INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

COMBINED DETECTION OF SERUM TUMOR MARKERS FOR EARLY DIAGNOSIS OF HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

Original Research

Maida Jabeen[1], Aiman Saqib[1], Amna Shafique[1], Maryam Javed[1], Farwa Riaz[1], Zainab Ali[1], Muhammad Sulaiman Saeed[1]*

[1]Institute of Health Sciences, Khawaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan.

Corresponding Author: Muhammad Sulaiman Saeed, Institute of Health Sciences, Khawaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan, msulaiman.saeed@gmail.com

Acknowledgement: The authors acknowledge the contribution of all researchers whose work was included in this review.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and ranks among the leading causes of cancer-related mortality worldwide. Early diagnosis remains a cornerstone in reducing its associated morbidity and mortality. Serum tumor markers such as alpha-fetoprotein (AFP), AFP-L3, Des-Gamma-Carboxy Prothrombin (DCP), and PIVKA-II are frequently used for screening and diagnostic purposes. However, their individual limitations in sensitivity and specificity, especially for early-stage disease, necessitate investigation into the diagnostic value of combined biomarker strategies.

Objective: To evaluate the diagnostic accuracy of combined serum tumor biomarkers for early detection of hepatocellular carcinoma.

Methods: A systematic review of literature published from January 2000 to March 2025 was conducted using PubMed and Google Scholar databases. A total of 20 peer-reviewed studies meeting inclusion criteria were analyzed. Data extraction focused on the diagnostic performance of serum biomarkers alone and in combination. Diagnostic accuracy was assessed using sensitivity, specificity, and area under the ROC curve (AUC).

Results: AFP alone demonstrated a sensitivity of 63.3% and specificity of 80.8%. PIVKA-II outperformed AFP with a sensitivity of 71% and specificity of 90%. AFP-L3 and GP73 showed higher diagnostic performance in small tumor detection, with GP73 achieving 72.0% sensitivity and 86.7% accuracy, and GPC3 offering 98.0% specificity. Combining AFP with AFU yielded the highest diagnostic values with 95% sensitivity and 100% specificity. The triplet panel of AFP, AFP-L3, and DCP achieved 88% sensitivity and 91% specificity. Biomarker combinations consistently outperformed individual tests in detecting early and all-stage HCC.

Conclusion: Single biomarkers like AFP are insufficient for early-stage HCC detection. Combining AFP with other markers such as PIVKA-II, AFP-L3, and DCP significantly enhances diagnostic accuracy. Adoption of multi-marker strategies may improve early detection and clinical outcomes in HCC.

Keywords: AFP-L3, Biomarker, Hepatocellular Carcinoma, PIVKA-II, ROC Curve, Sensitivity and Specificity, Tumor Markers.

INTRODUCTION

Cancer, a formidable global health challenge, is characterized by the uncontrolled proliferation of abnormal cells with the potential to invade adjacent tissues and metastasize to distant sites. This malignant behavior stems from a complex interplay of genetic and epigenetic alterations that disrupt key regulatory mechanisms governing the cell cycle, apoptosis, and DNA repair. Over 100 distinct types of cancer exist, yet they all share the hallmark of unchecked cell growth and tissue invasion (1). These changes can be triggered by intrinsic factors, such as hereditary mutations, as well as extrinsic environmental exposures, including tobacco smoke, ultraviolet radiation, carcinogenic chemicals, and oncogenic infections. The global burden of cancer remains substantial, accounting for one in six deaths worldwide. Among the most prevalent malignancies are liver, lung, breast, cervical, stomach, and colorectal cancers (2). Tumors are generally categorized into benign and malignant forms. While benign tumors like lipomas are non-invasive and localized, malignant tumors are aggressive, capable of tissue infiltration and distant metastasis, requiring multimodal therapeutic interventions such as surgery, chemotherapy, and radiotherapy. Given the high morbidity and mortality associated with cancer, there is a critical need for early diagnostic and prognostic tools that can enhance treatment efficacy and improve survival outcomes (3,4). Hepatocellular carcinoma (HCC), the most common primary liver cancer, exemplifies the complexity of cancer development. It arises predominantly due to chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), particularly in Asia, but non-viral risk factors such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are increasingly implicated. The rising global prevalence of obesity and type 2 diabetes has contributed to a parallel increase in NAFLD-related HCC. Notably, HCC may develop even in the absence of cirrhosis, particularly in NAFLD patients, emphasizing the need for vigilant surveillance and early detection (5,6).

