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Efficacy of Fibronectin in Detecting Early Hepatocellular Carcinoma

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Abstract

Improving the effectiveness of early HCC identification can be achieved in part by developing non-invasive detection methods that are practical for use in medical and healthcare settings. In this work, we attempted to investigate the diagnostic accuracy of the extracellular matrix protein; fibronectin (FN) in detecting early HCC stages. Through examination that incorporates statistical and clinical approaches, we observed that increasing levels of FN in HCC patients were accompanied by progression of aggressive tumor features. Moreover, FN is promising in differentiating between cirrhotic liver and small size tumor (<3cm) patients producing area under receiver operating characteristic curve (AUC) of 0.86 with 79.4% sensitivity and 80.4% specificity. Furthermore, FN possesses the ability to discriminate between cirrhotic liver patients and HCC patients who didn't experience vascular invasion with AUC of 0.86, sensitivity of 79.5%, and specificity of 80.4%. These results were promising regarding to the early detection of HCC depending on sole biomarker, where diagnostic accuracy of FN exceeded those of alpha-fetoprotein; the most common biomarker used in detecting HCC.

Keywords: Early HCC, Cirrhosis, HCV, Serum biomarker, Fibronectin.

Introduction

Up to 58 million people worldwide still have chronic hepatitis C (HCV) infection, with 3.2 million of those instances occurring in children and adolescents. The primary causes of HCV derived mortality were found to be cirrhosis and hepatocellular carcinoma (HCC), the two common complications of the chronic viral infection (Taha *et al.*, 2023). Whereas about 30% of chronic hepatitis C (CHC) patients develop cirrhosis and possess the potentiality of developing HCC (Weigand *et al.*, 2022). The societies around the world, including Egyptian society are increasingly burdened due to the rising incidence of HCC; on both human and economic bases (Hucke *et al.*, 2023). One of the most leading causes of this rising incidence of HCC is late diagnosis, which can be directly attributed to the subtleness of the disease

manifestations (Busato *et al.*, 2019). In turn, diagnostic delays of HCC prevent patients from receiving the appropriate treatment, whereas only 30% of the new identified HCC patients can be admitted to appropriate treatments (Maan and Feld, 2017, Pinto Marques *et al.*, 2020).

The dependency on ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) for the detection of HCC, particularly early stages has changed over the years due to corresponding limitations to these techniques such as; poor sensitivity in detecting small lesions, high cost, and complexity in performance (Liang *et al.*, 2021). For instance, the most used technique for HCC surveillance; US, bears a significant limitation which is the dependency of its accuracy on several factors; including size of lesions, and proficiency of technique performer. These varying factors render the technique poorly dependent on, especially in detecting early stages (Parikh *et al.*, 2023). The two other techniques of CT and MRI are also used as screening methods for early HCC, but one major flaw of these techniques is the use of chemical agents in order to investigate the small lesions which represents a great risk for patients with other comorbidities (Tanaka, 2020). In an attempt to overcome these shortcomings, serum biomarkers were continually under investigations to be used as a convenient screening method for early HCC (Singal *et al.*, 2022). Although several biomarkers were tested to be used as a replacement for the previously mentioned techniques, they lacked adequate sensitivity for detecting early HCC. One extensively used biomarker for HCC management and identification is alpha-fetoprotein (AFP). However, as a separately test for screening, AFP is not thought to have sufficient performance characteristics; whereas its sensitivity rates doesn't exceed 45% when used independently (Tzartzeva *et al.*, 2018). An appropriate biomarker with enhanced accuracy rates in detecting early HCC stages is a priority for the sake of health care.

It has previously been highlighted how fibronectin (FN), a significant extracellular matrix (ECM) component, is involved in cancer progression. It was noticed that FN is involved in tumorigenesis by activating signals of some down-streaming pathways (Kim *et al.*, 2020, Zhou *et al.*, 2023). However, FN hasn't received much attention to be investigated as a sole diagnostic biomarker for early HCC detection. The identification of HCC patients at an early stage is a worthy seeking on both clinical and economic levels. Therefore, we focused in the present work on the determination of FN diagnostic performance among CHC patients, particularly in early stages of HCC.

