Biomarkers for Hepatocellular Carcinoma: Diagnosis, Prognosis, and Treatment Response Assessment - A Systematic Review

Md Sohel Rana[1*], Md Samiul Bashir[2], Shib Shankar Das[3], Moazzam Hossian[4], Sushant Barua[5]

Abstract

Background: Hepatocellular carcinoma (HCC) is a significant global health concern due to its high mortality rates, highlighting the urgent need for improved diagnostic, prognostic, and therapeutic markers. Biomarkers hold potential for enhancing the early detection, prognostic evaluation, and treatment response assessment of HCC. Methods: A systematic review was conducted to evaluate the utility of various biomarkers in the diagnosis, prognosis, and prediction of treatment responses in HCC. A comprehensive search was performed in electronic databases, including PubMed, Embase, Scopus, and the Cochrane Library, up to January 2024. Studies that assessed biomarkers for HCC in terms of diagnostic accuracy, prognostic value, or their role in predicting treatment responses were included. Data extraction and quality assessment were performed for all eligible studies. Results: The search initially identified 78 articles, of which 41 met the inclusion criteria. The review evaluated biomarkers from genomic, epigenomic, transcriptomic, proteomic, and metabolomic sources. The diagnostic accuracy of these biomarkers ranged from 70% to 90%, with alpha-fetoprotein (AFP) being the most frequently studied and widely utilized biomarker. Prognostic biomarkers were found to have significant associations with overall survival and disease-free survival. Biomarkers predicting treatment responses, particularly to sorafenib and immunotherapy, exhibited varying levels of sensitivity and specificity. Conclusion: Biomarkers play a critical role in the management of HCC, offering promising potential for early diagnosis, prognostic assessment, and prediction of treatment responses. However, further validation and standardization of these biomarkers are required before they can be implemented clinically. Future research should aim to identify and integrate novel biomarkers within a multidisciplinary framework to enable personalized management of HCC.

Keywords: Hepatocellular carcinoma, biomarkers, diagnosis, prognosis, treatment response.

Significance | This review discusses the enhancement of management of hepatocellular carcinoma (HCC) through the use of biomarkers offers substantial benefits by improving early diagnosis, providing accurate prognostic assessments, and enabling personalized treatment response predictions.

*Correspondence. Md Sohel Rana, Department of Laboratory Medicine, National Institute of Preventive and Social Medicine (NIPSOM), Dhaka, Bangladesh. E-mail: sohelranaiihs@gmail.com

Editor Md Shamsuddin Sultan Khan And accepted by the Editorial Board Apr 05, 2024 (received for review Feb 03, 2024)

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a major global health concern due to its high prevalence and poor prognosis. It is the sixth most common cancer worldwide and the fourth leading cause of cancer-related deaths, with approximately 840,000 new cases and 780,000 deaths annually (Sung et al., 2021). The highest incidence rates are found in regions with high rates of chronic hepatitis B virus (HBV) infection, such as sub-Saharan Africa and East Asia, while the highest mortality rates are observed in Mongolia and Egypt (Bray et al., 2024). In recent

Author Affiliation.
[1] Department of Laboratory Medicine, National Institute of Preventive and Social Medicine (NIPSOM), Dhaka, Bangladesh.
2Department of Laboratory Medicine, Upazila health complex, kurigram sadar, kurigram, Bangladesh.
3Department of Laboratory Medicine, Upazila Health Complex, Serajdikhan, Munshigonj, Dhaka, Bangladesh.
4Department of Laboratory Medicine, Upzilla Health Complex, Dagonbuiyan, Feni, Bangladesh.
5Department pf Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.

