Progression and Natural History of Nonalcoholic Fatty Liver Disease in Adults

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Andrea Marengo, MD, Ramy Ibrahim Kamal Jouness, MD,
Elisabetta Bugianesi, MD, PhD*

KEYWORDS

• Steatohepatitis • Hepatocellular carcinoma • Type 2 diabetes • Obesity • Cirrhosis

KEY POINTS

- Liver-related mortality is the third cause of death in patients with nonalcoholic fatty liver disease (NAFLD) and is significantly higher in patients with nonalcoholic steatohepatitis (NASH) compared with patients with simple steatosis (7.3% vs 0.9% respectively) within the first 15 years of follow-up.
- The presence and severity of fibrosis on liver biopsy is currently the best indicator of long-term liver outcomes in patients with NAFLD.
- The rate of fibrosis progression is at around 1 stage every 6 to 15 years in patients with NASH but is reduced by half in patients with simple steatosis. However, some patients with NAFLD, also with simple steatosis, can progress rapidly to clinically significant fibrosis.
- Patients with NAFLD with cirrhosis have lower rates of liver-related complications but similar overall mortality as compared with patients with hepatitis C virus because of a higher incidence of cardiovascular events.
- Hepatocellular carcinoma incidence is growing in patients with NAFLD with or without cirrhosis, particularly among those with multiple metabolic risk factors.

INTRODUCTION

The 3 leading causes of death in patients with nonalcoholic fatty liver disease (NAFLD) in descending order are cardiovascular disease, cancer, and liver disease. Although the extrahepatic complications of NAFLD are described elsewhere, this section is focused on the potential liver-related morbidity and mortality that, along with the large prevalence and increasing incidence of this disease in the general population, clearly forecast the future impact of NAFLD on health care.

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Division of Gastroenterology and Hepatology, Department of Medical Sciences, A.O. Città della Salute e della Scienza di Torino, University of Turin, Corso Bramante 88, Turin I-10126, Italy
* Corresponding author.
E-mail address: elisabetta.bugianesi@unito.it

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The burden of data on the liver-related complications of NAFLD comes from studies addressing both the clinical course and the progression of liver damage through paired liver biopsies, but tackling the natural history of NAFLD is one of the most difficult challenges for researchers. On one hand, the variety of criteria used to define NAFLD from the clinical point of view (abnormal liver enzymes, hepatic ultrasound, indices of liver fat, and liver biopsy), coupled with the lack of sensitivity and specificity of most of the tests used and the composite nature of NAFLD outcomes, has hampered most clinical studies. On the other hand, studies based on repeat biopsies are limited by sampling variability and by the lack of consensus on what is the best definition of nonalcoholic steatohepatitis (NASH). Several scoring systems have been described to classify liver histology in adults with NAFLD.[1–3] The NASH Clinical Research Network (CRN) classification is the most frequently used in recent studies; however, the NAFLD Activity Score (NAS) has often been used as a surrogate for the diagnosis of NASH, although it is not designed for it but rather for crude evaluation of disease severity, once the diagnosis has been established by the overall pathologic assessment. The prospectively designed Steatosis-Activity-Fibrosis score[2] has been recently introduced. Despite these caveats, the threat that NAFLD is going to replace chronic hepatitis C as major cause of liver morbidity and mortality should be no longer overlooked.

LIVER DISEASE PROGRESSION IN SIMPLE STEATOSIS AND NONALCOHOLIC STEATOHEPATITIS

Major prospective cohort studies have been derived from Western populations, whereas data in Asian, African, and Latin American populations are limited (**Table 1**). The overall long-term mortality of Western patients with the whole spectrum of NAFLD is 34% to 69% higher than the general population of the same age and sex within 15 years of follow-up and is mostly due to cardiovascular disease.[4] In a community-based study of 420 patients from the United States, liver disease was the third leading cause of death in patients with NAFLD, as compared with the 13 leading causes of death in the general Minnesota population.[5] However, only 21 (5%) patients were diagnosed with cirrhosis, and 3.1% developed liver-related complications, including one requiring liver transplantation (LT) and 2 developing hepatocellular carcinoma (HCC). Higher mortality was associated with age (hazard ratio [HR] per decade 2.2; 95% confidence interval [CI] 1.7–2.7), impaired fasting glucose (HR 2.6; 95% CI 1.3–5.2), and cirrhosis (HR 3.1; 95% CI 1.2–7.8).

