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Predictive Significance of the Inflammatory Activities and GGT in Hepatocellular Carcinoma Development

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Abstract: This study evaluated whether gamma-glutamyltransferase (GGT) and several non-invasive inflammatory and fibrotic markers could predict the development of hepatocellular carcinoma (HCC). The research included 37 patients with HCC, 45 with liver cirrhosis, and 20 healthy individuals. **Patients and Methods:** Serum levels of AFP and GGT with the inflammatory markers (AAR, NLR, PLR and Pt) and fibrotic indices (APRI and FIB-4) were investigated in 82 adult HCC and liver cirrhotic patients in addition to 20 healthy individuals as non-disease control (NDC). **Results:** Our results showed that GGT, along with indices such as AAR, APRI, FIB-4, NLR, and PLR, were significantly elevated in HCC and cirrhotic patients compared to healthy controls. Alpha-fetoprotein (AFP) was the most accurate diagnostic marker (AUC = 0.972). Regression analysis indicated that ALT, INR, and platelet count could serve as early predictors of tumor development. Overall, the findings support the usefulness of combining inflammatory and fibrotic indices with traditional markers to improve early detection of HCC. **Conclusion:** AAR, NLR, FIB4, APRI and GGT as inflammatory and fibrotic indices play an important role in HCC and liver cirrhosis. ALT, INR and Pt count could be used as early predictors for HCC development.

keywords: AAR; APRI; AFP; FIB4; GGT

1.Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in human **[1].** HCC is one of the most common cancers worldwide and a major frequent cause of cancer mortality **[2].** In Egypt, HCC is the 1st mortality related to cancer **[3].** Only 10% to 20% of the HCCs can be surgically excised, although attended with a high frequency of recurrence **[4].**

HCC is a complex disease with multiple steps and associated with many risk factors and cofactors **[5].** Most patients with HCC have a history of liver cirrhosis and chronic liver disease, with risk factors including infectious causes like hepatitis C virus and hepatitis B virus and noninfectious causes like nonalcoholic and alcoholic liver disease **[3,6].**

The incidence of HCC continues to rise despite the fast-paced period of direct acting antiviral regimens (DAA) in the treatment of HCV **[7].** Even when the virus has been successfully eradicated, individuals still experience chronic HCV complications such liver cirrhosis and HCC. Given the high rate of recurrence, postoperative HCC patients' long-term survival is inadequate. Therefore, there is a pressing need to uncover novel serological biomarkers with high accuracy and practicality for the early identification of HCC because serum α-Fetoprotein level detection of HCC is hampered by its low sensitivity **[8].**

The lack of readily available biomarkers that are both sensitive and specific is the main issue faced by physicians in HCC patient's management of HCC. Novel circulating indicators are highly needed to raise the rate of disease-free survival **[9].** The most popular

tumor marker for HCC patients identifying is serum alpha fetoprotein (AFP), which has also been shown to be able to predict prognosis **[10].** Therefore, the aim of this study was to investigate the potential role of the inflammatory markers and fibrotic indices with GGT for predicting HCC earlier.

2. Materials and methods

Patients

The present study was conducted on 82 patients hospitalized for liver transplantation attending at the Gastro Intestinal Surgical Center (GISC) from August 2021 to April 2024 after approval of the Ethics Committee at the Faculty of Medicine, Mansoura University (Approval code MPD.21.04.66) and written informed consent was obtained from all participants. They were diagnosed according to the American Association for the Study of Liver Diseases (AASLD) guidelines, based on AFP > 400 and the presence of hepatic focal lesion(s) detected by liver ultrasound and confirmed by triphasic computed tomography (CT) and/or dynamic magnetic resonance imaging (MRI). The second group included patients with liver cirrhosis defined by clinical, biochemical, and imaging findings such as splenomegaly. They were followed up for 6 months to ensure the absence of HCC; 37 patients having HCC on top of liver cirrhosis (HCC-LC, 32 men and 5 women; median age 58yrs) and 45 liver cirrhotic patients (LC, 30 men and 15 women; median age 53yrs), in addition to 20 healthy individuals as control group (these individuals had no clinical history of hepatitis and no symptoms or signs of liver disease). Demographic data were collected from all participants.

Exclusion criteria included patients infected with HBV or HIV, patients with prior or metastatic HCC, patients with malignancies other than HCC, or patients aged less than 18 years old **[11].**

Sample collection and biochemical analysis

5 milliliters of venous blood were drawn from both patient's group and control, placed in plain tubes, blood was allowed to clot and the serum was separated by centrifugation at 4000 rpm for 15 minutes. Sera were immediately assessed for the biochemical parameters; ALT, AST, GGT, viral markers and the rest of serum samples were stored at -80C° until used for analysis of AFP by ELISA.

