ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2024 August 27; 16(8): 2365-2747

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 16 Number 8 August 27, 2024

EDITORIAL

FRONTIER

REVIEW

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Retrospective Study

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 8 August 27, 2024

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 8 August 27, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Gaetano Gallo, FASCRS, FEBS (Coloproctology), MD, PhD, Academic Research, Professor, Department of Surgery, University of Rome, Rome 00161, Italy. ga.gallo@uniroma1.it

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGS* as 1.8; JIF without journal self cites: 1.7; 5-year JIF: 1.9; JIF Rank: 123/290 in surgery; JIF Quartile: Q2; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
August 27, 2024

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

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2024 August 27; 16(8): 2386-2392

DOI: 10.4240/wjgs.v16.i8.2386

ISSN 1948-9366 (online)

EDITORIAL

Clinical application value of long non-coding RNAs signatures of genomic instability in predicting prognosis of hepatocellular carcinoma

Xiao-Wen Xing, Xiao Huang, Wei-Peng Li, Ming-Ke Wang, Ji-Shun Yang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade D

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade C

P-Reviewer: Chisthi MM, India; Hashimoto N, Japan

Received: March 19, 2024

Revised: May 16, 2024

Accepted: June 5, 2024

Published online: August 27, 2024

Processing time: 150 Days and 1 Hours

Xiao-Wen Xing, Xiao Huang, Wei-Peng Li, Ming-Ke Wang, Department of Disease Control and Prevention, Naval Medical Center, Naval Medical University, Shanghai 200052, China

Ji-Shun Yang, Medical Care Center, Naval Medical University, Shanghai 200052, China

Co-corresponding authors: Ming-Ke Wang and Ji-Shun Yang.

Corresponding author: Ming-Ke Wang, MD, PhD, Associate Chief Physician, Department of Disease Control and Prevention, Naval Medical Center, Naval Medical University, No. 338 Huaihai West Road, Changning District, Shanghai 200052, China. wmke021@163.com

Abstract

Hepatocellular carcinoma (HCC) presents challenges due to its high recurrence and metastasis rates and poor prognosis. While current clinical diagnostic and prognostic indicators exist, their accuracy remains imperfect due to their biological complexity. Therefore, there is a quest to identify improved biomarkers for HCC diagnosis and prognosis. By combining long non-coding RNA (lncRNA) expression and somatic mutations, Duan *et al* identified five representative lncRNAs from 88 lncRNAs related to genomic instability (GI), forming a GI-derived lncRNA signature (LncSig). This signature outperforms previously reported LncSig and TP53 mutations in predicting HCC prognosis. In this editorial, we comprehensively evaluate the clinical application value of such prognostic evaluation model based on sequencing technology in terms of cost, time, and practicability. Additionally, we provide an overview of various prognostic models for HCC, aiding in a comprehensive understanding of research progress in prognostic evaluation methods.

Key Words: Hepatocellular carcinoma; Prognosis; Prognostic model; Biomarkers; Genomic instability long non-coding RNA; Clinical application value

Core Tip: Hepatocellular carcinoma (HCC), ranking as the third leading cause of cancer-related mortality globally, is characterized by high rates of recurrence and metastasis. Long non-coding RNAs related to genomic instability emerge as promising biomarkers for HCC prognosis. Here, we discuss their clinical significance as prognostic models and offer insights into ongoing efforts to develop diverse models, with an aim to enhance the scope of research on HCC prognosis and diagnosis.

Citation: Xing XW, Huang X, Li WP, Wang MK, Yang JS. Clinical application value of long non-coding RNAs signatures of genomic instability in predicting prognosis of hepatocellular carcinoma. *World J Gastrointest Surg* 2024; 16(8): 2386-2392
URL: https://www.wjgnet.com/1948-9366/full/v16/i8/2386.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i8.2386

INTRODUCTION

Hepatocellular carcinoma (HCC), also known as the "king of cancer", ranks fifth in incidence and third in mortality in China, underscoring the critical importance of early screening and prognosis assessment. With the recognition of long non-coding RNAs (lncRNAs) as potential prognostic factors in various cancers including HCC, exploration into lncRNAs related to genomic instability (GI) has surged. In a recent study published in the *World Journal of Gastrointestinal Surgery*, Duan *et al*[1] identified a GI-derived lncRNA signature (GI-LncSig) by integrating lncRNA expression and somatic mutation profiles. They conducted functional enrichment analyses, established a training set *via* Cox regression analysis, validated its predictive ability in the testing set and The Cancer Genome Atlas set, and assessed its prognostic efficacy in comparison to TP53 mutation status in HCC. The study identified five representative lncRNAs from a pool of 88 GI-lncRNAs, culminating in the establishment of a GI-LncSig capable of prognosticating HCC outcomes. Notably, statistical analyses revealed GI-LncSig to possess superior predictive power compared to TP53 mutation status or standalone tumor markers. Nevertheless, the rapid development of medicine has led to the development of various detection indicators and methods related to the diagnosis and prognosis assessment of HCC. This editorial article posts an exploration of the clinical utility of genome sequencing and GI-LncSig model construction based on somatic mutations in HCC prognosis.