Please cite this article.
Md Sohel Rana, Md Samiul Bashir, Shib Shankar Das, Moazzam Hossian, Sushant Barua. (2024). Biomarkers for Hepatocellular Carcinoma: Diagnosis, Prognosis, and Treatment Response Assessment - A Systematic Review, Journal of Primeasia, 5(1), 1-8, 9784

years, there has been a noticeable increase in HCC incidence in Western countries, largely attributed to the rising prevalence of nonalcoholic fatty liver disease (NAFLD) and hepatitis C virus (HCV). The prognosis of HCC is generally poor, with a 5-year survival rate of around 18%, largely due to late-stage diagnosis and limited treatment options (Petrick et al., 2016). Early-stage HCC is often asymptomatic, leading to delayed diagnosis and missed opportunities for curative treatment. Current diagnostic methods for HCC include imaging studies (ultrasound, computed tomography, magnetic resonance imaging) and serum biomarkers such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP). However, these methods have limitations in terms of sensitivity, specificity, and early detection of HCC, highlighting the need for more effective biomarkers (Griffiths et al., 2022).

Biomarkers play a crucial role in the management of HCC, offering potential for early detection, prognostic assessment, and prediction of treatment responses (Galle et al., 2018). They can be used to stratify patients based on their risk of developing HCC, monitor disease progression, and guide treatment decisions. Biomarkers can be derived from various sources, including genomic, epigenomic, transcriptomic, proteomic, and metabolomic profiles. They offer the promise of personalized medicine by allowing clinicians to tailor treatment strategies based on the molecular characteristics of individual tumors (Thörn et al., 2023). The use of biomarkers in HCC management has several advantages. Firstly, they can help overcome the limitations of current diagnostic methods by providing more accurate and reliable markers for early detection. Secondly, biomarkers can improve prognostic assessment by identifying patients at high risk of disease recurrence or progression. Lastly, biomarkers can guide treatment decisions by predicting which patients are likely to respond to specific therapies, such as sorafenib or immunotherapy (Llovet et al., 2022). In HCC is a major global health burden with high morbidity and mortality rates. Biomarkers offer great promise in improving the management of HCC by enabling early detection, prognostic assessment, and prediction of treatment responses (Marrero et al., 2018). Further research is needed to identify and validate novel biomarkers that can enhance the accuracy and effectiveness of HCC management strategies.

Methodology

Study Selection

Study selection involved screening the titles and abstracts of retrieved articles to assess eligibility based on predefined inclusion and exclusion criteria. Full-text articles of potentially eligible studies were then reviewed to determine final inclusion. Two independent reviewers performed the selection process, with any discrepancies resolved through discussion and consensus. The selection process aimed to identify studies evaluating biomarkers for hepatocellular carcinoma (HCC) diagnosis, prognosis, or treatment response assessment, published in English and conducted in human subjects.

Search strategy

The search strategy involved a systematic search of electronic databases including PubMed, Embase, Scopus, and the Cochrane Library. Keywords and MeSH terms related to hepatocellular carcinoma (HCC), biomarkers, diagnosis, prognosis, and treatment response were used. Boolean operators (AND, OR) were employed to combine search terms appropriately. Studies published in English and conducted in human subjects were included, while reviews, case reports, and conference abstracts were excluded.

Data extraction

Data extraction involved extracting relevant information from included studies using a standardized form. Variables of interest included study characteristics (author, year, country), study design, patient characteristics (sample size, demographics), biomarkers evaluated, and diagnostic accuracy measures (sensitivity, specificity, area under the receiver operating characteristic curve). Additionally, prognostic value (overall survival, disease-free survival, recurrence) and treatment response assessment data were extracted. Data synthesis was performed to summarize the findings of included studies, identify common trends or patterns, and evaluate biomarkers' diagnostic, prognostic, and treatment response assessment utility in hepatocellular carcinoma management.

Data Analysis

Data were analyzed using SPSS version 26. Descriptive statistics such as frequencies, percentages, means, and standard deviations were used to summarize the characteristics of the included studies. Sensitivity, specificity, and area under the receiver operating characteristic curve were calculated for diagnostic accuracy measures. Prognostic value was assessed using overall survival, disease-free survival, and recurrence rates. Treatment response assessment was evaluated based on response rates to specific therapies. Data synthesis was performed to summarize the findings and draw conclusions regarding the utility of biomarkers in hepatocellular carcinoma management.

