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SCREENING FOR HEPATOCELLULAR CARCINOMA IN CHRONIC LIVER DISEASE: A SYSTEMATIC REVIEW

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Abstract

Background: *Chronic liver disease is the most significant risk factors for the development of hepatocellular carcinoma (HCC). High-risk patients should undergo routine screening for HCC, but it is unclear how much data there is to support this suggestion.*

The aim: *This study aims to determine the screening options for hepatocellular carcinoma in chronic liver disease.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and ScienceDirect, were used to do this. It was decided not to take into account review pieces, identical works that had already been published, or works that were only half done.*

Results: *In the PubMed database, the results of our search brought up 110 articles, whereas the results of our search on ScienceDirect brought up 285 articles. The results of the search conducted by title screening yielded a total 29 articles for PubMed and 15 articles for ScienceDirect. We compiled a total of 6 papers, 2 of which came from PubMed and 4 of which came from ScienceDirect. We excluded 1 review article. In the end, we included five research that met the criteria.*

Conclusion: *Multitarget HCC panel; combined methylation (CDH1, DNMT3b or ESR1); CARD10; COP; combination of CRD9, CARD10, and COP; and PKCδ were accurate for HCC screening (any stage of severity) in CLD with pooled sensitivities more than 80%. However, there is not adequate data to make definite judgements about the balance between the advantages and disadvantages of routine screening for HCC.*

Keywords: *screening; early detection; hepatocellular carsinoma; chronic liver disease*

INTRODUCTION

The term "chronic liver disease" (CLD) refers to liver function decline that has persisted for longer than six months.[1] The most prevalent risk factors for chronic liver disease globally include viral hepatitis and excessive alcohol consumption, which continue to be among the most significant risk factors for the development of HCC.[2] The absolute number of CLD cases (inclusive of any stage of disease severity) is estimated at 1.5 billion worldwide. The most common causes of prevalent disease are nonalcoholic fatty liver disease (NAFLD) (59%), followed by HBV (29%), HCV (9%), and ALD (2%).[3,4]

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, accounting for approximately 75% of the total, which is also the main cause of cancer-related death globally.[2,5] According to the National Vital Statistics Report 2017 from the Centres for Disease Control and Prevention, 1.8 percent of adult Americans—or 4.5 million adults—had cirrhosis and chronic liver disease. There were 41,473 deaths from cirrhosis and chronic liver disease (12.8 deaths per 100,000 people).[1] Prognosis of HCC is poor in all regions of the world. As a result, incidence and mortality rates are roughly equivalent. In 2018, the estimated global incidence rate of liver cancer per 100,000 person-years was 9.3 while the corresponding mortality rate was 8.5.[5]

A recent review of observational studies found that HCC screening was associated with detection of earlier-stage HCC and improved survival. Currently, several professional societies advise HCC screening utilising imaging tests and tumour markers, particularly in individuals with cirrhosis or chronic hepatitis B who are at a higher risk for developing the disease.[6] The quality and scarcity of the available data, as well as concerns about overdiagnosis and patient harms identified in previous cancer screening programmes, are some of the reasons why recommendations for HCC screening remain debatable. The purpose of this systematic review is to determine the screening test option for hepatocellular carcinoma in chronic liver disease.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this systematic review, we compare and contrast screening option for hepatocellular carcinoma in chronic liver disease. It is possible to accomplish this by researching or investigating screening for hepatocellular carcinoma in chronic liver disease. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to investigated screening for hepatocellular carcinoma in chronic liver disease. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published within the last 10 years. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "screening"; "early detection"; "hepatocellular carsinoma"; and "chronic liver disease" as keywords. The search for studies to be included in the systematic review was carried out from October, 17th 2023 using the PubMed and ScienceDirect databases by inputting the words: "early detection of cancer"[MeSH Terms] OR "early detection of cancer"[MeSH Terms] OR "early detection of cancer"[MeSH Terms]) AND "carcinoma, hepatocellular"[MeSH Terms]) OR "liver neoplasms"[MeSH Terms] AND "chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields] AND "liver diseases"[MeSH Terms] OR "liver"[All Fields] AND "diseases"[All Fields]) OR "liver diseases"[All Fields] OR "liver"[All Fields] AND "disease"[All Fields]) OR "liver disease"[All Fields]) AND (y_10[Filter]) AND (clinicaltrial[Filter]) AND (english[Filter]) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