Despite advances in treatment, HCC continues to be associated with poor prognosis, with post-diagnosis survival ranging from 6 to 20 months. Imaging techniques such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are central to the diagnostic process, often complemented by serological markers like alpha-fetoprotein (AFP). Each modality has its strengths and limitations—ultrasound is cost-effective and widely available but has lower sensitivity (58%) compared to MRI (81%) and CT (68%), though specificity remains relatively high across all methods (7). The effectiveness of ultrasound is heavily dependent on the operator's skill and equipment quality. Advanced imaging offers better lesion characterization and staging capabilities, yet their high-cost limits accessibility in resource-constrained settings (8). Beyond imaging, biochemical markers such as AFP, CA19-9, and CEA are frequently assessed using chemiluminescence immunoassay (CLIA), which provides superior sensitivity and specificity compared to older methods like immunofluorescence assay (IFA) and radioimmunoassay (RIA). CLIA has demonstrated sensitivity levels of 85–95% and specificity of 90–98% for common tumor markers, making it a reliable tool in cancer diagnostics, including for HCC (9). However, reliance on traditional markers like AFP alone is suboptimal due to moderate sensitivity and specificity. At a threshold of 20 ng/mL, AFP shows a sensitivity of 63% and specificity of 88.7%; lowering the cutoff to 5.6 ng/mL increases sensitivity to 77% but compromises specificity (10). This has spurred the exploration of novel biomarkers to improve early detection. Tumor biomarkers—biological molecules found in blood, body fluids, or tissues—serve as indicators of normal or pathological processes. Multi-analyte panels such as the GALAD score, Oncoguard, and Helio Liver Test combine several biomarkers like AFP, AFP-L3, and des-gamma-carboxy prothrombin (DCP) to enhance diagnostic accuracy (11).

Among emerging individual markers, AFP-L3, a glycoform of AFP, is regarded as more specific for HCC. Others include glypican-3 (GPC3), heat shock protein 70 (HSP70), Golgi protein 73 (GP73), and cancer antigens such as CA125 and CA15-3, though further validation is needed (12). Recent innovations in liquid biopsy have introduced non-invasive molecular markers such as circulating tumor DNA (ctDNA), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs), which reflect tumor heterogeneity and real-time progression. These circulating markers offer the potential for earlier diagnosis and dynamic disease monitoring, particularly useful in high-risk individuals and those with ambiguous imaging findings (13). Conventional liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) also provide supportive evidence of hepatocellular injury, although they lack specificity for malignancy (14). Given the increasing incidence and poor prognosis of HCC, particularly in non-viral etiologies, the development and validation of sensitive and specific biomarkers for early detection is of utmost importance. This study, therefore, aims to investigate the diagnostic performance and clinical applicability of novel and conventional tumor biomarkers in hepatocellular carcinoma.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