Importantly, there is a prognostic association between the presence of NASH, the stage of liver disease (higher fibrosis stage), and the long-term prognosis of patients with NAFLD. In patients with NASH compared with patients with simple steatosis, both the prevalence of cirrhosis development (10.8% vs 0.7%, respectively) and the liver-related mortality are significantly higher (7.3% vs 0.9%) within the first 15 years of follow-up.[10] These findings have been repeatedly confirmed. In a landmark study,[9] although just 5% of the 129 patients with biopsy-proven NASH enrolled went on to develop end-stage liver disease, including 3 patients with HCC, liver-related mortality was increased 10-fold compared with the reference population. However, in patients with simple steatosis (or steatosis with mild inflammation/cellular injury), the overall and liver-related mortality risk was not different. In the long-term follow-up studies available thus far, only 1% of patients with simple steatosis developed cirrhosis and died a liver-related death after a mean 15.6 years of follow-up, compared with 11% of those with NASH having or developing cirrhosis, and 7.3% of those with NASH dying of a liver-related cause after a similar period of

Table 1
Prevalence of cirrhosis in patients with NAFLD diagnosed by liver biopsy

Author (Year)	Diagnosis	Number	Cirrhosis Prevalence (%)	Follow-up (y)	Main Findings
Teli et al,[6] 1995	Bland steatosis	40	0	9.6	There was no progression to NASH/cirrhosis.
Dam-Larsen et al,[7] 2004	Bland steatosis	109	1	16.7	Patients with NAFLD have a benign clinical course without excess mortality.
Matteoni et al,[8] 1999	NAFLD	98	20	8.3	Poor outcomes are more frequent in patients with NASH.
Adams et al,[5] 2005	NAFLD	420	5	7.6	Mortality among patients with NAFLD is higher than the general population.
Ekstedt et al,[9] 2006	NAFLD	129	7.8	13.7	NAFLD with elevated ALT/AST is associated with a significant risk of developing end-stage liver disease. Survival is lower in patients with NASH.
Söderberg et al,[10] 2010	NAFLD	143	9	28.0	Patients with NASH are at increased risk of death compared with the general population.
Lee,[11] 1989	NASH	39	16.3	3.8	NASH has the potential to progress into cirrhosis.
Powell et al,[12] 1990	NASH	42	7	4.5	NASH should be recognized as a further cause of CC.
Evans et al,[13] 2002	NASH	26	4	8.7	There is no evidence of progressive chronic liver injury in patients with NASH.
Hashimoto et al,[14] 2005	NASH septal fibrosis/cirrhosis	89	48	3.7	The most important consequence of patients with NAFLD with advanced fibrosis was HCC.
Sanyal et al,[15] 2006	Cirrhotic-stage NASH	152	100	10.0	NASH-cirrhosis has a lower mortality rate compared with HCV-cirrhosis but a greater CV mortality.
Ascha et al,[16] 2010	Cirrhotic-stage NASH	195	100	3.2	Patients with NASH-cirrhosis have an increased risk of HCC.
Bhala et al,[17] 2011	NASH septal fibrosis/cirrhosis	247	54	7.4	Patients with NAFLD-cirrhosis have lower rates of liver-related complications and HCC than patients with HCV infection but similar overall mortality.
Stepanova et al,[18] 2013	NASH	289	NA	12.5	Patients with NASH have a higher risk of liver-related mortality than non-NASH.