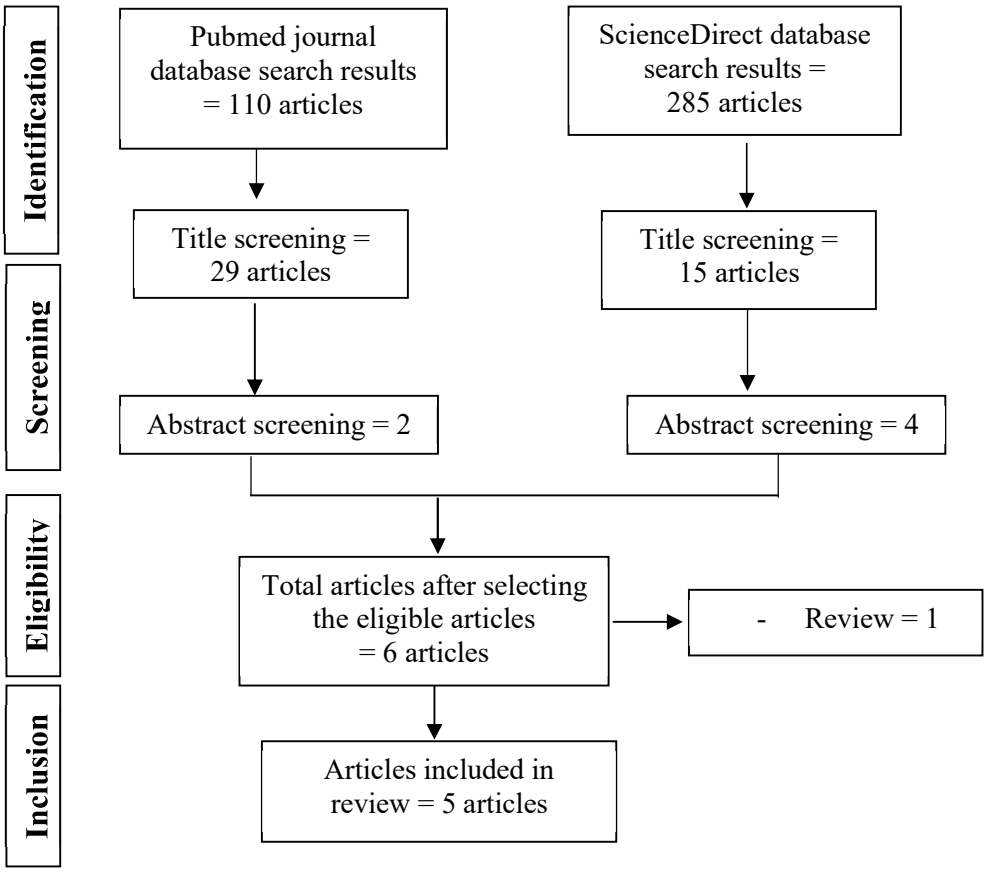

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 110 articles, whereas the results of our search on ScienceDirect brought up 285 articles. The results of the search conducted by title screening yielded a total 29 articles for PubMed and 15 articles for ScienceDirect. We compiled a total of 6 papers, 2 of which came from PubMed and 4 of which came from ScienceDirect. We excluded 1 review article. In the end, we included five research that met the criteria.

