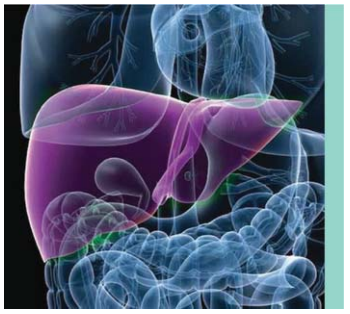

Natural History of Nonalcoholic Steatohepatitis/Nonalcoholic Fatty Liver Disease-Hepatocellular Carcinoma: Magnitude of the Problem From a Hepatology Clinic Perspective

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PREDICTED IMPACT OF NONALCOHOLIC FATTY LIVER DISEASE/NONALCOHOLIC STEATOHEPATITIS-HEPATOCELLULAR CARCINOMA IN THE HEPATOLOGY CLINIC

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western countries. It is estimated that NAFLD affects more than 10% of the adult population in the United States,[1] but this number can increase up to 35% when considering fatty liver diagnosed by imaging.[2] NAFLD prevalence has increased in the last decades,[1] across all ethnic groups. This also affects the pediatric population, with a 2-fold increase in the last 15 years.[3] Insulin resistance and metabolic

Abbreviations: BCLC, Barcelona Clinic Liver Cancer Staging; BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NR, not reported.

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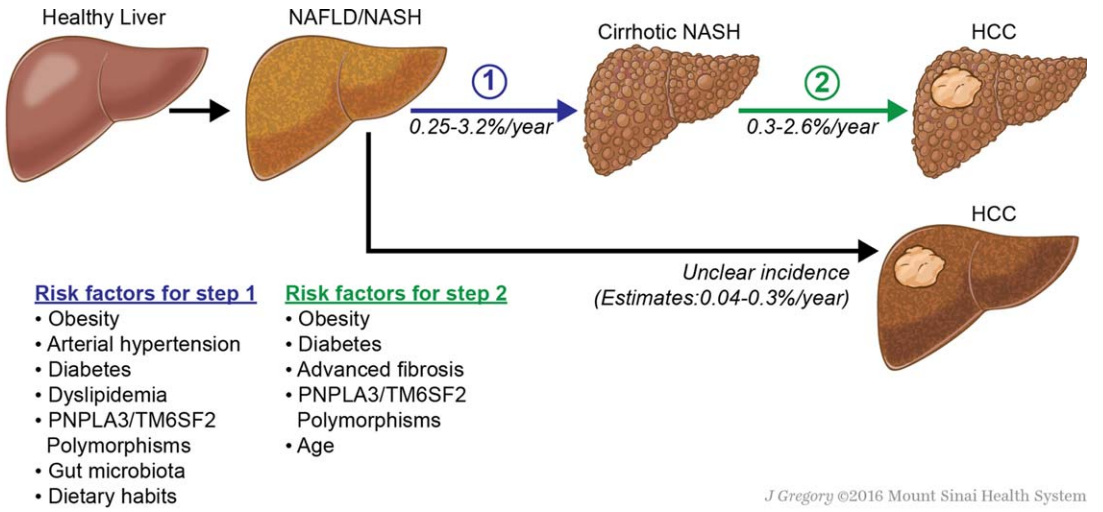

FIG 1 Natural history of NASH/NAFLD-related HCC. Illustration by Jill K. Gregory, CMI. Mount Sinai Health System.

syndrome are almost invariably associated to NAFLD and to certain extent, NAFLD is viewed as the hepatic manifestation of metabolic syndrome. The spectrum of NAFLD includes a variety of different clinical conditions from simple steatosis with normal liver function to active inflammation [nonalcoholic steatohepatitis (NASH)] and subsequent fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Arterial hypertension and type 2 diabetes are frequently associated with fibrosis progression[4] (Fig. 1), but many other factors are involved, including gut microbiota, dietary habits, and genetic factors, such as *PNPLA3* and *TM6SF2* polymorphisms. In patients with simple steatosis, the average progression of one stage of fibrosis is estimated to be 14 years, whereas for patients with NASH this time is shorter, being around 7 years.[4] NASH is a leading cause of liver cirrhosis in Western countries, and considering the recent advancements in the field of anti–hepatitis C virus (HCV) therapies, it is likely that in the next 30 years NASH will become a major cause of advanced liver disease. Parallel to the increase in NASH-cirrhosis cases, there has been an increase in the prevalence of NASH-related HCC.[5]

