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# Evaluation of The Role of Serum Epidermal Growth Factor Like Domain 7 as A New Non-Invasive Diagnostic Marker for Hepatocellular Carcinoma in Egyptian Cirrhotic Patients

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## ABSTRACT

**Background**: Hepatocellular carcinoma (HCC) remains a major contributor to liver-related deaths globally, with a particularly high impact in Egypt, where delayed diagnosis hinders optimal treatment. Alpha-fetoprotein (AFP) is commonly used for HCC screening; however, its diagnostic sensitivity and specificity are limited. Serum Epidermal Growth Factor-Like Domain 7 (EGFL7) has emerged as a promising, non-invasive biomarker with the potential to enhance diagnostic accuracy. This study aimed to assess the effectiveness of EGFL7 as a diagnostic tool for HCC in Egyptian patients with cirrhosis.

**Methods**: This cross-sectional study included 90 participants, divided into two groups: 45 patients with HCC and liver cirrhosis and 45 cirrhotic patients without HCC. AFP and EGFL7 serum levels were measured using enzyme-linked immunosorbent assay (ELISA). Diagnostic accuracy was evaluated using ROC curve analysis, comparing sensitivity, specificity, and cutoff values for both markers.

**Results**: EGFL7 levels were considerably higher in HCC patients compared to cirrhotic controls (37.03 ± 15.11 ng/ml vs. 6.41 ± 3.59 ng/ml, P-value <0.001). ROC curve revealed that EGFL7 had a sensitivity of 97.78% and a specificity of 93.33% at a cutoff value of 12.65 ng/ml, outperforming AFP, which had a 93.33% sensitivity and 97.78% specificity at a cutoff of 22.4 ng/ml.

**Conclusion**: EGFL7 demonstrates higher sensitivity and comparable specificity to AFP, suggesting its utility as a superior diagnostic marker for early detection of HCC in cirrhotic patients. Incorporating EGFL7 into screening protocols may enhance early detection and improve patient outcomes.

**Keywords**: Hepatocellular carcinoma, EGFL7, Alpha-fetoprotein, Non-invasive marker, Cirrhosis.

## INTRODUCTION

Worldwide, 70–85% of instances of liver cancer with a bad prognosis are caused by hepatocellular carcinoma (HCC). While the equivalent death rate was 8, the predicted global incidence rate of HCC per 100,000 person-years was 9.3 [1]. A considerable portion of these instances had a delayed diagnosis. This lowers their likelihood of recovery, which is why we require new markers for early detection and monitoring [2].

For the diagnosis or surveillance of HCC, the combination of serum biomarkers and radiographic techniques proved to be more effective than either technique alone. With a sensitivity of 63% and specificity of 84%, alpha-fetoprotein (AFP) with concurrent ultrasonography enhanced the early diagnosis of HCC in this way [3].

In clinical practice, AFP is currently the most commonly utilized serum marker for the screening of HCC and initial diagnosis. At a 20 ng/mL cut-off value, AFP's sensitivity is only roughly 60%, and its specificity is poor [3]. About 15–30% of patients with advanced HCC stages may have AFP levels that are within normal ranges. On the other hand, AFP levels may rise in certain individuals with liver cirrhosis, chronic hepatitis, and other liver illnesses, which can result in high rates of false-positive and negative results. As a result, new markers are required for HCC screening and more precise diagnosis in order to supplement the shortcomings of AFP [4].

Serum EGFL7 is upregulated during liver regeneration and functions as a mitogen for hepatocytes cultured in vitro. EGFL7 may also be crucial for the development and spread of tumors. A number of findings revealed a notably elevated amount in HCC patients compared to healthy individuals and patients with different malignancies, providing insight into the possible use of EGFL7 as a serum diagnostic marker for HCC [5]. Therefore, the purpose of this study was to assess the utility of serum EGFL7 as a diagnostic marker in individuals with HCC who also had cirrhosis.

## PATIENTS AND METHODS

This cross-sectional study was performed on 90 adult participants, with age > 18 years old recruited from Internal Medicine and Hepatology Outpatient Clinics and Inpatient Wards at Ain Shams University Hospitals over a period of six months, from January 2023 to June 2023.

