criteria.

The classification system of varices described by Sarin *et al.*^[23] was used in our endoscopy unit. Accordingly, varices are endoscopically classified as gastroesophageal varices type I (lesser curvature), gastroesophageal varices type II (greater curvature), isolated gastric varices type I (gastric fundus), or isolated gastric varices type II (gastric-excluding the fundus).

Statistical analysis

Data were coded and recorded electronically using an IBM Statistical Package for the Social Sciences (SPSS; Armonk, NY, United States) for Windows version 17.0 (2007). The χ^2 and Fisher's exact test was used to compare the groups for the distribution of cirrhosis, PVT, HCC, and mortality. Mean age compared by one-way ANOVA test in four groups and compared by Student's *t*-test between both genders. After the statistically significant ANOVA, we used post-hoc multiple comparison tests Bonferroni in order to identify statistically significant pairs. Kaplan-Meier Log Rank test was used to compare survival in four groups. $P < 0.05$ was considered statistically significant in all of the tests.

RESULTS

Primary end-point of the study was to use this cohort of patients with esophageal varices to evaluate the relationship between this disease and several etiologies, including NAFLD (in the presence or absence of cirrhosis), hepatitis B, hepatitis C or other liver-related

diseases. Second end-point was to draw this comparison in terms of PVT, HCC, survival and mortality.

Etiology

As shown in Table 1, the etiology of the total 258 patients with esophageal varices was attributed to: NAFLD in 39.0% (101 patients), hepatitis B virus in 29.1% (75 patients) and HCV in 11.2% (29 patients). In the rest of the patients (20.5%, 53 patients), the etiology was: Hepatoportal sclerosis in 7.8%, isolated portal vein thrombosis without any other pathology in 4.3%, chronic alcohol consumption in 3.1%, primary sclerosing cholangitis in 1.9%, autoimmune hepatitis in 1.2%, primary biliary cirrhosis in 1.2%, Wilson Disease in 0.8% and chronic pancreatitis in 0.4% of this group of patients.

Age

As Table 1 reveals, there is no statistical difference in the mean age between groups with NAFLD, hepatitis B and hepatitis C. However, the mean age of patients with these three etiologies (about 60 years) was higher than that in patients with other liver-related diseases (48 years) (Table 1; $P < 0.0001$). The mean age of women with esophageal varices (60.4 ± 14.8 years, median: 64, and range: 27-90) was higher than that in men (53.5 ± 14.6 , median: 56; and range: 24-84), $P < 0.001$. In terms of etiology, men exhibited a higher percentage of hepatitis B than NAFLD, hepatitis C and others (80% vs 62.4%, 58.6% and 58.5%, respectively, $P = 0.027$) (Table 1).

We also compared and found a difference in the mean age of patients with and without PVT (52 ± 15 years vs 58.5 ± 14.5 years, respectively, $P = 0.001$), with and without cirrhosis (56.3 ± 15 years vs 51.9 ± 13.8 years, respectively, $P < 0.05$), with and without HCC (62.7 ± 9.7 years vs 54.6 ± 15.4 years, respectively, $P = 0.001$) and the mean age of patients that have died and those that are still alive (61.1 ± 13.3 years vs 51.8 ± 15 years, respectively; $P < 0.0001$). However, there was no difference in the mean age of patients with and without fundic varices (54.9 ± 15.3 years vs 56.5 ± 14.8 years, respectively, $P > 0.05$).

PVT

The incidence rate of PVT was 41.9% (being detected in 108 out of 258 patients with esophageal varices) (Table 2). As Figure 1 and Table 2 indicate, PVT was observed in 47.5% of patients with NAFLD, 29.3% of patients with hepatitis B, 17.2% of patients with hepatitis C, and 62.3% of patients with other liver-related diseases ($P < 0.0001$). The incidence of PVT was 36.8% and 42.7% in patients with and without HCC, respectively ($P > 0.05$), 40.4% and 53.6% in patients with and without cirrhosis, respectively ($P > 0.05$), and 56.9% and 29.8% in patients with and without fundic varices, respectively ($P < 0.0001$). Of the 111 patients (43%) that died during the study period, 72 patients (64.9%) had no PVT ($P = 0.057$).

