

Fatty Liver and Hepatocellular Carcinoma

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Received date: October 17, 2020, **Accepted date:** December 21, 2020

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is showing an increasing trend world-wide and, in Western countries, it has been recognized as the most common cause of chronic elevation of liver enzymes.

Its definition includes a wide range of conditions that exhibit different histopathological patterns that lead to a distinct evolution of the natural history of the disease.

In this contest liver inflammation and fibrosis play the most relevant prognostic role, because of their strict relationship with all the liver-associated causes of morbidity and mortality.

Several noninvasive methods for the detection of liver fibrosis have been developed and tested in selected population but still liver biopsy remains the gold-standard for diagnosis and stadiation of liver disease.

Thus, recognizing patient at major risk of advanced fibrosis represents the most relevant goal in clinical practice, in order to identify patients who could benefit from a systematic screening program for an early detection of cirrhosis complications and hepatocellular carcinoma (HCC).

As matter of fact, NAFLD-related HCC is becoming a tricky issue for clinicians, mostly because it often spreads in a non-cirrhotic liver, when the surveillance programs fail.

The aim of this paper is to review the recent knowledge about NAFLD, underlying its epidemiological burden and discuss NAFLD-associated HCC.

Keywords: Fatty liver, Non alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Cirrhosis, Hepatocellular carcinoma

NAFLD Prevalence

Fatty liver (FL) is the most common wide-world liver disease that is nowadays demonstrating an increasing prevalence trend. In sharp contrast, the most common causes of liver diseases, such as viral causes, are decreasing thanks to advances in antiviral therapies. Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic fat accumulation, often associated with insulin resistance (IR), and defined by the presence of steatosis in at least 5% of hepatocytes in absence of relevant alcohol intake. [1]

The prevalence of FL is variable, ranging from 17 to 46% in

adults and is dependent on the diagnostic method besides varying with the ethnicity, sex and age [2]. Many studies have been carried out in primary, secondary and tertiary care centers and few studies of FL are still available in the general population [3].

Taking into account the “ecology of medical care model”, according to which only a minority of citizens with a given illness will actually search for and get medical care, the real burden of disease attributable to FL can be estimated only from data obtained from the general population.

There are different estimates of NAFLD prevalence. Some

studies reported a prevalence of 17-51% [4] while a meta-analysis of studies from 2006-2014 estimated a prevalence of 24% in general population [2].

In the Dionysos study, performed in the general population of Northern Italy, 44% of citizens with suspect liver disease had FL compared to 35% of those without suspected liver disease [5].

The Bagnacavallo study, also performed in the general population of Northern Italy, showed the presence of FL in 74% of citizens with altered liver enzymes and in 35% of those with normal liver enzymes [6]. Importantly, both the Dionysos and the Bagnacavallo studies showed that FL is quite common in citizens with normal liver enzymes.

The increasing trend of NAFLD was confirmed in South Italy by Pendino, who revealed a prevalence of NAFLD of about 24% in individual with abnormal liver transaminases [7].

In a recent study, a Markov model was employed to tentatively forecast NAFLD progression. The prevalence of NAFLD was forecasted to increase, from 83.1 million (2015) to 100.9 million (2030) cases worldwide, while that of non-alcoholic steatohepatitis (NASH) was projected to increase from 16.52 million (2015) to 27.00 million cases (2030). The incidence of decompensated liver cirrhosis is forecasted to increase of 168%, that of hepatocellular carcinoma (HCC) of 137%, and that of liver-related mortality of 178% [8].

NAFLD and NASH represent, therefore, a large and growing public health problem.

NAFLD is considered the hepatic manifestation of the metabolic syndrome and its increased prevalence parallels that of obesity, diabetes mellitus, dyslipidemia and hypertension.

Since NAFLD is commonly associated with obesity and type 2 diabetes, it is not surprising that it is associated with an increase not only of liver mortality but of all causes of death, especially cardiovascular. The contribution of FL to overall mortality, taking known risk factors into account, is however complex and needs further study [9].

Diagnosis

The NAFLD diagnosis can be apparently simple and requires the exclusion of other causes of hepatic damage and alcohol consumption out of the safe dose, considered for men ≥ 30 g daily and ≥ 20 g for women [1]. The real impact on liver caused by alcohol consumption still has many points of discussion before being proven, depending on many cofactors such as the type of alcohol beverage,

drinking patterns, duration of exposure, physical activity and genetic susceptibility.

Some studies have suggested a protective role of moderate alcohol consumption [10] while other studies have shown that a “safe limit” of alcohol consumption is unlikely to exist [11].

A group of experts has recently proposed to replace the definition of NAFLD with that of metabolic fatty liver disease (MAFLD), which does not include the quantification of alcohol intake for its diagnosis. Nevertheless, the contribution of alcohol consumption to MAFLD requires further investigation.

Similarly to the metabolic syndrome, for which many competing definitions have been proposed over the years, MAFLD is a very heterogeneous disease and its clinical phenotype is likely to depend from many factors such as ethnicity, sex, age, hormonal status, metabolic status, diet, smoking habits, alcohol intake, genetic background, and microbiota [12].