CLINICAL APPLICATION OF ASSAY INDICES IN HCC

Five common HCC markers are routinely employed in clinical settings: Alpha-fetoprotein (AFP), carbohydrate antigen (CA) 199, cancer-derived CA 125 (cCA125), AFP anisoplasts (AFP-L3), and abnormal prothrombin (PIVKA-II) (Figure 1). The following sections provide a brief description of the representative significance, detection scope, and prognostic value of each marker.

AFP

AFP, primarily synthesized by HCC, exhibits elevated levels in 60%-70% of HCC patients, making it the most frequently utilized tumor marker. Both the United States National Comprehensive Cancer Network Guidelines and the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2022 edition)[2] recommend AFP as a standard tumor marker for HCC screening, aiming to enhance early detection rates. Normally, serum AFP concentration remains below 20 ng/mL. Routine screening for HCC involves ultrasound with or without AFP assessment every 6 months. The combination of ultrasound and AFP has shown marginal improvements in detection (6%-8% higher than ultrasound alone)[3]; however, this may also increase false-positive results, which limits the specificity of AFP. Despite its strong prognostic significance in patients with HCC undergoing systemic therapy, elevated AFP levels were also observed in various other conditions including acute and chronic hepatitis, cirrhosis, viral and neonatal hepatitis, pregnancy and germ cell tumors, gastrointestinal tumors, liver injury, and telangiectasia. Additionally, certain patients with HCC were negative for AFP (AFP < 20 ng/mL)[4], indicating AFP's limited sensitivity and specificity for HCC.

AFP-L3

AFP-L3, a subfraction of AFP originating from malignant hepatocytes, serves as a valuable indicator for HCC. Given that AFP is negative in approximately 30% of patients with HCC, AFP-L3 acts as a complementary marker for AFP[5]. The ratio of AFP-L3 to total AFP aids in distinguishing between non-malignant hepatic disease and HCC. In 2005, the United States Food and Drug Administration approved AFP-L3 for HCC diagnosis. Normally, the serum AFP-L3 to AFP ratio remains below 10%; however, even with low AFP levels, an AFP-L3 ratio exceeding 10% suggests HCC occurrence. In a prospective study, AFP-L3 (AFP bound to lens culinaris agglutinin) and des-γ-carboxyprothrombin (DCP) biomarkers exhibited strong predictive capabilities for early HCC recurrence, surpassing AFP alone and effectively reducing false-negatives and false-positives[6]. In China, AFP, AFP-L3, and DCP have been included in the "13th Five-Year Plan" for infectious disease prevention and control, which is expected to become a common diagnostic criterion for HCC globally. Nonetheless, the relationship between pre-treatment serum AFP-L3% levels and tumor invasion, metastasis, and other clinicopathological parameters (such as tumor grade, stage, and cirrhosis) reported in some studies lacks reliability,

