

# Cartilage oligomeric matrix protein as a non-invasive biomarker for diagnosis of hepatocellular carcinoma in patients with liver cirrhosis

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## ABSTRACT

**Aim:** The current study purposed to evaluate serum COMP (Cartilage oligomeric matrix protein) as a diagnostic marker for HCC in patients with cirrhosis and to correlate it with other parameters of disease progression.

**Background:** COMP is known to promote fibrosis in various tissues. Emerging evidence shows that COMP plays critical roles in tumor development. It can serve as a fibrosis and cancer biomarkers.

**Methods:** The study included 24 subjects who serve as the healthy control, 24 cirrhotic patients without HCC, and 24 HCC patients with cirrhosis. All participants were subjected to liver function tests, AFP, calculation of fibrotic indices (APRI and FIB-4), and serum COMP by ELISA.

**Results** COMP was significantly increased in cirrhotic patients when compared to healthy controls and in HCC patients when compared to cirrhotic patients and healthy controls. A significant positive correlation was observed between COMP and APRI and FIB-4 in cirrhotic and HCC patients. Based on receiver operating characteristic (ROC) curve analysis, COMP had an area under curve (AUC) of 0.943 with 87.5% sensitivity and 79.2% specificity for diagnosis of HCC in cirrhotic patients. In combination with AFP, the sensitivity was increased to 100%.

**Conclusion:** COMP might act as a promising non-invasive biomarker for HCC either alone or in combination with AFP. It was correlated with the degree of fibrosis and associated with advanced cancer staging.

**Keywords:** Cartilage oligomeric matrix protein, Hepatocellular carcinoma, Liver cirrhosis.

(Please cite as: **Abdel-Azeez HA, Elhady HA, Fikry AA. Cartilage oligomeric matrix protein as a non-invasive biomarker for diagnosis of hepatocellular carcinoma in patients with liver cirrhosis. Gastroenterol Hepatol Bed Bench 2022;15(2):139-145.**)

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third leading cause of cancer-related death worldwide (1). It represents the sixth most common cancer worldwide (2) and the fourth most common cancer in Egypt (3). The major risk factors for the development of HCC are chronic liver diseases such as hepatitis and liver cirrhosis. More than 80% of HCC arises from cirrhosis, which is an irreversible end result of chronic liver disease (4). HCC shows a growing incidence in Egypt, which may be the

result of a shift in the relative importance of HBV and HCV as primary risk factors (5).

Diagnosis of early-stage HCC is difficult because of the lack of specific symptoms and the comparatively limited prognostic value of the serological and radiological approaches currently used for surveillance. The prognosis of HCC is generally poor due to the aggressive nature of the disease, synchronous liver decompensation, and sometimes limited availability of potential treatment choices (6). Screening of serum alpha-fetoprotein (AFP) levels and ultrasonography every 6 months appear to identify only a few cases with early-stage HCC, and therefore, its use is not prescribed by several international authorities (7).

Received: 11 January 2022 Accepted: 12 March 2022

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Cartilage oligomeric matrix protein (COMP) is a pentameric particle found in various extracellular matrices (ECMs) that has been suggested to modulate collagen turnover by different systems, most notably by catalyzing collagen fibril formation (8). It is localized in the extracellular matrix of chondrocytes, synovial, tendons, and ligaments (9). COMP has been used primarily to assess the destruction of cartilage in patients with rheumatoid arthritis and osteoarthritis (10).

The process of viral hepatitis-cirrhosis-HCC is the main epidemiological development path of HCC in the world (11). Increased hepatic matrix stiffness resulting from the deposition and cross-linking of large amounts of matrix proteins not only occurs extensively in most solid tumors, but also promotes cell growth, motility, proliferation, metabolism, and tumor metastasis (12). Several publications have revealed that COMP is involved with the process of cirrhosis and HCC progression (13, 14).

The current study aimed to evaluate serum COMP as a diagnostic marker for HCC in patients with cirrhosis and to correlate it with other parameters of disease progression.