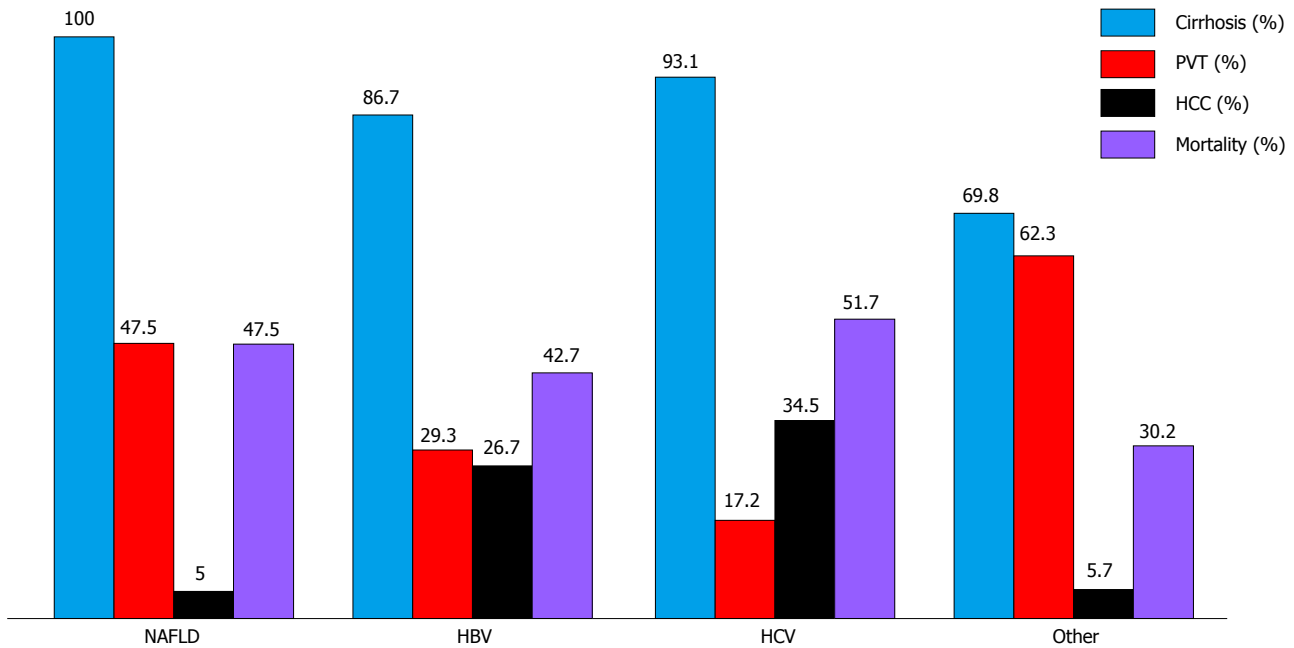


Figure 1 Incidence of portal vein thrombosis, cirrhosis, and hepatocellular cancer, in addition to mortality rate in patients with non-alcoholic fatty liver disease, hepatitis B, hepatitis C and other liver-related diseases (others). PVT: Portal vein thrombosis; HCC: Hepatocellular cancer; NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 1 Classification of study groups

	NAFLD	Hepatitis B	Hepatitis C	Others	Total	P value
n (%)	101 (39.0)	75 (29.1)	29 (11.2)	53 (20.5)	258 (100)	
Mean age (median; range of years)	56.4 ± 16.0 (59; 24-83)	57.8 ± 13.3 (58; 24-90)	62.9 ± 12.2 (65; 28-79)	48.1 ± 13.9 (48; 25-81) ^b	55.8 ± 15.0 (58; 24-90)	< 0.0001
% men	62.4%	80.0% ^a	58.6%	58.5%	66.3%	< 0.05

Study groups were classified per etiology: NAFLD, hepatitis B, hepatitis C and others. Mean age in patients with NAFLD, hepatitis B and C that was higher than the mean age of patients with other etiologies (^b $P < 0.0001$ others *vs* each of NAFLD, hepatitis B and C *vs* other etiologies). Percentage of men with hepatitis B was higher than those with NAFLD, hepatitis C and other etiologies (^a $P < 0.05$ patients with hepatitis B *vs* NAFLD, hepatitis C and other etiologies). NAFLD: Non-alcoholic fatty liver disease.

