



Research Article

A Review on Biomarkers for Early Detection of Liver Cancer

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Liver cancer, particularly hepatocellular carcinoma (HCC), remains a leading cause of cancer-related mortality worldwide due to late-stage diagnosis and limited treatment options. Early detection plays a crucial role in improving patient survival and therapeutic outcomes. The use of biomarkers—measurable biological indicators—offers a promising, non-invasive strategy for identifying liver cancer at its earliest stages. Traditional biomarkers such as alpha-fetoprotein (AFP) have long been used but show limited sensitivity and specificity. Recent advances in molecular biology have introduced novel biomarkers including des-gamma- carboxy prothrombin (DCP), Golgi protein 73 (GP73), glypican-3 (GPC3), and circulating microRNAs (e.g., miR-21, miR-122), which demonstrate greater diagnostic accuracy. Integrating multiple biomarkers through advanced detection techniques such as liquid biopsy, proteomics, and genomic profiling enhances the reliability of early diagnosis. Approach not only facilitates timely intervention but also supports personalized treatment and better prognosis. Therefore, the use of biomarker-based screening represents a significant advancement toward early detection and effective management of liver cancer.

Keywords: Hepatocellular Carcinoma (HCC), Early Detection of Cancer, Biomarkers, Tumor / analysis, Alpha-Fetoproteins (AFP), Des-Gamma-Carboxy Prothrombin (DCP), Glypican-3 (GPC3), MicroRNAs / blood, Circulating Tumor DNA (ctDNA), Liquid Biopsy, Proteomics, Genomics.

INTRODUCTION

Liver cancer, particularly hepatocellular carcinoma (HCC), is one of the leading causes of cancer-related mortality worldwide. The major challenge in its management lies in the fact that symptoms often appear only at advanced stages, limiting treatment options and survival rates. Therefore, early detection is critical for improving prognosis and reducing mortality. Biomarkers, measurable biological indicators found in blood, tissues, or other body fluids, offer a promising approach for early diagnosis. [1] The application of biomarkers enables clinicians to detect molecular changes preceding clinical symptoms, thereby identifying liver cancer at its initial stages. Recent advancements in proteomics, genomics, and metabolomics have accelerated the discovery of specific biomarkers, such as alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin

(DCP), and Golgi protein-73 (GP73). These markers hold significant diagnostic, prognostic, and therapeutic potential. [2]

History of Biomarker:

Liver cancer, primarily hepatocellular carcinoma (HCC), is one of the most prevalent and deadly malignancies worldwide. Its strong association with chronic hepatitis B and C infections, alcohol consumption, and non-alcoholic fatty liver disease (NAFLD) has made early diagnosis a major focus of research for decades. Historically, diagnosis relied mainly on imaging and clinical symptoms, which often appear only in the advanced stages of the disease. To improve early detection and patient outcomes, scientists began exploring biochemical and molecular markers, known as biomarkers, in the mid-20th century. [3] The first biomarker used clinically

for liver cancer detection was Alpha-Fetoprotein (AFP), discovered in the 1960s by Abelev and colleagues in the serum of hepatoma patients. AFP became the gold standard biomarker for HCC screening for several decades due to its easy detection in blood. However, its diagnostic accuracy was limited, as elevated AFP levels were also found in benign liver diseases and pregnancy. [4] To overcome these limitations, new biomarkers such as Des-gamma-carboxy prothrombin (DCP or PIVKA-II) were introduced in the 1980s, offering improved specificity for HCC. Later, in the early 2000s, Golgi protein 73 (GP73) and glypican-3 (GPC3) emerged as promising candidates, showing better performance for early-stage detection compared to AFP alone. [5-6] Advancements in molecular biology and omics technologies (genomics, proteomics, and metabolomics) during the 2010s revolutionized biomarker discovery. [7] Researchers identified novel molecular markers such as microRNAs (miR-21, miR-122), circulating tumor DNA (ctDNA), and exosomal proteins, which provided non-invasive

options for liquid biopsy-based detection. [8] These modern biomarkers reflect tumor biology and genetic alterations, offering superior diagnostic, prognostic, and therapeutic insights. [9] Currently, the trend has shifted toward multi-marker panels and integrated diagnostic systems that combine protein, gene, and metabolic biomarkers with advanced imaging and artificial intelligence (AI) tools. [10] This holistic approach aims to enhance sensitivity, specificity, and early detection accuracy, ultimately enabling timely treatment and improved survival rates. [11]..