The studied subjects included 45 patients with liver cirrhosis only as a control group and 45 patients with liver cirrhosis and HCC based on the characteristic vascular enhancement in triphasic CT abdomen, according to the 2011 American Association for the Study of Liver Diseases (AASLD) guidelines [6]. Exclusion criteria were patients diagnosed with malignancy other than HCC, and patients with any other



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organ dysfunction, or those who refused to participate in the study.

Before enrolment, each patient underwent a comprehensive clinical evaluation, which included a detailed history of chronic liver conditions, signs of hepatic decompensation (such as ascites, hepatic encephalopathy, lower limb edema, melena, or hematemesis), and any extrahepatic manifestations or involvement of other systems. A complete physical examination was undertaken. Initial laboratory examinations covered a complete blood count (CBC), coagulation profiles, and liver function tests, including ALT, AST, serum albumin, total bilirubin, INR, ALP, and GGT. Renal function was examined using BUN, serum creatinine, sodium (Na), and potassium (K) values. Viral serology for HBsAg and HCV antibodies, coupled with measures of AFP and serum EGFL7, was conducted for all patients. Radiological examinations comprised abdominal ultrasonography, concentrating on liver size, echotexture, splenic bi-polar diameter, portal vein diameter, and details of hepatic focal lesions. Any potential hepatic lesions discovered by ultrasound were subsequently studied using triphasic CT or dynamic MRI, defined by classic imaging patterns of HCC, such as washout in the portal venous or delayed phases, and arterial phase hyperenhancement.

EGFL7 levels were quantified using an ELISA. The assay plate was pre-coated with antibodies specific to human EGFL7. Upon introducing the sample, EGFL7 bound to the immobilized antibodies on the plate wells. This was followed by the addition of a biotinylated human EGFL7 antibody, which attacheed to the bound EGFL7. Next, Streptavidin-HRP was added, binding to the biotin-labeled antibody. After a period of incubation, unbound Streptavidin-HRP was washed away. A substrate solution was then applied, resulting in a color change that corresponds to the concentration of EGFL7 in the sample. The reaction was stopped by an acidic solution, and absorbance was read at 450 nm. Results were calculated by plotting a standard curve, using the average optical density (OD) of each standard on the Y-axis against its concentration on the X-axis. A best-fit curve was then generated, ideally using computerized curve-fitting software, with regression analysis determining the most accurate line.

**Ethical considerations:**

**The study was done after being accepted by the Research Ethics Committee, Ain Shams University Faculty of Medicine (FMASU M S 56/2019). All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This research has been conducted in compliance with the World Medical Association's Code of Ethics (Declaration of Helsinki) for studies involving human subjects.**

***Statistical analysis***

Data management and statistical analysis were conducted using SPSS version 26 (IBM, Armonk, New York, United States). Quantitative data were expressed as mean ± standard deviation. The Student's t-test was used to compare the means of two groups. Qualitative data was articulated in terms of frequency and proportion. The relationship between qualitative data was analyzed using the Chi-square test. The ROC curve was developed to assess the efficacy of various tests and to distinguish between the included groups. The P value was deemed significant at 0.05.

**RESULTS**

Patients with HCC were significantly older than those with cirrhosis. There were no significant differences between the groups in terms of BMI, gender distribution, or smoking status. Additionally, the prevalence of diabetes mellitus did not differ significantly between the groups. However, hypertension was more common in the HCC group compared to the cirrhotic group (**Table 1)**.