Table 2 Incidence of pathologies and mortality

	Cirrhosis	PVT	HCC	Fundic varices	Mortality
NAFLD	100%	47.5%	5.0% ^d	45.5%	47.5%
Hepatitis B	86.7%	29.3%	26.7%	52.0%	42.7%
Hepatitis C	93.1%	17.2% ^b	34.5%	27.6%	51.7%
Others	69.8% ^f	62.3%	5.7% ^d	43.4%	30.2%
Total	89.1%	41.9%	14.7%	45.0%	43.0%
P value	< 0.0001	< 0.0001	< 0.0001	> 0.05	> 0.05

The distribution of portal vein thrombosis (PVT), cirrhosis, hepatocellular cancer (HCC), fundic varices, and mortality rate in patients with NAFLD, hepatitis B, hepatitis C and other liver-related diseases (others) is shown. ^b $P < 0.0001$; ^d $P < 0.0001$; and ^f $P < 0.0001$. Different symbols were used in order to emphasize comparison within each etiology group. NAFLD: Non-alcoholic fatty liver disease.

Fundic varices

The condition of fundic varices was found in 116 (45%) patients; evenly spread among women and men (46% and 44.4%, respectively, $P > 0.05$). Etiology among patients with fundic varices was as follows: NAFLD in 39.7% (46 patients); hepatitis B in 33.6% (39 patients),

hepatitis C in 6.9% (8 patients) and other diseases in 19.8% (23 patients) ($P > 0.05$). The incidence of fundic varices was 47.4% and 44.5% in patients with and without HCC, respectively ($P > 0.05$), 43.9% and 53.6% in patients with and without cirrhosis, respectively ($P > 0.05$), and 61% and 33% in patients with and without PVT, respectively ($P < 0.0001$). Of the 111 patients (43%) that died during the follow-up study, 70 (63.1%) had no fundic varices ($P = 0.024$). The mortality rate was 35.6% and 51.9% in those with and without fundic varices, respectively ($P = 0.014$).

HCC

HCC was detected in 14.7% of patients (38 out of 258 total study pool). As shown in Figure 1 and Table 2, the incidence rate of HCC was: 5.0% in patients with NAFLD, 26.7% in patients with hepatitis B, 34.5% in patients with hepatitis C, and 5.7% in other diseases ($P < 0.0001$). Of the 38 patients with HCC, 13% had PVT (Table 3). Moreover, HCC increased the mortality rate in almost all the groups. The mortality rate in hepatitis B group increased from 31% (17/55) in patients with-

Table 3 Incidence of portal vein thrombosis

	Cirrhosis ($P > 0.05$)	HCC ($P > 0.05$)	Fundic varices ($P < 0.0001$)	Mortality rate ($P = 0.057$)
PVT (+)	86% (93 patients)	13% (14 patients)	61% ^b (66 patients)	36.1% (39 patients)
PVT (-)	91% (137 patients)	16% (24 patients)	33% (50 patients)	48.0% (72 patients)

The incidence of portal vein thrombosis (PVT) in patients with cirrhosis, hepatocellular cancer (HCC) and fundic varices are shown. Also reported is the relationship between PVT and the mortality rate. Each of these pathologies and mortality rate was compared in patients with and without PVT. ^b $P < 0.0001$ in the presence *vs* absence of PVT.

Table 4 Relationship among fundic varices, cirrhosis, hepatocellular cancer, and mortality rate

Fundic varices	Cirrhosis	HCC	Mortality rate
Yes	Yes	Yes	70.6%
		No	28.6%
	No	Yes	100%
No		No	28.6%
	Yes	Yes	85%
		No	23.1%
	No	Yes	No patients in this group
		No	23.1%

HCC: Hepatocellular cancer.

out HCC to 75% (15/20) in patients with HCC ($P = 0.001$). In the group with hepatitis C, the mortality rate increased from 32% (6/19) in patients without HCC to 90% (9/10) in patients with HCC ($P = 0.005$). The mortality rate in NAFLD patients increased from 47.5% during follow-up to 80% after HCC developed.