Materials

Patients

Sera of 280 CHC patients were gathered from Mansura university hospital after receiving confirmed consents from all of the patients; following 1975 Helsinki guideline (**Shephard, 1976**). Inclusion criteria for the presence of HCV were considered, and exclusion criteria for any other etiology for HCC other than HCV were considered as well. Patients' cohorts were classified into two groups. The first group; HCC patient group was classified according to the presence of AFP levels ≥ 400 ng/ml, confirmed by the presence of liver focal lesions using US, CT scan, and needle liver biopsy. The second group; cirrhotic liver patient group (F4) was classified according to METAVIR (Group and Bedossa, 1994, Bedossa and Poynard, 1996). The HCC patient group was further sub-classified according to some histological features of the disease including; tumor size, number of nodules, vascular invasion, and Child Pugh Turcotte score (Child and Turcotte, 1964).

Clinical data of patients

Clinical and laboratory parameters of patients including liver enzyme activity, albumin, bilirubin, and AFP were measured. Levels of FN were tested using enzyme-linked immune-sorbent assay (ELISA) in each group of patients; the technique was performed as (Attallah *et al.*, 2007) with adjustments; samples were diluted up to 1:50, the FN monoclonal antibody was diluted at a ratio of 1:50, while the goat anti-mouse IgG conjugate alkaline phosphatase (Sigma) was diluted at a ratio of 1:300. The ELISA reader (Robonik, India) was used to detect the generated color absorbance at 490 nm.

Statistics

The GraphPad Prism package v.5.0 (GraphPad Software, San Diego, CA) and SPSS software v.15.0 (SPSS Inc., Chicago, IL) were used for each of the statistical analyses. Data that did not have a regular distribution were displayed as median± interquartile range (IQR), whereas data with a normal distribution were represented as mean± standard deviation (SD). Kurskal-Wallis's analysis or Tukey's post-hoc analysis combined with a simple ANOVA, if applicable, was used to check significant difference between the groups. The *P* value less than 0.05 is deemed significant. To evaluate the diagnostic precision of FN in the identification of HCC, the area under the receiver-operating characteristic (ROC) curve (AUC) was employed. The optimal performance test has an AUC of 1.0. ROC analysis was used to establish the equilibrium between sensitivity and specificity for a variety of test results. The performance test's upper cut-off value was selected with specificity, sensitivity, and accuracy in reference (Metz, 1978).

Results

Classification of HCC patients

Histopathological features were assessed among HCC patients, where patients were classified according to tumor size, number of nodules, vascular invasion, and Child Pugh Turcotte score; showed in figure (1). It was noted that about 70.9% of HCC patients developed large size tumor ≥ 3 cm, and 64.1% of the patients displayed multiple nodules. Above that, around 29.1% of HCC group suffered from vascular invasion, and nearly 23.9 % of the patients were end-stage (class C) Child Pugh Turcotte score.

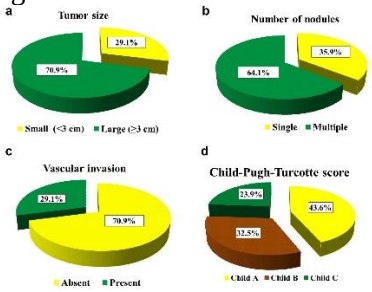

Figure 1. Classification of HCC (n=117) according to (**a**): tumor size, (**b**): number of nodules, (c): vascular invasion and (**d**): Child-Pugh-Turcotte score.

Distribution of clinical data among study groups

Some laboratory parameters showed characteristic differences between cirrhotic and HCC groups; represented in figure (2). Whereas bilirubin and aspartate aminotransferase (AST) showed increasing levels in HCC patient group than cirrhotic liver patient group, albumin levels were lower in HCC patients than cirrhotic liver patients, with *p* value < 0.0001. Moreover, AFP was measured in both groups of patients and displayed increasing levels in HCC group than cirrhotic liver patient group with *p* value < 0.0001.

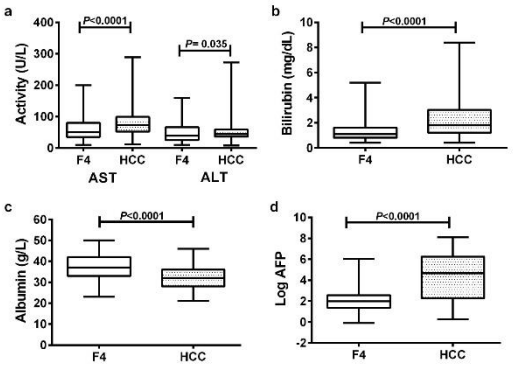

Figure 2. Distribution of (**a**): liver enzyme activity, (**b**): total bilirubin, (**c**): albumin, (**d**): Log α-fetoprotein (AFP) in HCC patients in comparison to cirrhotic F4 patients.