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**Table 1: Demographic characteristics among the studied groups**

| | | Group | | | Test | |
|---|---|---|---|---|---|---|
| | | **HCC** | **Cirrhotic** | **Total** | **t / $X^2$** | **p** |
| **Age (years):** Mean ±SD | | 60.6±7.414 | 56.111±9.939 | | 2.428 | 0.017* |
| **BMI (kg/m$^2$):** Mean ±SD | | 21.656±2.225 | 22.058±1.921 | | -0.918 | 0.361 |
| **Gender** | Male | 34(75.56%) | 29(64.44%) | 63(70%) | 1.323 | 0.25 |
| | Female | 11(24.44%) | 16(35.56%) | 27(30%) | | |
| **Smoking** | No | 30(66.67%) | 29(64.44%) | 59(65.56%) | 0.326 | 0.849 |
| | Current | 11(24.44%) | 13(28.89%) | 24(26.67%) | | |
| | Ex-smoker | 4(8.89%) | 3(6.67%) | 7(7.78%) | | |
| **DM** | No | 25(55.56%) | 32(71.11%) | 57(63.33%) | 2.344 | 0.126 |
| | Yes | 20(44.44%) | 13(28.89%) | 33(36.67%) | | |
| **HTN** | No | 23(51.11%) | 33(73.33%) | 56(62.22%) | 4.727 | 0.03 |
| | Yes | 22(48.89%) | 12(26.67%) | 34(37.78%) | | |

HCC: Hepatocellular carcinoma; DM: Diabetes mellitus; HTN: Hypertension, *: Significant.

PVT was notably more common in the HCC group compared to the cirrhotic group. Additionally, a significant difference was found in the distribution of Child class between the groups, with a higher proportion of Child C cases in the HCC group. In contrast, no significant differences were observed between the HCC and cirrhotic groups regarding HBsAg positivity or HCV Ab positivity (**Table 2)**.

**Table 2: Viral markers, portal vein thrombosis and Child class in the studied groups**

| | Group | | | Chi-Square | |
|---|---|---|---|---|---|
| | HCC | Cirrhotic | Total | | |
| | N (%) | N (%) | N (%) | $X^2$ | p |
| **HBsAg** | | | | | |
| No | 39(86.67%) | 40(88.89%) | 79(87.78%) | 0.104 | 0.748 |
| Yes | 6(13.33%) | 5(11.11%) | 11(12.22%) | | |
| **HCV Ab** | | | | | |
| No | 17(37.78%) | 15(33.33%) | 32(35.56%) | 0.194 | 0.66 |
| Yes | 28(62.22%) | 30(66.67%) | 58(64.44%) | | |
| **PVT** | | | | | |
| No | 17(37.78%) | 39(86.67%) | 56(62.22%) | 22.878 | <0.001* |
| Yes | 28(62.22%) | 6(13.33%) | 34(37.78%) | | |
| **Child class** | | | | | |
| Child A | 0(0%) | 10(22.22%) | 10(11.11%) | 11.458 | 0.003* |
| Child B | 17(37.78%) | 15(33.33%) | 32(35.56%) | | |
| Child C | 28(62.22%) | 20(44.44%) | 48(53.33%) | | |

HCC: Hepatocellular carcinoma; HBsAg: Hepatitis B surface antigen; HCV Ab: Hepatitis C virus antibody; PVT: Portal vein thrombosis, *: Significant.

Total bilirubin and direct bilirubin levels were significantly higher in the HCC group compared to the cirrhotic group. AST, ALP and GGT levels were also significantly elevated in the HCC group. Additionally, albumin levels were lower in the HCC group (**Table 3)**.

No significant differences were observed between the groups in terms of WBCs (P = 0.464), hemoglobin, platelet counts, BUN, creatinine, sodium, potassium, ALT, or INR (**Table 3)**.