### **Methods**

#### **Study population**

This case control study was conducted on 72 subjects classified into three age- and sex-matched groups; 24 subjects served as the healthy control group; 24 cirrhotic patients without HCC and 24 HCC patients with cirrhosis served as the case groups. Patients were recruited from the in-patient sections and out-patient clinics of the Internal Medicine Department, Zagazig University Hospital from November 2019 to April 2020.

Liver cirrhosis is diagnosed by its characteristic findings on clinical examination, laboratory tests, and/or radiological imaging. HCC is diagnosed on the basis of the results of serological AFP determination, radiological imaging (i.e. liver ultrasound scan, triphasic computed tomography, or magnetic resonance imaging techniques) (15) or liver biopsy. Patients who had other malignancies or diseases that cause abnormalities in COMP, such as rheumatoid arthritis, osteoarthritis, other autoimmune rheumatic disease,

systemic sclerosis, pulmonary fibrosis, cardiomyopathy, or skeletal dysplasia, were excluded from the study.

Written informed consent was obtained from all individual participants included in the study. Approval for the study was obtained from the Research Ethics Committee, Faculty of Medicine, Zagazig University.

#### **Methods**

All patients were subjected to history taking, clinical examination, and radiological imaging. Patients were classified according to Child-Pugh classification of severity of liver disease (16). Staging of HCC patients was carried out by Barcelona Clinic Liver Cancer (BCLC) (17).

Laboratory tests included liver function tests, AFP (Cobas 8000, Roche Diagnostics), platelets count (Sysmex XN-2000, Siemens), prothrombin time, INR (CA 1500, Sysmex), calculation of fibrotic indices (APRI (18) and FIB-4 (19)). Serum COMP levels were determined by enzyme-linked immunosorbent assay ELISA kit (Nova, China).

#### **Statistical Analysis**

Sample size was calculated by Epi-Info 6 at a confidence level 95% and power of test of 80%. Data analysis was performed using the SPSS (Statistical Package for the Social Sciences) version 20 (SPSS INC., Chicago, IL, USA) software. Categorical variables were described using their absolute frequencies, and chi-square test ( $\chi^2$ ) was used to compare frequencies of the data. The Kolmogorov-Smirnov (distribution type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. Quantitative variables were described using their means and standard deviations or median and range. To compare two groups, the independent sample (t) test or the Mann-Whitney test (MW) was used, as appropriate. To compare more than two groups, the Kruskal Wallis test (KW) or analysis of variance ANOVA test (F test) was used, as appropriate. Correlations between two quantitative parameters were done by Pearson or Spearman Rank correlation, as appropriate. Multiple stepwise logistic regression analysis was used to identify independent predictor variables for COMP. Receiver operating characteristic (ROC) curve analysis was used to assess the best cutoff of studied parameters. Sensitivity, specificity, positive predictive value (PPV), negative predictive value

(NPV), and accuracy were calculated. The level statistical significance was set at 5% ( $p < 0.05$ ). A highly significant difference was present if  $p \leq 0.001$ .

## Results

Demographic and clinical data of the studied groups are presented in Table (1). Laboratory findings of the studied groups are presented in Table (2). COMP was significantly increased in the cirrhotic group when compared to the control group and in the HCC group when compared to the other groups (Table 2). There were significant positive correlations between COMP and APRI and FIB-4 in the cirrhotic and HCC groups, while COMP was not significantly correlated with other studied parameters (Table 3). COMP levels were not significantly different according to the Child-Pugh classification of severity of liver disease in cirrhotic and HCC patients (KW= -0.650 & MW= 0.391, respectively, and  $p > 0.05$ ), while it was significantly increased in the BCLC stage (D) when compared with other stages (F=11.143,  $p < 0.001$ ). Regression analysis demonstrated that FIB-4, APRI, and BCLC are independently associated with COMP in HCC patients (Table 4).

