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Contents

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EDITORIAL

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Retrospective Cohort Study

Observational Study

LETTER TO THE EDITOR

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LETTER TO THE EDITOR

Nonalcoholic steatohepatitis and hepatocellular carcinoma: Beyond the boundaries of the liver

Tarana Gupta

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Abstract

The burden of non-alcoholic steatohepatitis (NASH) related hepatocellular carcinoma (HCC) is drawing attention due to the emerging epidemic of obesity and metabolic syndrome and is expected to increase in the near future. Antidiabetic medications, air pollutants, and newer genetic mutations are latest concerns as risk factors for HCC development in patients with NASH. Although molecular signatures are very accurate, they are not cost-effective and cannot be applied in larger population due to logistic issues. We need multicentric longitudinal studies including diverse geographical areas to evaluate the complex interplay of different risk factors and genetics in these patients.

Key Words: Non-alcoholic steatohepatitis; Hepatocellular carcinoma; Cirrhosis; Genetic factors; Lifestyle factors; Surveillance

Core Tip: Nonalcoholic steatohepatitis (NASH) is a metabolic liver disease which also involves multiple organs like the heart, lungs, and kidneys. NASH may arise primarily, followed by involvement of other organs, or it may come late in the course of metabolic syndrome. The multidisciplinary approach is needed towards a patient with diabetes, obesity, and metabolic syndrome to address all issues related to the liver, heart, *etc.* Genetic and molecular signatures have provided a ray of hope for estimating risk in these patients; however, it has many practical issues. The impact of environmental pollutants and toxins as a causative factor in NASH, especially lean patient population, should also be considered. We need population based studies from different geographical areas for estimation of metabolic, environmental, and genetic risk factors.

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TO THE EDITOR

Chrysavgis *et al*[1] have extensively reviewed the literature on non-alcoholic steatohepatitis (NASH) related hepatocellular carcinoma (HCC) with regard to its risk stratification, screening, and surveillance strategies. Metabolic syndrome is a systemic disease involving the heart, kidneys, lungs, and liver, *etc.* NASH is the liver manifestation of metabolic syndrome. With the emerging epidemic of obesity and metabolic syndrome, NASH is expected to supersede all other etiologies of liver cirrhosis as well as HCC. In various studies as discussed by Chrysavgis *et al*[1], the prevalence of HCC in non-cirrhotic non-alcoholic fatty liver disease (NAFLD) patients ranges from 15%-55%. Factors like age, male sex, concomitant smoking and alcohol intake, obesity, and type 2 diabetes mellitus have been shown to increase the risk of HCC in non-cirrhotic NASH. Recently, use of insulin and sulfonylureas has also been shown to increase the long-term risk of HCC in patients with diabetes. In an Italian study[2], an increased HCC risk with an odds ratio of 3.7 for insulin, 1.3 for sulfonylureas, and 2.1 for repaglinide was found in patients with diabetes. Even the duration of treatment with insulin, though not with other therapies, increased the risk of HCC. The same has also been confirmed in a nationwide nested case-control study[3] in Korea which showed an increased HCC risk with glimepiride instead of other sulfonylureas. And yet we do not have long-term data for GLP-1 agonists and DPP4 inhibitors. Chinese data[4] recently showed an increased association of air pollutants of particulate matter (PM) with an aerodynamic diameter of < 1 (PM_1), < 2.5 ($PM_{2.5}$), and < 10 μm (PM_{10}) with metabolic associated fatty liver disease. The role of intestinal dysbiosis has also been investigated in animal models and found to be associated with an increased risk of NASH and HCC.

In a multicentric trial, Pinyol *et al*[5] collected samples from NASH-HCC and NASH patients, performed expression array and whole exome sequencing, and compared it with HCC from non-NASH etiologies like viral/alcohol. They found *TERT* promoter, *CTNNB1*, *TP53*, and *ACVR2A* most frequently to be present in NASH-HCC patients. The *ACVR2A* (activin type 2 receptor gene) mutation was found in a higher number of patients with NASH-HCC as compared to those with HCC of other etiologies. The molecular signature revealed higher expression of bile acid and fatty acid signaling pathways. The Wnt/TGF-β proliferation subclass was more common in NASH-HCC. The upcoming data suggests that the molecular signature of NASH-HCC is different from that of HCC due to other etiologies. Collectively, the development of NAFLD-HCC results from a complex interplay of multiple factors related to unhealthy life style, environment, and genetics of an individual.

The authors have included abbreviated magnetic resonance imaging (MRI) in their suggested algorithm for HCC surveillance in NAFLD due to a poor window of ultrasound in obese patients. We have concerns regarding this strategy. First, a large number of individuals would need surveillance, so its cost-effectiveness, availability on large scale, and practicality need to be addressed. Second, how frequently MRI would have to be repeated is a practical issue. Third, when during the clinical course of NASH, screening should be performed. Although authors have included HCC risk model as suggested by Ioannou *et al*[6] in their algorithm, we believe that future prospective longitudinal studies are needed to determine the weightage of different risk factors in determining HCC risk in patients with cirrhotic and non-cirrhotic NAFLD, separately. The role of extracellular vesicles (EVs) for molecular characterization of HCC in patients with NASH may further be evaluated for HCC surveillance also. NAFLD is a risk factor not only for HCC but also for colorectal and breast cancers. Instead of screening for each carcinoma separately, we need to have studies on a common platform targeting the molecular signatures in blood for surveillance of different carcinomas in the body which share the pathogenetic mechanisms or pathways. The challenges involved are large population-based studies in different geographical regions, mapping of molecular signatures, and implementation. It has to be cost-effective, easily accessible, and readily available.

In patients with NAFLD, all-cause mortality includes mortality related to issues of the liver, heart, kidneys, lungs, *etc.* It is time to recognise the need for multidisciplinary approach towards a patient with diabetes, obesity, and metabolic syndrome to address all issues related to the liver, heart, kidneys, *etc.* Large prospective, multicentric studies including diverse geographical regions and dietary habits are needed to evaluate for risk stratification in these patients regarding need for HCC surveillance.

FOOTNOTES

Author contributions: Gupta T wrote and critically revised the manuscript.

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