Identification of fibronectin (FN) level among HCC patients in association with histopathological features

Levels of FN were quantified using ELISA and analysis of the results; represented in table (1), showed that FN levels were increasingly higher in HCC group (838.7±263) than cirrhotic patient group (492.4±136). Above all, these increasing levels were noted to be associated with progression of the disease according to some histopathological features. Patients who developed large tumor size ≥ 3cm expressed higher levels of FN (852.1±197) than patients who had small size tumor <3cm (782.1±212), and patients with multiple nodules displayed increasing levels of FN (825.5±146.0) than patients who had single nodule (802.6±222.2). Moreover, patients who exhibited vascular invasion were associated with higher levels of FN (913.7±152.0) than patients without vascular invasion (829.9±287.9), and patients with advanced Child Pugh Turcotte score (class

C) displayed increasing levels of FN (987.7±243.7) than patients with class A (752.6±166.2); *p* value of all mentioned results were 0.0001 in comparison to the non-malignant cirrhotic liver patient group (F4).

Table1. Distribution of Fibronectin level in HCC patients according to different histological features

Categories	**Fibronectin level (mg/L) Mean± SD**	***P* value***
Cirrhotic (F4)	492.4±136	0.0001
HCC patients	838.7±263	
Size of nodules		
small tumor size <3 cm	782.1±212	0.0001
large tumor size ≥3 cm	852.1±197	0.0001
Number of nodules		
Single	802.6±222.2	0.0001
Multiple	825.5±146.0	0.0001
Vascular invasion		
Absent	829.9±287.9	0.0001
Present	913.7±152.0	0.0001
Child-Pugh-Turcotte score		
Child A	752.6±166.2	0.0001
Child B	790.3±143.5	0.0001
Child C	987.7±243.7	0.0001

*$P<0.05$ is considered significant whereas F4 is the reference group

Evaluating diagnostic performance of fibronectin (FN) in different HCC stages

Single biomarkers with accurate detection rate for HCC, especially early stages are great concern for all medical aspect solicitous. Based on the favorable results of FN in our present work, ROC curves were used to assess the diagnostic ability of FN in detecting early HCC; presented in figure (3). Interestingly, ROC curves showed that FN could discriminate between cirrhotic liver patient group (F4) and HCC patient group that have small tumor size <3cm with AUC of 0.86 and sensitivity was 79.4% and specificity was 80.4%. Furthermore, FN provided AUC of 0.81, sensitivity of 76.2%, and specificity of 80.4%; this was for the discrimination between cirrhotic liver patient group and HCC patients with single nodule. Moreover, AUC, sensitivity, and specificity of FN differentiation between cirrhotic liver patient group and non-vascular invasion patients were 0.86, 79.5%, and 80.4%; respectively. Above that, ROC curves of FN separation between cirrhotic liver patients and patients with Child Pugh Turcotte class A provided AUC of 0.83, sensitivity of 74.5%, and specificity of 80.4%.

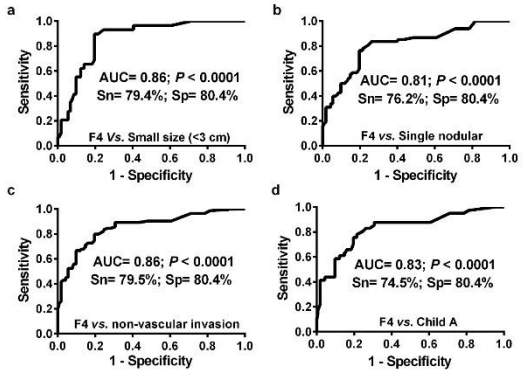

Figure 3. Area under receiver-operating characteristic curve (AUC) of fibronectin for separating patients with early HCC stages (a): small HCC tumor sizes (<3 cm), (b): single nodular, (c): non-vascular invasion and (d): Child-Pugh-Turcotte score A from patients with liver cirrhosis. Sn=sensitivity and Sp= specificity.