**Table 3: Laboratory data among studied groups**

| Laboratory parameter | Group | | T-Test | |
|---|---|---|---|---|
| | HCC | Cirrhotic | t | p |
| **WBCs ($\times10^3$/uL)** | 6.796±1.236 | 6.358±1.334 | 0.736 | 0.464 |
| **Hb (g/dl)** | 9.751±1.216 | 9.991±1.488 | -0.838 | 0.404 |
| **PLTs ($\times10^3$/uL)** | 103.556±8.511 | 103.889±7.395 | -0.037 | 0.971 |
| **BUN (mg/dl)** | 25.489±2.127 | 22.400±5.341 | 0.705 | 0.483 |
| **Creatinine (mg/dl)** | 1.056±0.072 | 0.964±0.173 | 0.442 | 0.659 |
| **Na (mEq/L)** | 138.156±5.148 | 137.422±5.778 | 0.636 | 0.527 |
| **K (mEq/L)** | 4.098±0.594 | 4.031±0.572 | 0.542 | 0.589 |
| **Total Bilirubin (mg/dl)** | 3.156±0.909 | 1.584±0.211 | 3.345 | 0.001* |
| **Direct Bilirubin (mg/dl)** | 1.840±0.058 | 0.730±0.136 | 3.502 | 0.001* |
| **AST (IU/L)** | 58.800±7.496 | 41.756±3.601 | 2.271 | 0.026* |
| **ALT(IU/L)** | 38.822±3.504 | 35.911±4.666 | 0.466 | 0.642 |
| **ALP(IU/L)** | 148.356±58.52 | 115.778±35.744 | 3.187 | 0.002* |
| **GGT(IU/L)** | 73.600±7.352 | 45.222±2.361 | 5.388 | <0.001* |
| **Albumin (g/dl)** | 2.578±0.449 | 2.831±0.694 | -2.057 | 0.043* |
| **INR** | 1.508±0.321 | 1.379±0.331 | 1.889 | 0.062 |

HCC: Hepatocellular carcinoma; BUN: Blood urea nitrogen; Na: Sodium; K: Potassium; AST: Aspartate transaminase; ALT: Alanine transaminase; WBCs: White blood cells; Hb: Hemoglobin; PLTs: Platelets; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio, *: Significant.

EGFL7 levels were notably higher in the HCC group compared to the cirrhotic group. AFP levels were also considerably elevated in the HCC group compared to the cirrhotic group (**Table 1)**.

**Table 4: AFP and EGFL7 levels among studied groups**

| | Group | | T-Test | |
|---|---|---|---|---|
| | HCC | Cirrhotic | T | p |
| **AFP (ng/ml)** Mean ±SD | 2118.589±342.211 | 4.458±1.057 | 2.236 | 0.028* |
| **EGFL7 (ng/ml)** Mean ±SD | 37.034±5.107 | 6.408±1.588 | 13.231 | <0.001* |

HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; EGFL7: Epidermal growth factor-like domain 7, *: Significant.

The Child score was significantly higher in the HCC group compared to the cirrhotic group. Similarly, the MELD score was considerably elevated in the HCC group compared to the cirrhotic group (**Table 5)**.

**Table 5: Child and MELD score among studied groups**

| | Group | | T-Test | |
|---|---|---|---|---|
| | HCC | Cirrhotic | T | p |
| **Child Score** Mean ±SD | 10.267±1.993 | 8.733±2.147 | 3.511 | <0.001* |
| **MELD Score** Mean ±SD | 16.533±4.511 | 13.756±2.153 | 2.721 | 0.008* |

HCC: Hepatocellular carcinoma; MELD: Model for End-Stage Liver Disease, *: Significant.

In the HCC group, EGFL7 revealed significant positive correlations with AFP, INR, Child score, MELD score, number of focal lesions, and size of focal lesions. In the cirrhotic group, EGFL7 showed significant positive correlations with AFP, BUN, creatinine, and MELD score. No significant correlations were observed between EGFL7 and other parameters in the HCC group and in the cirrhotic group (**Table 6)**.