Area under ROC curve (AUC) of AFP was 0.971. A cutoff of 200 ng/mL for AFP in the diagnosis of HCC was chosen (20). At this cut-off, 17 out of 24 HCC

patients were correctly diagnosed, while 2 out of 24 cirrhotic patients were falsely diagnosed as HCC (Table 5). ROC curve analysis of COMP as a diagnostic biomarker of HCC in cirrhotic patients revealed an AUC of 0.943. The best cutoff of COMP for the diagnosis of HCC is 15.6 ng/mL. At this cutoff, 21 out of 24 HCC patients were correctly diagnosed, while 5 of the cirrhotic patients were falsely diagnosed as HCC. By using both AFP and COMP in combination for the diagnosis of HCC at the same cutoff points, all HCC patients were correctly diagnosed (Figure 1 and Table 5).

## Discussion

Although great progress has been made in HCC treatment, HCC prognosis remains poor (21). HCC is frequently diagnosed late in its course because of the absence of symptoms and the reluctance of many primary care physicians to provide surveillance for their high-risk patients (22); as a result, some patients had incurable disease at the time of diagnosis (23).

Alpha-fetoprotein has been the most widely used biomarker for hepatocellular carcinoma during the past several decades and is considered the gold standard by which other markers for the disease are judged (24). However, the clinical value of serum AFP to detect early HCC has been questioned because of its low

**Table 1.** Demographic criteria and clinical data of the studied groups

Demographic & clinical data	Control n=24	Cirrhosis n=24	HCC n=24	P
Gender				
Male	12 (50)	13 (54.2)	15 (62.5)	0.675
Female	12 (50)	11 (45.8)	9 (37.5)	
Age (years) *	58.83 ± 6.53	57 ± 5.82	60.83 ± 7.38	0.140
Disease				
HBV		0 (0)	2 (8.3)	0.221
HCV		23 (95.8)	22 (91.7)	
Combined		1 (4.2)	0 (0)	
Disease duration(years) *		4.92 ± 2.36	6.08 ± 2.99	0.209
Child-Pough				
A		1 (4.2)	0 (0)	0.143
B		22 (91.7)	19 (79.2)	
C		1 (4.2)	5 (20.8)	
BCLC				
A1			1 (4.2)	
A4			2 (8.3)	
B			2 (8.3)	
C			11 (45.8)	
D			33.3)	

n: number of subjects; Data are represented as number (%) or mean ± SD \*,  $P > 0.05$  is non significant

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sensitivity and specificity (25). These problems direct us to the necessity and urgency of identifying additional biomarkers with the potential of being used alone or complementary to AFP for HCC diagnosis.

Cartilage oligomeric matrix protein, a cartilage metabolism marker, is an extracellular matrix protein that modulates the cellular phenotype during tissue genesis and remodeling (26). COMP is known to promote fibrosis in skin, lung, and liver. Emerging evidence shows that COMP plays critical roles in the development of cancerous tumors, including those of breast cancer, colon cancer, and hepatocellular carcinoma (27).

In the present study, a highly significant increase in mean values of COMP was observed in cirrhotic patients compared to the controls. These findings are in

agreement with those of Norman et al. (14) and Zachou et al. (28). Liver fibrosis is associated with major alterations in both quantity and composition of ECM (29), and COMP directly indicates ECM turnover in the liver (30). COMP increases type I collagen synthesis in the liver and stiffens the ECM contributing to cellular and organ dysfunction (31).

The current study demonstrated a positive correlation between COMP and fibrosis indices (APRI and FIB-4) in both the HCC and the cirrhosis groups. Regression analysis revealed that fibrosis indices (FIB-4 and APRI) are independently associated with COMP in HCC patients. Zachou et al. (30) reported that COMP levels are correlated positively with FIB-4 score in cirrhosis, and COMP was as good in detecting cirrhosis as the APRI and FIB-4 indices. Andréasson et