Fibronectin also yielded a valuable performance for the identification of HCC late stages (figure 4); represented in large tumor ≥3 cm, presence of multiple nodules, presence of vascular invasion, and Child Pugh Turcotte score B-C, with AUCs of 0.92, 0.92, 0.96, and 0.94; respectively, cirrhotic liver patient group (F4) was used as reference.

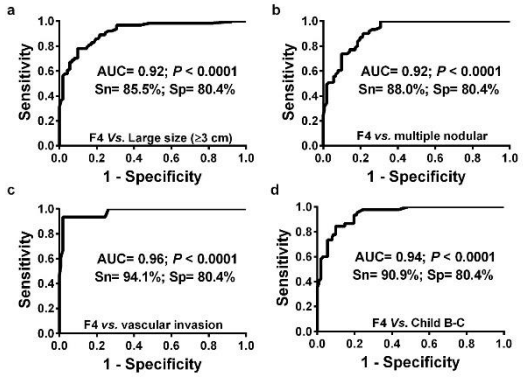

Figure 4. Area under receiver-operating characteristic curve (AUC) of fibronectin for separating patients with advanced HCC stages (**a**): large HCC tumor sizes (≥3 cm), (**b**): multiple nodular, (**c**): vascular invasion and (**d**): Child-Pugh-Turcotte score B-C from patients with liver cirrhosis. Sn=sensitivity and Sp= specificity.

Discussion

Liver cancer represents an enormous health burden to the society, particularly HCC which is the most common type of primary liver cancers. Mostly, HCC arises as a complication of chronic liver injury, including viral

infections. Unfortunately, HCV represents a common etiology for HCC in Egypt and worldwide. It was discovered that 30% of CHC patients develop cirrhosis and 90% of HCC cases are developed in a cirrhotic environment (Khatun *et al.*, 2021). What turns this cancer into a recondite health dilemma is its subtle morphological manifestations which decreases early diagnosis opportunities. Diagnostic delay of HCC prevents patients from receiving the appropriate treatment at the appropriate time. Less than 50% of the new identified HCC patients can be admitted to appropriate treatment regimens (Chang *et al.*, 2022).

Although several HCC diagnosis techniques are available, yet nearly 70–80% of HCC patients have a late diagnosis, mainly a consequence of inadequate early detection and monitoring for high-risk individuals (de Martel *et al.*, 2020). Over the years the use of serum biomarkers was widely introduced into the process of tumor detection. The most common biomarker used in the detection of HCC is AFP. The cutoff values have a significant impact on the AFP's sensitivity and specificity, so that decreased sensitivity and increased specificity are associated with higher AFP cut-off values (**Stefaniuk *et al.*, 2010, Yang *et al.*, 2019**). The European Association for the Study of the Liver (EASL) excluded AFP from the association's policy regarding risk-based management for HCC among cirrhotic patients, owing to its deficiency of sensitivity and specificity (**Liver, 2023**). These shortcomings necessitate the search for new efficient and accurate biomarkers to be used as diagnostic markers for HCC particularly early stages. The dynamic protein of ECM; FN has presented the evidence of its manifest role in carcinogenesis including HCC progression (Torbenson *et al.*, 2002, Roy *et al.*, 2023).