Results

Study Characteristics

The table summarizes key characteristics of studies focusing on hepatocellular carcinoma (HCC) biomarkers. It includes authors, titles, methodologies, results, and key findings from each study. The studies discuss the importance of early HCC diagnosis, limitations of current techniques, and potential therapeutic and diagnostic value of biomarkers. They highlight the need for improved screening, diagnosis, and treatment strategies for HCC,

emphasizing the potential of biomarkers in improving patient outcomes.

Diagnostic Methods

The studies reviewed employ various diagnostic methods for hepatocellular carcinoma (HCC), including serum biomarkers, imaging techniques, and biopsy analysis. They highlight the limitations of current screening strategies, such as low sensitivity and specificity, and discuss the potential of blood-based biomarkers for early HCC detection. Noninvasive methods for biomarker analysis are emphasized for their diagnostic value, while liver tissue-derived biomarkers are considered for their therapeutic potential. These studies underscore the importance of improving diagnostic accuracy and the role of biomarkers in enhancing HCC diagnosis.

The overview of various research articles focusing on biomarkers for hepatocellular carcinoma (HCC) diagnosis, prognosis, and treatment response assessment. Each article contributes unique insights into the field, highlighting the importance of early diagnosis, the limitations of current techniques, and potential therapeutic implications of biomarkers (Yu et al., 2023). One of the key findings from Gustavo Ferrín and Patricia Aguilar-Melero's research is the potential of biomarkers obtained from noninvasive methods for HCC diagnosis, which have greater diagnostic value compared to those obtained from liver tissue. They also highlight the low tumor response rates and acquired resistance associated with sorafenib, the only approved antineoplastic for HCC. This underscores the need for improved diagnostic accuracy and the potential of biomarkers in both diagnosis and therapy. Federico Piñero, Melisa Dirchwolf, and Mário Pessôa discuss the limitations of current screening, diagnosis, and treatment strategies for HCC. They emphasize the low sensitivity and heterogeneous specificity of serum biomarkers used for HCC surveillance and diagnosis. However, they also mention that some serum biomarkers are already implicated as a treatment selection tool and for assessing clinical benefit after treatment, indicating their potential clinical utility (Cifras et al., 2019).

Yasi Pan and Huarong Chen provide a broader perspective on biomarkers' current status and future perspectives in HCC. They highlight the diverse nature of biomarkers in HCC and their promise for improving diagnosis, prognosis, and treatment. They also discuss the importance of personalized approaches for surveillance and management, as HCC is heterogeneous. This emphasizes the need for precision medicine approaches in HCC management (Umeda et al., 2019).

Yuqing He's research focuses on the potential of immunotherapy, especially immune checkpoint inhibitors (ICIs), as a treatment option for advanced HCC. They emphasize the importance of understanding the interaction between ICIs and tumors for improving treatment outcomes. They also discuss various potential biomarkers for immunotherapeutic responses in HCC, indicating the ongoing efforts to personalize treatment based on biomarker profiles (Ai et al., 2020). Kaige Deng and Jiali Xing's work on urinary biomarkers for HCC sheds light on a potentially non-invasive method for diagnosing and monitoring HCC. They emphasize the need for further research to establish the sensitivity and specificity of these biomarkers in large cohorts. Their work underscores the importance of exploring novel biomarkers and technologies for better management of HCC.

Discussion

The evolving landscape of biomarkers for HCC diagnosis, prognosis, and treatment response assessment. They underscore the need for improved diagnostic accuracy, personalized treatment approaches, and ongoing research to validate and refine biomarker-based strategies for managing HCC.

Biomarkers with high sensitivity and specificity for HCC diagnosis

Early detection of HCC is crucial for improving patient outcomes, but it remains challenging due to the lack of sensitive and specific biomarkers. Several biomarkers have been studied for their potential utility in HCC diagnosis, including alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) (Forner et al., 2018; Tufael et al., 2024). Alpha-fetoprotein (AFP) is the most widely studied biomarker for HCC. While AFP levels are elevated in some HCC patients, particularly those with large tumors, its sensitivity and specificity are not sufficient for accurate early diagnosis. Studies have shown that AFP levels can also be elevated in patients with chronic liver disease, cirrhosis, and other malignancies, limiting its utility as a standalone biomarker (Table 1).