Chalasani, et al. (2021)[7] showed the multitarget HCC panel was superior compared with other biomarker-based tests for both very early-stage and early-stage HCC and any-stage HCC in chronic liver disease. At any-stage HCC, the sensitivity (95% CI) of multitarget HCC panel was 80% (72–86), the specificity (95% CI) was 90% (87–94), and area under the curve (AUC) (95% CI) was 0.92 (0.90–0.94). At very early/early HCC the sensitivity of multitarget HCC panel was 71% (60–81), at late stage was 92% (81–97). This study also showed the sensitivity, specificity, and any-stage AUC of the other tests, including AFP ($\geq 20\ ng/mL$), AFP-L3 (10%), DCP (≥7.5 ng/mL), and GALAD score (≥–0.63). AFP achieved 43% any-stage sensitivity, and 98% specificity. AFP-L3 achieved 56% any-stage sensitivity, and 93% specificity. DCP achieved 39% any-stage sensitivity, and 93% specificity. Serum biomarkers DCP and AFP-L3 similarly generated lower sensitivity percentages than the marker panel. In addition, at 90% specificity, the multitarget HCC panel performance (71% early-stage and 80% any-stage sensitivity) was superior to AFP (45% early-stage and 62% any-stage sensitivity; 7.32-ng/mL cutoff), the GALAD score (41% sensitivity and 62% any-stage sensitivity; ≥–0.182 cutoff), and DCP or AFP-L3 alone.

Chen, et al. (2023)[8] showed that the GAAP model achieved a better performance in section A for the detection of HCC and in section C for the detection of HBV-HCC than the ASAP model. This study included four sections. Section A

included 262 HCC, 393 CHB, 173 LC patients, and 110 HC. Section B included 199 HBV-HCC, 393 CHB, 173 LC, and 110 HC. Section C included 199 HBV-HCC, 393 CHB, and 115 HBV-LC. Section D included 143 HCC with LC and 173 LC. GAAP and ASAP models had greater AUC values than the patient markers des-gamma-carboxy prothrombin (DCP), AFP, and AFP&DCP in the population of sections A to D. The AUC of the GAAP model for HCC detection in the population of section A was 0.862 (95% confidence interval [CI): 0.838-0.883] which was superior to that of AFP (0.655, p<0.0001), DCP (0.746, p<0.0001), AFP&DCP (0.781, p<0.0001), and the ASAP model (0.850, p=0.0077). At an optimal cut-off of -0.7995, the GAAP score had a sensitivity of 74.43% and a specificity of 81.36% for HCC detection. The AUC of the GAAP model for HBV-HCC detection in the population of section C was 0.897 (95% confidence interval (CI): 0.872- 0.918) which was superior to that of AFP (0.668, p<0.0001), DCP (0.773, p<0.0001), AFP and DCP (0.784, p<0.0001), and the ASAP model (0.878, p=0.0006). At an optimal threshold of -0.7995, the GAAP score had a sensitivity of 75.38% and a specificity of 88.19% for HBV-HCC detection.

Dou, et al. (2016)[9] showed that combined methylation might be a biomarker to discriminate HBV-related HCC from CHB and LC. Combined methylation positive was identified as presence of at least one of the three methylated genes (CDH1, DNMT3b and ESR1). Combined methylation showed a sensitivity of 84.48 %, specificity of 66.26 %, positive likelihood ratio of 2.50 and negative likelihood ratio of 0.23. An ROC curve of combined methylation was constructed to discriminate HBV-related HCC from CHB patients. The area under the ROC curve (AUC) was 0.75 [standard error (SE) 0.03, 95 % confidence interval (CI) 0.70–0.80], which was significantly higher than serum AFP levels (AUC = 0.63, SE = 0.03, 95 % CI 0.57–0.68; p = 0.003). In addition, the AUC of combined methylation was 0.73 (SE = 0.04, 95 % CI 0.66–0.79) to discriminate HBV-related HCC from LC patients, which was also significantly higher than serum AFP levels (AUC = 0.62, SE = 0.04, 95 % CI 0.55–0.68; p = 0.045).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Chalasani, 2021[7]	Indiana, USA	Case-control study	135 cases	This study identified a multi-target HCC panel of 3 MDMs (HOXA1, EMX1, and TSPYL5), B3GALT6 and 2 protein markers (AFP and AFP-L3) with a higher sensitivity (71%, 95% CI: 60–81%) at 90% specificity for early-stage HCC than the GALAD score or AFP.
Chen, 2023[8]	China	Retrospective study	262 cases	This results showed that the GAAP model was more effective than the AFP, DCP, AFP&DCP, as well as the ASAP model in the whole population for the identification of HCC and in the HBV subset for the detection of HBV-HCC.
Dou, 2016[9]	China	Cross sectional study	183 cases	This findings provided novel information that combined methylation of CDH1, DNMT3b and ESR1 promoters might serve as a promising biomarker to predict HBV-related HCC.
Oikawa, 2023[10]	Japan	Cohort	187 cases	This study showed that serum PKCδ can be a novel biomarker for HCC and is complementary to conventional HCC markers, AFP and DCP. Specifically, PKCd is useful for detecting very early-stage or AFP/DCP double-negative HCC.
Zekri, 2013[11]	Egypt	Cross sectional study	40 cases	This study showed that CADs, CARD9, CARD10 and COP play an important role in HCV-associated hepatocarcinogenesis, however only CARD9 is associated with the development fibrosis in those. Together with AFP, they could be used as surrogate markers for prediction of HCC in chronic HCV-infected patients with or without cirrhosis either singly or in combination.