In our work, we embrace the duty of investigating FN's role in progression of HCC, moreover we focused on determining its diagnostic ability in early-stage HCC patients. Notably, when FN was measured in sera of CHC patients using ELISA, patients with HCC expressed more FN (838.7±263) than cirrhotic patients (492.4±136) with *p* value of 0.0001. Interestingly, the increasing levels of FN were associated with progression of some tumor hallmarks, where large tumor size patients ≥3cm expressed more FN levels than small tumor size <3cm patients. Therefore, we statistically analyzed data of FN levels to investigate its ability in differentiation between cirrhosis and early HCC using ROC curves. The AUC of FN produced levels ranging from 0.81-0.86, this was for the identification of HCC early stages; represented in small size tumor <3cm, single nodule, non-vascular invasion, and Child Pugh Turcotte score (class A). The sensitivity levels ranged from 74.5%-79.5%, and specificity levels were 80.4%. These outstanding results showing diagnostic ability of FN as a single used biomarker exceeded results of other biomarkers and other surveillance techniques. Where, previous studies showed the low sensitivity of AFP and ultrasound (US) in detecting early HCC (39%-64%), and (47%); respectively (Tzartzeva *et al.*, 2018). Moreover, the modest sensitivity of AFP in the diagnosis of small HCC was confirmed by a multi-center research, whereas AFP sensitivity is decreased when there is a single small HCC lesion 54% (Farinati *et al.*, 2006). In contrast, our work showed that FN could detect single HCC nodule with sensitivity of 76.2%. Another multidisciplinary investigation showed that, the sensitivity of AFP for HCC diagnosis dropped to 23.4% in identifying the small HCC <2 cm (Zhang *et al.*, 2012), while our work provided us with insights about FN's sensitivity in detecting small HCC lesions <3cm of 79.4%. Also, the biomarker Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) identified small HCC <3cm with lower sensitivity 61.2% (**Lim *et al.*, 2016**) than FN according to our results. Other biomarker des-gamma-carboxy-prothrombin (DCP) also displayed poor sensitivity in detecting early HCC 34%-62% (Parikh *et al.*, 2020). Also, the sensitivity of DCP and AFPL3 was shown in retrospective research involving 416 patients and it was, respectively, 50.0% and 41.0%. The sensitivity could be increased up to 69.9% by using DCP and AFP-L3% together (Huang *et al.*, 2023). On the other hand, FN in singular presented superior results of sensitivity in detecting early HCC (74.5%-79.5%). These findings highlight the FN's effective function and capacity to identify HCC in its early stages. Additionally, the protein showed that it could detect cancer in its later stages with enhanced diagnostic performance, where sensitivity levels of FN differentiation between cirrhotic patients and patients with advanced stages; large size of tumor ≥3cm, presence of multiple nodules, presence of vascular invasion, and Child Pugh Turcotte score B-C ranged from 85.5%-94.1%,

with specificity of 80.4%.

Conclusion

A recurring goal for medical attention is the development of an ideal biomarker that accurately diagnoses early HCC in extremely vulnerable (cirrhotic) patients, thereby reducing the associated health and social damage. We thus investigated the diagnostic potential of FN in identifying early HCC stages in an effort to improve the accuracy of diagnosing biomarkers that detect early HCC with low sensitivity. Compared to other biomarkers that are frequently employed for this issue, particularly AFP, FN in this investigation gave us remarkable sensitivity levels against diagnosing early stages of HCC.

References

Attallah, A. M., F. Zahran, H. Ismail, M. M. Omran, I. El-Dosoky, G. E. J. J. o. i. Shiha and immunochemistry (2007). "Immunochemical identification and detection of serum fibronectin in liver fibrosis patients with chronic hepatitis C." Journal of immunoassay & immunochemistry 28: 331-342.

Bedossa, P. and T. Poynard (1996). "An algorithm for the grading of activity in chronic hepatitis C." Hepatology 24: 289-293.

Busato, D., M. Mossenta, L. Baboci, F. Di Cintio, G. Toffoli and M. Dal Bo (2019). "Novel immunotherapeutic approaches for hepatocellular carcinoma treatment." Expert Review of Clinical Pharmacology 12: 453-470.

Chang, S.-S., H.-Y. Hu, Y.-C. Chen, Y.-F. Yen and N. Huang (2022). "Late hepatitis C virus diagnosis among patients with newly diagnosed hepatocellular carcinoma: a case–control study." BMC Gastroenterology 22: 425.

Child, C. G. and J. G. Turcotte (1964). "Surgery and portal hypertension." Major Problems in Clincal Surgery 1: 1-85.

de Martel, C., D. Georges, F. Bray, J. Ferlay and G. M. Clifford (2020). "Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis." Lancet Glob Health 8: e180-e190.

Farinati, F., D. Marino, M. De Giorgio, A. Baldan, M. Cantarini, C. Cursaro, G. Rapaccini, P. Del Poggio, M. A. Di Nolfo, L. Benvegnù, M. Zoli, F. Borzio, M. Bernardi and F. Trevisani (2006). "Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither?" Official journal of the American College of Gastroenterology| ACG 101: 524-532.

Group, F. M. C. S. and P. J. H. Bedossa (1994). "Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C." Hepatology 20: 15-20.

Huang, C., X. Xiao, L. Zhou, F. Chen, J. Wang, X. Hu, C. Gao and M. D. S. o. S. M. A. Clinical Laboratory Society of Chinese Rehabilitation Medicine Association, Tumor Immunology Branch of Shanghai Society for Immunology (2023). "Chinese expert consensus statement on the clinical application of AFP/AFP-L3%/DCP using GALAD and GALAD-like algorithm in HCC." Journal of clinical laboratory analysis 37: e24990.

