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FRONTIER

- 1850 Management of obstructive colon cancer: Current status, obstacles, and future directions
Yoo RN, Cho HM, Kye BH

REVIEW

- 1863 Role of endoscopic ultrasound in anticancer therapy: Current evidence and future perspectives
Bratanic A, Bozic D, Mestrovic A, Martinovic D, Kumric M, Ticinovic Kurir T, Bozic J
- 1880 Pancreatic intraductal papillary mucinous neoplasms: Current diagnosis and management
Jabłońska B, Szmigiel P, Mrowiec S
- 1896 Combined treatments in hepatocellular carcinoma: Time to put them in the guidelines?
Sparchez Z, Radu P, Bartos A, Nenu I, Craciun R, Mocan T, Horhat A, Spârchez M, Dufour JF
- 1919 Unique situation of hepatocellular carcinoma in Egypt: A review of epidemiology and control measures
Ezzat R, Eltabbakh M, El Kassas M
- 1939 Moving forward in the treatment of cholangiocarcinoma
Manzia TM, Parente A, Lenci I, Sensi B, Milana M, Gazia C, Signorello A, Angelico R, Grassi G, Tisone G, Baiocchi L
- 1956 Solid extraintestinal malignancies in patients with inflammatory bowel disease
Mala A, Foteinogiannopoulou K, Koutroubakis IE
- 1981 Mesenchymal stem cell-derived exosomes for gastrointestinal cancer
Zhao LX, Zhang K, Shen BB, Li JN
- 1997 Diabetes mellitus contribution to the remodeling of the tumor microenvironment in gastric cancer
Rojas A, Lindner C, Schneider I, González I, Araya H, Morales E, Gómez M, Urdaneta N, Araya P, Morales MA
- 2013 Macrophages play a role in inflammatory transformation of colorectal cancer
Lu L, Liu YJ, Cheng PQ, Hu D, Xu HC, Ji G

MINIREVIEWS

- 2029 Advancement of chimeric antigen receptor-natural killer cells targeting hepatocellular carcinoma
Dai K, Wu Y, She S, Zhang Q
- 2038 Current status of first-line therapy, anti-angiogenic therapy and its combinations of other agents for unresectable hepatocellular carcinoma
Alqahtani SA, Colombo MG

- 2050** Endoscopic or percutaneous biliary drainage in hilar cholangiocarcinoma: When and how?
Mocan T, Horhat A, Mois E, Graur F, Tefas C, Craciun R, Nenu I, Spârchez M, Sparchez Z
- 2064** Current status of non-surgical treatment of locally advanced pancreatic cancer
Spiliopoulos S, Zurlo MT, Casella A, Laera L, Surico G, Surgo A, Fiorentino A, de'Angelis N, Calbi R, Memeo R, Inchingolo R
- 2076** Prospect of lenvatinib for unresectable hepatocellular carcinoma in the new era of systemic chemotherapy
Sho T, Morikawa K, Kubo A, Tokuchi Y, Kitagataya T, Yamada R, Shigesawa T, Kimura M, Nakai M, Suda G, Natsuizaka M, Ogawa K, Sakamoto N

ORIGINAL ARTICLE**Basic Study**

- 2088** Dysbiosis of the duodenal microbiota as a diagnostic marker for pancreaticobiliary cancer
Sugimoto M, Abe K, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Takasumi M, Hashimoto M, Kato T, Kobashi R, Hikichi T, Ohira H
- 2101** MutL homolog 1 methylation and microsatellite instability in sporadic colorectal tumors among Filipinos
Cabral LKD, Mapua CA, Natividad FF, Sukowati CHC, Cortez ER, Enriquez MLD
- 2114** Propofol induces ferroptosis and inhibits malignant phenotypes of gastric cancer cells by regulating miR-125b-5p/STAT3 axis
Liu YP, Qiu ZZ, Li XH, Li EY
- 2129** BRAF^{V600E} mutant colorectal cancer cells mediate local immunosuppressive microenvironment through exosomal long noncoding RNAs
Zhi J, Jia XJ, Yan J, Wang HC, Feng B, Xing HY, Jia YT