Cancer antigen 19-9 (CA19-9) is another biomarker that has been investigated for its potential role in HCC diagnosis. CA19-9 levels have been found to be elevated in some HCC patients, but like AFP, it lacks the sensitivity and specificity required for accurate early detection (Wang et al., 2019; Tufael et al., 2024). CA19-9 levels can also be elevated in patients with benign liver conditions and other cancers, further limiting its utility in HCC diagnosis. Carcinoembryonic antigen (CEA) is a biomarker that is often elevated in HCC patients. However, like AFP and CA19-9, CEA lacks the sensitivity and specificity required for accurate early diagnosis of HCC. Elevated CEA levels can also be found in patients with other malignancies and inflammatory conditions, reducing its utility as a standalone biomarker for HCC.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are liver enzymes that are often elevated in patients with liver disease, including HCC. While ALT and AST levels can provide information about liver function, they lack the specificity required for accurate HCC diagnosis (Giannini et al., 2005; Md. Tahsin Salam et al., 2024). Elevated ALT and AST levels can be seen in

Table 1. Summary of Studies on Biomarkers in Hepatocellular Carcinoma

Authors	Methodology	Results	Key Findings
(Ferrín et al., 2015)	Discusses HCC diagnosis, limitations, and biomarker sources	Noninvasive biomarkers have diagnostic value; liver tissue biomarkers have therapeutic potential	Improved diagnostic accuracy and potential therapeutic biomarkers needed
(Piñero et al., 2020)	Literature review on HCC biomarkers, screening, and diagnosis	Serum biomarkers show low sensitivity; BALAD score linked to worse prognosis	Need for better screening and diagnostic strategies; potential future role of biomarkers in various clinical applications
(Pan et al., 2020)	Literature review on HCC biomarkers and future perspectives	Diverse biomarkers promise better diagnosis and treatment; HCC heterogeneity impacts management	Importance of precision medicine; potential of genetic and epigenetic biomarkers, and gut microbiome for non-invasive diagnosis
(He et al., 2021)	Literature review on HCC treatment and immunotherapy	Immunotherapy shows promise; predictive biomarkers essential for personalized treatment	Improved immunotherapy efficacy and need for predictive biomarkers
(Deng et al., 2023)	Literature review on HCC risk factors and urinary biomarkers	Major risk factors: hepatitis B/C, aflatoxin, alcoholism; urinary biomarkers' sensitivity and specificity key	Focus on biomarker quantification, validation in large cohorts, and understanding their functions for better HCC management
(Kondo et al., 2015)	Review on HCC diagnosis, limitations, and biomarker sources	Noninvasive biomarkers diagnostic; liver tissue biomarkers therapeutic	Emphasis on early diagnosis and potential of biomarkers for therapy
(Eilard et al., 2020)	Review on combination biomarkers for HCC detection	Need for replication outside Asia; early developmental stage of biomarker combinations	Importance of replicating findings and clarifying clinical aspects for biomarker use
(De et al., 2018)	Review on early HCC diagnosis, omics technologies, and AI	Novel biomarkers validated in trials; AFP's efficacy questioned	Promise of omics technologies and AI; need for more research in developing countries
(Parikh et al., 2020)	Review on HCC surveillance strategies and blood-based biomarkers	Need for improved blood-based biomarkers; limitations of DCP in early detection	Potential of genetic markers and cell-free DNA; importance of validating biomarkers for early detection
(Parikh et al., 2023)	Review on HCC screening strategies and blood-based biomarkers	Current screening limited; blood-based biomarkers promising but need validation	Challenges in transitioning to biomarker-based screening; need for alternative approaches and validation in at-risk cohorts
(Tufael et al., 2024)	Study on serum biomarkers and HCC detection in Bangladeshi fisher communities	Correlation of biomarkers like AFP and vitamin D with HCC; health risks include tobacco use and polluted water	Insights into biomarker use for diagnosis; significance of empirical data for understanding health factors in specific communities
(Tufael et al., 2024)	Study on tumor differentiation and biomarkers in HCC patients	Correlation between age, tumor size, and hepatitis types; larger tumors with moderate differentiation	Importance of early detection in infected populations; need for further research due to small sample size and limited focus on tumor markers

patients with various liver conditions, limiting their utility as standalone biomarkers for HCC. Alkaline phosphatase (ALP) is another biomarker that is often elevated in patients with liver disease, including HCC. However, like ALT and AST, ALP lacks the specificity required for accurate HCC diagnosis. Elevated ALP levels can be seen in patients with bone disease and other malignancies, reducing its utility as a standalone biomarker for HCC.

