

World Journal of *Gastroenterology*

World J Gastroenterol 2022 July 21; 28(27): 3282-3534



REVIEW

- 3282** Hepatitis B and circadian rhythm of the liver
Skrlec I, Talapko J
- 3297** Tumor microenvironment in pancreatic ductal adenocarcinoma: Implications in immunotherapy
Smith C, Zheng W, Dong J, Wang Y, Lai J, Liu X, Yin F
- 3314** Crosstalk between dietary patterns, obesity and nonalcoholic fatty liver disease
Ristic-Medic D, Bajerska J, Vucic V

MINIREVIEWS

- 3334** Application of intravoxel incoherent motion diffusion-weighted imaging in hepatocellular carcinoma
Zhou Y, Zheng J, Yang C, Peng J, Liu N, Yang L, Zhang XM
- 3346** Regulatory T cells and their associated factors in hepatocellular carcinoma development and therapy
Zhang CY, Liu S, Yang M
- 3359** Single-incision laparoscopic surgery to treat hepatopancreatobiliary cancer: A technical review
Chuang SH, Chuang SC
- 3370** Probiotics and postbiotics in colorectal cancer: Prevention and complementary therapy
Kvakova M, Kamlarova A, Stofilova J, Benetinova V, Bertkova I
- 3383** Interventional strategies in infected necrotizing pancreatitis: Indications, timing, and outcomes
Purschke B, Bolm L, Meyer MN, Sato H
- 3398** Artificial intelligence in liver ultrasound
Cao LL, Peng M, Xie X, Chen GQ, Huang SY, Wang JY, Jiang F, Cui XW, Dietrich CF
- 3410** Risk factors and diagnostic biomarkers for nonalcoholic fatty liver disease-associated hepatocellular carcinoma: Current evidence and future perspectives
Ueno M, Takeda H, Takai A, Seno H

ORIGINAL ARTICLE

Basic Study

- 3422** Accumulation of poly (adenosine diphosphate-ribose) by sustained supply of calcium inducing mitochondrial stress in pancreatic cancer cells
Jeong KY, Sim JJ, Park M, Kim HM

- 3435** RING finger and WD repeat domain 3 regulates proliferation and metastasis through the Wnt/ β -catenin signalling pathways in hepatocellular carcinoma

Liang RP, Zhang XX, Zhao J, Lu QW, Zhu RT, Wang WJ, Li J, Bo K, Zhang CX, Sun YL

- 3455** Associations of gut microbiota with dyslipidemia based on sex differences in subjects from Northwestern China

Guo L, Wang YY, Wang JH, Zhao HP, Yu Y, Wang GD, Dai K, Yan YZ, Yang YJ, Lv J

Retrospective Cohort Study

- 3476** Prognostic significance of hemoglobin, albumin, lymphocyte, platelet in gastrointestinal stromal tumors: A propensity matched retrospective cohort study

Zhao Z, Yin XN, Wang J, Chen X, Cai ZL, Zhang B

Retrospective Study

- 3488** Contrast-enhanced ultrasound Liver Imaging Reporting and Data System: Lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis

Vidili G, Arru M, Solinas G, Calvisi DF, Meloni P, Sauchella A, Turilli D, Fabio C, Cossu A, Madeddu G, Babudieri S, Zocco MA, Iannetti G, Di Lembo E, Delitala AP, Manetti R

- 3503** Novel index for the prediction of significant liver fibrosis and cirrhosis in chronic hepatitis B patients in China

Liao MJ, Li J, Dang W, Chen DB, Qin WY, Chen P, Zhao BG, Ren LY, Xu TF, Chen HS, Liao WJ

SYSTEMATIC REVIEWS

- 3514** Percutaneous transhepatic cholangiography *vs* endoscopic ultrasound-guided biliary drainage: A systematic review

Hassan Z, Gadour E

CASE REPORT

- 3524** Isolated gastric variceal bleeding related to non-cirrhotic portal hypertension following oxaliplatin-based chemotherapy: A case report

Zhang X, Gao YY, Song DZ, Qian BX

LETTER TO THE EDITOR

- 3532** Hepatitis B core-related antigen: Are we near a treatment endpoint?

Gupta T

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Govind K Makharia, MD, DM,DNB, Professor, Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. govindmakharia@aiims.edu

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Wen-Wen Qi; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

July 21, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Risk factors and diagnostic biomarkers for nonalcoholic fatty liver disease-associated hepatocellular carcinoma: Current evidence and future perspectives

Masayuki Ueno, Haruhiko Takeda, Atsushi Takai, Hiroshi Seno

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ulasoglu C, Turkey;
Wang YL, China

Received: February 2, 2022

Peer-review started: February 2, 2022

First decision: April 10, 2022

Revised: April 24, 2022

Accepted: June 15, 2022

Article in press: June 15, 2022

Published online: July 21, 2022



Masayuki Ueno, Haruhiko Takeda, Atsushi Takai, Hiroshi Seno, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto 6068507, Japan

Corresponding author: Atsushi Takai, MD, PhD, Assistant Professor, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 6068507, Japan. atsushit@kuhp.kyoto-u.ac.jp

Abstract

High rates of excessive calorie intake diets and sedentary lifestyles have led to a global increase in nonalcoholic fatty liver disease (NAFLD). As a result, this condition has recently become one of the leading causes of hepatocellular carcinoma (HCC). Furthermore, the incidence of NAFLD-associated HCC (NAFLD-HCC) is expected to increase in the near future. Advanced liver fibrosis is the most common risk factor for NAFLD-HCC. However, up to 50% of NAFLD-HCC cases develop without underlying liver cirrhosis. Epidemiological studies have revealed many other risk factors for this condition; including diabetes, other metabolic traits, obesity, old age, male sex, Hispanic ethnicity, mild alcohol intake, and elevated liver enzymes. Specific gene variants, such as single-nucleotide polymorphisms of patatin-like phospholipase domain 3, transmembrane 6 superfamily member 2, and membrane-bound O-acyl-transferase domain-containing 7, are also associated with an increased risk of HCC in patients with NAFLD. This clinical and genetic information should be interpreted together for accurate risk prediction. Alpha-fetoprotein (AFP) is the only biomarker currently recommended for HCC screening. However, it is not sufficiently sensitive in addressing this diagnostic challenge. The GALAD score can be calculated based on sex, age, lectin-bound AFP, AFP, and des-carboxyprothrombin and is reported to show better diagnostic performance for HCC. In addition, emerging studies on genetic and epigenetic biomarkers have also yielded promising diagnostic potential. However, further research is needed to establish an effective surveillance program for the early diagnosis of NAFLD-HCC.

Key Words: Nonalcoholic fatty liver disease; Hepatocellular carcinoma; Risk factors; Biomarkers; Tumor markers; Genetics

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This review summarizes the risk factors and diagnostic biomarkers for nonalcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma (HCC). The highlighted risk factors include liver fibrosis, diabetes, age, sex, race, alcohol intake, elevated liver enzymes, and specific genetic variants. Currently available diagnostic biomarkers include alpha-fetoprotein (AFP), des-carboxyprothrombin, and the AFP isoform L3. The combined use of these biomarkers may increase the diagnostic sensitivity of NAFLD-HCC detection. However, more discussion will be necessary on the cost-effectiveness of these approaches. This review also summarizes emerging means of discovering novel biomarkers using omics techniques. A better understanding of these risk factors and diagnostic biomarkers will facilitate the effective surveillance of NAFLD-HCC.

Citation: Ueno M, Takeda H, Takai A, Seno H. Risk factors and diagnostic biomarkers for nonalcoholic fatty liver disease-associated hepatocellular carcinoma: Current evidence and future perspectives. *World J Gastroenterol* 2022; 28(27): 3410-3421

URL: <https://www.wjgnet.com/1007-9327/full/v28/i27/3410.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v28.i27.3410>

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers[1]. It is the sixth most common form of cancer and the fourth leading cause of worldwide cancer-related deaths[2]. By contrast to the declining trends for other major cancers, mortality rates from liver cancer have increased by almost 3% *per year*[3]. Chronic liver infection from hepatitis B or C virus (HBV or HCV, respectively) and alcohol abuse are the most common causes of HCC[1,4]. However, there is a growing concern about the rapid increase in nonalcoholic fatty liver disease (NAFLD) as another cause of HCC.