**Table 2.** Laboratory findings of the studied groups:

Laboratory finding	Control n=24	Cirrhosis n=24	HCC n=24	P
T.bilirubin (mg/dL)	0.45 <sup>∞</sup> (0.3 – 0.8)	1.7(0.67 – 6.6)	1.44(0.6 – 16)	<0.001
D.bilirubin (mg/dL)	0.2(0.0 – 0.2)	0.3 6 <sup>∞</sup> (0.1 – 4.8)	0.65 <sup>∞</sup> (0.1 – 8.5)	0.001
T. protein (g/dL) *	7.22 ± 0.62	6.88 ± 0.45	6.35 ± 0.7 <sup>∞</sup>	<0.001
Albumin (g/dL) *	3.85 ± 0.49	3.15 ± 0.69 <sup>∞</sup>	2.79 ± 0.5 <sup>∞</sup>	<0.001
ALT (U/L)	27 <sup>∞</sup> (16 – 40)	57.5(15 – 850)	53(18 – 842)	<0.001
AST (U/L)	25 <sup>∞</sup> (19-35)	59(18 – 321)	50.5(25-527)	<0.001
Alkaline phosphatase (U/L)	95.5 <sup>∞</sup> (68-114)	234(158-980)	244(130 – 480)	<0.001
Platelets count/mL	239.5 <sup>∞</sup> (152 – 393)	113(54 – 232)	121(29 – 426)	<0.001
PT (seconds) *	13.04 ± 0.86	13.75 ± 1.47	16.68 ± 3.43 <sup>∞</sup>	<0.001
INR*	1.13 ± 0.14	1.17 ± 0.21	1.45 ± 0.39 <sup>∞</sup>	0.001
AFP (ng/mL)	5.9(2.1 – 9.3)	52(6 – 261)	337.5 <sup>∞</sup> (7 – 3810)	<0.001
APRI	0.26 <sup>∞</sup> (0.15 – 0.45)	2.37(1.2 – 12.9)	2.18(1.16 – 10.6 )	<0.001
FIB-4	1.28 <sup>∞</sup> (0.71 – 1.85)	4.14(1.18 – 10.19)	3.54(0.58 – 18.8)	<0.001
COMP (ng/ mL)*	7.7 ± 1.7	13.23 ± 3.6 <sup>∞</sup>	19.24 ± 4.0 <sup>∞</sup>	<0.001

n: number of subjects; Data are represented as median(range) or mean± SD \*; ∞: significant with other group; p≤0.001 is highly significant

**Table 3.** Correlation between COMP levels and other parameters in patients groups

Laboratory finding	Cirrhosis group		HCC group	
	r	p	r	p
Age	-0.028	0.896	-0.09	0.673
Disease duration	-0.053	0.806	0.026	0.903
T. bilirubin	0.226	0.289	0.398	0.054
D. bilirubin	-0.134	0.531	0.328	0.118
T. protein	-0.023	0.914	0.038	0.861
S. albumin	-0.311	0.139	-0.233	0.296
ALT	0.117	0.586	0.122	0.57
AST	0.014	0.984	0.067	0.756
Alkaline phosphatase	0.288	0.173	0.181	0.396
AFP	0.267	0.208	-0.096	0.654
Platelets count	-0.081	0.787	-0.160	0.454
INR	-0.04	0.851	0.196	0.359
APRI	0.694	0.004*	0.633	<0.001**
FIB-4	0.654	0.009*	0.809	<0.001**

\*p<0.05 is significant; \*\*p≤0.001 is highly significant

**Table 4.** Multiple stepwise regression analysis showing variables independently associated with serum COMP in HCC patients

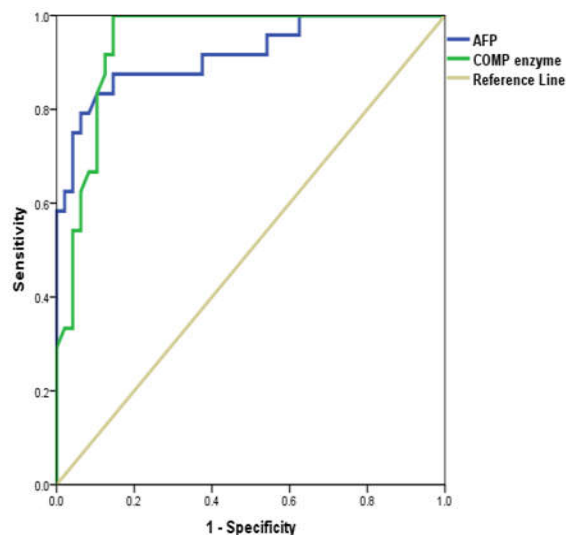
	Unstandardized coefficient		Standardized coefficient	t	p
	Beta	Standard error	Beta		
APRI	1.112	0.320	0.694	3.477	0.004*
FIB-4	0.782	0.199	0.643	3.395	0.001**
BCLC	2.650	0.646	0.658	4.13	<0.001**