Abbreviations: ALT/AST, alanine/aspartate aminotransferase; CC, cryptogenic cirrhosis; CV, cardiovascular; HCC, hepatocellular carcinoma; NA, not available.

follow-up,[4] leading to the concept that simple steatosis is a relatively "benign state," whereas NASH represents the form of NAFLD potentially progressive to cirrhosis and its complications (Fig. 1).

However, it is important to discriminate which of the histologic features of NASH are true determinants of long-term prognosis. In a cohort of 256 Swedish subjects, after a follow-up of up to 28 years, 40% of the 118 subjects with a histologic diagnosis of NAFLD died.[10] Compared with the total Swedish population, adjusted for sex, age, and calendar period, subjects with bland steatosis exhibited a 55% increased mortality and subjects with NASH 86%. Quite surprisingly, the study reported similar overall-related and liver-related mortality between the groups with and without definitive NASH (classified with the NASH CRN scoring system). However, 67% of patients classified as non-NASH in this study had liver fibrosis or even well-established cirrhosis, as fibrosis is not included in the NAS score. Thus, most likely the difference between the prognosis of NASH and simple steatosis is due to the greater likelihood of fibrosis being present in patients with NASH. This concept is supported by several studies. A more recent survey[19] conducted on 209 patients with NAFLD with a median 12 years of follow-up showed the presence of NASH correlated with liver mortality only when fibrosis was included in its definition, and the risk was highest with bridging fibrosis and cirrhosis (HR 5.68, 95% CI 1.5–21.5). Thus, it would seem likely that the presence and severity of fibrosis at liver biopsy would be the most important histologic determinant of long-term prognosis. Further evidence comes from recent studies demonstrating that noninvasive scoring systems correlating with the degree of fibrosis are capable of predicting liver-related events, LT, and death in patients with NAFLD.[20]

The rate of fibrosis progression in NAFLD is generally slow, and regression may also occur; but a subset of patients either with NASH or simple steatosis can develop severe liver damage quite rapidly (see Fig. 1). In a systematic review and meta-analysis[21] including 411 patients with biopsy-proven NAFLD (63% with NASH), over 2145.5 person-years of follow-up, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. The annual fibrosis progression rate in patients with NASH was doubled compared with that in patients with

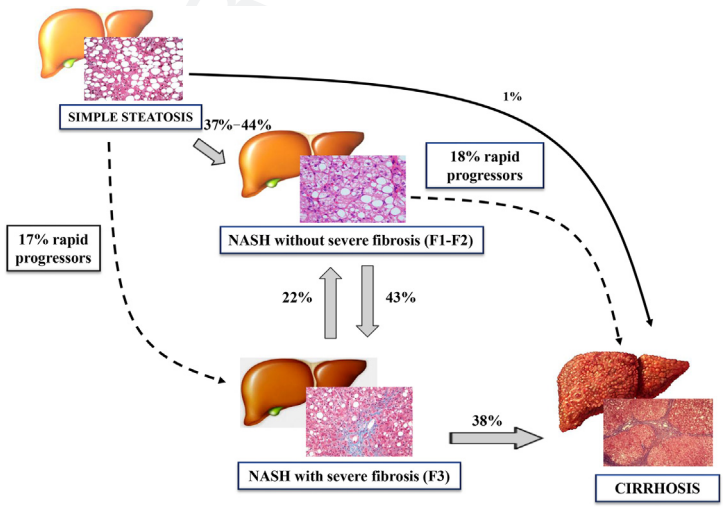

Fig. 1. Risk stratification for fibrosis progression in NAFLD.