NAFLD is a spectrum of chronic liver diseases characterized by excess fat accumulation in hepatocytes[5]. The prevalence of NAFLD is rapidly increasing worldwide, with recent studies reporting a global percentage of approximately 25%[6]. Unsurprisingly, the incidence of NAFLD-associated HCC (NAFLD-HCC) is also increasing in many areas of the world. In the United States, the proportion of NAFLD-HCC among all HCC patients has significantly increased from 9.3% to 13.6% over the past decade[7]. In a French cohort of patients who underwent liver resection, the prevalence of NAFLD-HCC increased from 2.6% (1995-1999) to 19.5% (2010-2014)[8]. Similar trends are also seen in Asian countries. According to a nationwide survey conducted in Japan, the proportion of nonalcoholic steatohepatitis (NASH)-related HCC has increased from 1.5% (2007 or before) to 7.2% (2014–2016)[9]. Universal HBV vaccination and widespread use of direct-acting antiviral agents for HCV are expected to decrease the number of virus-related HCC cases. Nonetheless, NAFLD-HCC is expected to continue to rise in the future[10,11].

NAFLD-HCC is often diagnosed at an advanced stage due to a lack of efficient surveillance policies [11]. In the Veteran Affairs population, only 40% of NAFLD-HCC patients underwent HCC surveillance compared to more than 80% of patients with HCV-related HCC[12]. From the perspective of cost-effectiveness, HCC screening should be considered when the annual risk of HCC exceeds 0.4–2.0%[13,14]. However, in a large-scale retrospective cohort study, out of 2382289 person-years of follow-up, only 490 patients with NAFLD were diagnosed with HCC (0.21/1000 person-years)[15]. Thus, it is necessary to more effectively identify high-risk patients who will benefit from HCC surveillance. Additionally, the diagnostic performance of the implemented examination is important for effective surveillance. Although ultrasonography with or without alpha-fetoprotein (AFP) is recommended for HCC screening [16], the sensitivity and specificity of these examinations are insufficient in patients with NAFLD. The high prevalence of obesity in patients with NAFLD impairs ultrasonography performance[17]. Therefore, many researchers have been searching for alternative NAFLD-HCC surveillance tools to increase the chances of early diagnosis. Recent advances in omics technology have enabled easier genetic and epigenetic benchmark analysis. Thus, many potential biomarkers are currently under investigation.

In this review, we discuss the current evidence for clinical and genetic HCC risk factors. We also summarize previous reports on the diagnostic biomarkers of NAFLD-HCC, including those under development. Finally, we briefly address future perspectives on HCC surveillance for NAFLD patients.

CLINICAL RISK FACTORS

Liver fibrosis

Liver fibrosis is the most important risk factor for the development of HCC in patients with NAFLD[18,

19]. In a large retrospective cohort study, the annual HCC incidence rates amongst NAFLD patients with and without cirrhosis were 10.6 and 0.08 *per* 1000 person-years, respectively[15]. This indicates that the presence of liver cirrhosis increases the risk of NAFLD-HCC by more than 10-fold (Table 1).

Liver biopsy is the gold standard for evaluating the fibrotic stage of the liver[20]. However, noninvasive examinations are more widely used in clinical practice. Available serum biomarkers for assessing fibrosis include the aspartate transaminase (AST)-to-platelet ratio index, Fibrosis-4 (FIB-4) index, and enhanced liver fibrosis score[21]. The FIB-4 index is calculated using various factors; including age, AST, alanine aminotransferase (ALT), and platelet count. Furthermore, a significant association between the FIB-4 index and HCC risk in NAFLD patients has been reported[15,22]. The Mac-2-binding protein glycosylation isomer is a novel serum biomarker that shows relatively high efficacy at assessing liver fibrosis[23]. It may also be useful in predicting the risk of hepatocarcinogenesis among NAFLD patients[24].

Additionally, elastography techniques using ultrasound or magnetic resonance imaging are useful tools for noninvasive evaluation of degree of fibrosis[21]. A retrospective study from Japan suggested that shear wave velocity measurements can be used for HCC risk assessment in NAFLD patients[25].

Diabetes mellitus and other metabolic traits

Several studies have demonstrated that (mostly type 2) diabetes mellitus is associated with an increased risk of HCC development in NAFLD patients. The hazard ratio for HCC in diabetic patients has been reported to be around 2.2–4.2[22,26,27] (Table 1). In a nationwide Japanese study, the annual incidence of HCC was only 0.11% in diabetes patients overall. However, it increased to 1.0% when they had an FIB-4 index of 3.5 or more[14]. Therefore, the degree of liver fibrosis, together with presence or absence of diabetes, should be assessed to predict the risk of NAFLD-HCC.

There have been conflicting reports regarding the association between other metabolic traits such as hypertension, dyslipidemia, with NAFLD-HCC[28]. However, a recent study showed that these conditions were also risk factors for NAFLD-HCC (Table 1). Furthermore, the hazard ratio for HCC was 5.6 in patients with diabetes, hypertension, and dyslipidemia[27,29].

Obesity

Regardless of underlying liver diseases, obesity is associated with an increased risk of HCC[30]. This relationship has also been confirmed in patients with NAFLD[29,31]. In a cohort of NAFLD-HCC patients treated with curative radiofrequency ablation, the degree of visceral fat accumulation, but not body mass index (BMI), was independently associated with an increased risk of HCC recurrence[32]. A propensity score-matched study showed that the incidence of both NASH and HCC were significantly lower in patients who underwent bariatric surgery, indicating a protective role of sustained weight loss by bariatric surgery[33].

Age, sex, and race

Old age, male sex, and Hispanic ethnicity are also known risk factors for NAFLD-HCC (Table 1); the details are described in another review article[31]. In the United States, a multicenter case-control study showed that old age (*per* year) and male sex were independently associated with a higher NAFLD-HCC risk [odds ratios (OR), 1.08 and 4.34, respectively][34]. In another study, age \geq 65 years was associated with a 1.83 times higher NAFLD-HCC risk compared to age < 65 years[15]. Regarding ethnicity, a previous study showed that Hispanic patients had a lower NAFLD-HCC risk (OR, 0.3). By contrast, another study showed the opposite result (hazard ratio, 1.59)[15,34]. Several other studies have shown that Hispanic ethnicity is, in itself, a risk factor for NAFLD, partly because of the high prevalence of patatin-like phospholipase domain 3 (*PNPLA3*) variants among Hispanic people[35,36].

Alcohol intake and smoking

NAFLD is defined as hepatic steatosis without harmful alcohol intake (more than 30 g/day for men and 20 g/day for women). However, mild alcohol intake can also be a risk factor for NAFLD-HCC[37]. Previous studies have shown that mild drinking habits were associated with 3.6–4.8 times higher risk of HCC in NAFLD patients compared to no habits of drinking[38,39] (Table 1). No study has specifically investigated the association between smoking and NAFLD-HCC. However, smoking is associated with an increased risk of HCC. Additionally, it has been reported to be associated with advanced liver fibrosis in NAFLD patients[31,40]. Because these factors are modifiable, NAFLD patients should be informed that cessation of alcohol intake and smoking may reduce the risk of future HCC development.

Elevated liver enzymes

Patients with NASH are thought to have a higher risk of HCC than those with NAFLD[18]. However, liver biopsy is required to accurately distinguish these conditions. Therefore, elevated liver enzyme levels are often used as surrogate markers for NASH in clinical practice. Several studies have shown that elevated liver enzymes in NAFLD patients are significantly associated with an increased risk of HCC (hazard ratio, 2.07–8.20)[41–43] (Table 1). At the same time, however, normal transaminase levels do not exclude the possibility of advanced liver fibrosis[44].