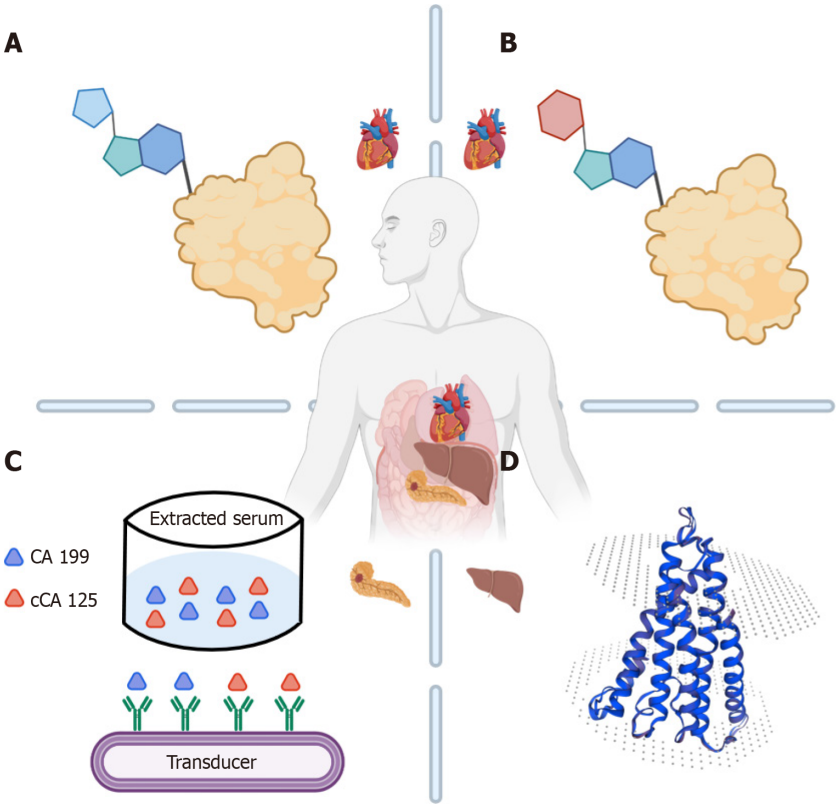

Figure 1 Five assay indices of hepatocellular carcinoma in clinical application. A: Alpha-fetoprotein; B: Alpha-fetoprotein heterosomes; C: Carbohydrate antigen (CA) 199 and cancer-derived CA 125, which belong to glycoprotein macromolecules that can be recognized as antigens; D: Abnormal prothrombin-II. CA199: Carbohydrate antigen 199; cCA125: Cancer-derived carbohydrate antigen 125.

hindering the estimation of their impact on overall survival (OS) or disease-free survival (DFS)[7]. Conflicting data have also emerged regarding the ability of pre-treatment serum AFP-L3% to predict DFS and OS in HCC, thereby reducing the confidence of AFP-L3% for HCC patient prognosis.

CA199 and cCA125

CA199 and cCA125, two glycoprotein macromolecules, are commonly utilized markers for adenocarcinoma, notably elevated in lung, pancreatic, colorectal, endometrial, ovarian, and other cancers[8]. Approximately 10% of HCC cases originate from bile duct epithelial cells or rare tumor types, wherein AFP is negative while CA199 is elevated. Furthermore, in cases of metastatic tumors, such as liver metastasis from colorectal cancer, CA199 elevation serves as a reference for differential diagnosis[9]. Both cCA125 and CA199 serve as relative reference indicators. Serum cCA125 elevation is observed in 80% of patients with HCC; however, it remains unaltered in nearly half of early-stage cases, limiting its utility as a standalone marker for early diagnosis. Notably, serum cCA125 in 90% of patients has been correlated to the course of the disease, making it valuable for disease detection and treatment efficacy evaluation. Normally, cCA125 Levels in healthy adult women are below 40U/mL, although the reported reference value is 35 U/mL[10]. Under normal physiological conditions, trace amounts of CA199 exist in the serum. While detectable in most normal individuals, a small fraction (6%-10%) may have undetectable CA199 Levels in the serum[11].

PIVKA-II

PIVKA-II arises in the presence of glutamyl carboxylase and vitamin K deficiency. When hepatocytes fail to synthesize normal vitamin K-dependent clotting factors, abnormal serum prothrombin concentrations are elevated. Since 2015, China's "Guidelines for the Prevention and Treatment of Chronic Hepatitis B" have recommended PIVKA-II as a crucial indicator for HCC diagnosis, serving as a complementary marker to AFP to enhance early detection rates of primary liver cancer[12]. Under normal conditions, PIVKA-II concentrations are below 40 mAU/mL, with a diagnostic rate of 74% for early-stage liver cancer[13]. PIVKA-II holds significant diagnostic value in preoperative diagnosis and postoperative monitoring of liver cancer, with levels typically decreasing post-surgery. A rise in PIVKA-II levels post-surgery indicates tumor recurrence. However, the pathological mechanism underlying the elevation of PIVKA-II in HCC remains incompletely understood, rendering it a serological marker with clinically significant associations. The clinical sensitivity of PIVKA-II-positive HCC stands at 55%, only positioning it as a reference marker in clinical diagnosis[14].

ADVANTAGES OF GI-LNCSIG

The elevation of tumor markers often correlates with tumor occurrence and progression, albeit influenced by benign diseases, inflammation, physiological changes, lifestyle habits, and other factors. Frequently, a single tumor marker alone may not conclusively indicate cancer; rather, multiple markers and detection methods are required for accurate identification. Cancer is characterized by abnormal and uncontrolled cell growth due to genetic mutations, a trait often referred to as GI[15].

Zhou *et al*[2] validated the GI-LncSig model, constructed using five GI-lncRNAs, which was established at the genetic level related to pathogenesis, thus circumventing environmental and individual differences affecting changes in HCC markers. Utilizing the risk score derived from this model, patients with HCC in the database were categorized into high-risk and low-risk groups. A comparison of the 5-year survival rates between these groups revealed a survival rate of 9.3% for high-risk patients and 19.8% for low-risk patients. The prognostic performance of GI-LncSig was assessed *via* receiver operating characteristic curve analysis, yielding an area under the curve (AUC) of 0.736, surpassing that of GulncSig (AUC = 0.664) or WulncSig (AUC = 0.725). These findings indicate that GI-LncSig exhibits superior prognostic performance compared to other published lncRNA signatures[1].