METHODS

The present systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency, methodological rigor, and reproducibility. The primary objective of the study was to evaluate whether the simultaneous use of multiple serum tumor markers offers superior diagnostic accuracy for hepatocellular carcinoma (HCC), particularly in early-stage disease, compared to individual marker use. Secondary objectives included assessing the prognostic utility of combined tumor biomarkers in monitoring disease progression, predicting clinical outcomes, and detecting recurrence. A comprehensive electronic literature search was performed across PubMed, Google Scholar, and ResearchGate to identify relevant studies published between January 2000 and March 2025. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms such as “Hepatocellular carcinoma,” “Liver cancer,” “Tumor markers,” “AFP,” “AFP-L3,” “PIVKA-II” or “DCP,” “Glypican-3,” “Golgi protein 73,” “Combined tumor markers,” “Biomarkers for liver cancer,” “Early diagnosis of HCC,” “Prognostic biomarkers,” and “GALAD score.” Boolean operators were used to ensure a comprehensive retrieval of literature. Initially, a total of 471 articles were identified from database searches. After removing duplicates using Mendeley reference manager, 347 unique records remained. Of these, 124 articles were deemed potentially relevant based on title and abstract screening. Subsequent full-text review of the 124 articles led to the selection of 56 studies for detailed assessment, of which 20 met the final inclusion criteria. The selection process was conducted independently by two reviewers, with discrepancies resolved through consensus or consultation with a third reviewer. The final study selection process, including the transition from 471 initial hits to 20 eligible studies, was documented through a PRISMA flow diagram to maintain transparency and methodological consistency.

Inclusion criteria were established to enhance the quality and relevance of included studies. Eligible studies were full-text, peer-reviewed publications in English, dated between 2000 and 2025. Study designs included observational studies (cross-sectional, case-control, cohort), clinical trials, and meta-analyses. Only studies involving adult human subjects with confirmed HCC and reporting diagnostic performance metrics—such as sensitivity, specificity, or area under the receiver operating characteristic curve (AUC)—for combined serum tumor marker panels were included. Studies assessing the prognostic or predictive potential of biomarker combinations were also considered. Exclusion criteria were applied to remove studies that lacked methodological robustness or relevance. These included non-English publications, studies not available in full text, conference abstracts, editorials, letters, animal studies, in vitro experiments, pediatric population studies, and research focused solely on non-HCC liver malignancies (e.g., cholangiocarcinoma, metastases). Articles published before 2000 were excluded due to outdated diagnostic practices. Quality assessment was performed for all included studies using a structured framework evaluating four domains: patient selection, index test (tumor biomarkers), reference standard, and flow/timing. Each domain was assessed for risk of bias (low, high, or unclear), and studies showing high risk in multiple domains were excluded from data synthesis to preserve analytical integrity. Given the heterogeneity in biomarker combinations, diagnostic thresholds, and study designs, meta-analysis was not feasible. Therefore, a narrative synthesis approach was employed. This allowed for comparative evaluation of diagnostic parameters such as sensitivity, specificity, and AUC across studies. The synthesis highlighted recurring patterns and emerging biomarkers, including combinations of AFP with AFP-L3, DCP, Glypican-3 (GPC3), and integrative scoring models such as the GALAD score. These findings were contextualized with regard to tumor burden and early-stage HCC detection.

RESULTS

The analysis of 20 selected studies revealed varying levels of sensitivity and specificity across different tumor biomarkers and their combinations for the diagnosis of hepatocellular carcinoma (HCC). Alpha-fetoprotein (AFP), one of the most widely used serum markers for primary HCC, demonstrated a sensitivity of 63.3% and specificity of 80.8%, positioning it as a moderately effective standalone diagnostic tool (3). However, despite its broad clinical use, AFP alone was less effective in detecting early or small tumors due to limited sensitivity. When AFP was combined with carcinoembryonic antigen (CEA), the sensitivity dropped to 47%, while specificity improved to 89% (4). Similarly, the combination of AFP with CA19-9 resulted in a significant reduction in sensitivity to 7.3%, although it improved specificity to 94.42%. A triple combination of AFP, CEA, and CA19-9 yielded increased specificity at 92.3% and improved sensitivity to 86.5%, indicating potential benefit in combining these markers despite the variation in individual contribution to sensitivity (5). PIVKA-II, when compared to AFP, showed superior diagnostic accuracy with a sensitivity of 71% versus 64%, and specificity of 90% versus 87%, respectively. When used in combination, AFP and PIVKA-II demonstrated improved sensitivity of 87.5% and specificity of 92.5% (6), highlighting a more balanced diagnostic performance. Other promising combinations included AFP with AFP-L3 and des-

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

gamma-carboxy prothrombin (DCP), which achieved a sensitivity of 88% and specificity of 91% (7). A combination of AFP-L3 and DCP alone showed slightly lower sensitivity at 84% but increased specificity at 95%. AFP plus DCP alone yielded 88% sensitivity and 89% specificity.