Table 1 Clinical risk factors for nonalcoholic fatty liver disease-associated hepatocellular carcinoma

Risk factors	Reported evidence	Ref.
Liver fibrosis	The annual incidence rate of HCC in NAFLD patients with cirrhosis was more than 10 times higher than in those without Non-invasive fibrosis markers (<i>e.g.</i> , FIB-4 index, M2BPGi, and shear wave velocity in VTQ) also had significant associations with the risk of NAFLD-HCC	[15,22,24,25]
Diabetes	Associated with increased risk of HCC in NAFLD patients (hazard ratio: 2.2–4.2)	[22,26,27]
Hypertension	May be an independent risk factor for NAFLD-HCC	[29]
Dyslipidemia	May be an independent risk factor for NAFLD-HCC	[29]
Age	Increased age was an independent risk factor for HCC in patients with NASH-related cirrhosis NAFLD patients aged ≥ 65 had 1.83 times higher risk of HCC than those aged < 65	[15,34]
Male sex	Male patients with NASH-related cirrhosis had 4.34 times higher risk of HCC than female patients	[34]
Ethnicity	Hispanic ethnicity was associated with 1.59 times higher risk of HCC in NAFLD patients compared to white ethnicity (however, there have been conflicting results)	[15]
Mild alcohol intake	Associated with increased risk of HCC in NAFLD patients (hazard ratio: 3.6–4.8)	[38,39]
Elevated liver enzymes	Associated with increased risk of HCC in NAFLD patients (hazard ratio: 2.1–8.2)	[41–43]

HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease; FIB-4: Fibrosis-4; M2BPGi: Mac-2-binding protein glycosylation isomer; VTQ: Virtual touch quantification; NASH: Nonalcoholic steatohepatitis.

Combined risk assessment

As we described above, many factors influence the risk of HCC in NAFLD patients. Therefore, integrating multiple factors will improve the accuracy of risk assessment. Lee *et al*[45] proposed a risk prediction model consisting of age, platelet count, and liver stiffness. This showed relatively good prediction performance in the validation cohort (*i.e.*, area under the receiver operating characteristic curve (AUROC), 0.78)[45]. Ioannou *et al*[46] reported another prediction model with a similar predictive value (AUROC, 0.75), consisting of age, sex, diabetes, BMI, platelet count, serum albumin, and AST/√ALT ratio[46].

GENETIC RISK FACTORS

Although NAFLD development and progression is largely determined by environmental factors, several genetic factors are involved in NAFLD pathogenesis. These genes included *PNPLA3*, transmembrane 6 superfamily member 2 (*TM6SF2*), glucokinase regulator (*GCKR*), membrane-bound O-acyl-transferase domain-containing 7 (*MBOAT7*), and 17-beta-hydroxysteroid dehydrogenase 13 (*HSD17B13*)[5,47]. Epigenetic factors, such as DNA methylation, histone modification, and non-coding RNAs, also play roles in the progression of NAFLD and hepatocarcinogenesis[48]. The risk of severe liver fibrosis has been reported to be 12.5-fold higher in patients with first-degree relatives with NAFLD-related cirrhosis than those without[49].

Single-nucleotide polymorphisms (SNPs) of *PNPLA3* have been the most studied for its association with HCC[50]. In a cohort of European Caucasian patients with NAFLD, the *PNPLA3* rs738409 polymorphism was significantly associated with HCC risk. GG carriers were found to evince a 5-fold increased risk compared to CC carriers[51]. This association was confirmed by subsequent studies[52, 53]. The *TM6SF2* rs58542926 polymorphism has been reported to be another risk factor for HCC and advanced fibrosis/cirrhosis[54,55]. In addition, the *MBOAT7* rs641738 variant has also been reported as a risk factor for NAFLD-HCC. Furthermore, in an Italian cohort, the rs6417338 C-to-T variant was associated with a 1.65-fold increased risk of HCC[56]. Other reported SNPs associated with NAFLD-HCC risk include Toll-like receptor 5 rs5744174[57], signal transducer transcription 6 rs167769[58] activator, yes-associated protein 1 rs11225163[58], *HSD17B13* rs72613567[55], and dystrophy-associated fer-1-like protein rs17007417[59] (Table 2).

Zhang *et al*[55] reported a combined risk assessment model consisting of *PNPLA3*, *TM6SF2*, and *HSD17B13* variants[55]. In this study, patients with the highest score had a 29-fold higher risk of developing HCC. Bianco *et al*[60] reported another polygenic risk assessment model consisting of *PNPLA3*, *TM6SF2*, *GCKR*, *MBOAT7*, and *HSD17B13*[60]. The sensitivity and specificity for diagnosing HCC were 0.43 and 0.79%, respectively (AUROC, 0.65).

Table 2 Genetic risk factors for nonalcoholic fatty liver disease-associated hepatocellular carcinoma

Risk factors	Reported evidence	Ref.
<i>PNPLA3</i>	Carriage of rs738409 GG polymorphism is associated with 5.1–6.4-fold increased risk of HCC in NAFLD patients <i>PNPLA3</i> G variant (GG <i>vs</i> CG <i>vs</i> CC) was not significantly associated with the risk of cardiovascular events extrahepatic cancers or overall death, but was associated with HCC (HR: 2.66) and liver-related death (HR: 2.42) Used for developing polygenic risk scores	[51–53,60]
<i>TM6SF2</i>	<i>TM6SF2</i> minor allele carriage (rs58542926 C>T) was associated with advanced fibrosis/cirrhosis and HCC (OR, 2.8) in NAFLD patients Combined assessment with <i>PNPLA3</i> and <i>HSD17B13</i> variants were useful for risk stratification of NAFLD-HCC Used for developing polygenic risk scores	[54,55,60]
<i>MBOAT7</i>	<i>MBOAT7</i> rs641738 C>T variants were associated with higher risk of HCC in NAFLD patients (OR, 1.65–2.10) Used for developing polygenic risk scores	[56,60]
<i>TLR5</i>	<i>TLR5</i> rs5744174 TT genotype was a risk factor of HCC in patients with steatohepatitis-related cirrhosis (OR, 1.9)	[57]
<i>STAT6</i>	<i>STAT6</i> rs167769 CC genotype was inversely associated with the risk of HCC in NASH patients (OR, 0.015)	[58]
<i>YAP1</i>	Carriage of <i>YAP1</i> rs11225163 C allele was inversely associated with the risk of HCC in NASH patients (OR, 0.047)	[58]
<i>HSD17B13</i>	Combined assessment with <i>PNPLA3</i> and <i>TM6SF2</i> variants were useful for risk stratification of NAFLD-HCC	[55]
<i>DYSF</i>	<i>DYSF</i> rs17007417 T allele carriage was associated with increased risk of HCC in NAFLD patients (OR, 2.74)	[59]
<i>GCKR</i>	<i>GCKR</i> rs1260326 T allele carriage was associated with increased risk of HCC in NAFLD patients (OR, 1.38) Used for developing polygenic risk scores	[59,60]

PNPLA3: Patatin-like phospholipase domain 3; HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease; HR: Hazard ratio; TM6SF2: Transmembrane 6 superfamily member 2; HSD17B13: 7-beta-Hydroxysteroid dehydrogenase 13; OR: Odds ratio; MBOAT7: Membrane-bound O-acyl-transferase domain-containing 7; TLR5: Toll-like receptor 5; STAT6: Signal transducer activator of transcription 6; NASH: Nonalcoholic steatohepatitis; YAP1: Yes-associated protein 1; DYSF: Dystrophy-associated fer-1-like protein; GCKR: Glucokinase regulator.

DIAGNOSTIC BIOMARKERS

Currently available biomarkers

The currently available serum biomarkers for diagnosing HCC include AFP, des-carboxyprothrombin (DCP), and AFP isoform L3 (AFP-L3) (Table 3). Only AFP is recommended for HCC surveillance as per the major guidelines[31]. However, patients with NAFLD-HCC tend to have lower AFP levels than those with viral HCC[12,61]. Thus, the combined use of multiple tumor markers may be considered to increase the detection rate of HCC[62]. The GALAD score is a scoring system for the diagnosis of HCC. This score can be calculated by sex, age, lectin-bound AFP, AFP, and DCP. In a German cohort of NASH patients with and without HCC, the GALAD score exhibited excellent diagnostic performance (AUROC, 0.96). This was significantly better than AFP (AUROC, 0.88), DCP (AUROC, 0.87), and AFP-L3 (AUROC, 0.86) alone[63]. However, it must be noted that only 20% of the HCC patients included in this study were within the Milan criteria. In addition, further research is needed from the perspective of cost effectiveness to determine whether this scoring system should be recommended for routine HCC screening in patients with NAFLD.