Background For Selection Of Topic:

5-Year Survival Rate
When cancer is detected at stage 1
90%

5-Year Survival Rate
When cancer is detected at stage 4
15%

Early detection Late detection



Fig. No.1: - Cancer Survival Rate [37].

Liver cancer, especially hepatocellular carcinoma (HCC), is a leading cause of cancer-related deaths due to late diagnosis and limited treatment options. [13] Early detection using biomarkers such as alpha-

fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) offers a non-invasive and reliable approach to identify the disease at an earlier stage. [14] This improves prognosis, enables timely treatment, and enhances overall patient survival.[15]

Table no 1 Types of biomarkers: [36]

Biomarker	Type	Source	Diagnostic Significance
Alpha-fetoprotein (AFP)	Serum protein	Blood serum	Traditional biomarker; elevated in HCC but limited sensitivity at early stages.
AFP-L3	Glycoform of AFP	Blood serum	More specific for malignant HCC; used with AFP to improve accuracy.
Des-gamma-carboxy prothrombin (DCP/PIVKA-II)	Abnormal prothrombin protein	Blood plasma	Useful for early diagnosis, often combined with AFP.
Glypican-3 (GPC3)	Oncofetal protein	Blood serum, tissue	Overexpressed in HCC, not in normal liver tissue.
Golgi protein-73 (GP73)	Golgi membrane protein	Blood serum	More sensitive than AFP in some cases; elevated in HCC.
Osteopontin (OPN)	Glycoprotein	Blood serum	Correlates with tumor progression and metastasis.
Circulating tumor DNA (ctDNA)	Genetic biomarker	Blood (cell-free DNA)	Detects tumor-specific mutations and methylation changes.
MicroRNAs (e.g., miR-21, miR-122, miR-221)	Small non-coding RNAs	Serum/plasma, exosomes	Dysregulated in HCC; promising for early detection.
DNA methylation markers	Epigenetic alterations	Cell-free DNA	Hypermethylation of tumor suppressor genes indicates HCC.
Exosomal markers (proteins, miRNAs)	Extracellular vesicle biomarkers	Blood, urine	Reflect tumor microenvironment, emerging non-invasive biomarkers.

Emerging Trends in Biomarker-Based Early Detection of Liver Cancer: -

1. Multi-biomarker Panels:

Instead of relying on a single biomarker like AFP (Alpha-fetoprotein), researchers are combining multiple markers (e.g., AFP-L3, DCP, GP73, GPC3) to improve accuracy.

These panels increase sensitivity and specificity for early-stage hepatocellular carcinoma (HCC).[16]

2. Liquid Biopsy:

A non-invasive technique using blood, urine, or saliva to detect tumor-derived materials such as:

- i. Circulating tumor DNA (ctDNA)
- ii. Circulating tumor cells (CTCs)
- iii. Exosomes and microRNAs (miRNAs)
- iv. Liquid biopsy allows real-time tumor monitoring and early diagnosis. [17]

a. MicroRNA (miRNA) and Long Non-coding RNA (lncRNA) Biomarkers:

Specific RNAs (e.g., miR-122, miR-21, HULC, and MALAT1) are emerging as sensitive biomarkers. They reflect early molecular changes in liver cells before visible tumors appear. [18]

3. Proteomic and Metabolomic Profiling:

Advanced mass spectrometry and metabolomics help identify unique protein and metabolite patterns in early liver cancer. This approach provides comprehensive molecular signatures of tumor development [19].

