Distinctive features of hepatocellular carcinoma in non-alcoholic fatty liver disease

Elisabetta Degasperi, Massimo Colombo

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AM and A Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy
(E Degasperi MD, Prof M Colombo MD)

Correspondence to:
Dr Elisabetta Degasperi, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, 20122 Milan, Italy
elisabetta.degasperi@unimi.it

Hepatocellular carcinoma is the fifth most common cancer and the second leading cause of cancer-related death worldwide. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis have been identified as emergent risk factors for this primary liver cancer. Incidence of NAFLD is increasing as a consequence of the epidemic spread of metabolic syndrome, which can result in progressive liver disease, leading to cirrhosis and its complications. Most data about the prevalence and incidence of hepatocellular carcinoma in patients with NAFLD are from a few population and cohort studies; its incidence is increasing and it is likely to become a leading indication for liver transplantation, especially in industrialised countries. In patients with NAFLD, hepatocellular carcinoma can arise in the context of non-cirrhotic liver, suggesting a specific carcinogenic pathway. Pathology studies have also described steatohepatitic hepatocellular carcinoma as a specific histological variant. NAFLD is underdiagnosed as causative liver disease, and patients are often diagnosed with hepatocellular carcinoma in the advanced stage because of the absence of efficient surveillance policies in this patient population. Management of hepatocellular carcinoma in patients with NAFLD is also complicated by comorbidities, mainly cardiac disease and diabetes, which negatively affect eligibility for radical treatments, including hepatic resection and, especially, liver transplantation. Finally, the effect of hepatocellular carcinoma treatments on postoperative morbidity, mortality, and disease-free survival remains to be precisely defined.

Introduction

Hepatocellular carcinoma is currently the fifth most common cancer and the second leading cause of cancer-related death worldwide.[1] Chronic infection with hepatitis C virus and hepatitis B virus and alcohol-related disease are the most important risk factors for this primary liver cancer; however, concern is growing about the pathogenic role of non-alcoholic fatty liver disease (NAFLD).[2,3] NAFLD has a vast disease spectrum, from simple steatosis to the combined association of steatosis with hepatocellular inflammation and fibrosis, known as non-alcoholic steatohepatitis (NASH), which has a greater propensity to progress to cirrhosis and eventually to hepatocellular carcinoma.[4] Because of the increasing burden of metabolic syndrome and its hallmarks—type 2 diabetes, dyslipidaemia, and arterial hypertension—in the setting of overweight and obesity, NAFLD resulting from liver involvement in the context of metabolic syndrome is becoming a new epidemic disease, especially in North American and western European countries.[5,6] A growing incidence has also been reported in east Asia and developing countries, particularly in those with high income.[7] Although increased short-term mortality in metabolic syndrome is mainly due to cardiovascular diseases, the liver disease burden is largely underestimated. This underestimation is mainly caused by absence of reliable epidemiological data about the incidence or prevalence of NAFLD and the prospective long-term outcomes of liver-related complications and hepatocellular carcinoma. The scarcity of data reflects the vast underdiagnosis of NAFLD, and consequently, reduced patient access to specialised tertiary centres for targeted surveillance and effective therapy for hepatocellular carcinoma.[8] Indeed, early diagnosis is important in determining treatment outcome in patients with hepatocellular carcinoma.[9] Since NAFLD is also increasing in younger generations who are more prone to development of long-term complications, hepatocellular carcinoma in patients with NAFLD is likely to become the first indication for liver transplantation in future decades. Thus, increased concern and awareness is needed to improve patient management and care.[10]

Epidemiology

The incidence and prevalence of hepatocellular carcinoma in patients with NAFLD are not well defined. Most data are from a few population-based studies and large cohort studies of hepatocellular carcinoma management and treatment, and from large liver transplant databases.

High-income countries

A population study by Younossi and colleagues[11] using the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database between 2004 and 2009, assessed incidence, prevalence, and hepatocellular carcinoma risk factors in 4979 patients with hepatocellular carcinoma with 14 937 matched controls. NAFLD was the underlying liver disease in 701 patients with hepatocellular carcinoma, representing 14·1% of the total hepatocellular carcinoma cases, and was the third most common liver disease after hepatitis C and alcohol-related disease. During the 6-year study period, an overall 11% annual increase in the number of cases of hepatocellular carcinoma was reported, with an increase of 9% in patients with NAFLD compared with a 13% increase in patients with hepatitis C. This trend can probably be explained by increasing awareness of the need for hepatocellular carcinoma screening in clinical practice. The main bias in population studies assessing