Retrospective Cohort Study

- 2149** Hepatocellular carcinoma surveillance and quantile regression for determinants of underutilisation in at-risk Australian patients
Low ES, Apostolov R, Wong D, Lin S, Kutaiba N, Grace JA, Sinclair M
- 2161** Comparison of tumor regression grading systems for locally advanced gastric adenocarcinoma after neoadjuvant chemotherapy
Liu ZN, Wang YK, Zhang L, Jia YN, Fei S, Ying XJ, Zhang Y, Li SX, Sun Y, Li ZY, Ji JF

Retrospective Study

- 2180** Clinical features of intracerebral hemorrhage in patients with colorectal cancer and its underlying pathogenesis
Deng XH, Li J, Chen SJ, Xie YJ, Zhang J, Cen GY, Song YT, Liang ZJ

Prospective Study

- 2190** Anatomic resection improved the long-term outcome of hepatocellular carcinoma patients with microvascular invasion: A prospective cohort study
Zhou JM, Zhou CY, Chen XP, Zhang ZW

SYSTEMATIC REVIEWS

- 2203** Minimally invasive surgical treatment of intrahepatic cholangiocarcinoma: A systematic review
Patrone R, Izzo F, Palaia R, Granata V, Nasti G, Ottaiano A, Pasta G, Belli A

LETTER TO THE EDITOR

- 2216** Gender differences in the relationship between alcohol consumption and gastric cancer risk are uncertain and not well-delineated
Verma HK, Bhaskar L
- 2219** Critical biomarkers of hepatocellular carcinoma in body fluids and gut microbiota
Nath LR, Murali M, Nair B

ABOUT COVER

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Critical biomarkers of hepatocellular carcinoma in body fluids and gut microbiota

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and one of the major causes of cancer-related death. The development of specific non-invasive or diagnostic markers from blood, urine and feces may represent a valuable tool for detecting HCC at an early stage. Biomarkers are considered novel potential targets for therapeutic intervention. It helps in the prediction of prognosis or recurrence of HCC, and also assist in the selection of appropriate treatment modality. We summarize the most relevant existing data about various biomarkers that play a key role in the progression of HCC.

Key Words: Hepatocellular carcinoma; Biomarker; Body fluids; Blood; Gut microbiota

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Core Tip: Hepatocellular carcinoma (HCC) ranks fourth among the leading causes of cancer-related mortality. The development of specific noninvasive or diagnostic markers from blood, urine and feces may represent a valuable tool for detecting HCC at an early stage. Biomarkers help in the prediction of prognosis or recurrence, selection of appropriate treatment modality, and signify novel potential targets for therapeutic interventions. We summarize the most relevant existing data about various biomarkers involved in the progression of HCC.

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TO THE EDITOR

We were interested to read the review reported by Guan *et al*[1] that clearly emphasized the substantial role of biomarkers from different body fluids such as blood, urine and feces for the early detection of primary and recurrent hepatocellular carcinoma (HCC). From the study reports, detection of biomarkers through screening of body fluids or feces is regarded as beneficial due to the quick and easy extraction procedures, stability, proper time management, cost-effectiveness and accessibility in comparison with conventional screening methods. The review highlights the clinical significance of several diagnostic biomarkers of HCC, including proteins, metabolites, circulating nucleic acids, circulating tumor cells (CTCs), extracellular vesicles (EVs), and gut microbiota from blood, urine and feces.