Oikawa, at al. (2023)[10] suggested that high level of serum PKCδ is indicative of the presence of HCC and that the diagnostic performance of PKCδ for HCC is not inferior to conventional tumor markers, and serum PKCδ can be more useful in detecting very early-stage HCC than conventional markers. In this study, they included 313 CLD patients with and without HCC. These patients were divided into 2 groups according to the time of sample collection (2018–2020 and 2021–2022): cohort A (CLD with HCC [“HCC”], n = 108; and CLD without HCC [“non-HCC”], n = 74)and cohort B(HCC = 79; and non-HCC = 52). PKCδ clearly distinguished between HCC patients and healthy subjects (AUC, 0.968; sensitivity, 88.9%; specificity, 100.0%; PKCδ also discriminated HCC patients from non-HCC patients (including those with chronic hepatitis [CH] and liver cirrhosis [LC]) and from those with LC alone. The AUC and cut-off values of PKCδ for HCC diagnosis were 0.686 (vs non-HCC patients with CH and LC) and 0.548 (vs non-HCC patients with LC alone) and 57.7 ng/mL for both. When PKCδ of >57.7 ng/mL was set as abnormal and considered positive, PPV for PKCδ (95.3%) was not inferior or comparable to that of AFP (>20.0 ng/mL; 97.0%) or DCP (>40.0 mAU/mL; 91.5%; vs AFP, P = .212; and vs DCP, P = .118). There were no significant differences in sensitivity or specificity between PKCδ and conventional markers. In cohort A, PKCδ yielded the highest sensitivity (45.0%) with high specificity, PPV, NPV, and

accuracy (97.3%, 81.8%, 86.7%, and 86.2%, respectively) compared with AFP and DCP. In contrast, AFP and DCP had low sensitivity (only 15.0% for both). The combination of AFP and DCP did not exceed the diagnostic performance of PKCδ. Moreover, PKCd had the highest AUC among the 3 markers (0.762, 0.710, and 0.562 for PKCd, AFP, and DCP, respectively).

Zekri, at al. (2013)[11] showed the best cut-off for each marker, which can differentiate between HCC and other non HCC lesions. The best cut-off for CARD9 was 47 with 80% sensitivity, 80% specificity, 61% positive predictive value (PPV) and 85.7% negative predictive value (NPV). For CARD10, the best cut-off was 89.5% with 90% sensitivity, 63% specificity, 51.4% PPV and 93.3% NPV. For COP, the best cut-off was 203 with 90% sensitivity, 81% specificity, 69.2% PPV and 94.8% NPV whereas; the best cut-off for AFP was 10.35 with 87% sensitivity, 68% specificity, 54% PPV and 91% NPV. A combination of CRD9, CARD10 and COP showed 100% sensitivity and 48% specificity with 47% PPV and 100% NPV. The combination of AFP with each of the studied markers (CARD9 then CARD 10 then COP) showed (93%, 100%, 100% sensitivity), (57%, 46%, 57% specificity), PPVs (49%, 45%, 51%) and NPVs (94%, 100%, 100%); respectively.

