

## Is Screening of Hepatocellular Carcinoma in Patients Without Cirrhosis Reasonable?

Viera Kissova\*, Gabriel Hajas, Adrian Kiss, Tomas Fazekas, Zuzana Straussova, Jaroslav Rosenberger and Maria Majernikova

Teaching Hospital Nitra, Nitra, Slovakia

### Abstract

Occurrence of hepatocellular carcinoma (HCC) in a non-cirrhotic condition of liver disease is now already well known. Non-cirrhotic condition was defined in our study as the presence of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). The rising onset of obesity, metabolic syndrome (MS) and Type 2 Diabetes Mellitus (T2DM) is associated with NAFLD or NASH. Currently only cirrhotic patients are required to be regularly (semi-annually) screened for liver neoplasma. The goal of this study was to describe the onset of HCC in patients admitted to an Internal Ward due to nonspecific symptoms of neoplasma and to identify a specific group of patients that could benefit from screening of hepatocellular carcinoma so that the disease is diagnosed in its early stages with promising prospects for successful treatment.

**Keywords:** Screening; Hepatocellular carcinoma; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Type 2 Diabetes Mellitus; Metabolic syndrome

### Introduction

The rising onset of obesity, Metabolic Syndrome, and Type 2 Diabetes Mellitus is often associated with hepatal disorder [1]. It can present itself in a range from simple steatosis of liver up to non-alcoholic steatohepatitis (NASH), the latter possibly being a serious condition progressing to hepatal cirrhosis and hepatocellular carcinoma (HCC) [1,2]. It is the most common chronic liver disorder in clinical settings of Western countries in Europe [1,2]. NAFLD or NASH are also regarded as clinical presentations of the Metabolic Syndrome in liver [3]. NAFLD or NASH could be associated with obesity, high energy diet, insulin resistance, arterial hypertension, and dyslipidaemia [3].

HCC has in the last three decades been on the rise in the US and Western Europe. The age adjusted occurrence has doubled in this time period [4]. Majority of HCC presents itself in the setting of hepatal cirrhosis; however up to 20% of patients have no signs of cirrhosis [5]. Cirrhosis of liver does not seem to be necessary for a development of HCC. Other well-known diseases that lead to liver cirrhosis are hepatitis B virus (HBV), hepatitis C virus (HCV) and alcoholic liver disease (ALD) [1,3,5]. They are easier to recognise and the autoimmune hepatal disorders are not such frequent causes of liver cirrhosis. Some patients with NAFLD/NASH may be at a higher risk for HCC; obesity seems to be an independent risk factor for HCC [6]. Ascha [7] found the annual cumulative HCC incidence to be at 2.6% for NASH-related cirrhosis. HCC can occur in NASH patients regardless of the degree of cirrhosis [8]. Therefore, NASH and the Metabolic Syndrome itself are significant independent risk factors for HCC [9,10]. Another important risk factor for HCC is T2DM, which is associated with a 2.9 fold increase in risk of HCC [10]. Old age and any life alcohol consumption are significant factors for a progression to NASH related cirrhosis and development of HCC [4,5,8].

Although HCV is still considered the main cause of HCC, NASH has been found to be the second leading hepatal disorder for HCC [11]. Therefore, the United States and European countries recommend regular semi-annual screening to study hepatal disorders [12]. Generally, the risk of progression to cirrhosis in NAFLD is low, with incidence rate estimated at 3.1% [13]. However, this estimate may be low due to lack of overall systemic screening in diabetic patients and patients with T2DM where up to 30% of patients may have NASH [14]. It would be valuable to perform the HCC screening in NASH patients and once a year should be sufficient [11].

Therefore, the aim of this study is to explore whether elderly patients with the Metabolic syndrome and Type 2 Diabetes Mellitus with NAFLD/NASH has to be checked for early onset of HCC and how is their chance of older cancer-stricken for successful treatment since HCC is likely to be in early stages.