The pathogenesis of HCC in the context of NAFLD is only partially understood; interestingly, close to 30% of NASH-related HCCs are diagnosed in the setting of noncirrhotic liver.[5,6] Older age, diabetes, advanced fibrosis, and obesity are the main risk factors associated with HCC development (Table 1). Typical patients with HCC developing in a setting of noncirrhotic NASH are males, older, and display criteria of metabolic syndrome.[7,8] Obesity is known to increase significantly the risk for different types of cancer including liver cancer. In obese men, the excess risk of death for liver cancer is 4 times higher than that of nonoverweight individuals.[9] The association of diabetes and HCC has also been reported in different series. A US study showed that the relative risk of HCC in patients with diabetes is 2 compared with those without diabetes, and similar figures have been reported in Europe.[10,11] Among the genetic factors, the *PNPLA3* rs738409 C>G polymorphism is associated with an increased risk for HCC development through a mechanism yet ill-defined.[12] Overall, these data suggest that NASH will become the dominant cause of HCC in Western countries in the next decades.

TRENDS AND CLINICAL SINGULARITIES OF NASH-HCC

Most NASH-related HCC cases are diagnosed in the context of cirrhosis. However, the incidence of HCC in these patients varies widely depending on the population studied and the diagnostic criteria used. Indeed, patients with advanced cirrhosis may lose the typical histological features of NASH, and in many retrospective series, patients with cryptogenic cirrhosis and clinical features of metabolic syndrome are considered to have NASH-cirrhosis. The cumulative incidence rate of HCC in NASH-cirrhosis ranges between 0.3% and 2.6% per year.[13,14] This risk increases with older age at diagnosis of cirrhosis and concomitant diabetes and obesity.[14,15]

TABLE 1. STUDIES REPORTING HCC INCIDENCE IN NASH

Author, Year, Publication	NASH/NAFLD Diagnostic Criteria	Study Population	Follow-up (years)	Annual HCC Incidence	Risk Factors for HCC Development
Sanyal, 2006, Hepatology[17]	Biopsy proven, alcohol intake <40 g/week, negative tests for other causes of cirrhosis	152 NASH-cirrhosis	10	0.2%	Not identified
Bhala, 2011, Hepatology[13]	Biopsy proven	247 NASH (cirrhosis 52%, advanced fibrosis 48%)	7.1	0.3%	Not identified
Kawamura, 2012, Am J Gastroenterol[15]	Fatty liver at ultrasound, alcohol intake <20 g/day, negative tests for other causes of cirrhosis	6508 NAFLD (not reported % of significant fibrosis/cirrhosis)	5.6	0.04%	Age Elevated alanine aminotransferase Low platelet count Diabetes
Adams, 2005, Gastroenterology[18]	Fatty liver at ultrasound or biopsy, alcohol intake <140 g/week, HCV/HBV-negative, or cryptogenic cirrhosis with criteria of metabolic syndrome	420 NAFLD (cirrhosis 2%)	7.6	0.06%	Not analyzed
Ascha, 2010, Hepatology[14]	Biopsy-proven or cryptogenic cirrhosis with metabolic syndrome without history of significant alcohol intake	195 NASH-cirrhosis	3.2	2.6%	Older age Any alcohol consumption

Although HCC predominantly occurs in a cirrhotic background liver, its incidence in noncirrhotic patients has been increasingly reported. An analysis of 128 HCC patients compared cases caused by metabolic syndrome versus other chronic liver disease.[16] The authors observed that patients with metabolic syndrome tended to be older and were less likely to have cirrhosis. Subsequent studies conducted mostly in Japan showed consistent results. In a study of 87 HCC patients with underlying NASH, cirrhosis was intriguingly less frequent in male compared with female patients.[7] Using the aspartate aminotransferase/platelet ratio index as a surrogate marker of fibrosis, a Japanese report described the cumulative rate of HCC in a cohort of 6324 patients without significant fibrosis. Estimated HCC rates were 0.02%, 0.06%, and 0.39% at 4, 8, and 12 years of follow-up, respectively.[15] Strikingly, 184 patients with significant fibrosis enrolled in the same study showed HCC rates up to 4% at 12 years. Although data from the United States are still scarce, two recent studies evaluated this using data from the Veterans Administration hospitals. The first study showed that compared with HCV-HCC, patients with NASH-HCC were significantly less likely to be cirrhotic.[6] A higher proportion of patients with NASH-HCC did not receive HCC surveillance during the 3 years preceding diagnosis. The second study sought to identify risk factors of HCC in the absence of cirrhosis.[8] In this cohort of 1500 patients with HCC, NASH and metabolic syndrome was the main risk factor in patients without cirrhosis.