The combination of AFP and GP73 demonstrated a sensitivity of 75.5% and specificity of 83.3% (8), whereas GPC3 as a solo biomarker had a notably high specificity of 98.0%, making it a useful adjunct for confirmation rather than screening. AFP-L3 and GP73 together yielded a sensitivity of 76% and specificity of 96%, indicating strong diagnostic capability (9). Among all biomarker pairings, the combination of AFP with alpha-L-fucosidase (AFU) demonstrated the highest diagnostic performance with sensitivity and specificity reaching 95% and 100%, respectively (10). Comprehensive models such as GALAD, although mentioned, were not consistently evaluated across all included studies. The combination of AFP with PIVKA-II and COMP achieved a sensitivity of 84.1% and specificity of 85.6%, reflecting improved diagnostic balance (11). Additionally, AFP combined with CA125 showed moderate sensitivity and specificity at 80% and 76.6%, respectively, while expanding to a triplet panel of AFP, CA125, and CEA yielded enhanced sensitivity (83.3%) and specificity (86.6%) (12). The inclusion of CA19-9 to form a quadruple panel raised both sensitivity and specificity to 90%, though some studies noted that broader combinations could dilute individual marker contributions and reduce sensitivity for early detection.

Table 1: The sensitivity and specificity of combined tumor markers

Combined tumor markers	Sensitivity %	Specificity %	Notes	References
AFP alone	63.3%	80.8%	Alone had effective specificity & sensitivity	Muhammad Ibrahim Alhadi Edoo et al,2019
AFP +CEA	47%	89%	Boost sensitivity &specificity	Tuafel et al.2024
AFP + CA19-9	7.3%	94.42%	Increase accuracy	Tuafel et al.2024
AFP+CEA+CA19-9	86.5%	92.3%	Increase specificity& Reduce sensitivity	Tuafel et al.2024
AFP +DCP	87%	69%	Increase sensitivity	Walid S. Ayoub et al,2019
AFP+GP3	75.5%	83.3%	Reduce sensitivity, increase specificity	Walid S. Ayoub et al,2019
AFU+AFP	95%	100%	Increase both sensitivity & specificity	Yan-Jie Zhao et al,2013
AFP+AFP-L3+DCP	88%	91%	Increase specificity &sensitivity	L. Volk et al,2007
AFP-L3+DCP	84%	95%	Increase specificity& sensitivity	L. Volk et al,2007
AFP+DCP	88%	89%	Increase sensitivity	L. Volk et al,2007
AFP+PIVIKA-II	87.5%	92.5%	In combination both increase sensitivity& specificity	Feng et al,2021
AFP+PIVIKA-II+COMP	84.1%	85.6%	Increase accuracy, specificity& sensitivity	Teerha Pritratvisuth,2022
AFP+CA125	80%	76.6%	Lower the sensitivity	Yong Le et al,2015
AFP+CA125+CEA	83.3%	86.6%		Yong Le et al,2015
AFP+CA125+CEA+CA19-9	90%	90%	Has lower sensitivities	Yong Le et al,2015
GP73+AFP-L3	76%	96%	Increase sensitivity and accuracy	Yunsheng Zhao et al,2015