Directly using lncRNA expression profiles and somatic cell mutation profiles at the molecular level enables the prediction of HCC patient prognosis, offering greater sensitivity and accuracy compared to biochemical indicators influenced by various factors. Some patients with HCC undergo chemotherapy, radiotherapy, and immunotherapy as part of their treatment regimen, aiming to eliminate cancer cells with high proliferative activity or relative sensitivity to radiation. While these approaches often result in tumor volume reduction and achieve certain therapeutic effects, they do not alter the tumor genotype, potentially allowing surviving cancer cells to reemerge post-treatment[16]. In such scenarios, sequencing lncRNAs in the tumor tissue enables an accurate assessment of the patient's tumor survival status and prognosis.

TEST METHOD AND COST OF GI-LNCSIG

Current screening methods for cancer include ultrasound imaging and serum antigen detection, despite their limited sensitivity (ranging from 47% to 84%) and specificity (from 67% to over 90%)[17]. However, their quickness and convenient sampling render them widely used in clinical practice. The GI-LncSig HCC prognostic model, constructed from genome-unstable lncRNAs, comprised five lncRNAs (miR210HG, AC016735.1, AC116351.1, AC010643.1, and LUCAT1), with varying lengths of 2303 nt, 174772 nt, 180464 nt, 30623 nt, and 582 nt, respectively. Tissue samples from patients were utilized for total RNA isolation, followed by confirmation of integrity, concentration, and purity. Subsequently, ribosomal RNA removal and RNA sequencing library generation for sequencing were performed[18]. The cost of constructing the HCC prognostic model for each patient is about 2000 yuan, which is higher than the 700 yuan cost of the commonly used five HCC tests in clinical practice. Additionally, it often takes 2 months to perform human lncRNA sequencing, thus resulting in longer detection times. In contrast, traditional clinical detection methods yield results and prognosis assessment within 1-2 d at a cost ranging from 400-800 yuan, which is economically convenient and can better meet the needs of patients with HCC. However, with the rapid advancement of sequencing technology, overcoming the challenges of prolonged sequencing time and high costs associated with lncRNA sequencing could enhance the clinical application of the GI-LncSig model, owing to its high prognostic accuracy for patients with HCC.

OTHER POTENTIAL BIOMARKERS FOR PROGNOSIS IN HCC

The current arsenal of serum biomarkers for predicting HCC prognosis remains insufficient, characterized by low sensitivity and heterogeneous specificity. Currently, apart from AFP and those mentioned above, new biomarkers have yet to be integrated into routine clinical practice. Therefore, researchers are diligently exploring alternative biomarkers for early diagnosis, personalized treatment approaches, and post-treatment prognosis using proteomics, metabolomics, genomics, and other novel technologies such as microbiome analysis[19].

Currently, researchers have mined genetic information associated with HCC-related processes, including cell senescence, cuproptosis, cell necrosis, cell-free DNA, natural killer cells, basement membrane, and cell cycles, to identify biomarkers that accurately assess patient prognosis. Integrating proteomic studies with gene-editing models enables the analysis of HCC patient prognosis, shedding light on post-translational modifications and complex pathological processes underlying tumorigenesis. Additionally, cancer cell mutations and oncogenes disrupt human metabolic processes, including aerobic glycolysis, glutaminolysis, and one-carbon metabolism, resulting in the production of amino acids, nucleotides, fatty acids, and other substances required for cancer cell growth and proliferation[20]. Cancer is considered a metabolic disease due to its metabolic disorder characteristics, thus metabolomics can be used as a means to identify novel diagnostic markers for liver cancer. Moreover, gut and tumor microbes have emerged as promising prognostic indicators for patients with HCC. Moreover, several imaging features, termed prognostic imaging features, may correlate with pathologic and molecular drivers of outcomes in HCC. Table 1 summarizes such biomarkers of various types.

Table 1 Typical biomarkers in different groups

Species	Name	Feature	Ref.
Genomics	PDXK	Cuproptosis-related gene signature	Chen *et al*[21]
	m6A/m5C/m1A	Poor prognosis and immune microenvironment in HCC	Li *et al*[22]
	CANT1	Histologic grade	Liu *et al*[23]
	CTSA	The most critical basement membrane-related genes	Sun *et al*[24]
	Mutation Capsule Plus	Multiple analyses of a cfDNA sample to obtain its whole genome information	Wang *et al*[25]
	IL18RAP, CHP1, VAMP2, PIK3R1, PRKCD	5-NKRLSig, associated with natural killer cells	Xi *et al*[26]
	CDCA8, CENPA, SPC25, TTK	Four central genes involved in cellular senescence	Zhang *et al*[27]
	PHF19	As a crucial constituent part of Polycomb repressive complex 2, PHD finger protein 19 plays a pivotal role in epigenetic regulation	Zhu *et al*[28]
Proteomics	Lysine crotonylation	Higher crotonylation in HCC cells facilitated cell invasiveness	Zhang *et al*[29]
	SLC1A4	SLC1A4 inhibited cell proliferation, migration, and cell cycle progression, and promoted cell apoptosis in HCC	Peng *et al*[30]
Metabolomics	MG (monoacylglyceride)	It might accumulate in patients with advanced HCC due to the deficit of MGLL	Lin *et al*[31]
	NrLR	Neutrophil times γ-glutamyl transpeptidase to lymphocyte ratio	Wu *et al*[32]
	IL-6	Interleukin-6 promotes the growth of the HCC microenvironment	Dalbeni *et al*[33]
Others	Gut microbiome	Strong diagnosis potential for early HCC and even advanced HCC	Ren *et al*[34]
	Intratumor microbiome	It can affect HCC patients' prognosis by modulating the cancer stemness and immune response	Song *et al*[35]
	LI-RADS	Liver imaging reporting and data system	Ronot *et al*[36]
	A combined clinicoradiological MR-based model integrating radiomics features	This model was shown to be associated with recurrence-free survival	Song *et al*[37]