**Table 6: Correlation between EGFL7 and age, labs, imaging data, Child and MELD score**

| Correlations | | | | |
|---|---|---|---|---|
| | EGFL7 | | | |
| | HCC | | Cirrhotic | |
| | r | p | r | p |
| **Age (years)** | 0.269 | 0.074 | 0.039 | 0.8 |
| **AFP (ng/ml)** | 0.41 | 0.005* | 0.663 | <0.001* |
| **BMI (kg/m$^2$)** | 0.002 | 0.991 | -0.156 | 0.307 |
| **WBCs (×10$^3$/uL)** | 0.084 | 0.585 | 0.159 | 0.296 |
| **Hb (g/dl)** | -0.113 | 0.46 | 0.103 | 0.502 |
| **PLTs (×10$^3$/uL)** | -0.039 | 0.8 | -0.032 | 0.835 |
| **BUN (mg/dl)** | -0.014 | 0.929 | 0.609 | <0.001* |
| **Creat. (mg/dl)** | 0.065 | 0.672 | 0.62 | <0.001* |
| **Na (mEq/L)** | -0.014 | 0.929 | -0.024 | 0.874 |
| **K (mEq/L)** | -0.007 | 0.963 | 0.119 | 0.437 |
| **Total Bilirubin (mg/dl)** | 0.278 | 0.064 | -0.127 | 0.407 |
| **Direct Bilirubin (mg/dl)** | 0.199 | 0.189 | -0.109 | 0.476 |
| **AST (IU/L)** | 0.084 | 0.585 | -0.073 | 0.636 |
| **ALT (IU/L)** | 0.169 | 0.267 | -0.09 | 0.557 |
| **ALP (IU/L)** | 0.12 | 0.433 | 0.137 | 0.368 |
| **GGT (IU/L)** | 0.135 | 0.378 | 0.1 | 0.512 |
| **Albumin(g/dl)** | -0.021 | 0.894 | -0.056 | 0.713 |
| **INR** | 0.382 | 0.01* | 0.006 | 0.968 |
| **Child Score** | 0.344 | 0.021* | -0.029 | 0.851 |
| **MELD Score** | 0.357 | 0.016* | 0.375 | 0.011* |
| **No. Focal Lesion** | 0.435 | 0.003* | . | . |
| **Size Focal Lesion** | 0.488 | 0.001* | . | . |

EGFL7: Epidermal growth factor-like domain 7; HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; BMI: Body mass index; WBCs: White blood cells; Hb: Hemoglobin; PLTs: Platelets; BUN: Blood urea nitrogen; Creat.: Creatinine; Na: Sodium; K: Potassium; ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio, *: Significant.

ROC curve analysis was conducted for EGFL7 and AFP to differentiate between HCC and cirrhotic patients. For EGFL7, the best cutoff value was 12.65 ng/ml, with an accuracy of 99.1%. For AFP, the best cutoff value was 22.4 ng/ml, with an accuracy of 97.3% (**Table 7)**.

**Table 7: Sensitivity specificity EGFL 7 AFP as markers in HCC**

| ROC curve between HCC Cirrhotic | | | | | | |
|---|---|---|---|---|---|---|
| | **Cutoff** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
| **EGFL7 (ng/ml)** | 12.65 | 97.78 | 93.33 | 93.6 | 97.7 | 99.1% |
| **AFP (ng/ml)** | 22.4 | 93.33 | 97.78 | 97.7 | 93.6 | 97.3% |

ROC: Receiver operating characteristic; HCC: Hepatocellular carcinoma; PPV: Positive predictive value; NPV: Negative predictive value; EGFL7: Epidermal growth factor-like domain 7; AFP: Alpha-fetoprotein.