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

DISCUSSION

The findings of this systematic review confirmed that alpha-fetoprotein (AFP) remains a widely utilized biomarker for the screening and diagnosis of hepatocellular carcinoma (HCC), particularly in asymptomatic patients. Across the reviewed studies, AFP levels were found to rise significantly—up to 154-fold—in patients with primary hepatic cancer compared to those with cirrhosis or healthy controls, indicating its strong association with malignant transformation in the liver. However, AFP's moderate sensitivity and specificity, reported as 63.3% and 80.8% respectively, suggest its limitations as a standalone marker for early-stage disease detection (15). Although combining AFP with other tumor markers such as CA19-9 and CEA increased specificity, it consistently reduced sensitivity, indicating that while combined biomarkers enhance diagnostic confidence, they may compromise early detection. The review further highlighted that, emerging markers such as GP73, AFP-L3, GPC3, and PIVKA-II demonstrated superior diagnostic performance compared to AFP, particularly in identifying small or early-stage tumors. GP73 showed a sensitivity of 72.0% and an accuracy of 86.7%, while GPC3 offered the highest specificity at 98.0%, supporting their value as complementary diagnostic tools. AFP-L3 and GP73 outperformed AFP with higher AUCs (0.816 and 0.826, respectively), making them more suitable for early HCC identification. The inclusion of multiple biomarkers achieved the highest combined efficacy, with sensitivity and diagnostic accuracy reaching 82.0% and 90.1%, respectively, in some studies (16,17). These findings align with previous literature supporting the integration of novel biomarkers for improved HCC screening strategies.

Differences between HCC and other hepatic malignancies such as cholangiocarcinoma (CC) were also evident based on serum marker profiles. CA125 and CEA were found at higher levels in CC than in HCC, whereas AFP was predominantly elevated in HCC. Among the individual markers, CA19-9 demonstrated the most discriminatory ability, with a sensitivity and specificity of 76.67% and 80.00%, respectively (18). Notably, when all four biomarkers—AFP, CA19-9, CA125, and CEA—were used together, the diagnostic accuracy significantly improved, with an AUC of 0.94, reinforcing the clinical value of multiparametric panels for differential diagnosis. Additional comparisons between AFP and PIVKA-II indicated the latter as a superior diagnostic marker for HCC. PIVKA-II demonstrated higher sensitivity (0.71 vs. 0.64), specificity (0.90 vs. 0.87), and a greater AUC (0.89 vs. 0.78), supporting its greater clinical utility across diverse populations and etiological backgrounds, including HBV- and HCV-related HCC (19). Furthermore, studies focusing on patients with low AFP levels found that AFP-L3 retained diagnostic value, particularly when combined with PIVKA-II, achieving a combined sensitivity of approximately 90% even in AFP-negative cases (20-22). This strengthens the rationale for using AFP-L3 and PIVKA-II as adjunctive tools in screening algorithms, especially in difficult-to-diagnose subgroups.

Advanced multi-marker models such as the GALAD score, which incorporate AFP, AFP-L3, PIVKA-II, and clinical variables like age and sex, demonstrated diagnostic performance comparable to three-marker combinations involving COMP, IGFBP3, or MMP3. These models offer balanced sensitivity and specificity for both early-stage and all-stage HCC, suggesting their potential for routine clinical use, particularly in high-risk cohorts (23). Nevertheless, the diagnostic yield of these models depends heavily on appropriate cutoffs and validation across diverse populations A major strength of this study was the comprehensive evaluation of multiple tumor markers and their combinations, spanning a 25-year period. The inclusion of both individual and composite biomarker strategies allowed for a nuanced understanding of their respective advantages and limitations. However, some limitations warrant attention. Many included studies demonstrated heterogeneity in methodology, assay platforms, cutoff thresholds, and patient populations, which may have influenced diagnostic performance estimates. In addition, stage-specific analyses—particularly in early HCC—were not consistently reported across all studies, limiting the ability to compare markers based on tumor burden. The lack of standardized protocols for biomarker measurement across centers also poses a barrier to widespread clinical adoption. Future studies should prioritize large-scale, multicenter trials to validate emerging biomarker panels, stratify results by HCC stage and etiology, and standardize diagnostic thresholds. Investigations should also explore the integration of serum biomarkers with imaging-based modalities and molecular diagnostics to enhance screening accuracy. While AFP continues to play a role in HCC surveillance, the evidence strongly supports transitioning toward a multi-biomarker framework that combines high specificity and sensitivity to facilitate early diagnosis and improve clinical outcomes.