DISCUSSION

The purpose of this research was to review studies published after January of 2013 and up to October of 2023 that investigated screening for HCC in CLD patients. Identified studies reported sensitivity, specificity, AUC of several screening tests. Multitarget HCC panel; combined methylation (CDH1, DNMT3b or ESR1); CARD10; COP; combination of CRD9, CARD10, and COP; and PKCδ had high sensitivity (80%; 84.48 %, 90%; 90%; 100%; 88.9%). PKCδ had high specificity, 100.0% while combination of CRD9, CARD10 and COP had 48% specificity. They were accurate for HCC (any stage of severity) with pooled sensitivities more than 80%.

When it comes to cancer incidence globally and cancer-related mortality, hepatocellular carcinoma (HCC) comes in third place.[12] The incidence of HCC is among the fastest rising of all cancers, primarily because of aging cohorts of chronic viral hepatitis and rising incidence of obesity and alcohol-related liver disease. Although survival from HCC has improved to a median of 12.1 months, prognosis remains poor. The cost burden to health systems is substantial with mean treatment costs for HCC in Australia of ~A$50 000/person and liver transplantation costing A$166 000/person. Consequently, prevention and early detection may offer substantial benefits for patients and healthcare systems.[13] Assessments of three parameters—tumor burden, liver function, and patient performance status—are used to guide the therapy of HCC patients. A study has proved that patients who benefited from a regular screening were diagnosed at an earlier stage and were eligible more frequently for curative treatments.[12]

Prior to implementing population-wide screening programmes, health systems must evaluate the benefits, risks, and cost-effectiveness of screening. Without devoted resources, public education campaigns, population-wide support from community stakeholders, and uptake-optimization procedures, it is difficult for new screening programmes to be adopted. To maximise health benefits and reduce the use of unnecessary healthcare resources, one potential option is to focus screening on high-risk patients. To risk stratify individuals with cirrhosis, blood tests like biochemical analytes, protein and/or tumour DNA panels, microRNAs, and metabolomics have been established.[13] According to a systematic review, screening can help find more patients who are candidates for treatments that may be curative at an earlier stage of their illness. However, there is insufficient evidence to draw firm conclusions about the balance between the advantages and disadvantages of routine screening for HCC.[6]

The goal of screening is to find undiagnosed disease as a secondary way of prevention. However, there is presently no screening approach for HCC that can reliably identify disease at an early stage. In order to avoid missing disease, doctors employ surveillance tests with relatively high sensitivity (true-positive rates) and relatively poor specificity (true-negative rates). The American Association for the Study of Liver Diseases (AASLD) advises that patients with cirrhosis and some patients with chronic liver disease without cirrhosis undergo surveillance for HCC using ultrasonography (USG) every six months.[14] Effective cancer screening requires several steps along a continuum of care, including recognition of patients who are at risk, clinicians recommending and ordering screening, and patients adhering to complete surveillance tests in a timely manner.[15]

At present, only one meta-analysis, published by Singal et al. in 2022, has summarized the evidence on HCC screening-related harms. However, it only describes proportions of screening-related physiological harm reported by current articles. In addition, high-quality systematic reviews performed by the USPSTF on breast cancer, cervical cancer, colorectal cancer, lung cancer, and others have shown that cancer screening causes psychological harms such as psychological anxiety.[16] A study published by Yang et al. in 2023 has concluded that the benefits of HCC screening outweigh those of not screening, according to the currently available, relatively poor-quality evidence. There is not enough proof at this time of the hazards of HCC screening. Future research should focus on high-quality trials that weigh the advantages and disadvantages of HCC screening in people with chronic liver disease and other high-risk populations.[17]

CONCLUSION

Multitarget HCC panel; combined methylation (CDH1, DNMT3b or ESR1); CARD10; COP; combination of CRD9, CARD10, and COP; and PKCδ were accurate for HCC screening (any stage of severity) in CLD with pooled sensitivities more than 80%. However, there is not adequate data to make definite judgements about the balance between the advantages and disadvantages of routine screening for HCC.