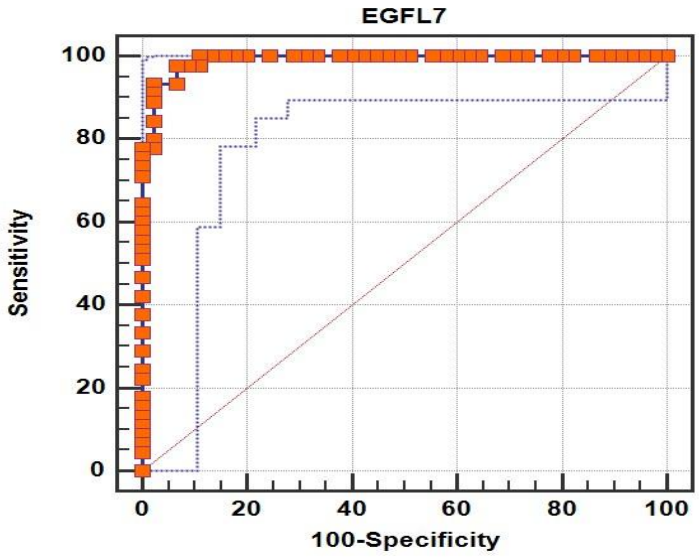


**Figure 1**: The sensitivity and specificity of EGFL 7 as a marker in HCC.

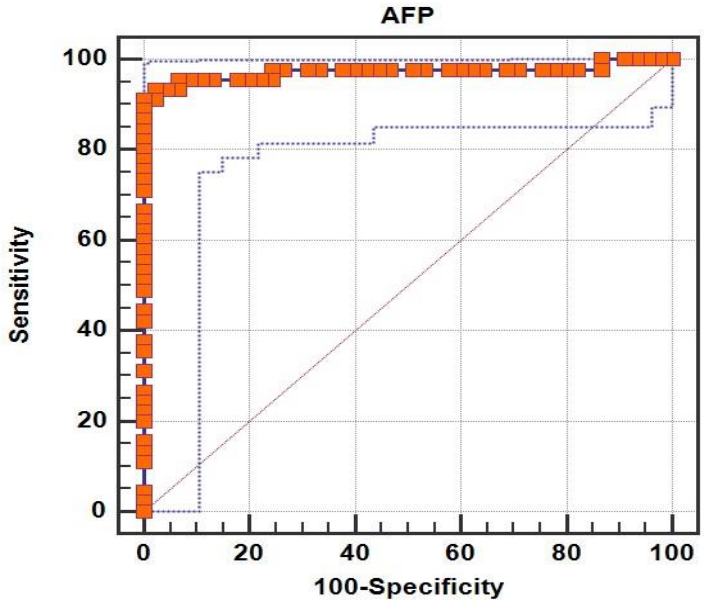


**Figure 2:** The sensitivity and specificity of AFP as a marker in HCC.

## DISCUSSION

HCC is the sixth most prevalent cancer globally and ranks as the fourth most common in Egypt [7]. Multiple hospital-based studies have reported a rise in HCC incidence, which is attributed to factors such as improved screening and diagnostic capabilities, better survival rates among patients with cirrhosis—leading to an elevated risk of HCC—and an increase in hepatitis C virus (HCV) prevalence and its associated complications, a primary contributor to liver cancer in Egypt [8]. HCC screening involves the use of ultrasound imaging and the measurement of AFP levels in high-risk groups, including those with cirrhosis and/or HBV/HCV infections, regardless of cirrhosis status [9]. During surveillance, any suspicious lesion identified by ultrasound in cirrhotic patients is further confirmed using contrast-enhanced computed tomography (CT) or dynamic magnetic resonance imaging (MRI) [10].

A substantial portion of liver cancer cases are detected at an advanced stage, limiting the potential for recovery. Therefore, novel biomarkers are essential for early detection and monitoring of liver cancer [11]. EGFL7 is a protein consisting of an N-terminal signaling sequence, a cysteine-rich Emilin-like (EMI) domain, and two epidermal growth factor-like (EGF-like) domains [12].

Our findings indicated that EGFL7 levels were markedly elevated in HCC tissues, and increased EGFL7 expression was significantly associated with clinical features such as vascular invasion, presence of multiple nodules, and capsule formation, all of which correlate with poorer prognosis in HCC [13].

This study enrolled 90 subjects, aged between 28 and 80 years, from Ain Shams University Hospitals. Participants provided informed consent and were divided into two groups: Group A, consisting of 45 patients with HCC, and Group B, comprising 45 patients with liver cirrhosis without HCC.

Regarding our findings, the age of HCC patients (60.6 ± 7.414 years) was in the 6-decade on top of liver cirrhosis in our Egyptian patients, agreeing with previous reports that HCC affects patients in the $5^{th}$ to $6^{th}$ decades, as reported by **Le *et al.*** [14] in their study, which was carried out on 382 HCC patients for ages of HCC occurrence, showed that the mean age of HCC patients was 54.1 ± 14.6 years.