simple steatosis; overall, one stage of fibrosis progression in patients with NASH occurred over 7.1 years in NASH versus 14.3 years in those with simple steatosis. However, the proportion of fibrosis progressors who moved from stage 0 to advanced (stage 3 or 4) fibrosis (rapid progressors) was identical in the 2 histologic subgroups (17% of patients with steatosis and 18% of patients with NASH). Similarly, a recent study has challenged the current concept that simple steatosis is a benign disease and cannot progress to significant liver damage. In a cohort of 108 patients from the United Kingdom with serial biopsies,[22] 81 had a baseline histologic diagnosis of NASH (75%) and 27 (25%) of NAFLD. The mean annual rate of fibrosis progression was 0.08 ± 0.25 stages. Remarkably, 44% of patients with baseline NAFLD developed NASH, including 10 patients in which fibrosis worsened over time (3 of 10 progressed by 1 stage, 5 by 2 stages, and 2 by 3 stages). No difference in the proportion exhibiting fibrosis progression was found between patients with steatosis or NASH at index biopsy (37% vs 43%), although all patients with steatosis developing fibrosis had also developed NASH on follow-up biopsy (see **Fig. 1**). Of note, 44% of the patients with steatosis developed NASH after a median 8 years of follow-up, suggesting that NASH usually develops after steatosis. Overall, these data suggest that the necroinflammatory damage per se is not as important as fibrosis for the long-term prognosis of patients with NAFLD and accordingly the major focus of therapy should be in the resolution of fibrosis rather than of the other histologic features of NASH.

RISK FACTORS FOR DISEASE PROGRESSION IN SIMPLE STEATOSIS AND NONALCOHOLIC STEATOHEPATITIS

Provided that the presence and severity of fibrosis is the key factor determining long-term, liver-related mortality, the key question is which are the main determinants of NAFLD progression that can be identified without a liver biopsy. Age, body mass index (BMI), type 2 diabetes mellitus (T2DM) or metabolic syndrome (MetS), and insulin resistance assessed by homeostasis model assessment are well-recognized risk factors for advanced fibrosis in multiple cross-sectional studies; but few of them have also been examined in longitudinal studies and in relation to their ability to predict the progression of NAFLD. In the previously cited meta-analysis,[21] the presence of hypertension (odds ratio [OR] 1.94; 95% CI 1.00–3.74) and a low aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio at the time of baseline biopsy was associated with the progression of fibrosis, whereas in the most recent study,[22] most (80%) of the patients with NAFLD in which fibrosis worsened were diabetic and had a longer disease duration. Fibrosis progressors had also a significantly lower platelet count ($P = .04$) and higher AST/ALT ratio ($P = .04$) and Fibrosis 4 (FIB-4) score ($P = .02$) than nonprogressors. The same study identified the FIB-4 score as the only significant baseline factor able to predict fibrosis progression, whereas the presence of T2DM (OR 6.25; CI 1.88–20) and FIB-4 score (OR 3.1; CI 1.4–6.8, $P = .004$) at the time of follow-up liver biopsy were indicators of the presence of fibrosis.

Among genetic factors, homozygosity for the patatin-like phospholipase domain-containing protein (PNPLA3) 148M allele has been associated with a 3.3-fold increased risk of both NASH and liver fibrosis independent of BMI, T2DM, and steatosis (for NASH) and age, BMI, T2DM, steatosis, and NASH (for fibrosis).[23] The association between PNPLA3 I148M and the severity of fibrosis in NAFLD has been almost contemporarily replicated by independent groups in adults[24,25] and in the pediatric population[26] and confirmed by a recent meta-analysis.[27] Studies on the ability of genetic and other factors to predict the risk of disease progression are

definitely needed, not only in the Western population but also in other developed and developing countries where the risk of NAFLD is paralleling the economic development.

LIVER DISEASE PROGRESSION IN NONALCOHOLIC STEATOHEPATITIS–RELATED CIRRHOSIS

It is well established that patients with severe liver damage are more likely to develop liver-related complications, and pooled data from long-term (~10 years) follow-up studies of patients with NAFLD with advanced fibrosis and cirrhosis demonstrate a 16% mortality with 60% of the deaths liver-related compared with only approximately 9% liver-related in long-term (~15 years) follow-up studies of patients with NAFLD without advanced fibrosis or cirrhosis.[4] However, the natural history of cirrhosis due to NASH has been addressed by only few studies.

