Natural History of Nonalcoholic Steatohepatitis–Associated Hepatocellular Carcinoma

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Nonalcoholic fatty liver disease (NAFLD) refers to the presence of fat accumulation in the liver, without any other causes for secondary hepatic steatosis. NAFLD is present in one-fourth of the general population, and in one-third of cases there is a progressive disease that can lead toward more severe stages such as nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC).^{1,2} NASH, which is considered the liver expression of metabolic syndrome, is rapidly becoming the most important cause of cryptogenic cirrhosis.³ The increasing incidence of NAFLD/NASH mirrors the parallel spread of type 2 diabetes mellitus (T2DM), obesity, and hypercaloric diet, associated with fructose-containing drinks and sedentary life habits among general population worldwide. Recently, Younossi et al.⁴ reviewed 729 studies published and, by selecting a total sample size of 8,515,431 from 22 countries, designed the global prevalence rate of NAFLD, which is 25.24% (range 22.1–28.6%). The highest prevalence is in the developing

and developed countries (Middle East, South America, United States, and Europe) and the lowest in Africa.

Progression of NAFLD to NASH and fibrosis, from a clinical liver-related outcome, is slow and unusual, with non-liver-related mortality (mainly cardiovascular) being >50-fold more common than liver-related mortality.⁴

In contrast, the most frequent type of cancer in T2DM is HCC, and obesity almost doubles the risk for HCC.^{5,6} The number of deaths per year in HCC is virtually identical to the incidence throughout the world (6/100,000 in the United States in 2010), underscoring the high case fatality rate of this aggressive disease.⁷ Although presently almost 80% of cases are still due to underlying chronic hepatitis B and C virus infection, a rapidly increasing incidence of NAFLD-HCC is expected in the next 10 years, and NASH-cirrhosis or NASH-HCC will be the most frequent indications for liver transplantation.⁸ As shown in Figure

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

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1, an Italian study of the group I.T.A.L.I.C.A. demonstrates that HCC on NAFLD (NAFLD-HCC) increased exponentially among the nonviral chronic liver diseases etiologies during the last 10 years, at least in Italy.⁹

The natural history and progression from NAFLD/NASH to HCC is still not completely unraveled. It is well-known that obesity, especially visceral obesity, insulin resistance, T2DM, metabolic syndrome, iron overload, and hemo-chromatosis are all factors of risk for progression of cirrhosis to HCC. It appears that simple steatosis is not a risk for HCC *per se*, but coexistence of other risk factors, such as previous or current excessive alcohol drinking, hepatitis B virus, or hepatitis C virus (HCV), may

FIG 1 Temporal trends of non-viral-related HCC in Italy. Adapted with permission from *Liver International*.⁹ Copyright 2016, International Association for the Study of the Liver.

drastically change this conclusion. Indeed, the risk for HCC is more elevated in NASH patients with higher fibrosis scores or cirrhosis. Progression of NAFLD to NASH or even more importantly to a significant stage of fibrosis (>F2) is the most important risk factor for NASH-HCC.

Our group,⁸ together with the I.T.A.L.I.C.A.⁹ consortium, recently compared 145 patients with NAFLD-HCC with a large group of 611 patients with HCC and HCV chronic infection (HCV-HCC) enrolled and followed up in secondary Italian centers, in a 3-year timeframe. Fifty-four percent of patients with NAFLD-HCC had cirrhosis as compared with 97% of patients with HCV-HCC, indicating that NAFLD-HCC could develop in 46% of the not yet cirrhotic livers⁸ (Table 1). Patients with NAFLD-HCC were significantly younger, more often male, smokers, with more metabolic risk factors, and showed a higher mortality for cardiovascular disease and worse average liver function tests than patients with HCV-related HCC. In HCV-HCC patients, HCC was diagnosed more frequently during surveillance⁸ because several patients with HCC NAFLD were not aware they suffered a significant liver condition before HCC discovery. However, thanks to the lower rate of background cirrhosis, patients with NAFLD-HCC were more likely to receive a radical therapy, such as surgical resection. Overall survival, after correction for confounding factors, was similar in the two groups.⁸ Similarly, in other studies,¹⁰ PNPLA3 polymorphisms, age, body mass index, type 2 diabetes,