PDXK: Pyridoxal kinase; m6A: N^6-methyladenosine; m5C: 5C-methyltransferase; m1A: 1A-methyltransferase; CANT1: Calcium-activated protein nucleotidase 1; CTSA: Cathepsin A; IL18RAP: Interleukin 18 receptor accessory protein; CHP1: Calcineurin-like EF-hand protein 1; VAMP2: Vesicle-associated membrane protein 2; PRKCD: Protein kinase C delta; CDCA8: Cell division cycle-associated 8; CENPA: Centromere protein A; SPC25: SPC25 component of NDC80 kinetochore complex; TTK: TTK protein kinase; PHD: Plant homeodomain; PHF19: Plant homeodomain finger protein-19; SLC1A4: Solute carrier family 1 member 4; MG: Monoacylglyceride; NrLR: Neutrophil times γ-glutamyl transpeptidase to lymphocyte ratio; IL-6: Interleukin-6; LI-RADS: Liver imaging reporting and data system; HCC: Hepatocellular carcinoma; MGLL: Monoacylglycerol lipase; 5-NKRLSig: 5-Natural killer-related signature; cfDNA: Cell-free DNA; PIK3R1: Phosphoinositide-3-kinase regulatory subunit 1.

CONCLUSION

This literature review provides an overview of biomarkers utilized in the diagnosis and prognosis of patients with HCC in clinical practice, comparing their detection time and cost with those of the GI-LncSig prognostic model. AFP, AFP-L3, CA199, cCA125, PIVKA-II, and other indicators exhibit varying degrees of deficiencies and inaccuracies in terms of accuracy, sensitivity, applicability, as well as representativeness. In contrast, the GI-LncSig model effectively addresses these limitations and demonstrates superior alignment with the database, resulting in enhanced prognostic accuracy. However, the current implementation of GI-LncSig is hindered by cumbersome detection sampling, high costs, and prolonged detection times. If these issues can be resolved, GI-LncSig technology will offer higher accuracy than traditional detection indicators and hold significant clinical application value. Furthermore, various methods are employed in the screening and determination of prognostic biomarkers for patients with liver cancer, including genomics, proteomics, metabolomics, microbiology, and imaging. The combined application of multiple technologies will enable a more accurate assessment of the prognosis of patients with HCC.

FOOTNOTES

Author contributions: Wang MK and Yang JS conceptualized, designed, and revised the manuscript; Xing XW wrote the draft; Huang X and Li WP collected the literature. All authors have read and approved the final manuscript. Both Wang MK and Yang JS conceptualized, proposed, designed, and supervised the whole process of the article, and played important and indispensable roles in the manuscript preparation and revision as the co-corresponding authors.

Supported by The National Key R&D Program of China (Key Special Project for Marine Environmental Security and Sustainable Development of Coral Reefs 2022-3.3), No. 2022YFC3103-004001; and Scientific Research Foundation of Shanghai Municipal Health Commission of Changning District, No. 20234Y038.

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

Country of origin: China

ORCID number: Xiao-Wen Xing 0009-0009-9601-4418; Xiao Huang 0009-0007-9466-3305; Wei-Peng Li 0000-0002-8993-5536; Ming-Ke Wang 0000-0001-9918-0491; Ji-Shun Yang 0000-0001-7160-706X.

S-Editor: Liu H
L-Editor: Wang TQ
P-Editor: Zhao YQ

REFERENCES

1 **Duan BT**, Zhao XK, Cui YY, Liu DZ, Wang L, Zhou L, Zhang XY. Construction and validation of somatic mutation-derived long non-coding RNAs signatures of genomic instability to predict prognosis of hepatocellular carcinoma. *World J Gastrointest Surg* 2024; **16**: 842-859 [PMID: 38577085 DOI: 10.4240/wjgs.v16.i3.842]