In an Australian study of 23 patients with NASH cirrhosis identified from a hospital database, the 10-year survival rate was 84%. Comparing these patients to subjects affected by hepatitis C virus (HCV)–related cirrhosis, the study showed no difference between liver-related deaths or all-cause mortality between the two groups after adjustment for baseline differences, despite a trend toward improved survival in NASH.[28] In a larger study,[15] the 10-year survival in the NASH group was 80.9%, significantly better than in the HCV controls of similar age, sex, and Child-Pugh score, principally because of a lower risk of hepatic decompensation in the NASH cohort. In subjects with NASH-related cirrhosis, ascites was the first and most common clinical feature of decompensation but occurred at a slower rate than in patients with HCV. Once ascites developed, the rate of hepatorenal syndrome was similar in the two groups. Development of varices and the rates of variceal hemorrhage were similar in NASH-related and HCV-related cirrhosis, whereas the incidence of hepatic encephalopathy was intermediate between that for ascites and variceal hemorrhage. Remarkably, subjects with NASH-related cirrhosis had a significantly higher rate of cardiovascular mortality compared with HCV-related cirrhosis. These data have been corroborated in another independent cohort.[16] In a multicenter prospective study,[17] the long-term morbidity and mortality of 247 patients with NAFLD advanced fibrosis or cirrhosis was compared with 264 patients with HCV cirrhosis. Both cohorts were Child-Pugh class A and had cirrhosis confirmed by liver biopsy. In the NAFLD cohort, liver-related complications occurred in 19.4% of cases and deaths or LT in 13.4%, compared with 16.7% and 9.4%, respectively, in the HCV cohort. When adjusting for baseline differences in age and sex, the cumulative incidence of liver-related complications was lower in the NAFLD than the HCV cohort, including incident HCC; but cardiovascular events and overall mortality were similar in both groups. Thus, NAFLD seems to have lower rates of liver-related complications but a similar overall mortality compared with patients with HCV. Fibrosis stage and standard clinical and biochemical parameters are relevant in assessing the risk of future liver complications.

HEPATOCELLULAR CARCINOMA IN NONALCOHOLIC FATTY LIVER DISEASE

The exact burden of HCC related to NAFLD remains uncertain, but it is clear that NAFLD is going to be the most common underlying etiologic risk factor for HCC. In a population–based study in the United States, NAFLD accounted for 59% of HCC cases, with a cumulative incidence of 0.3% over a 6-year follow-up.[29] The mortality rates for HCC ranged from 0.25% to 2.3% over 8.3 and 13.7 years of follow-up in 2 further studies.[8,9] In the largest prospective community-based study performed so

far,[30] after a mean follow-up of 7.6 years, only 0.5% patients developed HCC; but the rate among cirrhotic patients was 10%. As expected, the risk of HCC is more elevated when examining patients with advanced liver disease; but patients with NAFLD with HCC have a lower prevalence of cirrhosis than patients with HCC in HCV-related and other liver diseases. This prevalence is an important characteristic of HCC in NAFLD, which has been reported in multiple publications (**Table 2**).

Hepatocellular Carcinoma in Nonalcoholic Steatohepatitis–Related Cirrhosis

Two longitudinal studies on the natural history of NASH-related cirrhosis in the United States[15] and Japan[30] confirmed that HCC was the cause of 47% of deaths in patients with NASH, representing an independent risk factor for liver-related mortality (HR 7.96). Overall, the relative HCC risk and mortality rate in NASH-related cirrhosis seems to be lower in comparison with viral or alcohol-related cirrhosis. In a large cohort study, HCC was significantly more common in HCV than NAFLD (6.8% vs 2.4%, respectively)[17] and the HCV cohort had an approximate 0.15% risk per year of HCC development versus 0.05% in NAFLD. However, the perception that HCC is a rare and late complication of NAFLD has been denied by recent reports. In North East England, the overall incidence of HCC increased 1.8-fold from 2000 to 2010; but most shocking was a more than 10-fold increase in HCC associated with NAFLD, accounting for 34.8% of all the cases in 2010 and making it the single most common underlying cause.[39] Not surprisingly, this increasing incidence of HCC was associated with an increasing prevalence of overweight and obesity (61.0% in 2000 and 65.5% in 2010). This finding confirms that the apparently lower rates of HCC arising in NAFLD-cirrhosis compared with other causes of chronic liver disease are definitely outweighed by the much larger spread of NAFLD in the general population and open future scenarios in the approach to HCC.

Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease Without Cirrhosis

The most worrisome issue consistently emerging in the last years is the onset of HCC in patients with NAFLD who do not have cirrhosis yet. A French study analyzed a cohort of 31 patients with HCC with MetS as the only risk factor for liver disease and found mild or no fibrosis in most cases, compared with those harboring HCC associated with an overt cause of liver disease (65% vs 26%, $P<.0001$).[38] The absence of cirrhosis was further confirmed in 38% of Japanese patients[41] and in one-third of patients from North East England with NAFLD-related HCC.[41] As patients without cirrhosis are not in surveillance programs, most (62.3%) presented symptomatically with larger tumors, and their median survival was just 7.2 months.[39]

In conclusion, HCC in NAFLD should not be underestimated for several reasons. First, once cirrhosis had developed, HCC represents a frequent complication, with an incidence of up to 10% over a 7-year follow-up. Secondly, HCC can also arise in the absence of cirrhosis in patients with NASH with multiple metabolic risk factors, mainly obesity and T2DM. These observations arouse an urgent need to better understand the risk factors linked to the development of HCC, especially in noncirrhotic livers, and to update screening programs.

Nonalcoholic Fatty Liver Disease in Lean Patients

A small but significant proportion of patients (7%–21%) develops NAFLD despite normal BMI, and they are defined as lean or normal weight NAFLD.[42–46] They are generally described in the Asian populations; but within the National Health and

Table 2
Principal studies on the association between NAFLD and HCC

Author (Year)	Diagnosis	Study Population	Main Findings
Bugianesi et al,[31] 2002	Cirrhosis	641 patients with cirrhosis-associated HCC	NAFLD-related features are more frequent in HCC arising in CC than viral or alcoholic cirrhosis.
Marrero et al,[32] 2002	Cirrhosis	105 patients with HCC	CC-related HCC was less likely to have undergone HCC surveillance and had larger tumors at diagnosis.
Regimbeau et al,[33] 2004	Cirrhosis	210 patients who underwent resection for HCC	Obesity and T2DM may be important risk factors for HCC, via NAFLD and CC.
Ascha et al,[16] 2010	Cirrhosis	510 patients with cirrhosis	Patients with NASH cirrhosis have an increased risk of HCC yearly cumulative incidence (2.6% vs 4.0% in HCV).
Yasui et al,[34] 2011	Cirrhosis and NAFLD/NASH	87 HCC cases; no cirrhosis in 43 patients	Most patients with NASH who develop HCC are men with features of MetS and at a less advanced stage of liver fibrosis.
Mittal et al,[35] 2015	Cirrhosis	1500 patients with HCC	NAFLD is the third most common risk factor for HCC. Cirrhosis was less common in NAFLD-related cases compared with alcoholic or HCV-related HCC.
Wong et al,[36] 2014	Cirrhosis	10,061 adult LT recipients for HCC	NAFLD is the most rapidly growing indication for LT in HCC cases in the United States.
Tateishi et al,[37] 2015	Cirrhosis	33,782 patients with HCC (596 NAFLD related)	Most cases of nonviral HCC are related to lifestyle factors, including obesity and T2DM.
Paradis et al,[38] 2009	NAFLD/NASH	31 patients with HCC with MetS as the only risk factor for liver disease	NAFLD contributes to noncirrhotic HCC.
Dyson et al,[39] 2014	Cirrhosis and NAFLD/NASH	623 patients with HCC	HCC cases without cirrhosis most commonly occurred in NAFLD. Patients without cirrhosis were not in surveillance programs, and most presented symptomatically with larger tumors.
Leung et al,[40] 2015	Cirrhosis and NAFLD/NASH	54 patients with NAFLD-associated HCC	HCC can develop in NAFLD without cirrhosis. At diagnosis, such tumors are larger than those in cirrhotic patients.