REFERENCES

[1]. Sharma A, Nagalli S. Chronic Liver Disease [Internet]. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554597/#:~:text=Chronic

[2]. Balogh J, Victor D, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma [Internet]. 2016 Oct;Volume 3:41–53. Available from: https://www.dovepress.com/hepatocellular-carcinoma-a-review-peer-reviewed-article-JHC

[3]. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. Vol. 17, Clinical Liver Disease. John Wiley and Sons Inc; 2021. p. 365–70.

[4]. Li J, Yang HI, Yeh ML, Le MH, Le AK, Yeo YH, et al. Association between Fatty Liver and Cirrhosis, Hepatocellular Carcinoma, and Hepatitis B Surface Antigen Seroclearance in Chronic Hepatitis B. Journal of Infectious Diseases. 2021 Jul 15;224(2):294–302.

[5]. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. Vol. 73, Hepatology. John Wiley and Sons Inc; 2021. p. 4–13.

[6]. Kansagara D, Papak J, Pasha AS, O'Neil M, Freeman M, Relevo R, et al. Screening for hepatocellular carcinoma in chronic liver disease: A systematic review. Vol. 161, Annals of Internal Medicine. American College of Physicians; 2014. p. 261–9.

[7]. Chalasani NP, Ramasubramanian TS, Bhattacharya A, Olson MC, Edwards V DK, Roberts LR, et al. A Novel Blood-Based Panel of Methylated DNA and Protein Markers for Detection of Early-Stage Hepatocellular Carcinoma. Clinical Gastroenterology and Hepatology. 2021 Dec 1;19(12):2597-2605.e4.

[8]. Chen Y, Yang X, Shao Y, Zhao H, Jiang J, Huang P, et al. Comparison of diagnostic performance of AFP, DCP and two diagnostic models in hepatocellular carcinoma: a retrospective study. Ann Hepatol. 2023 Jul 1;28(4).

[9]. Dou CY, Fan YC, Cao CJ, Yang Y, Wang K. Sera DNA Methylation of CDH1, DNMT3b and ESR1 Promoters as Biomarker for the Early Diagnosis of Hepatitis B Virus-Related Hepatocellular Carcinoma. Dig Dis Sci. 2016 Apr 1;61(4):1130–8.

[10]. Oikawa T, Yamada K, Tsubota A, Saeki C, Tago N, Nakagawa C, et al. Protein Kinase C Delta Is a Novel Biomarker for Hepatocellular Carcinoma. Gastro Hep Advances. 2023;2(1):83–95.

[11]. Zekri AR, El-Kassas M, Saad Y, Bahnassy A, Khatab Sameh Seif El-Din H, Darweesh SK, et al. Caspase recruitment domains. New potential markers for diagnosis of hepatocellular carcinoma associated with HCV in Egyptian patients. Vol. 12. 2013.

[12]. Hasani A. Factors affecting screening for hepatocellular carcinoma. Ann Hepatol. 2014;13(2):204–10.

[13]. Carter HE, Jeffrey GP, Ramm GA, Gordon LG. Cost-Effectiveness of a Serum Biomarker Test for Risk-Stratified Liver Ultrasound Screening for Hepatocellular Carcinoma. Value in Health. 2021 Oct 1;24(10):1454–62.

[14]. Fitzmorris P, Singal AK. Surveillance and Diagnosis of Hepatocellular Carcinoma. Vol. 11, Gastroenterology & Hepatology. 2015.

[15]. Parikh ND, Tayob N, Al-Jarrah T, Kramer J, Melcher J, Smith D, et al. Barriers to Surveillance for Hepatocellular Carcinoma in a Multicenter Cohort. JAMA Netw Open. 2022 Jul 22;5(7):E2223504.

[16]. Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. J Hepatol. 2022 Jul 1;77(1):128–39.

[17]. Yang J, Yang Z, Zeng X, Yu S, Gao L, Jiang Y, et al. Benefits and harms of screening for hepatocellular carcinoma in high-risk populations: Systematic review and meta-analysis. Journal of the National Cancer Center. 2023 Sep 1.