4. Epigenetic Biomarkers

DNA methylation patterns (like methylated SEPT9, RASSF1A) are being explored for early detection. These markers are detectable in circulating free DNA (cfDNA) from blood samples.[20]

a. Artificial Intelligence (AI) and Machine Learning

AI models analyze large biomarker datasets to detect hidden patterns. Integration of clinical data + imaging + biomarkers leads to more accurate risk prediction.[21]

5. Integration with Imaging Biomarkers

Combining molecular biomarkers with advanced imaging (MRI, CT, PET) improves detection and reduces false negatives. [22]

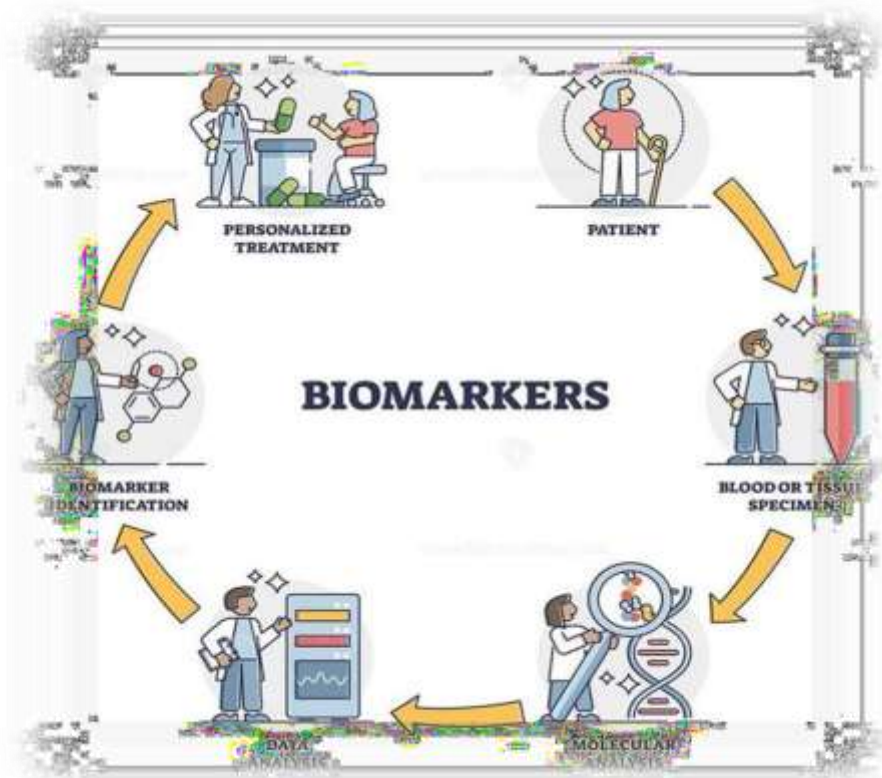


Fig No 2: Process of Detection of Liver Cancer By Using Biomarker: [33]

1. Sample Collection:

Blood, urine, or tissue samples are collected from the patient. Blood samples are most commonly used because they are easy to obtain and less invasive. [23]

2. Biomarker Identification:

- Specific biomarkers (molecules that indicate liver cancer) are targeted for detection.
- Common liver cancer biomarkers include:
 - a. AFP (Alpha-fetoprotein)
 - b. DCP (Des-gamma-carboxy prothrombin)
 - c. GPC3 (Glypican-3)
 - d. microRNAs (miR-21, miR-122)
 - e. AFP-L3 (a specific type of AFP) [24]

3. Laboratory Testing:

- The collected samples are analyzed in the lab using advanced techniques such as:

- ELISA (Enzyme-Linked Immunosorbent Assay) – measures protein biomarkers like AFP.
- PCR (Polymerase Chain Reaction) – detects genetic biomarkers such as microRNAs.
- Mass spectrometry or immunoassays – for detailed biomarker profiling. [25]

4. Data Analysis:

- The biomarker levels are compared with normal reference values.
- High or abnormal levels of certain biomarkers (e.g., AFP > 400 ng/mL) may indicate liver cancer. [26]

5. Diagnosis Confirmation:

- If biomarker tests suggest liver cancer, imaging tests such as ultrasound, CT scan, or MRI are performed for confirmation. Sometimes, a biopsy (tissue sample) is also taken to confirm cancerous cells. [27]

Future Scope of Biomarker-Based Early Detection of Liver Cancer:**1. Early Diagnosis:**

Biomarkers can detect liver cancer at very early stages before appearing improving survival rate

2. Risk Stratification:

Identify high-risk individuals (e.g., hepatitis or cirrhosis patients) for targeted screening.

3. Non-Invasive Testing:

Blood-based biomarkers and liquid biopsies reduce the need for invasive procedures like liver biopsy.