The epidemiology of NASH-HCC is changing as the number of patients with metabolic syndrome increases every year. A significant proportion of these patients develop HCC in the setting of a noncirrhotic liver, and hence outside surveillance programs.[6] Compared with patients with other causative factors, patients with NAFLD-HCC tend to be older, with less severe liver dysfunction,[6] and more frequently display comorbidities such as diabetes, obesity, dyslipidemia, and hypertension. These factors increase the clinical complexity of these patients, and ultimately, this makes more challenging their clinical management (Table 2).[13,14] Indeed, patients with NASH-related HCC are less likely to receive potentially curative treatment compared with patients with HCV.[6] There are still many uncertainties in terms of HCC risk at the different stages of NAFLD/NASH (Fig. 1) and whether other genetic factors could contribute to an

TABLE 2. MAIN CLINICAL CHARACTERISTICS OF PATIENTS WITH NASH-RELATED HCC COMPARED WITH OTHER CAUSATIVE FACTORS

Author, Year, Publication	Study Population	Age (years)	Diabetes	Dyslipidemia	Hypertension	BMI (kg/m^2)	Cirrhosis	Tumor Burden at Diagnosis		
								No. of Nodules	Size (cm)	
Dyson J, 2014, J Hepatol[5]	136 NAFLD/NASH	71	80%	NR	NR	32	77%	2.3	5.3	
	469 other causative factors	68.2	30%			26.4	70.9%	2.4	5.7	
Beste L, 2015, Gastroenterology[19]	1029 NAFLD/NASH	70.5	76%	NR	NR	31	NR	NR		
	6641 other causative factors	66.2	39.2%			28.2				
								BCLC		
								0-A	*B*	*C*
Piscaglia F, 2016, Hepatology[20]	145 NAFLD/NASH	67.8	73.1%	57%	73.1%	29.1	53.8%	42.8%	19.3%	33.1%
	611 HCV	71.1	24.9%	8.3%	37.1%	27.6	97.2%	53%	14.6%	23.9%
								BCLC		
								A	*B*	*C*
Weinmann A, 2015, BMC Cancer[21]	45 NAFLD/NASH	67.6	66.7%	0%	71.1%	29	77.8%	20%	24.4%	42.2%
	1074 other causative factors	65	37.8%	19.6%	45.2%	26.6	79.9%	24%	16.7%	42.6%
Wong RJ, 2014, Hepatology[22]	807 NAFLD/NASH	59.3	42.8%	NR	NR	33.6	NR	NR		
	7066 other causative factors	57.2	20.8%			27.3				
								>3 Nodules	Size (cm)	Vascular inv. or Metastasis
Tateishi R, 2015, J Gastroenterol[23]	596 NAFLD/NASH	69.7	32.7%	22.9%	55.5%	NR	64.9%	16.8%	3.0	6%
	4730 other causative factors	72	41.9%	12.5%	36.9%		63.4%	23%	3.06	11.6%

Abbreviations: BCLC, Barcelona Clinic Liver Cancer Staging; BMI, body mass index; NR, not reported.

increased risk in this population. Tailored surveillance programs using robust risk biomarkers could be an option to make surveillance in noncirrhotic NASH-HCC cost-effective, especially considering the increasing incidence of NASH. In summary, the irruption of NASH in the hepatology clinic will have a strong impact in the epidemiological landscape and clinical management of HCC. This may translate in older patients with frequent comorbidities and less advanced liver dysfunction that could impact the applicability of potentially curative therapies.

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