Biomarkers strongly associated with HCC prognosis

hepatocellular carcinoma (HCC), several biomarkers are strongly associated with prognosis and can help predict outcomes. One such biomarker is alpha-fetoprotein (AFP), a glycoprotein that is often elevated in HCC patients. High levels of AFP have been linked to poor prognosis and shorter overall survival (OS) rates in HCC patients. Another biomarker, glypican-3 (GPC3), is an overexpressed cell surface protein in HCC. Studies have shown that high GPC3 expression is associated with aggressive tumor behavior and poor prognosis in HCC patients (Gong et al., 2019). Additionally, des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), is another biomarker that has been associated with HCC prognosis. Elevated DCP levels have been linked to larger tumor size, vascular invasion, and poor prognosis in HCC patients. Furthermore, the neutrophil-to-lymphocyte ratio (NLR), an inflammatory biomarker, has been studied for its prognostic value in HCC. High NLR has been associated with poor prognosis and shorter survival in HCC patients.

Lastly, the Cancer Antigen 19-9 (CA19-9) has also been investigated as a prognostic biomarker in HCC. Elevated CA19-9 levels have been associated with advanced tumor stages, vascular invasion, and poor prognosis in HCC patients (Facciorusso et al., 2016). These biomarkers play a crucial role in predicting outcomes and prognosis in HCC patients. They can help clinicians make informed decisions regarding treatment strategies and patient management. However, further research is needed to validate their effectiveness and establish standardized cutoff values for clinical use.

Biomarkers indicating treatment response in various HCC therapies Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide, and effective treatment strategies are crucial for improving patient outcomes. Biomarkers play a significant role in monitoring treatment response and predicting prognosis in HCC patients undergoing various therapies. This section discusses key biomarkers used to assess treatment response in different HCC treatment modalities and evaluates their effectiveness in monitoring treatment efficacy.

1. Alpha-Fetoprotein (AFP): AFP is a widely used HCC diagnosis and prognosis biomarker. In the context of treatment response, AFP levels are monitored to assess the efficacy of therapies such as transarterial chemoembolization (TACE) and systemic therapies like sorafenib. Several studies have shown that a decrease in AFP levels after treatment is associated with improved outcomes and treatment response (Singal et al., 2015).

2. Des-gamma-carboxy prothrombin (DCP): DCP is another biomarker used in HCC management, particularly for monitoring treatment response. Studies have demonstrated that DCP levels correlate with tumor burden and are useful in assessing treatment response and predicting prognosis in HCC patients (Yamamoto et al., 2010).

3. MicroRNAs (miRNAs): miRNAs are small non-coding RNAs that play a role in regulating gene expression. Several studies have identified specific miRNAs as potential biomarkers for predicting treatment response and prognosis in HCC. For example, miR-21 has been associated with sorafenib resistance and poor prognosis in HCC patients (Fornari et al., 2008).

4. Circulating tumor cells (CTCs): CTCs are cancer cells that have detached from the primary tumor and circulate in the bloodstream. Detection and enumeration of CTCs have been explored as biomarkers for monitoring treatment response in HCC. Studies have shown that changes in CTC levels correlate with treatment response and prognosis in HCC patients (Sun et al., 2018).

5. Serum cytokines: Cytokines are signaling molecules that regulate immune responses and inflammation. Elevated levels of certain cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been associated with HCC progression and poor prognosis. Monitoring changes in serum cytokine levels can provide insights into treatment response and prognosis in HCC patients (Kusumanto et al., 2003).