\*p<0.05 is significant; \*\*p≤0.001 is highly significant

**Table 5.** Performance of AFP and COMP in diagnosis of HCC in cirrhotic patients

Parameter	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
AFP (ng/ml)	70.8	91.7	89.5	75.9	81.3
COMP (ng/ml)	87.5	79.2	80.8	86.4	83.3
AFP and COMP	100	66.7	75	100	83.3

al. (32) found that COMP is associated with the stage of liver fibrosis in chronic viral hepatitis C.

**Figure 1.** ROC curve showing performance of COMP and AFP in diagnosis of HCC.

The current study revealed a highly significant increase in COMP levels in patients with HCC compared to cirrhotic patients and controls. Elevated COMP levels were associated with a higher risk of HCC development in cirrhotic patients (28). Li et al. (27) found that the level of COMP was increased in the serum of HCC patients compared to the healthy control, and the transition from premalignant lesions to HCC was associated with an increase in COMP serum levels.

Xiao et al. (33) found that COMP was absent or rarely expressed in normal liver and liver cirrhosis tissues, but it was significantly overexpressed in HCC tissue samples when detected by northern blot and western blot analyses. When COMP mRNA and

protein expression were localized within the cytoplasm of the tumor cells by in situ hybridization and immunohistochemistry analysis, COMP was highly expressed within the tumor cells of HCC, suggesting that COMP might play a role in the pathophysiology of HCC. Xiao et al. also showed that COMP was only weakly expressed in cirrhotic liver tissues, indicating that this gene might have a function early in the course of liver carcinogenesis.

ECM is a major component of tumor microenvironment and plays critical roles in cancer development and progression (34). In HCC, the metastatic microenvironment consists of activated hepatic stellate cells, extracellular matrix, and their secreted or released various cytokines to regulate tumor metastasis (35). COMP plays a very important role in the development and progression of HCC by activating the ERK and AKT signaling pathways in a CD36-dependent manner (27).

Patients with end-stage disease (BCLC stage D) have poor liver function (Child–Pugh class C). They are not candidates for transplantation and have marked cancer-related symptoms. They have a poor prognosis and require supportive care (36). We found that COMP levels are significantly increased in the BCLC stage (D) when compared with other stages. Regression analysis found that BCLC staging is independently associated with COMP in HCC patients. Li et al. (27) found that patients with a high level of serum COMP showed more unfavorable disease progression, such as higher incidence of vascular invasion, large tumor size, and tumor recurrence. Additionally, HCC patients with high serum COMP levels had poorer survival and disease-free survival rates. Studies have shown that COMP is

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present in human arteries and may play a role in the adhesion and migration of vascular smooth muscle cells during vasculogenesis (37, 38).

Norman et al. (14) assessed serum COMP in the outcome of HCC and cirrhotic patients in a long-term follow-up. They demonstrated that the presence of COMP in the sera of patients with chronic liver diseases is strongly associated with liver cirrhosis and that increased COMP levels appear to identify a subgroup of patients who are at increased risk of their disease progressing to HCC and liver-related mortality. Furthermore, 73.7% of patients who developed HCC during follow-up were COMP positive prior to the diagnosis of HCC. Although the presence of cirrhosis is clearly associated with an increased risk of disease progression, the detection of COMP in cirrhotic patients is a potentially useful marker to identify a subgroup of cirrhotic patients with a higher likelihood of developing HCC.