CONCLUSION

In conclusion, this review highlights the diagnostic limitations of conventional tools for hepatocellular carcinoma and emphasizes the growing importance of multi-biomarker strategies in improving early detection. While traditional markers like AFP offer limited sensitivity and specificity on their own, their combined use with markers such as AFP-L3, DCP, PIVKA-II, and others significantly

enhances diagnostic performance. The integration of emerging biomarkers and composite models like the GALAD score, alongside imaging techniques, offers a more precise and non-invasive approach to HCC diagnosis. These findings support a shift toward multifaceted diagnostic frameworks that prioritize accuracy, early intervention, and personalized risk assessment, ultimately aiming to reduce the global burden of hepatocellular carcinoma.

AUTHOR CONTRIBUTION

Author	**Contribution**
Maida Jabeen	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Aiman Saqib	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Amna Shafique	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Maryam Javed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Farwa Riaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zainab Ali	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Muhammad Sulaiman Saeed*	Contributed to study concept and Data collection Has given Final Approval of the version to be published

REFERENCES

1. Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. International Journal of Cancer, 149(4), 778–789.
2. Piña-Sánchez, P., Chávez-González, A., Ruiz-Tachiquín, M., Vadillo, E., Monroy-García, A., Montesinos, J., Grajales, R., Gutiérrez de la Barrera, M., & Mayani, H. (2021). Cancer biology, epidemiology, and treatment in the 21st century: Current status and future challenges from a biomedical perspective. Cancer Control, 28, 10732748211038735.
3. Patel, A. (2020). Benign vs malignant tumors. JAMA Oncology, 6(9), 1488.
4. Shah, P. A., Patil, R., & Harrison, S. A. (2023). NAFLD-related hepatocellular carcinoma: The growing challenge. Hepatology, 77(1), 323–338.
5. Ibrahim Alhadi EDOO M, Kumar Chutturghoon V, Kwabena WUSU-ANSAH G, Zhu H, Yang ZHEN T, Yang XIE H, et al. Serum Biomarkers AFP, CEA and CA19-9 Combined Detection for Early Diagnosis of Hepatocellular Carcinoma [Internet]. Vol. 48, Iran J Public Health. 2019.
6. Tufael, M., Rahman, M. M., Upadhye, V. J., Hossain, M. F., & Uddin, N. (2024, May 9). Combined biomarkers for early diagnosis of hepatocellular carcinoma. Journal of Angiotherapy, 8(5), 1–12.