Mortality

As shown in Table 4 and Figure 2, 111 (43%) patients died in this study during follow-up. Of the patients, 50.0% with NAFLD, 33.3% with hepatitis B, 26.3% with hepatitis C, and 58.3% with other diseases were alive at the end of the 5-year period with a significant difference according to the Kaplan-Meier log Rank test ($P = 0.04$). Risk for mortality, measured by risk ratio (RR), did not change per gender (RR: male/female = 43.3%/42.5%, $P > 0.05$) or with the occurrence of cirrhosis (RR: 44.8%/28.6%, $P > 0.05$). However, it changed with the existence of fundic varices (RR: 49.3/35.3, $P = 0.024$ in favor of fundic varices development) and HCC (RR: 78.9%/36.8%, $P < 0.0001$ in favor of HCC development).

NAFLD group

Of the 258 patients, 39.0% (101 patients) were diagnosed with NAFLD. The mean age of NAFLD was 56.4 ± 16.0 years and 62% of these patients were men (Table 1). Moreover, 47.5% had PVT, 5.0% had HCC, and 45.5% had fundic varices (Table 2 and Figure 1). The mortality rate was 47.5% during follow-up (Table 2 and Figure 1), but increased to 80% in the presence of HCC.

DISCUSSION

NAFLD-associated cirrhosis is predicted to rapidly

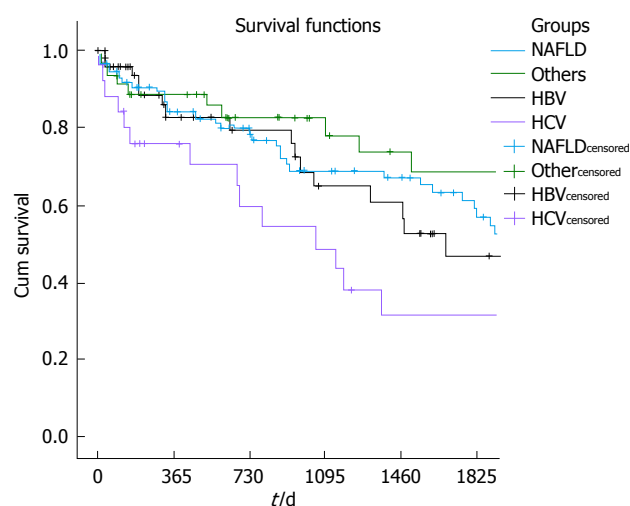


Figure 2 Survival functions in patients with non-alcoholic fatty liver disease, hepatitis B, hepatitis C and other liver-related diseases (others). Of the patients, 50.0% with NAFLD, 33.3% with hepatitis B, 26.3% with hepatitis C, and 58.3% with other diseases were alive at the end of the 5-year period with a significant difference according to the Kaplan-Meier log Rank test ($P = 0.040$). NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

become the leading indicator for liver transplant in the Western world^[24,25]. We herein show that NAFLD-associated cirrhosis is indeed the most common cause of end-stage liver disease at our liver center (Table 2 and Figure 1). By retrospectively evaluating national liver transplant database in the United States, Byrne *et al.*^[26] and Charlton^[27] and then, Wong *et al.*^[24,27] showed a significant increase in the proportion of patients undergoing liver transplant due to NASH. These findings differ from studies carried out in Japan where the rate of seronegative cirrhotic patients was 5%-20%. This finding could be explained by the relatively lower incidence of NASH (1%-3%) by comparison to hepatitis B, hepatitis C and alcoholic liver disease in Japan. Among the cohort of our patients who needed liver transplant, a significantly larger proportion developed decompensated cirrhosis due to NAFLD than hepatitis B or C.

In a prospective longitudinal cohort study, Hui *et al.*^[28] showed a comparable incidence and survival rate of cirrhosis related to hepatitis C to that related to NASH. Another large multi-center international study compared 247 patients with advanced fibrosis or cirrhosis secondary to NASH to 264 patients with chronic hepatitis C and similar stages of fibrosis^[29]. In that study, 19.4% of NASH patients developed liver-related