In the present study, serum AFP yielded an ROC-AUC of 0.917 for HCC versus liver cirrhosis. At a 200 ng/mL cutoff, sensitivity was 70.8% and specificity was 91.7%. AFP remains the most commonly used screening biomarker for HCC, although it suffers from poor sensitivity even at relatively low cutoffs and is even more limited in smaller tumors. Because AFP is secreted by regenerating hepatocytes as well as hepatic tumors, specificity is limited. AFP cannot be used reliably to distinguish malignant versus nonmalignant lesions, although specificity improves at higher levels. The presence of an elevated AFP, particularly an AFP that has increased from baseline, may alert the clinician to the possibility of HCC diagnosis (39). The current study revealed that COMP ROC-AUC for discriminating HCC patients from those with liver cirrhosis was 0.943, comparable with that of AFP. A cutoff of 15.6 ng/mL resulted in higher sensitivity than AFP (87.5%) and a specificity of 79.2%. When both AFP and COMP were used to diagnose HCC in cirrhotic patients, all HCC patients were correctly diagnosed (100% sensitivity). The lack of correlation between COMP and AFP in HCC patients encourages their use as complementary biomarkers in the diagnosis of HCC.

In conclusion, COMP might act as a promising non-invasive biomarker for HCC either alone or in combination with AFP. It is correlated with the degree

of fibrosis and associated with advanced cancer staging. Further studies on a larger number of patients are recommended to confirm these results. In addition, serial measurements of COMP during the follow up of HCC patients are needed to evaluate its prognostic value.

### Conflict of interests

The authors declare that they have no conflict of interest.

### References

1. Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. *Nat Rev Gastroenterol Hepatol* 2017;14:527–539.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018;391:1301–14.
3. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. *JAMA Oncol* 2017;3:1683-91.
4. Ramakrishna G, Rastogi A, Trehanpati N, Sen B, Khosla R, Sarin SK. From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. *Liver Cancer* 2013;2:367-383.
5. Gomaa AI, Hashim MS, Waked I. Comparing staging systems for predicting prognosis and survival in patients with hepatocellular carcinoma in Egypt. *PLoS One* 2014;9:e90929.
6. Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis* 2010;42:S206-214.
7. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908–943.
8. Halász K, Kassner A, Mörgelin M, Heinegård D. COMP acts as a catalyst in collagen fibrillogenesis. *J Biol Chem* 2007;282:31166-31173.
9. Hedbom E, Antonsson P, Hjerpe A, Aeschlimann D, Paulsson M, Rosa-Pimentel E, et al. Cartilage matrix proteins. An acidic oligomeric protein (COMP) detected only in cartilage. *J Biol Chem* 1992;267:6132–6136.
10. Tseng S, Reddi AH, Di Cesare PE. Cartilage Oligomeric Matrix Protein (COMP): a biomarker of arthritis. *Biomark Insights* 2009;4:33–44.
11. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127:S35–50.
12. Tilghman RW, Blais EM, Cowan CR, Sherman NE, Grigera PR, Jeffery ED, et al. Matrix rigidity regulates cancer cell growth