4. Multi-Biomarker Panels:

Combining multiple biomarkers increases sensitivity and specificity compared to single markers.

5. Integration with AI:

Machine learning can analyze complex biomarker patterns for more accurate early detection.

6. Personalized Surveillance:

Biomarker profiles can guide individualized monitoring schedules.

7. Recurrence Monitoring:

Detect tumor recurrence earlier after treatment through serial biomarker assessment.

8. Therapy Response Assessment:

Biomarkers can indicate how well a patient responds to treatments.

9. Development of Novel Biomarkers:

Research will continue to identify new molecular, protein, or genetic markers for HCC.

10. Point-of-Care Testing:

Portable biomarker assays could enable rapid screening in remote or low-resource areas.

11. Integration with Imaging:

Biomarkers combined with imaging modalities improve diagnostic accuracy.

1. Cost-Effective Screening:

Biomarkers may reduce the need for expensive imaging for routine surveillance.

2. Population-Based Screening Programs:

High-risk populations can be systematically monitored using biomarker-based tests.

3. Multi-Omics Approaches:

Combining genomics, proteomics, and metabolomics will enhance early detection capabilities.

4. Predictive Modeling:

Biomarkers can be used in algorithms to predict liver cancer risk before onset.

5. Reducing Late-Stage Diagnosis:

Early detection through biomarkers decreases the proportion of patients diagnosed at advanced stages.

6. Global Health Impact:

Accessible biomarker tests can significantly reduce liver cancer mortality worldwide.

7. Targeted Therapies Development:

Biomarkers can identify molecular pathways for novel drug targets.

8. Integration with Wearable Tech:

Future biosensors may allow continuous monitoring of biomarker levels.

9. Standardization and Validation:

Future research will establish standardized biomarker protocols for clinical use. [28]



Fig No 3: Challenges in digital biomarker in liver cancer [29]

Applications of Biomarkers in Early Detection of Liver Cancer:

1. Early Diagnosis:

Biomarkers like AFP, DCP, GP73, and microRNAs help detect liver cancer at its early stages—before symptoms appear—improving survival chances. [28]

2. Non-Invasive Screening:

Blood-based biomarkers (e.g., ctDNA, miRNAs) allow for non-invasive and routine screening, especially in high-risk groups (e.g., hepatitis B/C or cirrhosis patients). [29]

3. Monitoring Disease Progression:

Biomarker levels can be used to track tumor growth, monitor treatment response, and detect recurrence after therapy. [30]

4. Treatment Decision Support:

Molecular biomarkers provide insights into the tumor's biology, aiding in personalized treatment

planning (e.g., surgery, chemotherapy, or targeted therapy). [31]

5. Risk Stratification:

Helps categorize patients based on their biomarker profile for surveillance intensity and prognosis estimation. [32]

CONCLUSION:

Early detection of liver cancer, particularly hepatocellular carcinoma (HCC), is critical for improving patient prognosis, enabling timely therapeutic interventions, and significantly increasing survival rates. biomarkers like alpha-fetoprotein (AFP), while historically important, offer limited sensitivity and specificity, especially in early-stage diagnosis. Emerging biomarkers such as des-gamma-carboxy prothrombin (DCP), Golgi protein 73 (GP73), glypican-3 (GPC3), and circulating microRNAs (e.g., miR-21, miR-122) demonstrate superior diagnostic accuracy and provide non-invasive avenues for early detection. Recent advancements in technologies such as liquid biopsy, proteomics, genomics, and epigenetics have further

enhanced the ability to detect liver cancer at molecular levels before clinical symptoms arise. The integration of multiple biomarkers into diagnostic panels, coupled with artificial intelligence and advanced imaging, holds great promise in establishing more reliable, sensitive, and specific screening tools. Despite significant progress, no single biomarker currently offers ideal diagnostic performance on its own. A multi-marker, integrative approach that combines molecular profiling with clinical and imaging data represents the future of liver cancer screening. Continued research, validation in large-scale clinical studies, and the development of standardized protocols are essential to transition these biomarker-based strategies from the laboratory to clinical practice. Ultimately, biomarker-driven early detection will play a pivotal role in reducing liver cancer mortality and advancing personalized medicine.

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