complications and 13.4% either died or underwent liver transplantations during follow-up, as compared to patients with hepatitis C among whom 16.7% developed liver-related complications and 9.4% either died or required transplant surgery. Our observations of higher mortality rates in patients with NAFLD differ from previously reported survival data^[28,30]. The first study^[28] that investigated the survival rate in patients with NASH reported a 10-year survival rate of 84%. Then, Sanyal *et al.*^[30] reported a 10-year mortality rate of 19.1% in patients with NASH cirrhosis as opposed to 4.1% in patients with compensated cirrhosis. Yatsuji *et al.*^[31] observed a 5-year HCC rate of 11.3% for NASH-associated cirrhosis and 30.5% for HCV cirrhosis; and a 5-year survival rate was 75.2% in NASH-associated cirrhosis and 73.8% in HCV cirrhosis in a study carried out on Japanese patients. Our study found the mortality rate in NAFLD to be 46% during follow-up and 80% after HCC developed. These rates were higher than those in patients with hepatitis in whom mortality rate was 31%-32% in the absence of HCC, and increased to 75% and 90% in patients with hepatitis B and C after HCC developed, respectively. The cohort of this study showed significantly higher mortality in comparison to reports in other ethnic groups. This difference could be due to several factors, such as: (1) The severity of the disease in our cohort that included patients with cirrhosis and esophageal varices; and (2) a higher rate of consumption of diet rich in fat (red meat) and carbohydrates (sweets) in Turkey, as opposed to other countries where fish and white meat (chicken) are more commonly used. Although the role of ethnicity and/or genetics remains controversial, it is possible that the heterogeneity in terms of age, genetic and environmental factors in patients studied in other reports^[1-4,14] contributes to the difference between their observations and those in the current studies. The observed higher mortality rate in our cohort could in part be attributed to its relative ethnical homogeneity since it basically consists of Caucasian patients from a Turkish origin.

Although NAFLD is a risk factor for HCC, the prevalence rate of HCC in cirrhotic NAFLD has not been well established, despite its reported range of 2.4% to 12.8%^[32]. Scientists from Sweden described three and five cases of HCC in cohorts of 129 and 256 subjects with NAFLD followed for 13.7 and 21 years, respectively^[33]. Previous reports indicated that the risk of HCC due to NAFLD is less than the risk resulting from chronic hepatitis C. In a 10-year prospective study, 10 out of 149 American patients with NAFLD-associated cirrhosis developed HCC compared to 25 out of 147 patients with hepatitis C virus-associated cirrhosis^[4]. A large retrospective cohort study from South Korea evaluated 329 patients with HCC associated with fatty liver disease and demonstrated an increase in NAFLD-related HCC from 3.8% in 2001-2005 to 12.2% in 2006-2010^[34]. A United States based study evaluated 195 NASH-cirrhosis patients from 2003-2007 with serial

abdominal computed tomography and serum alpha-fetoprotein every 6 mo with a median follow up of 3.2 years^[35]. Among this cohort for NASH-related cirrhosis patients, 12.8% ($n = 25$) developed HCC with an annual cumulative incidence rate of 2.6%. In a prospective cohort study, Yatsuji *et al.*^[31] compared 68 patients with NASH-related cirrhosis to 69 age- and sex-matched patients with hepatitis C-related cirrhosis to determine HCC risk. Overall, the 5-year cumulative HCC rate was 11.3% for NASH patients and 30.5% for hepatitis C patients. This lower HCC risk among NAFLD-related cirrhosis patients compared with hepatitis C-related cirrhosis was also confirmed by our study. Our results with 5.0% NAFLD-related HCC with cirrhosis was lower than previously reported with 2.4%-12.8% in patients with NAFLD^[32].

The current studies revealed the prevalence of portal vein thrombosis in patients with NAFLD to be significantly higher than in patients with hepatitis B or hepatitis C ($P < 0.0001$). This could be related to the predisposition of patients with NAFLD to developing pro-coagulation and impaired blood flow, as well as a pro-inflammatory state. It is well known that these patients are commonly obese. Obesity is associated with low-grade chronic inflammation and is strongly associated with chronic macrophage accumulation to the hypertrophied adipose tissue^[36-39]. Adipose tissue macrophages produce proinflammatory cytokines such as tumor necrosis factor- α , interleukin-6, and C-reactive protein. These cytokines alter insulin signaling by protein kinase C θ , inhibitor κ B kinase β , suppressors of cytokine signaling and inducible nitric oxide synthase to contribute to insulin resistance. Similarly, increased fat accumulation in liver alters its inflammatory milieu, thus modifying insulin action^[40]. The metabolic syndrome and NAFLD are also independently associated with both atherosclerosis and endothelial vascular dysfunction, which are related to a prothrombotic state. Thus, increased systemic inflammation and increased procoagulant factor levels associated with insulin resistance could explain the higher prevalence of portal vein thrombosis in our cirrhotic patients with NAFLD.