2 **Zhou J**, Sun H, Wang Z, Cong W, Zeng M, Zhou W, Bie P, Liu L, Wen T, Kuang M, Han G, Yan Z, Wang M, Liu R, Lu L, Ren Z, Zeng Z, Liang P, Liang C, Chen M, Yan F, Wang W, Hou J, Ji Y, Yun J, Bai X, Cai D, Chen W, Chen Y, Cheng W, Cheng S, Dai C, Guo W, Guo Y, Hua B, Huang X, Jia W, Li Q, Li T, Li X, Li Y, Li Y, Liang J, Ling C, Liu T, Liu X, Lu S, Lv G, Mao Y, Meng Z, Peng T, Ren W, Shi H, Shi G, Shi M, Song T, Tao K, Wang J, Wang K, Wang L, Wang W, Wang X, Wang Z, Xiang B, Xing B, Xu J, Yang J, Yang J, Yang Y, Yang Y, Ye S, Yin Z, Zeng Y, Zhang B, Zhang B, Zhang L, Zhang S, Zhang T, Zhang Y, Zhao M, Zhao Y, Zheng H, Zhou L, Zhu J, Zhu K, Liu R, Shi Y, Xiao Y, Zhang L, Yang C, Wu Z, Dai Z, Chen M, Cai J, Wang W, Cai X, Li Q, Shen F, Qin S, Teng G, Dong J, Fan J. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition). *Liver Cancer* 2023; **12**: 405-444 [PMID: 37901768 DOI: 10.1159/000530495]

3 **Force M**, Park G, Chalikonda D, Roth C, Cohen M, Halegoua-DeMarzio D, Hann HW. Alpha-Fetoprotein (AFP) and AFP-L3 Is Most Useful in Detection of Recurrence of Hepatocellular Carcinoma in Patients after Tumor Ablation and with Low AFP Level. *Viruses* 2022; **14** [PMID: 35458505 DOI: 10.3390/v14040775]

4 **Lim DH**, Casadei-Gardini A, Lee MA, Lonardi S, Kim JW, Masi G, Chon HJ, Rimini M, Kim I, Cheon J, Hwang JE, Kang JH, Lim HY, Yoo C. Prognostic implication of serum AFP in patients with hepatocellular carcinoma treated with regorafenib. *Future Oncol* 2022; **18**: 3021-3030 [PMID: 35903991 DOI: 10.2217/fon-2022-0524]

5 **Kawahara I**, Fukuzawa H, Urushihara N, Kosaka Y, Kuroda Y, Fujieda Y, Takeuchi Y, Uemura K, Iwade T, Samejima Y, Morita K, Maeda K. AFP-L3 as a Prognostic Predictor of Recurrence in Hepatoblastoma: A Pilot Study. *J Pediatr Hematol Oncol* 2021; **43**: e76-e79 [PMID: 33093349 DOI: 10.1097/MPH.0000000000001971]

6 **Norman JS**, Li PJ, Kotwani P, Shui AM, Yao F, Mehta N. AFP-L3 and DCP strongly predict early hepatocellular carcinoma recurrence after liver transplantation. *J Hepatol* 2023; **79**: 1469-1477 [PMID: 37683735 DOI: 10.1016/j.jhep.2023.08.020]

7 **Cheng J**, Wang W, Zhang Y, Liu X, Li M, Wu Z, Liu Z, Lv Y, Wang B. Prognostic role of pre-treatment serum AFP-L3% in hepatocellular carcinoma: systematic review and meta-analysis. *PLoS One* 2014; **9**: e87011 [PMID: 24498011 DOI: 10.1371/journal.pone.0087011]

8 **Lin S**, Wang Y, Peng Z, Chen Z, Hu F. Detection of cancer biomarkers CA125 and CA199 *via* terahertz metasurface immunosensor. *Talanta* 2022; **248**: 123628 [PMID: 35660997 DOI: 10.1016/j.talanta.2022.123628]

9 **Gao Y**, Wang J, Zhou Y, Sheng S, Qian SY, Huo X. Evaluation of Serum CEA, CA19-9, CA72-4, CA125 and Ferritin as Diagnostic Markers and Factors of Clinical Parameters for Colorectal Cancer. *Sci Rep* 2018; **8**: 2732 [PMID: 29426902 DOI: 10.1038/s41598-018-21048-y]

10 **Huang Y**, Zeng J, Liu T, Lin X, Guo P, Zeng J, Zhou W, Liu J. Prognostic Significance of Elevated Preoperative Serum CA125 Levels After Curative Hepatectomy for Hepatocellular Carcinoma. *Onco Targets Ther* 2020; **13**: 4559-4567 [PMID: 32547086 DOI: 10.2147/OTT.S236475]

11 **Zhang J**, Qin SD, Li Y, Lu F, Gong WF, Zhong JH, Ma L, Zhao JF, Zhan GH, Li PZ, Song B, De Xiang B. Prognostic significance of combined α-fetoprotein and CA19-9 for hepatocellular carcinoma after hepatectomy. *World J Surg Oncol* 2022; **20**: 346 [PMID: 36258212 DOI: 10.1186/s12957-022-02806-9]