The diagnosis of MAFLD is “positive” in the sense that it is based on the presence of criteria related to metabolic dysfunction and not on the absence of other conditions. These criteria include the presence of FL, detected with different methods, and the presence of one of the three following criteria: overweight or obesity, type 2 diabetes mellitus, or metabolic abnormalities [13].

The method used to diagnose FL is of great importance for both clinical and epidemiological applications. The most commonly employed diagnostic method is liver ultrasonography (US), which, however, is known to underestimate the degree of fatty liver as compared to liver biopsy. This latter technique is still the gold standard, but it is performed only in a minority of cases even in tertiary care centers [2]. Magnetic resonance spectroscopy and magnetic resonance imaging can quantify the total amount of triglycerides, but are too expensive for clinical use and for epidemiological research [1].

Another option for the diagnosis of FL is the use of surrogate markers, such as the fatty liver index (FLI), the Liver fat score, and the Steato Test [1].

The variety of methods by which FL can be diagnosed has important implication for the epidemiology of FL and some researchers wonder whether it is appropriate to pool diagnoses of FL obtained with different methods [3].

To diagnose FL, the EASL-EASD-EASO clinical practice guidelines suggest using US or, when it is not available, a surrogate marker such as FLI, SteatoTest, or NAFLD score [1].

Inflammation and Fibrosis

An estimated 20% of FL is associated with inflammation, which may progress to fibrosis, cirrhosis and HCC [14]. Such progression may nonetheless happen, albeit rarely, also in the absence of inflammation.

With current diagnostic methods besides liver biopsy and especially those readily applicable to clinical practice, it is impossible to distinguish uncomplicated from complicated FL, although hints to the presence of severe fibrosis, cirrhosis or HCC can of course be obtained by liver US.

The “true prevalence” of liver fibrosis is currently unknown for the simple reason that liver biopsy cannot be performed in individuals from the general population. In recent years, there has literally been a race for the search of the best method to identify liver fibrosis. Liver stiffness measured by transient elastography (TE), is presently the best surrogate method to detect liver fibrosis and can be performed in the general population, but it is expensive and requires expertise. Cut-off points of 8 or 9 kPa for TE are presently suggested for the diagnosis of clinically relevant liver fibrosis in the general population [15].

Liver transaminases are not suitable for the assessment of liver fibrosis. Many non-invasive serum markers of liver fibrosis have been developed using a liver biopsy as reference standard [7]. Using data from the general population of the Bagnacavallo study, we found, not unexpectedly, that the association between liver stiffness measured by TE and markers of liver fibrosis developed in tertiary care centers (AST/ALT, APRI, Forns Index, FIB-4, GGT, BARD, BAAT), is low and of doubtful clinical relevance [6,16].

The effectiveness of NAFLD screening in the general population has been questioned both for the low positive predictive value of surrogate markers of fibrosis and for its cost [1].

For these reasons, screening programs are preferentially carried out in patients at high risk of NAFLD such as those with type 2 diabetes or metabolic syndrome.

In the Rotterdam–community study, the coexistence of type 2 diabetes and NAFLD was associated to the prevalence of advanced fibrosis [17]. The assessment of liver fibrosis by means of the NAFLD fibrosis score, TE, and liver biopsy in asymptomatic patients with type 2 diabetes, has revealed a prevalence of 7.8% of advanced fibrosis [18]. In a global study of 49,419 subjects with type 2 diabetes, the prevalence of NAFLD was 56%, with the highest value in Europe (68%), that of NASH was 38%, and that of advanced fibrosis was 17% [19].

Fibrosis is the most important prognostic factor in NAFLD, being associated with liver-related outcomes and mortality. The EASL algorithm suggests to calculate the NAFLD fibrosis score or FIB4 and to perform an ELF test for the patients with an indeterminate NAFLD fibrosis score (range: 1.455 to 0.672) or FIB4 (range: 1.3 to 3.25). These tests have generally a high negative predictive value so that they can be used to exclude advanced fibrosis and for risk stratification [20]. Combining TE elastography with serum markers may perform better than serum markers alone at diagnosis of liver fibrosis [21].

Hepatocellular Carcinoma and NAFLD

Liver disease is characteristically, clinically, and biochemically “silent” until end-stage organ impairment. The accurate identification of the stage of liver fibrosis plays a key role for the enrolment of patients in surveillance programs for the early detection of HCC.

All patients with advanced fibrosis or cirrhosis are in fact at risk for HCC, which is the primary liver cancer worldwide, and is one of five commonest cancers causing death [22,23].

HCC is more common in men than in women, and, in Western countries, rarely occurs before 50 years of age. HCC occurs frequently in patients with cirrhosis of different etiology, most commonly alcoholic and viral (HBV and HCV) [24].

The burden of NAFLD could lead to an increase of NAFLD-related HCC. It has been estimated that, in Western countries, NAFLD/NASH could be responsible for 30 to 40% of HCC cases [25].