Englesbe *et al.*^[41] carried out a retrospective study evaluating the survival of 148 cirrhotic patients with occlusive portal vein thrombosis followed over a large period (1995-2007). The reported rate of death was 54.7%; significantly higher than the 37.2% in patients without portal vein thrombosis. These results are similar to our mortality data that show 65% incidence of death in cirrhotic patients with portal vein thrombosis vs 35% in patients without portal vein thrombosis. Additionally, the incidence of gastric varices was higher in NAFLD associated cirrhosis than other groups in our cohort.

It has also been reported that the incidence of portal vein thrombosis rises to 10%-40% in cirrhotic patients upon developing HCC^[42]. Consistently, our study showed an elevated incidence of portal vein thrombosis in cirrhotic patients with hepatitis C or B after they developed HCC. In contrast, HCC failed to alter

the incidence of portal vein thrombosis in our cirrhotic patients with NAFLD.

Our studies suggest that increase in NASH-associated cirrhosis would be an indication for orthotopic liver transplantation in Turkey. Increased frequency of NASH-associated cirrhosis with portal vein thrombosis in clinical practice has been a subject of debate among transplant surgeons. Whereas the high incidence of PVT (up to 26%) in patients awaiting liver transplantation constitutes a risk factor for early post-liver transplantation mortality^[43,44], PVT is no longer considered an absolute contraindication for transplantation. Unfortunately, we could not reach the records of patients receiving transplant surgery in our studies to be able to assess more concretely the transplantation outcomes in our Turkish patients with NASH-associated cirrhosis and portal vein thrombosis. However, Quillin *et al*^[16] have recently observed a strong indication for NASH in orthotopic liver transplantation in 2356 patients in the United States^[16], despite their older age by comparison to patients with hepatitis C and alcoholic cirrhosis. Whether this is related in part to the potential dominance of Caucasians in that study is unclear, but the study supports an equivalent, if not a more favorable, outcome for orthotopic liver transplantation in patients with fatty liver disease as compared to other common indications for surgery.

In conclusion, our data revealed a proportionally greater rise in liver transplant candidacy due to NAFLD-associated cirrhosis with portal vein thrombosis. The mortality rate of patients with NAFLD-associated cirrhosis did not differ from that in patients with virally caused cirrhosis. We confirmed that NAFLD was the third leading cause of HCC on the transplantation waiting list. Older patients were more prone to developing more cirrhosis, HCC and high mortality rates. However, the younger group had more portal vein thrombosis and fundic varices. These findings should constitute a reliable guideline for evaluating patients at the transplant center and for health policy makers to develop better strategic preventive measures against liver diseases.

COMMENTS

Background

Non-alcoholic fatty liver disease (NAFLD) predisposes to non-alcoholic steatohepatitis, which progresses to cirrhosis and hepatocellular carcinoma (HCC).

Research frontiers

NAFLD-associated cirrhosis is predicted to rapidly become the leading indicator for liver transplant. The mortality rate of patients with NAFLD might differ from that in patients with virally caused cirrhosis.

Innovations and breakthroughs

The authors' data revealed a proportionally greater rise in liver transplant candidacy due to NAFLD-associated cirrhosis with portal vein thrombosis. This could be related to the predisposition of patients with NAFLD to developing pro-coagulation and impaired blood flow, as well as a pro-inflammatory state. Their observations of higher mortality rates in patients with NAFLD differ from previously reported survival data. Older patients with esophageal varices were

more prone to developing cirrhosis, HCC and a high mortality rate.

Applications

The authors' data revealed a proportionally greater rise in liver transplant candidacy due to NAFLD-associated cirrhosis with portal vein thrombosis. The underlying cause for this predisposition remains unclear, although both genetic and environmental factors could be implicated. These findings should constitute a reliable guideline to evaluate patients at the transplant center.

Peer-review

This retrospective study describes NAFLD-related clinical diagnosis over 250 patients in Turkish origin. One unique strength of this study is to show higher risk of portal vein thrombosis and fundic varices, on the other hand, elderlies are more prone to cirrhosis, HCC and high mortality rates.

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