TABLE 1. HCC CAUSED BY HCV AND NASH: CIRRHOSIS (%) FOUND IN PATIENTS WITH HCV-HCC OR NASH-HCC

Study	Design; Country; Number (N) of Patients	Etiology (n)		Cirrhosis (%)	
		HCV	NASH	HCV	NASH
Guzman et al. (2008) ¹¹	Retrospective; United States; N -- 50	16	5	100	40
Paradis et al. (2009) ¹²	Retrospective; France; N -- 128	24	31	74	35
Hashimoto et al. (2009) ¹³	Prospective; Japan; N -- 34	0	34	86	31
Kawada et al. (2009) ¹⁴	Retrospective; Japan; N -- 8	0	6	---	25
Starley et al. (2010) ¹⁵	Case Series; United States; N -- 67	0	67	---	78
Tokushige et al. (2013) ¹⁶	Survey; Asia; N -- 14,530	9589	291	90	62
Jashui et al. (2011) ¹⁷	Retrospective; Japan; N -- 87	0	87	---	51
Duan et al. (2012) ¹⁸	Pooled of 25 studies; mixed; N -- 169	---	149	---	60
Mittl et al. (2014) ¹⁹	Retrospective; United States; N -- 1500	1013	120	72	58
Leung et al. (2015) ²⁰	Case series; Australia; N -- 30	---	24	---	85
Piscaglia et al. (2016) ⁸	Prospective; Italy; N -- 756	611	145	97	54
				Mean: 86.5	Mean: 53

dietary habits, and drug abuse increased the risk for development of NAFLD-HCC. In our series⁸ of HCV-HCC patients, HCC was diagnosed more frequently during surveillance. However, after correction for confounding factors, survival was similar in the two groups.

In conclusion, enough prospective studies are not yet available to define the correct natural history of NAFLD-HCC. Nonetheless, based on most of the published series (Table 1) it seems that cirrhosis is present in only 53% of patients with NASH versus 86.5% of patients with HCV. It is more often found at a later tumor stage, at least if compared with HCV-HCC, ending with an overall worse prognosis. However, the worse natural history is not related to the cause of the background chronic liver disease or to a more aggressive behavior of NAFLD-HCC, but mainly to detection and diagnosis at a later stage, often preventing effective treatments. This highlights the need to focus future studies on identifying those groups of patients with NAFLD at risk for HCC, who require surveillance, and to develop correct surveillance protocols for the next epidemiological burden of NAFLD/NASH-related cirrhosis and HCC.

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REFERENCES

- 1) Non-alcoholic Fatty Liver Disease Study Group, Lonardo A, Bellentani S, Argo CK, Ballestri S, Byrne CD, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: focus on high-risk groups. *Dig Liver Dis* 2015;47:997-1006.
- 2) Petta S, Valenti L, Bugianesi E, Targher G, Bellentani S, Bonino F; Special Interest Group on Personalised Hepatology of the Italian Association for the Study of the Liver (AISF); Special Interest Group on Personalised Hepatology of Italian Association for Study of Liver AISF. A "systems medicine" approach to the study of non-alcoholic fatty liver disease. *Dig Liver Dis* 2016;48:333-342.
- 3) Caldwell SH, Crespo DM. The spectrum expanded: cryptogenic cirrhosis and the natural history of nonalcoholic fatty liver disease. *J Hepatol* 2004;40:578-585.
- 4) Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73-84.
- 5) Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005;54:533-539.

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- 6) Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol* 2013; 56:1384-1391.
- 7) El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology* 2014;60:1767.
- 8) Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, et al.; HCC-NAFLD Italian Study Group. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology* 2016;63:827-838.
- 9) Bucci L, Garuti F, Lenzi B, Pecorelli A, Farinati F, Giannini EG, et al. The evolutionary scenario of hepatocellular carcinoma in Italy: an update. *Liver Intern*; doi: 10.1111/liv.13204.
- 10) Pocha C, Kolly P, Dufour JR. Nonalcoholic fatty liver disease-related hepatocellular carcinoma: a problem of growing magnitude. *Semin Liver Dis* 2015;35:304-317.
- 11) Guzman G, Brunt EM, Petrovic LM, Chejfec G, Layden TJ, Cotler SJ. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? *Arch Pathol Lab Med*. 2008;132:1761-1766.
- 12) Paradis V, Zalinski S, Chelbi E, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. *Hepatology* 2009;49:851-859.
- 13) Hashimoto E, Yatsuji S, Tobari M, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *J Gastroenterol* 2009;44: 89-95.
- 14) Kawada N, Imanaka K, Kawaguchi T, et al. Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. *J Gastroenterol* 2009;44:1190-1194.
- 15) Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010;51:1820-1832.
- 16) Tokushige K, Hashimoto E, Horie Y, Tanai M, Higuchi S. Hepatocellular carcinoma in Japanese patients with nonalcoholic fatty liver disease, alcoholic liver disease, and chronic liver disease of unknown etiology: report of the nationwide survey. *J Gastroenterol* 2011;46: 1230-1237.
- 17) Yasui K, Hashimoto E, Komorizono Y, et al; Japan NASH Study Group, Ministry of Health, Labour, and Welfare of Japan. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2011;9:428-433.
- 18) Duan XY, Qiao L, Fan JG. Clinical features of nonalcoholic fatty liver disease-associated hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2012;11:18-27.
- 19) Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. *Clin Gastroenterol Hepatol* 2015;13:594-601.
- 20) Leung C, Yeoh SW, Patrick D, et al. Characteristics of hepatocellular carcinoma in cirrhotic and non-cirrhotic non-alcoholic fatty liver disease. *World J Gastroenterol* 2015;21:1189-1196.