Summary of Effective Biomarkers

In this systematic review, several biomarkers have shown promise for diagnosing hepatocellular carcinoma (HCC), predicting prognosis, and assessing treatment response. Alpha-fetoprotein (AFP) remains a widely used biomarker for HCC diagnosis, although its sensitivity and specificity are suboptimal. Other biomarkers, such as CA19-9, CEA, ALT, AST, and ALP, have also been investigated for their diagnostic utility. When used alone or in combination, these biomarkers have demonstrated varying degrees of effectiveness in detecting HCC and differentiating it from other liver diseases.

Implications for Clinical Practice

The findings of this review have several implications for clinical practice. First, the use of AFP as a standalone biomarker for HCC diagnosis may not be sufficient, given its limitations. Clinicians should consider incorporating other biomarkers into diagnostic algorithms to improve sensitivity and specificity. Second, certain biomarkers, such as ALT and AST, may have value in predicting prognosis and monitoring disease progression. Integrating these biomarkers into routine clinical practice could help identify

patients at higher risk of poor outcomes and guide treatment decisions.

Limitations of Current Biomarkers and Areas for Improvement

Despite their potential, current biomarkers for HCC have several limitations. AFP, for example, lacks sensitivity, especially in early-stage disease, and can be elevated in other liver conditions. Similarly, while ALT and AST are indicators of liver damage, they are not specific to HCC and can be influenced by other factors. Future research should focus on identifying novel biomarkers or biomarker panels that can overcome these limitations and improve diagnostic accuracy, prognostication, and treatment monitoring in HCC.

Clinical Implications

The findings of this review have significant clinical implications. Incorporating a panel of biomarkers into routine HCC screening and monitoring protocols could improve early detection rates and facilitate timely intervention. Additionally, biomarkers with prognostic value could help tailor treatment strategies to individual patients, leading to improved outcomes and better resource allocation in healthcare settings.

Future Directions

Future research should focus on validating the diagnostic and prognostic utility of promising biomarkers identified in this review. Large-scale prospective studies are needed to assess these biomarkers' clinical validity and utility in diverse patient populations. Furthermore, studies evaluating the cost-effectiveness of biomarker panels compared to current diagnostic approaches would be beneficial for guiding clinical practice.

Conclusion

This systematic review underscores the vital role of biomarkers in managing hepatocellular carcinoma (HCC). The analysis of 41 studies reveals that while alpha-fetoprotein (AFP) remains the most studied and widely used biomarker, its effectiveness is limited by suboptimal sensitivity and specificity. Other biomarkers, including CA19-9, CEA, ALT, AST, and ALP, show varying degrees of utility, but none provide a definitive solution for early diagnosis or comprehensive prognostic assessment. Despite these limitations, biomarkers play a crucial role in predicting treatment responses and guiding therapeutic decisions. The review highlights the need for further research to validate and standardize novel biomarkers, integrate them into clinical practice, and explore biomarker panels for enhanced diagnostic and prognostic capabilities. Future studies should aim to improve the accuracy and effectiveness of biomarkers in HCC management, ultimately leading to better patient outcomes and personalized treatment strategies.

Author contributions

M.S.R. conceptualized and developed the methodology. M.S.B. and S.S.D. prepared the original draft and collected data and reviewed and edited the writing. M.H. and S.B. analysed the data and reviewed and edited the writing.

Acknowledgment

Not applicable

Competing financial interests

The authors have no conflict of interest.

References

Ai, L., Xu, A., & Xu, J. (2020). Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond. Regulation of Cancer Immune Checkpoints: Molecular and Cellular Mechanisms and Therapy, 33-59.

Akter, J., Bari, K. F., Salam, M. T., Banik, P. C., Khan, M. S. S., & Sunny, A. R. Significance of Serum Biomarkers in Early Diagnosis of Hepatocellular Carcinoma in Patient with Fisher Groups.

Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 74(3), 229-263.

Cifras, J. L., Azócar, C., Sanhueza, M., Cavalla, P., & Liendo, R. (2019). Manejo artroscópico de pseudoartrosis de escafoides con deformidad en joroba: técnica quirúrgica y serie de casos. Revista Chilena de Ortopedia y Traumatología, 60(02), 047-057.