Hucke, F., H. Emmer, R. Emmer, M. Hucke, S. Bota, M. Fürstner, K. Hausegger, R. Mittermair and M. Peck-Radosavljevic (2023). "Changes in the Epidemiology of Hepatocellular Carcinoma in Carinthia, Austria, 2012–2023. ." cancers 15: 5215.

Khatun, M., R. Ray and R. B. Ray (2021). Chapter Three - Hepatitis C virus associated hepatocellular carcinoma. Advances in Cancer Research. D. Sarkar and P. B. Fisher, Academic Press. 149: 103-142.

Kim, S. A., E. J. Cho, S. Lee, Y. Y. Cho, B. Kim, J.-H. Yoon and T. Park (2020). "Changes in serum fibronectin levels predict tumor recurrence in patients with early hepatocellular carcinoma after curative treatment." Scientific Reports 10: 21313.

Liang, Y., F. Xu, Y. Guo, L. Lai, X. Jiang, X. Wei, H. Wu and J. Wang (2021). "Diagnostic performance of LI-RADS for MRI and CT detection of HCC: A systematic review and diagnostic meta-analysis." European Journal of Radiology 134: 109404.

Lim, T. S., D. Y. Kim, K.-H. Han, H.-S. Kim, S. H. Shin, K. S. Jung, B. K. Kim, S. U. Kim, J. Y. Park and S. H. J. S. j. o. g. Ahn (2016). "Combined use of AFP, PIVKA-II, and AFP-L3 as tumor markers enhances diagnostic accuracy for hepatocellular carcinoma in cirrhotic patients." Scandinavian journal of gastroenterology 51: 344-353.

Liver, E. A. F. T. S. O. T. (2023). "EASL Policy Statement: risk-based surveillance for hepatocellular carcinoma among patients with cirrhosis.". from https://easl.eu/publication/easl-policy-statement-risk-based/.

Maan, R. and J. J. Feld (2017). "Risk for Hepatocellular Carcinoma After Hepatitis C Virus Antiviral Therapy With Direct-Acting Antivirals: Case Closed?" Gastroenterology 153: 890-892.

Metz, C. E. (1978). "Basic principles of ROC analysis." Seminars in nuclear medicine 8: 283-298.

Parikh, N. D., A. S. Mehta, A. G. Singal, T. Block, J. A. Marrero and A. S. Lok (2020). "Biomarkers for the Early Detection of Hepatocellular Carcinoma." Cancer Epidemiology, Biomarkers & Prevention 29: 2495-2503.

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

Pinto Marques, H., S. Gomes da Silva, E. De Martin, V. G. Agopian and P. N. Martins (2020). "Emerging biomarkers in HCC patients: Current status." International Journal of Surgery 82: 70-76.

Roy, A. M., R. Iyer and S. Chakraborty (2023). "The extracellular matrix in hepatocellular carcinoma: Mechanisms and therapeutic vulnerability." Cell Reports Medicine 4: 101170.

Shephard, D. A. J. C. M. A. J. (1976). "The 1975 Declaration of Helsinki and consent." Canadian Medical Association Journal 115: 1191.

Singal, A. G., M. Reig and A. Villanueva (2022). "Emerging Tools for Hepatocellular Carcinoma Surveillance." The American Journal of Gastroenterology 117: 1948-1951.

Stefaniuk, P., J. Cianciara and A. J. W. j. o. g. W. Wiercinska-Drapalo (2010). "Present and future possibilities for early diagnosis of hepatocellular carcinoma." World journal of gastroenterology: WJG 16: 418.

Taha, G., L. Ezra and N. Abu-Freha (2023). "Hepatitis C Elimination: Opportunities and Challenges in 2023." Viruses 15: 1413.

Tanaka, H. (2020). "Current role of ultrasound in the diagnosis of hepatocellular carcinoma." Journal of Medical Ultrasonics 47: 239-255.

Torbenson, M., J. Wang, M. Choti, R. Ashfaq, A. Maitra, R. E. Wilentz and J. Boitnott (2002). "Hepatocellular Carcinomas Show Abnormal Expression of Fibronectin Protein." Modern Pathology 15: 826-830.