### Material and Methods

HCC cases were identified from a pool of patients admitted to the Internal Department at the Teaching Hospital of Nitra between January 2014 and June 2016. The adult patients with general nonspecific signs of discomfort or symptoms and sings attributable to liver disease or abnormal liver biochemistries were referred for a screening for NASH/NAFLD. NASH/NAFLD was identified using abdominal ultrasound and laboratory tests (ALT as the marker of hepatal cytolytic disorder). Regularity of alcohol consumption was evaluated via a questionnaire (see Liagnpunsakul) [15]. For all patients with a tumor suspicion in ultrasound screening, the diagnosis of HCC was determined by assessing their clinical history, oncomarkers (AFP) and radiology scans (three phase liver CT or liver MR scans) AFP (alpha fetoprotein) was estimated in all these patients. The radiological diagnosis was defined according to the American Association for the Study of Liver Diseases (AASLD) [16]. IDF criteria were used to diagnose the Metabolic Syndrome [17]. The diagnosis of Diabetes type 2 was determined according to EASD guidelines [18]. Presence of liver disease other than NAFLD/NASH was confirmed by a review of clinical notes and laboratory data.

The results were analysed statistically (using SAS), where associations were tested by contingency analysis. We used the Fischer Exact test for the 2 to 2 relationships. The significance level of 0.5 was used as a threshold for statistical significance.

### Results

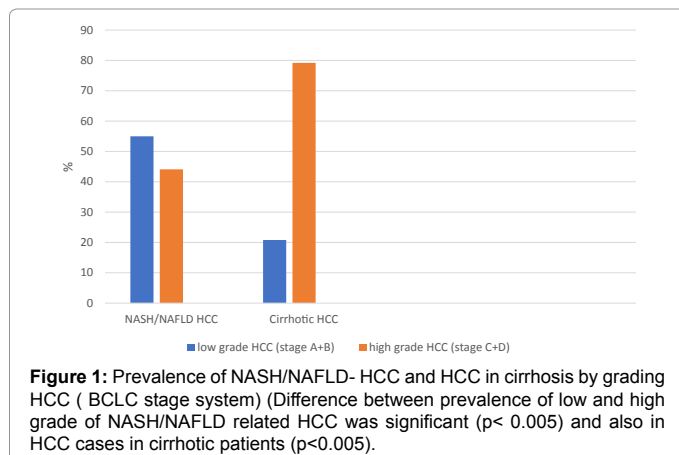
Seventy nine cases of liver cancer were identified in the analysed

\*Corresponding author: Viera Kissova, Teaching Hospital Nitra, Nitra, Slovakia, Tel: 00421 37 6545 699, E-mail: [kissovav@fnitra.sk](mailto:kissovav@fnitra.sk)

Received May 29, 2017; Accepted June 24, 2017; Published June 27, 2017

Citation: Kissova V, Hajas G, Kiss A, Fazekas T, Straussova Z, et al. (2017) Is Screening of Hepatocellular Carcinoma in Patients Without Cirrhosis Reasonable? J Gerontol Geriatr Res 6: 436. doi:10.4172/2167-7182.1000436

Copyright: © 2017 Kissova V, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



Diseases	Number
NASH/NAFLD	25
ALD Cirrhosis	43
Cryptogenic (cirrhosis)	5
HBV hepatitis	3
HCV hepatitis	1
Autoimmune hepatitis	1
Primary biliary cirrhosis	1
Total	79

**Table 1:** Liver diseases in liver cancer patients (n=79).

time period, of which there were 11 female patients. The mean age of patients was  $64.5 \pm 7$  years. Forty nine patients had liver cancer in a cirrhotic condition (62%). Twenty-five cases of liver cancer were without liver cirrhosis (31.6%) in NASH/NAFLD clinical settings. For the marginal distribution statistics: five liver cancer cases were observed in 3 Hepatitis B virus positive patients, 1 in a Hepatitis C virus positive patient, 1 in autoimmune hepatitis patients and 1 in a patient with primary biliary cirrhosis (Table 1). Among the patients with liver cancer associated with cirrhosis thirty nine consumed significant amounts of alcohol (81.2%). The threshold for significant alcohol consumption was set at 21 drinks or more per week in males, and more than 14 drinks per week in females. Due to a smaller cohort of patients were considered HCC cases according BCLC staging system of Stage A and Stage B as “low grade HCC”. These patients are considered to have good or very good treatment prospects.

Stages C and D of BCLC staging were considered as “high grade of HCC” with limited treatment possibilities of HCC. There were ten patients with liver cirrhosis (20.8%) and fourteen patients with NASH/NAFLD (55.0%) in the “low grade group”. In the “high grade group” the percentages were thirty-eight patients with liver cirrhosis (79.2%) and only eleven patients (44.1%), respectively. Diabetes mellitus type 2 or Metabolic Syndrome was present in 96% of patients with liver cancer in NASH/NAFLD (24 patients), but only 14% in patients with cirrhotic liver (7 patients).