Potential biomarkers under investigation

Many serum biomarkers are under investigation for more accurate diagnosis of NAFLD-HCC without imaging. These biomarkers include iron and transferrin saturation[64], glypican-3 and adiponectin[65], midkine[66], apoptosis inhibitor of macrophages[67,68], glycosylation patterns of glycoproteins[69], and specific types of glycopeptides[70,71] (Table 3). Recently, Kozumi *et al*[72] showed that intrahepatic and serum thrombospondin 2 (*THBS2*) expression levels are strongly associated with advanced fibrosis in patients with NASH[72]. In their study, HCC was observed only in patients with high serum levels of

Table 3 Currently available and potential diagnostic biomarkers for nonalcoholic fatty liver disease-associated hepatocellular carcinoma

Biomarkers	Reported evidence	Ref.
Currently available		
AFP	Modest diagnostic ability for HCC in NAFLD patients (AUROC, 0.71–0.88)	[63,84]
DCP	The diagnostic ability for NAFLD-HCC was similar to that of AFP Combined use with AFP improved the diagnostic performance Used for calculation of GALAD score	[63,84]
AFP-L3	The diagnostic ability for NAFLD-HCC was similar to that of AFP Used for calculation of GALAD score	[63]
Under development		
Iron status	Elevations of serum iron levels and transferrin saturation were associated with increased risk of HCC in NAFLD patients (HR, 2.91 and 2.02, respectively)	[64]
Proteins	Midkine increased the diagnostic yield in AFP-negative HCC in NAFLD patients; 59.2% of AFP-negative NAFLD-HCC patients had elevation of serum midkine levels IgM-free AIM had better diagnostic performance for NASH-HCC than AFP or DCP (AUROC, 0.905–0.929) Serum TSP-2 levels were significantly associated with advanced fibrosis in NASH patients. Among 164 patients with NAFLD, HCC occurred only in patients with high serum levels of TSP-2	[65–67,72]
Glycoprotein	Glycosylation patterns of alpha-1 acid glycoprotein may serve as a diagnostic biomarker for AFP-negative HCC in NAFLD patients	[69]
Proteoglycan	Glypican-3 had modest diagnostic ability (AUROC, 0.759), similar to AFP (AUROC, 0.763). When combined with age, sex, DCP and adiponectin, the AUROC increased to 0.948	[65]
Glycopeptide	Site-specific N-glycopeptides from vitronectin may serve as diagnostic biomarkers for NASH-HCC. When used together with AFP, the AUROC were 0.834 and 0.847, compared to 0.791 of AFP alone Site-specific N-glycopeptides from serum haptoglobin showed better diagnostic accuracy for NASH-HCC than AFP	[70,71]
Cytokine (adipokine)	Adiponectin had slightly better diagnostic ability (AUROC, 0.770) than AFP (AUROC, 0.763). When combined with age, sex, DCP and glypican-3, the AUROC increased to 0.948	[65]
Cell-free DNA	<i>TERT</i> promoter mutation (C228T) in serum cfDNA showed better diagnostic ability for early NAFLD-HCC than AFP and DCP Methylation biomarkers in cfDNA improved the diagnostic performance when combined with AFP	[76,78]
microRNA	The expression levels of exosomal miR-182, miR-301a and miR-373 in both serum and ascetic fluid were higher in NASH-cirrhosis patients with HCC than in those without HCC	[77]

AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease; AUROC: Area under receiver operating characteristic curve; DCP: Des-carboxyprothrombin; AFP-L3: AFP isoform L3; HR: Hazard ratio; IgM: Immunoglobulin M; AIM: Apoptosis inhibitor of macrophages; TSP-2: Thrombospondin-2; NASH: Nonalcoholic steatohepatitis; *TERT*: Telomerase reverse transcriptase; cfDNA: Cell-free DNA; miR: microRNA.

thrombospondin-2 (TSP-2). Thus, serum TSP-2 testing may also be useful for NAFLD-HCC surveillance.

Genetic and epigenetic biomarkers have attracted increasing attention in recent years (Table 3). For example, telomerase reverse transcriptase (*TERT*) promoter mutations, the most common form of HCC genetic alteration[73–75], can be analyzed using cell-free DNA (cfDNA). Akuta *et al*[76] reported that *TERT* C228T mutation could be detected in 63.9% of NAFLD-HCC patients by analyzing cfDNA[76]. Notably, it can be positive, even in patients with normal AFP and DCP levels. Another example of circulating biomarkers is non-coding RNAs, especially microRNAs. In a preliminary study, the serum expression levels of miR-182, miR-301a, and miR-373 were significantly higher in NASH-HCC patients than in NASH patients without HCC[77]. DNA methylation can also be analyzed using peripheral blood. In a recent study, methylation cfDNA biomarkers provided a modest diagnostic value for NAFLD-HCC with a sensitivity of 87.5% and specificity of 39.4%[78]. The combination of this DNA methylation panel and AFP led to a better cohort wide diagnostic performance than either of them used

alone. Although the utility of these biomarkers is yet to be validated, in the near future, advances in omics technology will surely provide better diagnostic tools for NAFLD-HCC than conventional tumor markers.

FUTURE PERSPECTIVES

A more effective surveillance approach is strongly desired to reduce the number of deaths due to NAFLD-HCC. As advanced liver fibrosis is the most common risk factor for NAFLD-HCC, current screening recommendations primarily focus on patients with cirrhosis. However, in a French study, only 37% of patients undergoing liver resection for NAFLD-HCC had bridging fibrosis or cirrhosis; with a frequency significantly lower than that of other etiologies[8]. Similar results were observed in a Japanese multicenter study; in which only 49% of patients with NAFLD-HCC had underlying cirrhosis [79]. Therefore, more than half of patients with NAFLD-HCC will lose the chance of early detection if no other risk factors are considered. As discussed above, other clinical factors and specific genetic variants have robust associations with NAFLD-HCC risk. We should make the best use of this evidence to enhance effective HCC surveillance. In addition, more accurate diagnostic biomarkers for NAFLD-HCC are needed. Among the currently available biomarkers, the GALAD score seems to be the most reliable. However, advances in omics technology will certainly provide more powerful diagnostic tools in the future. For instance, a recent study showed that fragmentomic cfDNA analysis offered excellent accuracy in detecting primary liver tumors (AUROC, 0.995), regardless of the underlying liver disease [80]. Moreover, it showed a sensitivity of over 95%, even for stage I tumors. Thus, further research on genetic and epigenetic biomarkers is very much needed.

Novel conceptional criteria for metabolic dysfunction-associated fatty liver disease (MAFLD) were proposed in 2020[81]. Although MAFLD has been reported as a more practical definition for identifying patients with fatty liver disease with high risk of disease progression[82], it remains unclear whether the evidence of risk factors and diagnostic markers for NAFLD-HCC can be extended to MAFLD-HCC. A nationwide cohort study conducted in Taiwan revealed that patients with NAFLD/MAFLD overlap had similar risk of HCC compared to those with NAFLD alone[83]. Nonetheless, further studies are warranted on this topic.

CONCLUSION

The incidence of NAFLD-HCC is increasing rapidly worldwide. Thus, an effective surveillance approach is required to reduce the number of deaths due to this condition. Although advanced fibrosis is the most important risk factor for NAFLD-HCC, other clinical risk factors such as diabetes, old age, male sex, and elevated liver enzymes should also be considered. Recent advances in omics technology have revealed that genetic factors such as the SNP of *PNPLA3* also affect the risk of hepatocarcinogenesis in patients with NAFLD. With regards to the diagnostic biomarkers for NAFLD-HCC, only AFP is recommended for surveillance as *per* major guidelines. A recent study showed that the GALAD score evinced a more effective diagnostic performance than when AFP was used alone. However, clinical implementation should be discussed from the perspective of cost-effectiveness. Specific gene mutations and DNA methylation can be detected in cfDNA and are expected to be novel biomarkers for the early NAFLD-HCC diagnosis, as well as specific proteins, glycopeptides, and adipokines.

ACKNOWLEDGEMENTS

We would like to thank Drs. Ken Takahashi, Takahiro Shimizu, Yuji Eso, Eriko Iguchi, Ken Kumagai, Masako Mishima, Mari Teramura, Shigeharu Nakano, Takahiko Ito, Haruka Amino, and Takahiro Inoue for their helpful discussions and comments on the manuscript.