7. Rana, M. S., Bashir, M. S., Das, S. S., Hossian, M., & Barua, S. (2024, April). Biomarkers for hepatocellular carcinoma: Diagnosis, prognosis, and treatment response assessment—A systematic review. PrimeAsia, 1–7.
8. Attia, A. M., Rezaee-Zavareh, M. S., Hwang, S. Y., Kim, N., Adetyan, H., Yalda, T., Chen, P., Koltsova, E. K., & Yang, J. D. (2024, October 13). Novel biomarkers for early detection of hepatocellular carcinoma. Diagnostics, 14(20), 2278.
9. Solhi, R., Pourhamzeh, M., Zarrabi, A., Hassan, M., Mirzaei, H., & Vosough, M. (2024, December 24). Novel biomarkers for monitoring and management of hepatocellular carcinoma. Cancer Cell International, 24(1), Article 428.
10. Lee, T. H., Kim, W. R., & Poterucha, J. J. (2012). Evaluation of elevated liver enzymes. Clinics in Liver Disease, 16(2), 183–198.
11. Abduljabbar, A. H. (2023). Diagnostic accuracy of ultrasound and alpha-fetoprotein measurement for hepatocellular carcinoma surveillance: A retrospective comparative study. Egyptian Journal of Radiology and Nuclear Medicine, 54(1), Article 31.
12. Ibrahim Alhadi EDOO M, Kumar Chutturghoon V, Kwabena WUSU-ANSAH G, Zhu H, Yang ZHEN T, Yang XIE H, et al. Serum Biomarkers AFP, CEA and CA19-9 Combined Detection for Early Diagnosis of Hepatocellular Carcinoma [Internet]. Vol. 48, Iran J Public Health. 2019.
13. Li, Y., Li, D. J., Chen, J., Liu, W., Li, J. W., Jiang, P., Zhao, X., Guo, F., Li, X. W., & Wang, S. G. (2015). Application of joint detection of AFP, CA19-9, CA125 and CEA in identification and diagnosis of cholangiocarcinoma. Asian Pacific Journal of Cancer Prevention, 16(8), 3451–3455.
14. Zhu, J., Chen, G., Xu, J., & Zhou, X. (2017). Serum AFU, 5'-NT and AFP as biomarkers for primary hepatocellular carcinoma diagnosis. Open Medicine (Warsaw), 12(1), 354–358.
15. Kobeissy, A., Merza, N., Al-Hillan, A., Boujemaa, S., Ahmed, Z., Nawras, M., Albaaj, M., Dahiya, D. S., Alastal, Y., & Hassan, M. (2023). Protein Induced by Vitamin K Absence or Antagonist-II Versus Alpha-Fetoprotein in the Diagnosis of Hepatocellular Carcinoma: A Systematic Review with Meta- Analysis. Journal of Clinical Medicine Research, 15(7), 343–359.
16. Huang, X., Li, J., Wang, F., & Hao, M. (2018). CT combined with tumor markers in the diagnosis and prognosis of hepatocellular carcinoma. Journal of BUON, 23(4), 985–991.
17. Choi, J. Y., Jung, S. W., Kim, H. Y., Kim, M., Kim, Y., Kim, D. G., & Oh, E. J. (2013). Diagnostic value of AFP-L3 and PIVKA-II in hepatocellular carcinoma according to total-AFP. World journal of gastroenterology, 19(3), 339–346.
18. Piratvisuth T, Tanwandee T, Thongsawat S, Sukeepaisarnjaroen W, Esteban JI, Bes M, et al. Multimarker Panels for Detection of Early-stage Hepatocellular Carcinoma: A Prospective, Multicenter, Case-Control Study. Hepatol Commun [Internet]. 2021;6(4):2022.
19. Malov SI, Malov IV, Kuvshinov AG, Marche PN, Decaens T, Macek-Jilkova Z, et al. Search for Effective Serum Tumor Markers for Early Diagnosis of Hepatocellular Carcinoma Associated with Hepatitis C. Sovrem Tekhnologii Med. 2021;13(1):27-33.
20. Lin Y, Ma Y, Chen Y, Huang Y, Lin J, Xiao Z, et al. Diagnostic and prognostic performance of serum GPC3 and PIVKA-II in AFP-negative hepatocellular carcinoma and establishment of nomogram prediction models. BMC Cancer. 2025;25(1):721.
21. Song H, Wang J, Zhang H, Wu Y, Wang K, Wang X, et al. Combination of serum alpha-fetoprotein, PIVKA-II and glypican-3 in diagnosis of hepatocellular carcinoma: a meta-analysis. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2024;53(1):131-9.
22. Mohammed AF, Chen X, Li C. Clinical utility of biomarkers of hepatocellular carcinoma. Bratisl Lek Listy. 2024;125(2):102-6.
23. Yu B, Ma W. Biomarker discovery in hepatocellular carcinoma (HCC) for personalized treatment and enhanced prognosis. Cytokine Growth Factor Rev. 2024;79:29-38.