Tzartzeva, K., J. Obi, N. E. Rich, N. D. Parikh, J. A. Marrero, A. Yopp, A. K. Waljee and A. G. Singal (2018). "Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis." Gastroenterology 154: 1706-1718.e1701.

Tzartzeva, K., J. Obi, N. E. Rich, N. D. Parikh, J. A. Marrero, A. Yopp, A. K. Waljee and A. G. J. G. Singal (2018). "Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis." Gastroenterology 154: 1706-1718. e1701.

Weigand, K., G. Peschel, J. Grimm, M. Müller, M. Höring, S. Krautbauer, G. Liebisch and C. Buechler (2022). "HCV Infection and Liver Cirrhosis Are Associated with a Less-Favorable Serum Cholesteryl Ester Profile Which Improves through the Successful Treatment of HCV." Biomedicines 10: 3152.

Yang, J. D., P. Hainaut, G. J. Gores, A. Amadou, A. Plymoth and L. R. Roberts (2019). "A global view of hepatocellular carcinoma: trends, risk, prevention and management." nature reviews gastroenterology & hepatology 16: 589-604.

Zhang, G., S. A. Ha, H. K. Kim, J. Yoo, S. Kim, Y. S. Lee, S. Y. Hur, Y. W. Kim, T. E. Kim, Y. G. Park, J. Wang, Y. Yang, Z. Xu, E. Y. Song, Z. Huang, P. Jirun, J. Zhongtian, Q. Shishi, C. Zhuqingqing, G. Lei and J. W. Kim (2012). "Combined analysis of AFP and HCCR-1 as an useful serological marker for small hepatocellular carcinoma: a prospective cohort study." Disease Markers 32: 265-271.

Zhou, F., J. Sun, L. Ye, T. Jiang, W. Li, C. Su, S. Ren, F. Wu, C. Zhou and G. Gao (2023). "Fibronectin promotes tumor angiogenesis and progression of non-small-cell lung cancer by elevating WISP3 expression via FAK/MAPK/ HIF-1α axis and activating wnt signaling pathway." Experimental Hematology & Oncology 12: 61.

الملخص العربي

عنوان البحث: فعالية الفيبرونكتين في التعرف على المراحل المبكرة من سرطان الخلايا الكبدية

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يمكن تحسين فعالية التعرف على سرطان خلايا الكبد المبكر جزئيًا عن طريق تطوير وسائل الكشف عن وجود السرطان بدون تدخل جراحي، وتكون هذه الطرق قابلة للتطبيق في الأماكن الطبية وأماكن الرعاية الصحية. ولقد حاولنا في هذا العمل اختبار الدقة التشخيصية لواحد من أكثر البروتينات تواجدًا في المواد الموجودة حول الخلية-وهو الفيبرونكتين - في الكشف عن مراحل سرطان خلايا الكبد المبكر. من خلال الفحص الشامل الذي يتضمن التحاليل الإحصائية والمعملية، لاحظنا أن المستويات المتزايدة من الفيبرونكتين في مرضى سرطان خلايا الكبد كانت مصحوبة بتطور سمات متقدمة للورم (زيادة حجم الورم (≤ ٣سم) - وجود عدة بؤر سرطانية-ظهور الأوعية الدموية الجديدة- Child Pugh score B-C. علاوة على ذلك أظهر الفيبرونكتين نتائج واعدة في التمييز بين تشمع الكبد والورم الكبدي صغير الحجم (< ٣ سم)، وكانت المنطقة تحت منحنى الخصائص (AUC=0.86) مع حساسية٧٩,٤٪ وتخصصية بنسبة ٨٠,٤٪. أيضًا يمتلك الفيبرونكتين القدرة على التمييز بين مرضى تشمع الكبد ومرضى سرطان خلايا الكبد الذي لم يظهر فيه غزو الأوعية الدموية بنسبة ٠,٨٦ = (AUC) وحساسية بنسبة ٧٩,٥٪ وتخصصية بنسبة ٨٠,٤٪. كانت هذه النتائج واعدة فيما يتعلق بالكشف المبكر عن سرطان خلايا الكبد اعتمادًا على مؤشر حيوي واحد فقط، حيث تجاوزت الدقة التشخيصية للفيبرونكتين بروتين دقة ألفا فيتو بروتين (AFP)؛ المؤشر الحيوي الأكثر استخدامًا في الكشف عن سرطان خلايا الكبد.