In a recent study about Italian study, among non-viral patients, pure alcoholic cases almost halved over time (from 20 to 13.3%), probably because of a shift towards mixed alcoholic + NAFLD cases (from 0.7% to 8%) and “pure” NAFLD associated HCCs may increase (from 1.5% to 7.1%) [26].

The number of patients with NAFLD-associated HCC who underwent liver transplantation had a 4-fold increase in last years and NAFLD-associated HCC is becoming a growing indication for liver transplantation [27].

Importantly a recent nationwide, matched cohort study including all individuals in Sweden with biopsy-confirmed NAFLD, showed an increased mortality associated with NAFLD driven primarily by the excess risk of cancer-specific and cirrhosis-specific mortality, together with a small, although significant, excess risk of HCC-specific mortality [28].

HCC and NAFLD Pathogenesis

The pathogenesis of NAFLD-associated HCC is largely unknown but both obesity and type 2 diabetes are likely to play a major role. Central to these conditions predisposing to NAFLD is insulin resistance, leading, in the so called “first hit”, to lipogenesis and accumulation of free fatty acids inside the hepatocytes [29]. In the “second hit”, free fatty acids lead to the formation of reactive oxygen species (ROS), especially in mitochondria. DNA damage made by ROS and autophagy are involved in NAFLD-associated HCC. It is likely that genetic predisposition and the intestinal microbiota do modulate ROS production [30].

The fact that HCC arises in NAFLD, even in the absence of cirrhosis, suggests that other risk factors contribute to HCC etiology. Such factors include hyperinsulinemia, which stimulates carcinogenesis, and genes such as the patatin-like phospholipase domain containing 3 (PNPLA3) gene, which is also associated with an increased risk of steatohepatitis [31].

HCC Diagnosis and Treatment

Early diagnosis plays a key role in the prognosis of HCC patients. In the early stages, radical treatments such as local ablation, surgical resection, and liver transplantation are viable options.

To diagnose HCC early in patients with cirrhosis, it is presently recommended to carry out US surveillance every six months. This can be easily done when one is aware of the natural history of the underlying disease, as it happens for HBV- and HCV-associated cirrhosis. In patients with NAFLD, commonly associated with obesity and type 2 diabetes mellitus, surveillance is not routinely performed because it is unfeasible and because there are no data on its effectiveness. Therefore, in NAFLD patients, HCC can be diagnosed later than in those with HBV- or HCV-associated cirrhosis. Moreover, importantly, ultrasound fails to detect early HCC in patients with visceral obesity [31].

Several staging systems are available to diagnose HCC and to guide its treatment: the Barcelona Clinic Liver Cancer (BCLC) is the commonly used system and takes into account the liver function, the performance status, the tumour size, its spread proposing a treatment for each identified stage of disease [32]. Etiology is not taken into account by BCLC, including whether HCC is NAFLD-related or not.

The analysis of the ITA.LI.CA (Italian liver cancers) database showed that at the time of HCC diagnosis, cirrhotic patients with ≥ 3 metabolic disorders have more preserved

liver function than those with none or just 1 metabolic risk factor confirming that, in patients with metabolic disease, HCC develops at an earlier stage of underlying disease [33]. Such patients have often an advanced tumor stage and a higher frequency of metastasis at the time of diagnosis.

On the other hand, some patients with large tumours do nonetheless undergo surgery because of an underlying better liver function [33]. Moreover, not all patients are fit for surgical interventions because some of them have comorbidities that can worsen the performance status, such as cardiac and renal disease, making them sometimes unsuitable also for systemic antiangiogenic therapy.

When considering the impact of five main metabolic features (diabetes, obesity, arterial hypertension, hypercholesterolemia, and hypertriglyceridemia) of NAFLD-related HCC, ITA.LI.CA found that only type 2 diabetes reduced the overall survival of HCC patients but its effect was marginal [33]. On the other hand, some studies showed that diabetes could increase not only the incidence but also the aggressiveness of HCC [34,35]. Clinical heterogeneity of different cross-sections and cohorts is likely to explain most of these discrepant findings. A recent cohort study found, for instance, that patients with NAFLD-related HCC had a shorter survival compared to patients with HCV-associated disease [36].

Treating the metabolic risk factors may be an option to reduce HCC incidence.

A recent meta-analysis showed that treating diabetes with metformin can result in a 50% decrease of HCC incidence, while insulin and sulfonylureas may increase it [37]. Statins can lower HCC incidence, possibly by means of anti-angiogenic, anti-proliferative, and pro-apoptotic effects [38].

Conclusion

In conclusion, the prevalence and possibly incidence of NAFLD-associated HCC is increasing worldwide. Strategies must be implemented to prevent the development of cirrhosis and to early detect HCC in at risk patients, e.g., those with type 2 diabetes, possibly by using surrogate markers of fibrosis. Specific surveillance programs should be developed and evaluated for their effectiveness at reducing the incidence of NAFLD-associated HCC.

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