FOOTNOTES

Author contributions: Ueno M drafted the manuscript and prepared the tables; Takeda H and Takai A designed the outline and coordinated the writing of the manuscript; Seno H supervised data interpretation and revised the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-

NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Japan

ORCID number: Masayuki Ueno 0000-0002-2497-9327; Haruhiko Takeda 0000-0002-8954-9133; Atsushi Takai 0000-0002-5233-4120; Hiroshi Seno 0000-0002-8509-8128.

S-Editor: Fan JR

L-Editor: A

P-Editor: Fan JR

REFERENCES

- Villanueva A. Hepatocellular Carcinoma. *N Engl J Med* 2019; **380**: 1450-1462 [PMID: 30970190 DOI: 10.1056/NEJMra1713263]
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin* 2020; **70**: 443-459 [PMID: 32940362 DOI: 10.3322/caac.21637]
- Takeda H, Takai A, Inuzuka T, Marusawa H. Genetic basis of hepatitis virus-associated hepatocellular carcinoma: linkage between infection, inflammation, and tumorigenesis. *J Gastroenterol* 2017; **52**: 26-38 [PMID: 27714455 DOI: 10.1007/s00535-016-1273-2]
- Brunt EM, Wong VW, Nobili V, Day CP, Sookoian S, Maher JJ, Bugianesi E, Sirlin CB, Neuschwander-Tetri BA, Rinella ME. Nonalcoholic fatty liver disease. *Nat Rev Dis Primers* 2015; **1**: 15080 [PMID: 27188459 DOI: 10.1038/nrdp.2015.80]
- Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 11-20 [PMID: 28930295 DOI: 10.1038/nrgastro.2017.109]
- Hester D, Golabi P, Paik J, Younossi I, Mishra A, Younossi ZM. Among Medicare Patients With Hepatocellular Carcinoma, Non-alcoholic Fatty Liver Disease is the Most Common Etiology and Cause of Mortality. *J Clin Gastroenterol* 2020; **54**: 459-467 [PMID: 30672817 DOI: 10.1097/MCG.0000000000001172]
- Pais R, Fartoux L, Goumard C, Scatton O, Wendum D, Rosmorduc O, Ratzu V. Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period. *Aliment Pharmacol Ther* 2017; **46**: 856-863 [PMID: 28857208 DOI: 10.1111/apt.14261]
- Enomoto H, Ueno Y, Hiasa Y, Nishikawa H, Hige S, Takikawa Y, Taniai M, Ishikawa T, Yasui K, Takaki A, Takaguchi K, Ido A, Kurosaki M, Kanto T, Nishiguchi S; Japan Etiology of Liver Cirrhosis Study Group in the 54th Annual Meeting of JSH. The transition in the etiologies of hepatocellular carcinoma-complicated liver cirrhosis in a nationwide survey of Japan. *J Gastroenterol* 2021; **56**: 158-167 [PMID: 33219410 DOI: 10.1007/s00535-020-01748-x]
- Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y, Geier A, Kondili LA, Kroy DC, Lazarus JV, Loomba R, Manns MP, Marchesini G, Nakajima A, Negro F, Petta S, Ratzu V, Romero-Gomez M, Sanyal A, Schattenberg JM, Tacke F, Tanaka J, Trautwein C, Wei L, Zeuzem S, Razavi H. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018; **69**: 896-904 [PMID: 29886156 DOI: 10.1016/j.jhep.2018.05.036]
- Degasperi E, Colombo M. Distinctive features of hepatocellular carcinoma in non-alcoholic fatty liver disease. *Lancet Gastroenterol Hepatol* 2016; **1**: 156-164 [PMID: 28404072 DOI: 10.1016/S2468-1253(16)30018-8]
- Mittal S, Sada YH, El-Serag HB, Kanwal F, Duan Z, Temple S, May SB, Kramer JR, Richardson PA, Davila JA. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. *Clin Gastroenterol Hepatol* 2015; **13**: 594-601.e1 [PMID: 25148760 DOI: 10.1016/j.cgh.2014.08.013]
- Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. *Am J Gastroenterol* 2020; **115**: 1642-1649 [PMID: 32530829 DOI: 10.14309/ajg.0000000000000715]
- Tateishi R, Matsumura T, Okanoue T, Shima T, Uchino K, Fujiwara N, Senokuchi T, Kon K, Sasako T, Taniai M, Kawaguchi T, Inoue H, Watada H, Kubota N, Shimano H, Kaneko S, Hashimoto E, Watanabe S, Shiota G, Ueki K, Kashiwabara K, Matsuyama Y, Tanaka H, Kasuga M, Araki E, Koike K; LUCID study investigators. Hepatocellular carcinoma development in diabetic patients: a nationwide survey in Japan. *J Gastroenterol* 2021; **56**: 261-273 [PMID: 33427937 DOI: 10.1007/s00535-020-01754-z]
- Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, Li L, Desiderio R, Thrift AP, Asch SM, Chu J, El-Serag HB. Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease. *Gastroenterology* 2018; **155**: 1828-1837.e2 [PMID: 30144434 DOI: 10.1053/j.gastro.2018.08.024]
- Kim TH, Kim SY, Tang A, Lee JM. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma: 2018 update. *Clin Mol Hepatol* 2019; **25**: 245-263 [PMID: 30759967 DOI: 10.3350/cmh.2018.0090]
- Harris PS, Hansen RM, Gray ME, Massoud OI, McGuire BM, Shoreibah MG. Hepatocellular carcinoma surveillance: An evidence-based approach. *World J Gastroenterol* 2019; **25**: 1550-1559 [PMID: 30983815 DOI: 10.3748/wjg.v25.i13.1550]
- Younossi ZM, Henry L. Epidemiology of non-alcoholic fatty liver disease and hepatocellular carcinoma. *JHEP Rep* 2021;