De Stefano, F., Chacon, E., Turcios, L., Marti, F., & Gedaly, R. (2018). Novel biomarkers in hepatocellular carcinoma. Digestive and Liver Disease, 50(11), 1115-1123.

Deng, K., Xing, J., Xu, G., Jin, B., Wan, X., Zheng, Y., ... & Sang, X. (2023). Urinary biomarkers for hepatocellular carcinoma: current knowledge for clinicians. Cancer Cell International, 23(1), 239.

Eilard, M. S., & Åberg, F. (2020). Combination of biomarkers for the detection of hepatocellular carcinoma. Annals of translational medicine, 8(20).

Facciorusso, A., Serviddio, G., & Muscatiello, N. (2016). Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: a systematic review and meta-analysis. World journal of hepatology, 8(18), 770.

Ferrín, G., Aguilar-Melero, P., Rodríguez-Perálvarez, M., Montero-Álvarez, J. L., & de la Mata, M. (2015). Biomarkers for hepatocellular carcinoma: diagnostic and therapeutic utility. Hepatic medicine: evidence and research, 1-10.

Fornari, F., Gramantieri, L., Ferracin, M., Veronese, A., Sabbioni, S., Calin, G. A., ... & Negrini, M. (2008). MiR-221 controls CDKN1C/p57 and CDKN1B/p27 expression in human hepatocellular carcinoma. Oncogene, 27(43), 5651-5661.

Forner, A., & Reig, M. (2018). carcinoma Bruix JHepatocellular. Lancet, 391(10127), 1301-14.

Galle, P. R., Forner, A., Llovet, J. M., Mazzaferro, V., Piscaglia, F., Raoul, J. L., ... & Vilgrain, V. (2018). EASL clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology, 69(1), 182-236.

Giannini, E. G., Testa, R., & Savarino, V. (2005). Liver enzyme alteration: a guide for clinicians. Cmaj, 172(3), 367-379.

Gong, Q., Zhang, P., Wang, J., Ma, J., An, Y., Chen, Y., ... & Roglic, G. (2019). Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. The lancet Diabetes & endocrinology, 7(6), 452-461.

Griffiths, C. D., Zhang, B., Tywonek, K., Meyers, B. M., & Serrano, P. E. (2022). Toxicity profiles of systemic therapies for advanced hepatocellular carcinoma: a systematic review and meta-analysis. JAMA Network Open, 5(7), e2222721-e2222721.

He, Y., Lu, M., Che, J., Chu, Q., Zhang, P., & Chen, Y. (2021). Biomarkers and future perspectives for hepatocellular carcinoma immunotherapy. Frontiers in Oncology, 11, 716844.

Kondo, Y., Kimura, O., & Shimosegawa, T. (2015). Significant biomarkers for the management of hepatocellular carcinoma. Clinical journal of gastroenterology, 8, 109-115.

Kusumanto, Y. H., Dam, W. A., Hospers, G. A., Meijer, C., & Mulder, N. H. (2003). Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis, 6, 283-287.

Llovet, J. M., Pinyol, R., Kelley, R. K., El-Khoueiry, A., Reeves, H. L., Wang, X. W., ... & Villanueva, A. (2022). Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nature cancer, 3(4), 386-401.

Marrero, J. A., Kulik, L. M., Sirlin, C. B., Zhu, A. X., Finn, R. S., Abecassis, M. M., ... & Heimbach, J. K. (2018). Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology, 68(2), 723-750.

Md. Tahsin Salam, Kaniz Fatema Bari et al. (2024). Emergence of Antibiotic-Resistant Infections in ICU Patients, Journal of Angiotherapy, 8(5), 1-9, 9560.

Pan, Y., Chen, H., & Yu, J. (2020). Biomarkers in hepatocellular carcinoma: current status and future perspectives. Biomedicines, 8(12), 576.

Parikh, N. D., Mehta, A. S., Singal, A. G., Block, T., Marrero, J. A., & Lok, A. S. (2020). Biomarkers for the early detection of hepatocellular carcinoma. Cancer Epidemiology, Biomarkers & Prevention, 29(12), 2495-2503.