- by modulating cellular metabolism and protein synthesis. *PLoS One* 2012;7:e37231.
13. Xiao Y, Kleeff J, Guo J, Gazdhar A, Liao Q, Di Cesare PE, et al. Cartilage oligomeric matrix protein expression in hepatocellular carcinoma and the cirrhotic liver. *J Gastroenterol Hepatol* 2004;19:296–302.
  14. Norman GL, Gatselis NK, Shums Z, Liaskos C, Bogdanos DP, Koukoulis GK, et al. Cartilage oligomeric matrix protein: a novel non-invasive marker for assessing cirrhosis and risk of hepatocellular carcinoma. *World J Hepatol* 2015;7:1875–1883.
  15. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona 2000 EASL conference. *J Hepatol* 2001;35:421–430.
  16. Sebastian A, Varghese SM. Fuzzy logic for Child-Pugh classification of patients with cirrhosis of liver. *International Conference on Information Science* 2016;168-171.
  17. Adhoute X, Penaranda G, Raoul JL, Le Treut P, Bollon E, Hardwigsen J, et al. Usefulness of staging systems and prognostic scores for hepatocellular carcinoma treatments. *World J Hepatol* 2016;8:703.
  18. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Vorácková F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol* 2008;7:350-357.
  19. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. Pol S. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology* 2007;46:32-36.
  20. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *HepatolInt* 2010;4:439-474.
  21. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. *Gut Liver* 2016;10:332–339.
  22. Simmons OL, Feng Y, Parikh ND, Singal AG. Primary care provider practice patterns and barriers to hepatocellular carcinoma surveillance. *Clin Gastroenterol Hepatol* 2019;17:766-773.
  23. Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology* 2015;61:191-199.
  24. Lopez JB. Recent developments in the first detection of hepatocellular carcinoma. *Clin Biochem Rev* 2005;26:65-79.
  25. Hu B, Tian X, Sun J, Meng X. Evaluation of individual and combined applications of serum biomarkers for diagnosis of hepatocellular carcinoma: a meta-analysis. *Int J Mol Sci* 2013;14:23559-23580.
  26. Vuga LJ, Milosevic J, Pandit K, Ben-Yehudah A, Chu Y, Richards T, et al. Cartilage oligomeric matrix protein in idiopathic pulmonary fibrosis. *PLoS One* 2013;8:e83120.
  27. Li Q, Wang C, Wang Y, Sun L, Liu Z, Wang L, et al. HSCs-derived COMP drives hepatocellular carcinoma progression by activating MEK/ERK and PI3K/AKT signaling pathways. *J Exp Clin Cancer Res* 2018;37:231.
  28. Zachou K, Gabeta S, Gatselis NK, Norman GL, Dalekos GN. Cartilage oligomeric matrix protein on the spot for liver fibrosis evaluation: Too early or too late? *Eur J Intern Med* 2017;43:e48-49.
  29. Scott LF. Hepatic Fibrosis. In: Eugene R Schiff, Michael F Sorrell, Willis C Maddrey, editors. *Schiff's Diseases of the Liver*. 11th edition. Singapore: Wiley-Blackwell; 2012. P.297–305.
  30. Zachou K, Gabeta S, Shums Z, Gatselis NK, Koukoulis GK, Norman GL, et al. COMP serum levels: a new non-invasive biomarker of liver fibrosis in patients with chronic viral hepatitis. *Eur J Intern Med* 2017; 38: 83–88.
  31. Magdaleno F, Arriazu E, Ruiz de Galarreta M, Chen Y, Ge X, et al. Cartilage oligomeric matrix protein participates in the pathogenesis of liver fibrosis. *J Hepatol* 2016;65:963–971.
  32. Andréasson K, Waldenström J, Westin J, Norrgren H, Jönsson G, Nyström K, et al. Cartilage oligomeric matrix protein associates with hepatic inflammation and fibrosis in hepatitis C virus infection. *J Hepatol* 2017;67:649-651.
  33. Xiao Y, Kleeff J, Guo J, Gazdhar A, Liao Q, Di Cesare, et al. Cartilage oligomeric matrix protein expression in hepatocellular carcinoma and the cirrhotic liver. *J Gastroenterol Hepatol* 2004;19:296–302.
  34. Kim BG, An HJ, Kang S, Choi YP, GAO MQ, Park H, et al. Laminin-332-rich tumor microenvironment for tumor invasion in the interface zone of breast cancer. *Am J Pathol* 2011;178:373-381.
  35. Kang N, Gores GJ, Shah VH. Hepatic stellate cells: partners in crime for liver metastases? *Hepatology* 2011;54:707–713.
  36. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology* 2010;51:1274–1283.
  37. Riessen R, Fenchel M, Chen H, Axel DI, Karsch KR, Lawler J. Cartilage oligomeric matrix protein (thrombospondin-5) is expressed by human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2001;21:47–54.
  38. Canfield AE, Farrington C, Dziobon MD, Boot-Handford RP, Heagerty AM, Kumar SN, et al. The involvement of matrix glycoproteins in vascular calcification and fibrosis: an immunohistochemical study. *J Pathol* 2002;196:228–234.
  39. Clark P. Serum markers for hepatocellular carcinoma. *Clin Liver Dis* 2016;8:29-33.