- 3: 100305 [PMID: 34189448 DOI: 10.1016/j.jhepr.2021.100305]
- 19 **Ito T**, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Hayashi K, Nishimura D, Toyoda H, Kumada T, Goto H, Hirooka Y. Utility and limitations of noninvasive fibrosis markers for predicting prognosis in biopsy-proven Japanese non-alcoholic fatty liver disease patients. *J Gastroenterol Hepatol* 2019; **34**: 207-214 [PMID: 30144360 DOI: 10.1111/jgh.14448]
- 20 **Berger D**, Desai V, Janardhan S. Con: Liver Biopsy Remains the Gold Standard to Evaluate Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Clin Liver Dis (Hoboken)* 2019; **13**: 114-116 [PMID: 31061705 DOI: 10.1002/cld.740]
- 21 **Castera L**, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2019; **156**: 1264-1281.e4 [PMID: 30660725 DOI: 10.1053/j.gastro.2018.12.036]
- 22 **Alexander M**, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, Waterworth DM, Kendrick S, Sattar N, Alazawi W. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. *BMC Med* 2019; **17**: 95 [PMID: 31104631 DOI: 10.1186/s12916-019-1321-x]
- 23 **Kamada Y**, Ono M, Hyogo H, Fujii H, Sumida Y, Yamada M, Mori K, Tanaka S, Maekawa T, Ebisutani Y, Yamamoto A, Takamatsu S, Yoneda M, Kawada N, Chayama K, Saibara T, Takehara T, Miyoshi E; Japan Study Group of Nonalcoholic Fatty Liver Disease (JSG-NAFLD). Use of Mac-2 binding protein as a biomarker for nonalcoholic fatty liver disease diagnosis. *Hepatol Commun* 2017; **1**: 780-791 [PMID: 29404494 DOI: 10.1002/hep4.1080]
- 24 **Kawanaka M**, Tomiyama Y, Hyogo H, Koda M, Shima T, Tobita H, Hiramatsu A, Nishino K, Okamoto T, Sato S, Hara Y, Nishina S, Kawamoto H, Chayama K, Okanoue T, Hino K. Wisteria floribunda agglutinin-positive Mac-2 binding protein predicts the development of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. *Hepatol Res* 2018; **48**: 521-528 [PMID: 29316028 DOI: 10.1111/hepr.13054]
- 25 **Takamura M**, Kanefuji T, Suda T, Yokoo T, Kamimura H, Tsuchiya A, Kamimura K, Tamura Y, Igarashi M, Kawai H, Yamagiwa S, Nomoto M, Aoyagi Y. Value of shear wave velocity measurements for the risk assessment of hepatocellular carcinoma development in patients with nonalcoholic fatty liver disease : HCC risk assessment by VTTQ. *Hepatol Int* 2014; **8**: 240-249 [PMID: 26202505 DOI: 10.1007/s12072-014-9517-9]
- 26 **Grgurevic I**, Bozin T, Mikus M, Kukla M, O'Beirne J. Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease: From Epidemiology to Diagnostic Approach. *Cancers (Basel)* 2021; **13** [PMID: 34830997 DOI: 10.3390/cancers13225844]
- 27 **Fassio E**, Barreiro FJ, Pérez MS, Dávila D, Landeira G, Gualano G, Ruffillo G. Hepatocellular carcinoma in patients with metabolic dysfunction-associated fatty liver disease: Can we stratify at-risk populations? *World J Hepatol* 2022; **14**: 354-371 [PMID: 35317172 DOI: 10.4254/wjh.v14.i2.354]
- 28 **Benhammou JN**, Lin J, Hussain SK, El-Kabany M. Emerging risk factors for nonalcoholic fatty liver disease associated hepatocellular carcinoma. *Hepatoma Res* 2020; **6** [PMID: 32685690 DOI: 10.20517/2394-5079.2020.16]
- 29 **Jarvis H**, Craig D, Barker R, Spiers G, Stow D, Anstee QM, Hanratty B. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. *PLoS Med* 2020; **17**: e1003100 [PMID: 32353039 DOI: 10.1371/journal.pmed.1003100]
- 30 **Chen Y**, Wang X, Wang J, Yan Z, Luo J. Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. *Eur J Cancer* 2012; **48**: 2137-2145 [PMID: 22446023 DOI: 10.1016/j.ejca.2012.02.063]
- 31 **Huang DQ**, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 223-238 [PMID: 33349658 DOI: 10.1038/s41575-020-00381-6]
- 32 **Ohki T**, Tateishi R, Shiina S, Goto E, Sato T, Nakagawa H, Masuzaki R, Goto T, Hamamura K, Kanai F, Yoshida H, Kawabe T, Omata M. Visceral fat accumulation is an independent risk factor for hepatocellular carcinoma recurrence after curative treatment in patients with suspected NASH. *Gut* 2009; **58**: 839-844 [PMID: 19174415 DOI: 10.1136/gut.2008.164053]
- 33 **Kwak M**, Mehafeff JH, Hawkins RB, Hsu A, Schirmer B, Hallowell PT. Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: A propensity matched analysis. *Am J Surg* 2020; **219**: 504-507 [PMID: 31575419 DOI: 10.1016/j.amjsurg.2019.09.006]
- 34 **Corey KE**, Gawrieh S, deLemos AS, Zheng H, Scanga AE, Haglund JW, Sanchez J, Danford CJ, Comerford M, Bossi K, Munir S, Chalasani N, Wattacheril J. Risk factors for hepatocellular carcinoma in cirrhosis due to nonalcoholic fatty liver disease: A multicenter, case-control study. *World J Hepatol* 2017; **9**: 385-390 [PMID: 28321274 DOI: 10.4254/wjh.v9.i7.385]
- 35 **Romeo S**, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]
- 36 **Thandra KC**, Barsouk A, Saginala K, Aluru JS, Rawla P. Epidemiology of non-alcoholic fatty liver disease and risk of hepatocellular carcinoma progression. *Clin Exp Hepatol* 2020; **6**: 289-294 [PMID: 33511275 DOI: 10.5114/ceh.2020.102153]
- 37 **Petroni ML**, Brodosi L, Marchignoli F, Musio A, Marchesini G. Moderate Alcohol Intake in Non-Alcoholic Fatty Liver Disease: To Drink or Not to Drink? *Nutrients* 2019; **11** [PMID: 31847199 DOI: 10.3390/nu11123048]
- 38 **Kimura T**, Tanaka N, Fujimori N, Sugiura A, Yamazaki T, Joshita S, Komatsu M, Umemura T, Matsumoto A, Tanaka E. Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic fatty liver disease with advanced fibrosis. *World J Gastroenterol* 2018; **24**: 1440-1450 [PMID: 29632425 DOI: 10.3748/wjg.v24.i13.1440]
- 39 **Protopapas AA**, Cholongitas E, Chrysavgis L, Tziomalos K. Alcohol consumption in patients with nonalcoholic fatty liver disease: yes, or no? *Ann Gastroenterol* 2021; **34**: 476-486 [PMID: 34276185 DOI: 10.20524/aog.2021.0641]
- 40 **Ou H**, Fu Y, Liao W, Zheng C, Wu X. Association between Smoking and Liver Fibrosis among Patients with Nonalcoholic Fatty Liver Disease. *Can J Gastroenterol Hepatol* 2019; **2019**: 6028952 [PMID: 31737583 DOI: 10.1155/2019/6028952]
- 41 **Kawamura Y**, Arase Y, Ikeda K, Seko Y, Imai N, Hosaka T, Kobayashi M, Saitoh S, Sezaki H, Akuta N, Suzuki F, Suzuki Y, Ohmoto Y, Amakawa K, Tsuji H, Kumada H. Large-scale long-term follow-up study of Japanese patients with non-alcoholic fatty liver disease for the onset of hepatocellular carcinoma. *Am J Gastroenterol* 2012; **107**: 253-261 [PMID: 22008893 DOI: 10.1038/ajg.2011.327]
- 42 **Natarajan Y**, Kramer JR, Yu X, Li L, Thrift AP, El-Serag HB, Kanwal F. Risk of Cirrhosis and Hepatocellular Cancer in