A large pool of evidence suggests the presence of elevated serum blood levels of bilirubin, albumin, α -fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) and des- γ -carboxy prothrombin (DCP) at the time of diagnosis of HCC. These biomarkers exhibit a close relation with HCC staging and prognosis of overall survival and disease-free survival. Elevated levels of AFP in cases of liver injury above the reference range (400-500 ng/mL) can be considered crucial for the prognosis of HCC. AFP-L3 possesses better sensitivity but low specificity for the early detection of HCC. To its expression in small tumors (< 2 cm in diameter) of aggressive types, the prognosis of early-stage HCC is relevant if the AFP-L3 level is greater than 10% in comparison with AFP. DCP can be regarded as an excellent prognostic biomarker since it can differentiate nonmalignant cirrhosis and HCC with a specificity of 93% and sensitivity of 92% at a cut-off value of about 150 mAU/mL[2]. With disease progression, metabolic markers such as methionine, proline and ornithine increase, whereas the levels of pimelylcarnitine and octanoylcarnitine decrease[3]. The applicability of phenylalanyl-tryptophan and glycocholate as a superior biomarker was demonstrated in a multicenter cohort study that indicated its diagnostic accuracy of 86.0%-92.5% in HCC[4].

The progression of HCC involves invasion, migration, proliferation and metastasis. Studies have shown that drug resistance is mainly mediated through the functional activation of miRNAs. Clinicians can predict the overall survival of patients based on the expression of miRNA. Single miRNAs like miR-130b, miR-150, miR-182, miR-215 and miR-96 are considered key candidates among all miRNAs but the use of multiple miRNAs as promising biomarkers for the prediction of early as well as recurring HCC is recent[5]. CTCs play a significant role in the prediction of HCC recurrence, prognostic evaluation for surveillance, and promotion of suitable adjuvant therapy. CTCs are generally categorized as a small subpopulation of malignant cells secreted from primary malignant tissue and they are usually expressed at the aggressive malignancy stage; therefore, liquid biopsy of CTCs facilitates timely diagnosis of HCC [6]. Another important category of biomarker with a functional role in the prediction of HCC progression is EVs. Increased circulating levels of EVs have contributed to poor survival and disease-free survival in HCC patients. Despite their high capability of being absorbed into host cells, EVs are considered an efficient tool for targeted approaches. This is by the incorporation of therapeutic agents to improve therapeutic efficacy and reduce side effects. The incorporation of sodium/iodide symporter protein to EVs has been used as one of the systemic targeted approaches to cancer treatment with the promotion of cytotoxicity and radioiodine therapy[7].

Another potential category of biomarkers for HCC are urine-based. Among the biomarkers, higher levels of 8-oxodeoxyguanosine improve DNA repair mechanisms by overcoming oxidative DNA damage with a reduction in risk of developing HCC. Enhanced levels of 15-F2t-isoprostane are also correlated with the risks of HCC. Urinary proteins such as urinary DJ-1, chromatin assembly factor-1, heat shock protein 60 and orosomucoid, and metabolites such as ethanolamine, lactic acid, aconitic acid, phenylalanine and ribose were found to be effective predictors for early HCC recurrence. Additionally, the overexpression of urinary trypsin inhibitor in HCC was revealed to be a risk factor for HCC recurrence[1]. In a study reported by Hann *et al* [8], detection of urinary markers such as TP53m, mSGTP and mRASSF1A were potential tools for the early detection of HCC recurrence (Figure 1).

Inflammation significantly decreases the expression of beneficial microflora which, in turn, enhances the risk of liver malignancy by accumulating harmful compounds.