We observed a significant association between female gender and HCC in NASH/NAFLD conditions ( $p < 0.01$ ) in our cohort. The low grade HCC was clearly associated with the presence of NASH/NAFLD ( $p < 0.01$ ), see Figure 1. Cirrhotic patients were associated with the high grade HCC ( $p < 0.05$ ) regardless of the level of alcohol consumption ( $p < 0.01$ ). Diabetes mellitus type 2 was highly associated with NASH/NAFLD ( $p < 0.01$ ).

## Discussion

It is a generally known fact that an onset of hepatal carcinoma can arise without the presence of an advanced liver disorder like cirrhosis. The screening tests are currently performed only in population at high risk of hepatocellular cancer (European and American guidelines [19]. The population at risk is defined by the presence of cirrhosis, which was diagnosed via ultrasonography of liver in a six months period. The occurrence of HCC due to NASH/NAFLD hepatal disorder is on the rise, partly due to better diagnostic schedules and medical availability, but much more due to the pandemy of diabetes and obesity in Western lifestyle countries. Diabetes mellitus signals an increased risk for HCC (RR=2.13) [4].

In our cohort of patients, we also observed a statistically significant association between NASH patients with HCC and diabetes mellitus ( $p < 0.01$ ). In cirrhotic patients with HCC the presence of diabetes was not significant. Occurrence of HCC in the context of NASH was significantly higher in female patients than in their male counterparts ( $p < 0.01$ ). Our results are comparable to those observed by Yasui [20]. In the low grade HCC group of our cohort (stage A, B by BCLC), 55% of HCC cases were induced by NASH versus 21% by cirrhosis ( $p < 0.01$ ). This means that the majority of HCC patients in the NASH setting had at the time of the diagnosis good prospects for a successful treatment. Only 44.1 % of HCC cases in the NASH setting but 79.2% of HCC cases in the cirrhosis setting had high grade HCC (BCLC C,D), irrespective of alcohol consumption ( $p < 0.01$ ). BCLC stages C and D represent mainly palliative or symptomatic treatment possibilities. The diagnosis has to be formulated in early stages of HCC for a good prognosis of patient’s life expectancy and therefore it is imperative to screen high risk patients as soon as possible.

Presence of HCC in a NASH setting observed in our cohort may suggest another specific risk population: female diabetic population with abnormal lab tests - ALT and nonspecific discomfort or signs attributable to liver disease. Majority of these cases of HCC in the NASH setting were in low grade HCC (BCLC Stages A and B). Reasonable screening of this population (ultrasonography and AFP) could determine the diagnosis in early or very early stages of HCC, thus giving patients good prospects for a successful cancer treatment. Although the ODDs ratio for HCC is much lower for diabetes/obesity -diabetes, OR=2.47, than for other risk factors, such as HCV, OR 39.89, but factor of obesity and diabetes have the greatest population attributable fraction [21].

A retrospective analysis of a cohort with 1500 HCC patients from Veterans Administration (VA) hospitals showed that patients with NAFLD-HCC underwent less frequent screening (43.3%) in the three years before HCC diagnosis compared to patients with alcohol (59.8%) or HCV-induced (86.7%) HCC [22,23]. Our findings suggest that a new group should be identified as patients with increased risk of HCC development without cirrhosis - female patients over 65 with Metabolic Syndrome or Diabetes mellitus type 2 and in NASH/NAFLD clinical setting. These patients should be screened regularly.

One impediment to successful diagnosis could be insufficient ultrasonography of liver in obese patients, requiring other methods of screening like CT or MR scans. Another study based on cirrhotic patients suggested that AFP has better sensitivity in NAFLD patients than in others (HCV patients) [24]. Early stages of HCC can be better treated and starting the treatment early significantly improves the odds for the patients. However, diagnosing HCC while still in early stages will remain a challenge for physicians engaged in the treatment of patients with NASH/NAFLD.