12 **You H**, Wang F, Li T, Xu X, Sun Y, Nan Y, Wang G, Hou J, Duan Z, Wei L, Jia J, Zhuang H; Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022). *J Clin Transl Hepatol* 2023; **11**: 1425-1442 [PMID: 37719965 DOI: 10.14218/JCTH.2023.00320]

13 **Feng H**, Li B, Li Z, Wei Q, Ren L. PIVKA-II serves as a potential biomarker that complements AFP for the diagnosis of hepatocellular carcinoma. *BMC Cancer* 2021; **21**: 401 [PMID: 33849479 DOI: 10.1186/s12885-021-08138-3]

14 **Fujita K**, Kinukawa H, Ohno K, Ito Y, Saegusa H, Yoshimura T. Development and evaluation of analytical performance of a fully automated chemiluminescent immunoassay for protein induced by vitamin K absence or antagonist II. *Clin Biochem* 2015; **48**: 1330-1336 [PMID: 26210849 DOI: 10.1016/j.clinbiochem.2015.07.023]

15 **Martínez-Jiménez F**, Muiños F, Sentís I, Deu-Pons J, Reyes-Salazar I, Arnedo-Pac C, Mularoni L, Pich O, Bonet J, Kranas H, Gonzalez-Perez A, Lopez-Bigas N. A compendium of mutational cancer driver genes. *Nat Rev Cancer* 2020; **20**: 555-572 [PMID: 32778778 DOI: 10.1038/s41568-020-0290-x]

16 **Caruso S**, Calatayud AL, Pilet J, La Bella T, Rekik S, Imbeaud S, Letouzé E, Meunier L, Bayard Q, Rohr-Udilova N, Péneau C, Grasl-Kraupp B, de Koning L, Ouine B, Bioulac-Sage P, Couchy G, Calderaro J, Nault JC, Zucman-Rossi J, Rebouissou S. Analysis of Liver Cancer Cell Lines Identifies Agents With Likely Efficacy Against Hepatocellular Carcinoma and Markers of Response. *Gastroenterology* 2019; **157**: 760-776 [PMID: 31063779 DOI: 10.1053/j.gastro.2019.05.001]

17 **Tzartzeva K**, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, Waljee AK, Singal AG. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. *Gastroenterology* 2018; **154**: 1706-1718.e1 [PMID: 29425931 DOI: 10.1053/j.gastro.2018.01.064]

18 **Qiu M**, Yu C, Zhu S, Liu S, Peng H, Xiong X, Chen J, Jiang X, Du H, Li Q, Zhang Z, Yang C. RNA sequencing reveals lncRNA-mediated non-mendelian inheritance of feather growth change in chickens. *Genes Genomics* 2022; **44**: 1323-1331 [PMID: 36087248 DOI: 10.1007/s13258-022-01304-2]

19 **Piñero F**, Dirchwolf M, Pessôa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. *Cells* 2020; **9** [PMID: 32492896 DOI: 10.3390/cells9061370]

20 **Yang C**, Huang X, Liu Z, Qin W, Wang C. Metabolism-associated molecular classification of hepatocellular carcinoma. *Mol Oncol* 2020; **14**: 896-913 [PMID: 31955511 DOI: 10.1002/1878-0261.12639]

21 **Chen Y**, Tang L, Huang W, Abisola FH, Zhang Y, Zhang G, Yao L. Identification of a prognostic cuproptosis-related signature in hepatocellular carcinoma. *Biol Direct* 2023; **18**: 4 [PMID: 36750831 DOI: 10.1186/s13062-023-00358-w]

22 **Li D**, Li K, Zhang W, Yang KW, Mu DA, Jiang GJ, Shi RS, Ke D. The m6A/m5C/m1A Regulated Gene Signature Predicts the Prognosis and Correlates With the Immune Status of Hepatocellular Carcinoma. *Front Immunol* 2022; **13**: 918140 [PMID: 35833147 DOI: 10.3389/fimmu.2022.918140]

23 **Liu T**, Li ZZ, Sun L, Yang K, Chen JM, Han XY, Qi LM, Zhou XG, Wang P. Upregulated CANT1 is correlated with poor prognosis in hepatocellular carcinoma. *BMC Cancer* 2023; **23**: 1007 [PMID: 37858061 DOI: 10.1186/s12885-023-11463-4]

24 **Sun W**, Wang J, Wang Z, Xu M, Lin Q, Sun P, Yuan Y. Combining WGCNA and machine learning to construct basement membrane-related gene index helps to predict the prognosis and tumor microenvironment of HCC patients and verifies the carcinogenesis of key gene CTSA. *Front Immunol* 2023; **14**: 1185916 [PMID: 37287981 DOI: 10.3389/fimmu.2023.1185916]