This study shows that within the HCC group and the cirrhotic group, males outnumbered female patients, aligning with prior research that identifies a higher prevalence of HCC among males than females [15]. A retrospective cohort study involving 1,087 HCC patients (917 males and 170 females) revealed that males had a significantly higher risk of developing HCC, largely due to the increased prevalence of risk factors like chronic viral hepatitis among men [15].

The findings also suggest that smoking does not appear to be a risk factor for HCC in this study, likely due to the limited sample size. However, this observation is at odds with **Matsuura *et al.*** [16] who reported that smoking might contribute to the risk of HCC.

Among the HCC patients in this study, 22 individuals (48.89%) had hypertension. This association underscores the role of hypertension in the development of liver cirrhosis, which in turn raises the risk of HCC. This finding aligns with the work of **Yu *et al.*** [17], which highlighted the impact of metabolic risk factors, including hypertension, on the development of HCC.

This study also found a notable elevation in serum AFP levels among HCC patients compared to the cirrhotic group, consistent with other studies [18,19] that regard elevated AFP as a key indicator of HCC, particularly when used alongside triphasic abdominal CT or dynamic MRI. Numerous guidelines recommend combining serum AFP testing with abdominal ultrasound for the screening of cirrhotic patients, aiding in the early detection of HCC, as supported by **Jasirwan *et al.*** [18] who emphasized that AFP remains a reliable marker for HCC.

This study found that blood levels of EGFL7 were significantly higher in patients with HCC compared to those with cirrhosis. These findings among our Egyptian cohort align with the results reported by **Yang *et al.*** [19].

All participants underwent comprehensive assessments, including medical history, physical examination, standard lab tests, AFP, EGFL7 measurements, and radiological evaluations. The analysis demonstrated that EGFL7 provided superior diagnostic accuracy for HCC compared to AFP, offering greater precision in distinguishing between cirrhotic and HCC patients, suggesting that EGFL7 could be a promising marker for HCC diagnosis and screening.

The observed significant correlation between AFP and EGFL7 in the HCC group differs from the findings of **Yang *et al.*** [19] whose study involved 1,081 subjects, highlighting the limitations posed by the smaller sample size in our study

Additionally, EGFL7 levels showed a significant positive correlation with both Child and MELD scores within the HCC group. A strong association was also found between EGFL7 levels and both the number and size of hepatic focal lesions, consistent with the findings of **Yang *et al.*** [19].

The results showed that EGFL7 had a sensitivity of 97.78% and a specificity of 93.33% as a biomarker for HCC, achieving an accuracy of 99.1% at a cutoff value of >12.65 ng/ml. These findings are in line with those of **Yang *et al.*** [19] who reported a sensitivity of 77.4%, a specificity of 82.7%, and an accuracy of 80.2% at a threshold of >26 ng/ml for EGFL7 as an HCC biomarker. In contrast, AFP demonstrated a sensitivity of 93.33% and a specificity of 97.78%, with an overall accuracy of 97.3%. These

results are consistent with **Abd El Moety *et al.*** [20] who found AFP to have a sensitivity of 88%, a specificity of 96%, and an accuracy of 92%. However, our study differs from the findings of **Turshudzhyan *et al.*** [21] which reported AFP's sensitivity at 60% and specificity at 35.8% for diagnosing HCC.

This study showed that EGFL 7 is more sensitive and accurate than AFP, so we can use it as a marker in diagnosis of early HCC.

The study had several limitations. First, the relatively small sample size may limit the generalizability of the findings. Second, the study was conducted at a single center, which could introduce selection bias. Third, the cross-sectional design prevents establishing a cause-and-effect relationship between EGFL7 levels and HCC progression. Finally, the lack of longitudinal follow-up limits the assessment of EGFL7's role in monitoring disease progression over time.

## CONCLUSION

EGFL7 emerges as a more sensitive and accurate marker than AFP for early HCC detection. Incorporating EGFL7 into diagnostic algorithms could enhance the effectiveness of surveillance programs for early HCC detection, ultimately leading to improved clinical outcomes and patient management.

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