- Patients With NAFLD and Normal Liver Enzymes. *Hepatology* 2020; **72**: 1242-1252 [PMID: [32022277](#) DOI: [10.1002/hep.31157](#)]
- 43 **Lee TY**, Wu JC, Yu SH, Lin JT, Wu MS, Wu CY. The occurrence of hepatocellular carcinoma in different risk stratifications of clinically noncirrhotic nonalcoholic fatty liver disease. *Int J Cancer* 2017; **141**: 1307-1314 [PMID: [28509327](#) DOI: [10.1002/ijc.30784](#)]
 - 44 **Makker J**, Tariq H, Kumar K, Ravi M, Shaikh DH, Leung V, Hayat U, Hassan MT, Patel H, Nayudu S, Chilimuri S. Prevalence of advanced liver fibrosis and steatosis in type-2 diabetics with normal transaminases: A prospective cohort study. *World J Gastroenterol* 2021; **27**: 523-533 [PMID: [33642826](#) DOI: [10.3748/wjg.v27.i6.523](#)]
 - 45 **Lee JS**, Sinn DH, Park SY, Shin HJ, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, Oh JH, Lee JI, Kim SU. Liver Stiffness-Based Risk Prediction Model for Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease. *Cancers (Basel)* 2021; **13** [PMID: [34572795](#) DOI: [10.3390/cancers13184567](#)]
 - 46 **Ioannou GN**, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. *J Hepatol* 2019; **71**: 523-533 [PMID: [31145929](#) DOI: [10.1016/j.jhep.2019.05.008](#)]
 - 47 **Carlsson B**, Lindén D, Brolén G, Liljeblad M, Bjursell M, Romeo S, Loomba R. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2020; **51**: 1305-1320 [PMID: [32383295](#) DOI: [10.1111/apt.15738](#)]
 - 48 **Tian Y**, Wong VW, Chan HL, Cheng AS. Epigenetic regulation of hepatocellular carcinoma in non-alcoholic fatty liver disease. *Semin Cancer Biol* 2013; **23**: 471-482 [PMID: [24018165](#) DOI: [10.1016/j.semcancer.2013.08.010](#)]
 - 49 **Causy C**, Soni M, Cui J, Bettencourt R, Schork N, Chen CH, Ikhwan MA, Bassirian S, Cepin S, Gonzalez MP, Mendler M, Kono Y, Vodkin I, Mekeel K, Halderson J, Hemming A, Andrews B, Salotti J, Richards L, Brenner DA, Sirlin CB, Loomba R; Familial NAFLD Cirrhosis Research Consortium. Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis. *J Clin Invest* 2017; **127**: 2697-2704 [PMID: [28628033](#) DOI: [10.1172/JCI93465](#)]
 - 50 **Anstee QM**, Day CP. The Genetics of Nonalcoholic Fatty Liver Disease: Spotlight on PNPLA3 and TM6SF2. *Semin Liver Dis* 2015; **35**: 270-290 [PMID: [26378644](#) DOI: [10.1055/s-0035-1562947](#)]
 - 51 **Oda K**, Uto H, Mawatari S, Ido A. Clinical features of hepatocellular carcinoma associated with nonalcoholic fatty liver disease: a review of human studies. *Clin J Gastroenterol* 2015; **8**: 1-9 [PMID: [25575848](#) DOI: [10.1007/s12328-014-0548-5](#)]
 - 52 **Seko Y**, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, Hara T, Okajima A, Umemura A, Nishikawa T, Yamaguchi K, Moriguchi M, Kanemasa K, Yasui K, Imai S, Shimada K, Itoh Y. Development of hepatocellular carcinoma in Japanese patients with biopsy-proven non-alcoholic fatty liver disease: Association between PNPLA3 genotype and hepatocarcinogenesis/fibrosis progression. *Hepatol Res* 2017; **47**: 1083-1092 [PMID: [27862719](#) DOI: [10.1111/hepr.12840](#)]
 - 53 **Wang Z**, Budhu AS, Shen Y, Wong LL, Hernandez BY, Tiirikainen M, Ma X, Irwin ML, Lu L, Zhao H, Lim JK, Taddei T, Mishra L, Pawlish K, Stroup A, Brown R, Nguyen MH, Koshiol J, Hernandez MO, Forgues M, Yang HI, Lee MH, Huang YH, Iwasaki M, Goto A, Suzuki S, Matsuda K, Tanikawa C, Kamatani Y, Mann D, Guarnera M, Shetty K, Thomas CE, Yuan JM, Khor CC, Koh WP, Risch H, Wang XW, Yu H. Genetic susceptibility to hepatocellular carcinoma in chromosome 22q13.31, findings of a genome-wide association study. *JGH Open* 2021; **5**: 1363-1372 [PMID: [34950780](#) DOI: [10.1002/jgh3.12682](#)]
 - 54 **Liu YL**, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, Allison ME, Alexander GJ, Piguet AC, Anty R, Donaldson P, Aithal GP, Francque S, Van Gaal L, Clement K, Ratzliff V, Dufour JF, Day CP, Daly AK, Anstee QM. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. *Nat Commun* 2014; **5**: 4309 [PMID: [24978903](#) DOI: [10.1038/ncomms5309](#)]
 - 55 **Zhang HB**, Su W, Xu H, Zhang XY, Guan YF. HSD17B13: A Potential Therapeutic Target for NAFLD. *Front Mol Biosci* 2021; **8**: 824776 [PMID: [35071330](#) DOI: [10.3389/fmolb.2021.824776](#)]
 - 56 **Donati B**, Dongiovanni P, Romeo S, Meroni M, McCain M, Miele L, Petta S, Maier S, Rosso C, De Luca L, Vanni E, Grimaudo S, Romagnoli R, Colli F, Ferri F, Mancina RM, Iruzubieta P, Craxi A, Fracanzani AL, Grieco A, Corradini SG, Aghemo A, Colombo M, Soardo G, Bugianesi E, Reeves H, Anstee QM, Fargion S, Valenti L. MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals. *Sci Rep* 2017; **7**: 4492 [PMID: [28674415](#) DOI: [10.1038/s41598-017-04991-0](#)]
 - 57 **Nischalke HD**, Fischer J, Klüners A, Matz-Soja M, Krämer B, Langhans B, Goeser F, Soyka M, Stickel F, Spengler U, Nattermann J, Strassburg CP, Berg T, Lutz P. A genetic variant in toll-like receptor 5 is linked to chemokine levels and hepatocellular carcinoma in steatohepatitis. *Liver Int* 2021; **41**: 2139-2148 [PMID: [34051061](#) DOI: [10.1111/liv.14980](#)]
 - 58 **El-Derany MO**. Polymorphisms in Interleukin 13 Signaling and Interacting Genes Predict Advanced Fibrosis and Hepatocellular Carcinoma Development in Non-Alcoholic Steatohepatitis. *Biology (Basel)* 2020; **9** [PMID: [32283835](#) DOI: [10.3390/biology9040075](#)]
 - 59 **Kawaguchi T**, Shima T, Mizuno M, Mitsumoto Y, Umemura A, Kanbara Y, Tanaka S, Sumida Y, Yasui K, Takahashi M, Matsuo K, Itoh Y, Tokushige K, Hashimoto E, Kiyosawa K, Kawaguchi M, Itoh H, Uto H, Komorizono Y, Shirabe K, Takami S, Takamura T, Kawanaka M, Yamada R, Matsuda F, Okanoue T. Risk estimation model for nonalcoholic fatty liver disease in the Japanese using multiple genetic markers. *PLoS One* 2018; **13**: e0185490 [PMID: [29385134](#) DOI: [10.1371/journal.pone.0185490](#)]
 - 60 **Bianco C**, Jamialahmadi O, Pelusi S, Baselli G, Dongiovanni P, Zanoni I, Santoro L, Maier S, Liguori A, Meroni M, Borroni V, D'Ambrosio R, Spagnuolo R, Alisi A, Federico A, Bugianesi E, Petta S, Miele L, Vespasiani-Gentilucci U, Anstee QM, Stickel F, Hampe J, Fischer J, Berg T, Fracanzani AL, Soardo G, Reeves H, Prati D, Romeo S, Valenti L. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. *J Hepatol* 2021; **74**: 775-782 [PMID: [33248170](#) DOI: [10.1016/j.jhep.2020.11.024](#)]
 - 61 **Than NN**, Ghazanfar A, Hodson J, Tehami N, Coldham C, Mergental H, Manas D, Shah T, Newsome PN, Reeves H, Shetty S. Comparing clinical presentations, treatments and outcomes of hepatocellular carcinoma due to hepatitis C and non-alcoholic fatty liver disease. *QJM* 2017; **110**: 73-81 [PMID: [27634970](#) DOI: [10.1093/qjmed/hw151](#)]
 - 62 **Ertle JM**, Heider D, Wichert M, Keller B, Kueper R, Hilgard P, Gerken G, Schlaak JF. A combination of α -fetoprotein and