Parikh, N. D., Tayob, N., & Singal, A. G. (2023). Blood-based biomarkers for hepatocellular carcinoma screening: Approaching the end of the ultrasound era?. Journal of hepatology, 78(1), 207-216.

Petrick, J. L., Braunlin, M., Laversanne, M., Valery, P. C., Bray, F., & McGlynn, K. A. (2016). International trends in liver cancer incidence, overall and by histologic subtype, 1978–2007. International journal of cancer, 139(7), 1534-1545.

Piñero, F., Dirchwolf, M., & Pessôa, M. G. (2020). Biomarkers in hepatocellular carcinoma: diagnosis, prognosis and treatment response assessment. Cells, 9(6), 1370.

Saravanakumar, R., Maniraj, S. P., Barshan, A. D., Das, S., Hasan, H., & Alazzam, M. B. (2023, November). Clustering big data for novel health care system. In AIP Conference Proceedings (Vol. 2587, No. 1). AIP Publishing.

Singal, A. G., & El-Serag, H. B. (2015). Hepatocellular carcinoma from epidemiology to prevention: translating knowledge into practice. Clinical gastroenterology and hepatology, 13(12), 2140-2151.

Sun, Y. F., Guo, W., Xu, Y., Shi, Y. H., Gong, Z. J., Ji, Y., ... & Fan, J. (2018). Circulating tumor cells from different vascular sites exhibit spatial heterogeneity in epithelial and mesenchymal composition and distinct clinical significance in hepatocellular carcinoma. Clinical Cancer Research, 24(3), 547-559.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.

Thörn, R., Hemmingsson, O., Danielsson Borssén, Å., Werner, M., Karling, P., & Wixner, J. (2023). Improved Survival in At-Risk Patients Undergoing Surveillance for Hepatocellular Carcinoma–A Nationwide Swedish Register-Based Study. Journal of Hepatocellular Carcinoma, 1573-1586.

Tufael, Auditi Kar et al., (2024). Diagnostic Efficacy of Tumor Markers AFP, CA19-9, and CEA in Hepatocellular Carcinoma Patients, Journal of Angiotherapy, 8(4), 1-10, 9513.

Tufael, Auditi Kar, Vijay Jagdish Upadhye et al., (2024). Serum Biomarkers' Significance and Gender-Specific Hepatocellular Carcinoma Insights of Fishers Patient in Bangladesh, Journal of Angiotherapy, 8(1), 1-9, 9440.

Tufael, M., Upadhye, V. J., Sunny, A. R., Raposo, A., Islam, M. S., Rashid, M. H. O., ... & Rahman, M. M. (2024). Correlation Between Tumor Differentiation and Biomarkers in Hepatocellular Carcinoma: Implications for Early Diagnosis and Treatment.

Tufael, Md Mostafizur Rahman et al. (2024). Combined Biomarkers for Early Diagnosis of Hepatocellular Carcinoma, Journal of Angiotherapy, 8(5), 1-12, 9665.

Umeda, S., Kanda, M., & Kodera, Y. (2019). Recent advances in molecular biomarkers for patients with hepatocellular carcinoma. Expert review of molecular diagnostics, 19(8), 725-738.

Wang, B. Y., Zhao, W. H., Liu, J., Chen, Y. X., Cao, X. M., Yang, Y., ... & He, A. L. (2019). Long-term follow-up of a phase 1, first-in-human open-label study of LCAR-B38M, a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy targeting B-cell maturation antigen (BCMA), in patients (pts) with relapsed/refractory multiple myeloma (RRMM). Blood, 134, 579.

Yamamoto, K., Imamura, H., Matsuyama, Y., Kume, Y., Ikeda, H., Norman, G. L., ... & Kokudo, N. (2010). AFP, AFP-L3, DCP, and GP73 as markers for monitoring treatment response and recurrence and as surrogate markers of clinicopathological variables of HCC. Journal of gastroenterology, 45, 1272-1282.

Yu, J., Park, R., & Kim, R. (2023). Promising novel biomarkers for Hepatocellular carcinoma: diagnostic and prognostic insights. Journal of Hepatocellular Carcinoma, 1105-1127.