25 **Wang P**, Song Q, Ren J, Zhang W, Wang Y, Zhou L, Wang D, Chen K, Jiang L, Zhang B, Chen W, Qu C, Zhao H, Jiao Y. Simultaneous analysis of mutations and methylations in circulating cell-free DNA for hepatocellular carcinoma detection. *Sci Transl Med* 2022; **14**: eabp8704 [PMID: 36417488 DOI: 10.1126/scitranslmed.abp8704]

26 **Xi D**, Wang J, Yang Y, Ji F, Li C, Yan X. A novel natural killer-related signature to effectively predict prognosis in hepatocellular carcinoma. *BMC Med Genomics* 2023; **16**: 211 [PMID: 37674210 DOI: 10.1186/s12920-023-01638-0]

27 **Zhang S**, Zheng Y, Li X, Zhang S, Hu H, Kuang W. Cellular senescence-related gene signature as a valuable predictor of prognosis in hepatocellular carcinoma. *Aging (Albany NY)* 2023; **15**: 3064-3093 [PMID: 37059592 DOI: 10.18632/aging.204658]

28 **Zhu ZY**, Tang N, Wang MF, Zhou JC, Wang JL, Ren HZ, Shi XL. Comprehensive Pan-Cancer Genomic Analysis Reveals PHF19 as a Carcinogenic Indicator Related to Immune Infiltration and Prognosis of Hepatocellular Carcinoma. *Front Immunol* 2021; **12**: 781087 [PMID: 35069553 DOI: 10.3389/fimmu.2021.781087]

29 **Zhang XY**, Liu ZX, Zhang YF, Xu LX, Chen MK, Zhou YF, Yu J, Li XX, Zhang N. SEPT2 crotonylation promotes metastasis and recurrence in hepatocellular carcinoma and is associated with poor survival. *Cell Biosci* 2023; **13**: 63 [PMID: 36949517 DOI: 10.1186/s13578-023-00996-7]

30 **Peng X**, Chen R, Cai S, Lu S, Zhang Y. SLC1A4: A Powerful Prognostic Marker and Promising Therapeutic Target for HCC. *Front Oncol* 2021; **11**: 650355 [PMID: 33777811 DOI: 10.3389/fonc.2021.650355]

31 **Lin Z**, Li H, He C, Yang M, Chen H, Yang X, Zhuo J, Shen W, Hu Z, Pan L, Wei X, Lu D, Zheng S, Xu X. Metabolomic biomarkers for the diagnosis and post-transplant outcomes of AFP negative hepatocellular carcinoma. *Front Oncol* 2023; **13**: 1072775 [PMID: 36845695 DOI: 10.3389/fonc.2023.1072775]

32 **Wu Q**, Zeng J, Zeng J. Inflammation-Related Marker NrLR Predicts Prognosis in AFP-Negative HCC Patients After Curative Resection. *J Hepatocell Carcinoma* 2023; **10**: 193-202 [PMID: 36789253 DOI: 10.2147/JHC.S393286]

33 **Dalbeni A**, Natola LA, Garbin M, Zoncapè M, Cattazzo F, Mantovani A, Vella A, Canè S, Kassem J, Bevilacqua M, Conci S, Campagnaro T, Ruzzenente A, Auriemma A, Drudi A, Zanoni G, Guglielmi A, Milella M, Sacerdoti D. Interleukin-6: A New Marker of Advanced-Sarcopenic HCC Cirrhotic Patients. *Cancers (Basel)* 2023; **15** [PMID: 37173873 DOI: 10.3390/cancers15092406]

34 **Ren Z**, Li A, Jiang J, Zhou L, Yu Z, Lu H, Xie H, Chen X, Shao L, Zhang R, Xu S, Zhang H, Cui G, Chen X, Sun R, Wen H, Lerut JP, Kan Q, Li L, Zheng S. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. *Gut* 2019; **68**: 1014-1023 [PMID: 30045880 DOI: 10.1136/gutjnl-2017-315084]

35 **Song Y**, Xiang Z, Lu Z, Su R, Shu W, Sui M, Wei X, Xu X. Identification of a brand intratumor microbiome signature for predicting prognosis of hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2023; **149**: 11319-11332 [PMID: 37380815 DOI: 10.1007/s00432-023-04962-1]

36 **Ronot M**, Chernyak V, Burgoyne A, Chang J, Jiang H, Bashir M, Fowler KJ. Imaging to Predict Prognosis in Hepatocellular Carcinoma: Current and Future Perspectives. *Radiology* 2023; **307**: e221429 [PMID: 37014244 DOI: 10.1148/radiol.221429]

37 **Song W**, Yu X, Guo D, Liu H, Tang Z, Liu X, Zhou J, Zhang H, Liu Y, Liu X. MRI-Based Radiomics: Associations With the Recurrence-Free Survival of Patients With Hepatocellular Carcinoma Treated With Conventional Transcatheter Arterial Chemoembolization. *J Magn Reson Imaging* 2020; **52**: 461-473 [PMID: 31675174 DOI: 10.1002/jmri.26977]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com