NAFLD-related complications is the difficulty of a differential diagnosis between the lower-risk NAFLD and the higher-risk NASH. This differential diagnosis should ideally be obtained by histological assessment, which is often not done in clinical practice. To reduce the risk of underestimating disease burden, many studies expand the NAFLD definition to include patients with cryptogenic liver disease and patients who are overweight or obese, or who have type 2 diabetes. Using this clinical-based definition of NAFLD, the global prevalence of NAFLD varies from 3% to 35% according to different studies, whereas NASH is limited to about 3–5% of patients in the general population, with large differences according to geographical areas.[12] Another important bias of population studies is the risk of underestimating both the incidence and prevalence of hepatocellular carcinoma because diagnosis is often not reported in cancer registries used as source databases for these studies. Together with population-based studies, cohort studies are a source of data about the incidence of hepatocellular carcinoma and long-term outcomes. The BRIDGE study,[13] a large multicentre observational study of hepatocellular carcinoma management in a real-world setting (2005–12), assessed 18 031 patients treated for hepatocellular carcinoma in 14 countries. NAFLD was reported as one of the main risk factors for hepatocellular carcinoma in Europe and North America, after hepatitis C, hepatitis B, and alcoholic liver disease, and accounting for about 10–12% of underlying liver diseases in patients with hepatocellular carcinoma. According to different cohort studies, 1-year cumulative incidence of hepatocellular carcinoma in patients with NAFLD has been estimated at around 2·5% compared with 4% in patients with hepatitis C. The 5-year incidence has been reported as 11% in patients with NAFLD compared with 30% in patients with hepatitis C, suggesting a lower risk of hepatocellular carcinoma in patients with NAFLD.[14] A prospective study assessing 195 liver transplantation candidates for NAFLD-related cirrhosis in Cleveland (OH, USA) during 2003–07, reported development of hepatocellular carcinoma in 25 (12·8%) patients over a median follow-up of 3·2 years (IQR 1·7–5·7 years), with a yearly cumulative incidence of 2·6%.[15] In a cohort of 315 patients with hepatitis C, the reported hepatocellular carcinoma incidence was 64 (20%) at the end of follow-up (3·2 years), with a yearly incidence of 4%.[15] In multivariate analysis, any grade of alcohol consumption was independently associated with risk of hepatocellular carcinoma development (hazard ratio 3·8 [95% CI 1·6–8·9], p=0·002) in the NAFLD cohort. When the cumulative incidence of hepatocellular carcinoma in the entire study population was assessed, social alcohol intake was associated with an increased risk of hepatocellular carcinoma both in the NAFLD cohort (p=0·001) and in the hepatitis C cohort (p=0·002).[15] Because of the specific subset of patients referred for liver transplant evaluation, the study could not provide data about compensated liver disease and could potentially overestimate or underestimate the risk of hepatocellular carcinoma. Despite these methodological uncertainties, published data concur that hepatocellular carcinoma in patients with NAFLD is an emerging problem and is rapidly growing. A retrospective study conducted in Newcastle upon Tyne (UK) between 2000 and 2010, reported that NAFLD was the cause of liver disease in 136 (21·5%) of 632 patients with hepatocellular carcinoma.[16] When the investigators prospectively considered the referrals for hepatocellular carcinoma during the study period, NAFLD-related hepatocellular carcinoma had the greatest increase, accounting for 41 (35%) of 118 cases at the end of the study period. Moreover, hepatocellular carcinoma in patients with NAFLD occurred in the absence of histological or radiological hallmarks of cirrhosis in 31 (23%) patients. The cause of liver disease remained undefined in 195 (31%) patients with hepatocellular carcinoma in the Newcastle cohort. However, these patients had an increased prevalence of metabolic risk factors (type 2 diabetes, obesity, hypertension, dyslipidaemia), suggesting that the link between metabolic disorders and hepatocellular carcinoma could be even stronger than that found when the classic NAFLD diagnosis criteria are used.[16] The disease is also growing as an indication for liver transplantation in most industrialised countries: according to the United Network for Organ Sharing (UNOS) registry, it is the most rapidly increasing indication for liver transplantation due to hepatocellular carcinoma in the USA.[10] In 10 061 patients receiving liver transplantation for hepatocellular carcinoma in the USA from 2002 to 2012, NAFLD-related hepatocellular carcinoma was the indication that showed the greatest increase (364%), becoming the second leading cause of liver transplantation after hepatitis C. NAFLD-related hepatocellular carcinoma is predicted to further increase in future decades, whereas widespread use of direct-acting antivirals could achieve an efficient cure for hepatitis C and lead to a decline in complications associated with the virus, including hepatocellular carcinoma.[10]

Growing burden in eastern countries

Data from the BRIDGE study[13] report a negligible NAFLD prevalence in east Asian countries: about 2–6% in China, Taiwan, and Japan. However, other studies suggest that NAFLD is becoming a major cause of liver disease in Asia.[7] Indeed, because of the lifestyle changes associated with a rapidly growing economy, the prevalence of NAFLD in Asian countries has increased from 13% before 1990 to 30% by 2008, with NAFLD accounting for about 50% of liver disease in obese adolescents.[17,18] By contrast, Asian countries also seem to report the highest prevalence of a specific NAFLD phenotypic variant—the lean NAFLD, defined as disease in patients with a body-mass index (BMI) less than 25 kg/m².[19]