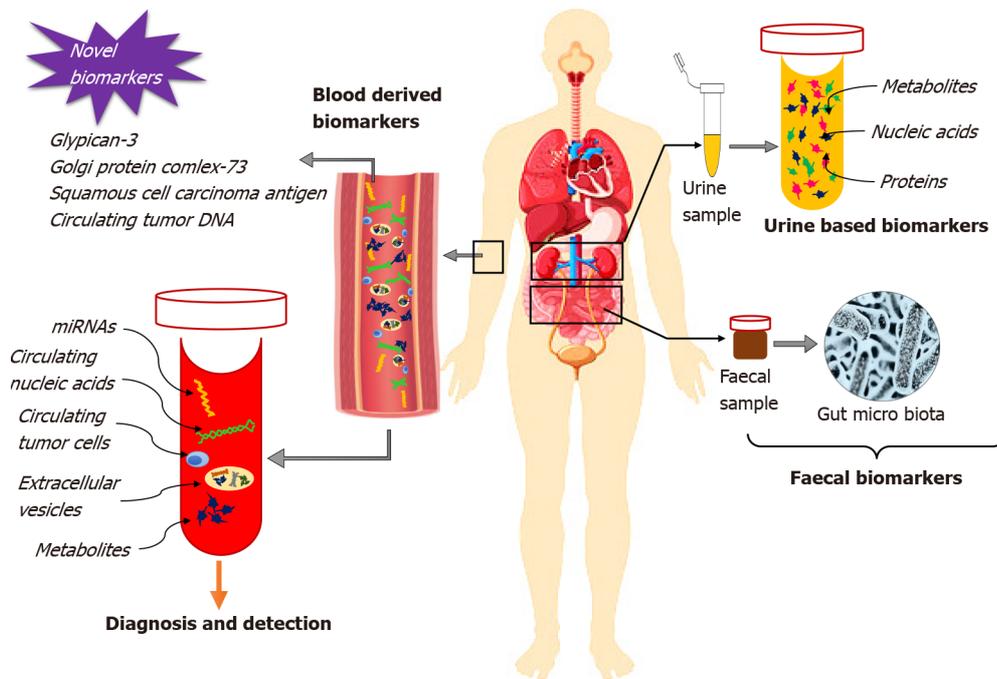


Figure 1 Pictorial representation of numerous biomarkers derived from different body fluids, namely, blood (serum), urine and feces. These biomarkers constitute a wide spectrum of proteins, nucleic acids and metabolites. Circulating tumor cells, miRNAs and gut microbiota which can be beneficial for the early detection, diagnosis and prognosis of hepatocellular carcinoma.

Translocated bacterial products such as lipopolysaccharides, peptidoglycans, muramyl-dipeptides and bacterial DNA from the infectious stage of the gut stimulate an inflammatory cascade by activation of signaling through Toll-like receptors (TLRs). Stimulation of interleukin-6, either directly or *via* the JAK/STAT3 pathway forces the gut microbiota to induce proliferation and progression of HCC. Gut microbiota can stimulate the generation of reactive free radical oxygen species indirectly *via* small molecular motifs derived from a pathogenic class of microbes by the activation of NADPH-oxidase (NOX1–NOX4). Microbial imbalance and enhancement of inflammation are directly correlated with fluctuating redox status. Modulation of farnesoid X receptor activation by gut microbiota enhances bile acid accumulation in the liver. This leads to damage of hepatocyte plasma membranes, resulting in activation of an inflammatory response and production of reactive oxygen species through stimulating the MAPK pathway. As a result, the secretion of inflammatory cytokines *via* the nuclear factor-B pathway is increased by induction of proliferation and immortalization of HCC cells directly or *via* the JAK/STAT3 pathway. Gut microbiota can exhaust the surveillance of the immune system within the tumor microenvironment of HCC through macrophage polarization *via* the activation of TLRs. This results in further diversification and progression of the tumor[9]. Additionally, several other biomarkers namely, glypican-3, Golgi protein complex-73, squamous cell carcinoma antigen and circulating tumor DNA are useful for early diagnosis of HCC, and might be clinically validated in the near future[10].

The supporting evidence gives an insight into novel biomarkers for early prediction and prevention of HCC. HCC accounts for almost 90% of primary liver malignancies and has a poor prognosis due to rapid metastasis and multidrug resistance. Diagnosis of HCC at an early stage is important for overcoming the hurdles associated with the disease[11]. To conclude, it is important to identify and develop promising biomarkers for early diagnosis and prognosis as well as therapy of HCC.

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