- des- γ -carboxy prothrombin is superior in detection of hepatocellular carcinoma. *Digestion* 2013; **87**: 121-131 [PMID: 23406785 DOI: 10.1159/000346080]
- 63 **Best J**, Bechmann LP, Sowa JP, Sydor S, Dechêne A, Pflanz K, Bedreli S, Schotten C, Geier A, Berg T, Fischer J, Vogel A, Bantel H, Weinmann A, Schattenberg JM, Huber Y, Wege H, von Felden J, Schulze K, Bettinger D, Thimme R, Sinner F, Schütte K, Weiss KH, Toyoda H, Yasuda S, Kumada T, Berhane S, Wichert M, Heider D, Gerken G, Johnson P, Canbay A. GALAD Score Detects Early Hepatocellular Carcinoma in an International Cohort of Patients With Nonalcoholic Steatohepatitis. *Clin Gastroenterol Hepatol* 2020; **18**: 728-735.e4 [PMID: 31712073 DOI: 10.1016/j.cgh.2019.11.012]
 - 64 **Yu YC**, Luu HN, Wang R, Thomas CE, Glynn NW, Youk AO, Behari J, Yuan JM. Serum Biomarkers of Iron Status and Risk of Hepatocellular Carcinoma Development in Patients with Nonalcoholic Fatty Liver Disease. *Cancer Epidemiol Biomarkers Prev* 2022; **31**: 230-235 [PMID: 34649958 DOI: 10.1158/1055-9965.EPI-21-0754]
 - 65 **Caviglia GP**, Armandi A, Rosso C, Gaia S, Aneli S, Rolle E, Abate ML, Olivero A, Nicolosi A, Guariglia M, Ribaldone DG, Carucci P, Saracco GM, Bugianesi E. Biomarkers of Oncogenesis, Adipose Tissue Dysfunction and Systemic Inflammation for the Detection of Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease. *Cancers (Basel)* 2021; **13** [PMID: 34064999 DOI: 10.3390/cancers13102305]
 - 66 **Vongsuvan R**, van der Poorten D, Iseli T, Strasser SI, McCaughan GW, George J. Midkine Increases Diagnostic Yield in AFP Negative and NASH-Related Hepatocellular Carcinoma. *PLoS One* 2016; **11**: e0155800 [PMID: 27219517 DOI: 10.1371/journal.pone.0155800]
 - 67 **Sumida Y**, Yoneda M, Seko Y, Ishiba H, Hara T, Toyoda H, Yasuda S, Kumada T, Hayashi H, Kobayashi T, Imajo K, Tada T, Kawaguchi T, Eguchi Y, Oeda S, Takahashi H, Tomita E, Okanoue T, Nakajima A; Japan Study Group Of Nafld Jsg-Nafld. Surveillance of Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease. *Diagnostics (Basel)* 2020; **10** [PMID: 32785100 DOI: 10.3390/diagnostics10080579]
 - 68 **Shimizu T**, Sawada T, Asai T, Kanetsuki Y, Hirota J, Moriguchi M, Nakajima T, Miyazaki T, Okanoue T. Hepatocellular carcinoma diagnosis using a novel electrochemiluminescence immunoassay targeting serum IgM-free AIM. *Clin J Gastroenterol* 2022; **15**: 41-51 [PMID: 34981443 DOI: 10.1007/s12328-021-01567-4]
 - 69 **Liang J**, Zhu J, Wang M, Singal AG, Odewole M, Kagan S, Renteria V, Liu S, Parikh ND, Lubman DM. Evaluation of AGP Fucosylation as a Marker for Hepatocellular Carcinoma of Three Different Etiologies. *Sci Rep* 2019; **9**: 11580 [PMID: 31399619 DOI: 10.1038/s41598-019-48043-1]
 - 70 **Zhu J**, Huang J, Zhang J, Chen Z, Lin Y, Grigorean G, Li L, Liu S, Singal AG, Parikh ND, Lubman DM. Glycopeptide Biomarkers in Serum Haptoglobin for Hepatocellular Carcinoma Detection in Patients with Nonalcoholic Steatohepatitis. *J Proteome Res* 2020; **19**: 3452-3466 [PMID: 32412768 DOI: 10.1021/acs.jproteome.0c00270]
 - 71 **Lin Y**, Zhu J, Pan L, Zhang J, Tan Z, Olivares J, Singal AG, Parikh ND, Lubman DM. A Panel of Glycopeptides as Candidate Biomarkers for Early Diagnosis of NASH Hepatocellular Carcinoma Using a Stepped HCD Method and PRM Evaluation. *J Proteome Res* 2021; **20**: 3278-3289 [PMID: 33929864 DOI: 10.1021/acs.jproteome.1c00175]
 - 72 **Kozumi K**, Kodama T, Murai H, Sakane S, Govaere O, Cockell S, Motooka D, Kakita N, Yamada Y, Kondo Y, Tahata Y, Yamada R, Hikita H, Sakamori R, Kamada Y, Daly AK, Anstee QM, Tatsumi T, Morii E, Takehara T. Transcriptomics Identify Thrombospondin-2 as a Biomarker for NASH and Advanced Liver Fibrosis. *Hepatology* 2021; **74**: 2452-2466 [PMID: 34105780 DOI: 10.1002/hep.31995]
 - 73 **Totoki Y**, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, Tsuji S, Donehower LA, Slagle BL, Nakamura H, Yamamoto S, Shinbrot E, Hama N, Lehmkuhl M, Hosoda F, Arai Y, Walker K, Dahdouli M, Gotoh K, Nagae G, Gingras MC, Muzny DM, Ojima H, Shimada K, Midorikawa Y, Goss JA, Cotton R, Hayashi A, Shibahara J, Ishikawa S, Guiteau J, Tanaka M, Urushidate T, Ohashi S, Okada N, Doddapaneni H, Wang M, Zhu Y, Dinh H, Okusaka T, Kokudo N, Kosuge T, Takayama T, Fukayama M, Gibbs RA, Wheeler DA, Aburatani H, Shibata T. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. *Nat Genet* 2014; **46**: 1267-1273 [PMID: 25362482 DOI: 10.1038/ng.3126]
 - 74 **Takeda H**, Takai A, Kumagai K, Iguchi E, Arasawa S, Eso Y, Shimizu T, Ueda Y, Taura K, Uemoto S, Kita R, Haga H, Marusawa H, Fujimoto A, Seno H. Multiregional whole-genome sequencing of hepatocellular carcinoma with nodule-in-nodule appearance reveals stepwise cancer evolution. *J Pathol* 2020; **252**: 398-410 [PMID: 32815153 DOI: 10.1002/path.5533]
 - 75 **Ki Kim S**, Ueda Y, Hatano E, Kakiuchi N, Takeda H, Goto T, Shimizu T, Yoshida K, Ikura Y, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Uemoto S, Chiba T, Ogawa S, Marusawa H. TERT promoter mutations and chromosome 8p loss are characteristic of nonalcoholic fatty liver disease-related hepatocellular carcinoma. *Int J Cancer* 2016; **139**: 2512-2518 [PMID: 27511114 DOI: 10.1002/ijc.30379]
 - 76 **Akuta N**, Kawamura Y, Kobayashi M, Arase Y, Saitoh S, Fujiyama S, Sezaki H, Hosaka T, Suzuki Y, Suzuki F, Ikeda K, Kumada H. TERT Promoter Mutation in Serum Cell-Free DNA Is a Diagnostic Marker of Primary Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease. *Oncology* 2021; **99**: 114-123 [PMID: 32998139 DOI: 10.1159/000510366]
 - 77 **Muhammad Yusuf AN**, Raja Ali RA, Muhammad Nawawi KN, Mokhtar NM. Potential biomarkers in NASH-induced liver cirrhosis with hepatocellular carcinoma: A preliminary work on roles of exosomal miR-182, miR-301a, and miR-373. *Malays J Pathol* 2020; **42**: 377-384 [PMID: 33361718]
 - 78 **Lewin J**, Kottwitz D, Aoyama J, deVos T, Garces J, Hasinger O, Kasielke S, Knaust F, Rath P, Rausch S, Weiss G, Zipprich A, Mena E, Fong TL. Plasma cell free DNA methylation markers for hepatocellular carcinoma surveillance in patients with cirrhosis: a case control study. *BMC Gastroenterol* 2021; **21**: 136 [PMID: 33765926 DOI: 10.1186/s12876-021-01714-8]
 - 79 **Yasui K**, Hashimoto E, Komorizono Y, Koike K, Arai S, Imai Y, Shima T, Kanbara Y, Saibara T, Mori T, Kawata S, Uto H, Takami S, Sumida Y, Takamura T, Kawanaka M, Okanoue T; 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**: 428-33; quiz e50 [PMID: 21320639 DOI: 10.1016/j.cgh.2011.01.023]
 - 80 **Zhang X**, Wang Z, Tang W, Wang X, Liu R, Bao H, Chen X, Wei Y, Wu S, Wu X, Shao Y, Fan J, Zhou J. Ultra-Sensitive and Affordable Assay for Early Detection of Primary Liver Cancer Using Plasma cfDNA Fragmentomics. *Hepatology* 2021 [DOI: 10.1002/hep.32308]

- 81 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: [32044314](#) DOI: [10.1053/j.gastro.2019.11.312](#)]
- 82 **Lin S**, Huang J, Wang M, Kumar R, Liu Y, Liu S, Wu Y, Wang X, Zhu Y. Comparison of MAFLD and NAFLD diagnostic criteria in real world. *Liver Int* 2020; **40**: 2082-2089 [PMID: [32478487](#) DOI: [10.1111/liv.14548](#)]
- 83 **Chen YG**, Yang CW, Chung CH, Ho CL, Chen WL, Chien WC. The association between metabolic risk factors, nonalcoholic fatty liver disease, and the incidence of liver cancer: a nationwide population-based cohort study. *Hepatol Int* 2022 [PMID: [35064545](#) DOI: [10.1007/s12072-021-10281-9](#)]
- 84 **Beale G**, Chattopadhyay D, Gray J, Stewart S, Hudson M, Day C, Trerotoli P, Giannelli G, Manas D, Reeves H. AFP, PIVKAI, GP3, SCCA-1 and follistatin as surveillance biomarkers for hepatocellular cancer in non-alcoholic and alcoholic fatty liver disease. *BMC Cancer* 2008; **8**: 200 [PMID: [18638391](#) DOI: [10.1186/1471-2407-8-200](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