Abbreviation: CC, cryptogenic cirrhosis.

Nutrition Examination Survey III cohort, 7.4% of subjects had a normal BMI (<25 kg/m^2).[47] Lean individuals with NAFLD constitute a subgroup of patients relatively free from MetS, although insulin resistance can be increased anyway compared with healthy controls.[48] The common variant in the PNPLA3 gene (I148M) can partially explain the onset of NAFLD in lean patients; but in a recent study,[46] PNPLA3 polymorphism did not contribute to incident NAFLD.

The pivotal question is whether lean patients with NAFLD have a different disease progression compared with obese patients with NAFLD, but the answer is still unknown because of the paucity of clinical and histologic outcome data. In a biopsy series, leaner Asian patients with NASH were less likely to have advanced fibrosis and cirrhosis than Caucasians.[49] However, the preliminary report of an international study indicated a more severe prognosis in lean subjects with biopsy-proven NAFLD compared with overweight/obese subjects.[50] In a cohort of 1090 NAFLD cases, only 125 (11.5%) were classified as lean at first diagnosis. In accordance with previous studies, lean patients with NAFLD were characterized by a lower prevalence of T2DM, hypertension, hypertriglyceridemia, low high-density lipoproteins cholesterol, central obesity, and MetS as well as more frequently normal liver enzymes and a lower prevalence or severity of insulin resistance. Histology was characterized by milder degrees of steatosis and fibrosis but more severe lobular inflammation. In a subgroup of 483 patients, whereby the index liver biopsy had been performed before 2005, the difference in overall mortality between the lean and nonlean NAFLD group was analyzed. Over a follow-up of 11 years, 71 of the 483 (14.7%) patients died; surprisingly, the cumulative survival was significantly shorter in lean patients with NAFLD as compared with non–lean NAFLD (log-rank test = 5.6; P<.02). This difference remained significant when adjusted in a Cox regression model, with only lean NAFLD (HR 11.8; 95% CI 2.8–50.1; P = .001) and age (HR 1.05; 95% CI 1.008–1.1; P = .02) identified as prognostic factors. These provocative data point out that the definition of risk factors for the progression of NAFLD is still an open issue and that we should not quickly discharge lean patients with NAFLD from the gastroenterology outpatients clinic, overlooking their potential liver-related complications.

SUMMARY

Patients with NAFLD are at risk of liver-related complications and death; but fibrosis progression is generally slow, taking around 8 years to progress from stage 0 to stage 1 fibrosis, although there is a subgroup of rapid progressors who can progress 3 to 4 stages within 2 to 6 years. There is a prognostic association between the histologic stage of liver disease and the long-term prognosis of patients with NAFLD. Currently the presence and severity of fibrosis at index biopsy is the best indicator of the long-term liver outcome. Pooled data from long-term follow-up studies of NAFLD demonstrate only approximately 9% of liver-related deaths in patients without advanced fibrosis or cirrhosis, whereas patients with NAFLD with advanced fibrosis and cirrhosis demonstrate a 16% mortality with 60% of the deaths liver related. Among nonhistologic predictors, hypertension and T2DM at presentation are the factors most consistently associated with the risk of disease progression that is observed also in lean patients. HCC is a worrisome growing complication of NAFLD at any stage. Scientific advances in the understanding of mechanisms of fibrosis and carcinogenesis in NAFLD are awaited with interest in order to provide clinical indexes to predict and prevent the risk of liver-related deaths.

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