## Conclusion

This study suggests that patients about 65 years old with the metabolic syndrome and Type 2 Diabetes Mellitus with NAFLD/NASH should be checked for early onset of HCC. These patients have much higher chances for successful treatment since HCC is likely to be in early stages. Robustness of these results should be assessed on a greater cohort of HCC patients and include a wider variety of identification markers. Further studies enrolling larger cohorts of patients are needed to create safe and effective consensus of HCC screening in patients with HCC without cirrhosis.

## References

1. Angulo P (2005) Non-alcoholic fatty liver disease. *Rev Gastroenterol* 70: 52-56.
2. Adams L, Lymp J, St. Sauer J, Schvuyler O, Keith D, et al. (2005) The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 129: 113-121.
3. Fabrini E, Sullivan S, Klein S (2010) Obesity and non alcoholic fatty liver disease: biochemical, metabolic and clinical implication. *Hepatology* 51: 679-689.
4. El Serag HB (2004) Hepatocellular carcinoma: Recent trends in the United States. *Gastroenterology* 127: S27-34.
5. Simonetti R, Camma C, Fiorello F, Politi F, Amico DG, et al. (1991) Hepatocellular carcinoma. A worldwide problem and the major risk factors. *Dig Dis Sci* 36: 962-972.
6. Leite N, Salles G, Araujo A, Nogueira VC, Cardoso C (2009) Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. *Liver Int* 29: 113-119.
7. Ascha SM, Hanouneh A, Lopez R, Hanouneh IA, Zein NN (2010) The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 51: 1972-1978.
8. Yasui K, Hashimoto E, Tokushige K, Koike K, Shima T, et al. (2012) Clinical and pathological progression of non-alcoholic steatohepatitis to hepatocellular carcinoma. *Hepatol Res* 42: 767-773.
9. Ertle J, Dechene A, Sowa J, Penndorf F, Herzer K, et al. (2011) Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer* 128: 2436-2443.
10. Wetzel T, Graubard B, Zeuzem S, El-Serag H, Davila J, et al. (2011) Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology* 54: 463-471.
11. Khan F, Perumpail R, Wong R, Ahmed A (2015) Advances in hepatocellular carcinoma: Nonalcoholic steatohepatitis-related hepatocellular carcinoma. *World J Hepatol* 7: 2155-2161.
12. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. *Hepatology* 53: 1020-1022.
13. Larsen DS, Becker U, Franzmann M, Larsen K, Christoffersen P, et al. (2009) Final results of a long-term, clinical follow-up in fatty liver patients. *Scand J Gastroenterol* 44: 1236-1243.
14. Matteoni C, Younossi ZM, Gramlich T, Navdeep B, Liu YC, et al. (1999) Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity. *Gastroenterology* 116: 1413-1419.
15. Liagnpunsakul S, Chalasani N (2012) What do we recommend our patients with NAFLD about alcohol consumption? *Am J Gastroenterol* 107: 976-978.
16. Bruix J, Sherman M (2011) AASLD Practice guideline. Management of hepatocellular carcinoma: An update. *Hepatology* 53: 1020-1022.
17. Alberti K, Zimmet P, Shaw J (2006) Metabolic syndrome - A new world wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetes Med* 23: 469-480.
18. Ryden L, Grant J, Anver S, Berne C, Cosentino I, et al. (2013) ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD. The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 34: 3035-3087.
19. Llovet J, Ducreux M, Iencions R, Bisceglie A, Galle P, et al. (2012) EASL: European Association For Study Of The Liver, European Organisation for Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol* 56: 908-943.
20. Yasui K, Hashimoto E, Komorizono Y, Koyke K, Aril S, et al. (2011) Characteristic of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 9: 428-433.
21. Welzel T, Graubard B, Quraishi S, Zeuzem S, Davila J, et al. (2013) Population attributable fractions of risk factor for hepatocellular carcinoma in the United States. *Am J Gastroenterol* 108: 1314-1321.
22. Mittal S, Sada Y, El Serag H, Kanwal F, Duan Z, et al. (2015) Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. *Clin Gastroenterol. Hepatol* 13: 594-601.
23. Gopal P, Yopp A, Waljee A, Chiang J, Nehra H, et al. (2014) Factors that affect accuracy of  $\alpha$ -fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol. Hepatol* 12: 870-877.
24. Kolly P, Dufour J (2016) Surveillance for hepatocellular carcinoma in patients with NASH. *Diagnostics* 6: 22.