Determination of noninvasive indices

Serum ALT and AST activities were calorimetrically determined according to the method described by Reitman and Frankel (1957), using a commercial kit supplied by Spin react, Santa Coloma, Spain.

The following ratios and indices (AAR, APRI, FIB4, PLR and NLR) were calculated as follow:

- **AAR** (AST to ALT Ratio) = AST/ALT. **[12]**
- **APRI** (AST to Platelet Ratio Index) was calculated using the following equation: (AST/upper limit of normal for AST) / platelet count ($\times 10^9$/L) $\times 10$ **[12].**
- **FIB-4** = (Age in years × AST) / (Platelet count × √ALT), where AST and ALT are measured in U/L and platelets are in 10^9/L. (a possible value of 0-10) **[13].**
- **NLR** (Neutrophil to Lymphocyte Ratio): Neutrophil / lymphocyte counts **[14].**
- **PLR** (Platelet to Lymphocyte Ratio)**:** Platelet count / absolute lymphocyte count.

Statistical analysis

The collected data were analyzed and presented graphically using SPSS 20 (Statistical Package for Social Sciences). For continuous variables, descriptive statistics are reported as median and interquartile range (IQR). Kruskal-Wallis and Mann-Whitney U tests were employed to determine significant differences between non-parametric variables, with a p-value less than 0.05 considered statistically significant. Spearman's correlation coefficient was used for correlative analysis between variables. The area under receiver operating characteristic (ROC) curve (AUC) was utilized for assessment the diagnostic performance of biomarkers **[15].**

3. Results and Discussion

Result

The current case-control study included 102 participants were divided as follow, Group I consisting of 37 HCC-LC patients [32 males (86.5%) and 5 females (13.5%), with a median age of 58 years]**,** Group II consisting of 45 LC

patients [30 males (66.7%) and 15 females (33.3%); with median age 53 years], and Group III consisting of 20 healthy subjects as Non-Disease control (NDC) group [18 males (90%) and 2 females (10%); with median age 34 years]. There was a significant difference in age **(p<0.0001**) and gender (**p = 0.033)** as shown in **Table (1)**. Significant elevation of ALT was recorded in HCC patients compared to LC **(p = 0.007)**, between HCC and NDC **(p<0.0001)** and between LC and NDC (**P = 0.003**). Higher expression was also detected in HCC and LC compared to NDC as regards to AST and CRP **(P< 0.05**). Considered to AAR, INR, APRI and FIB-4, substantial increase was recorded in HCC and LC compared to NDC **(p<0.0001).** Enhanced level was also noticed in HCC and LC compared to NDC concerning PLR **(p=0.002 and p=0.037**), NLR **(p=0.001 and p<0.0001)** and GGT **(p=0.002** and **p=0.038),** respectively). AFP showed higher activity **(p<0.0001)** in HCC and LC related to NDC and in HCC concerned to LC **(Table 1)**.

Table (1) Clinicopathological and demographic characteristics of all study groups

	Group I(HCC-LC) N = 37	**Group II (LC)N** = 45	**Group III (Non-Disease)N** = 20	***P Value***
M/F	32/ 5	30 /15	18/2	0.035
Age (Yrs)	58 (54.5-59.5)	53 (43.5-59.0)	34 (25.0-44.75)	^{a}*P= 0.004* ^{b,c}*P< 0.0001*
AST (U/ml)	44 (31.0-55.5)	36(26.5-59.5)	21 (20.0-23.0)	^{a}*P= 0.152* ^{b,c}*P< 0.0001*
ALT (U/ml)	28 (22.5-50.0)	23(20.0-30.0)	21 (20.0-21.0)	^{a}*P= 0.007* ^{b}*P< 0.0001* ^{c}*P=0.003*
Plt Count (10^9 /L)	64.0 (46.0-106.0)	53.0(37.0-68.7)	218.9 (211.0-312.5)	^{a}*P= 0.038* ^{b,c}*P< 0.0001*
INR	1.2 (1.2-1.55)	1.4 (1.2-1.6)	1.0 (1.0-1.083)	^{a}*P= 0.078* ^{b,c}*P< 0.0001*
CRP (mg/L)	4.0 (4.0-11.8)	4.0 (3.0-11.5)	4.0(2.25-4.0)	^{a}*P= 0.598* ^{b}*P= 0.001* ^{c}*P= 0.009*
APRI	1.77 (1.043-3.297)	1.805 (1.167-2.767)	0.245 (0.167-0.263)	^{a}*P= 0.625* ^{b,c}*P< 0.0001*
FIB4	6.257 (4.289-12.337)	6.99 (4.58-10.25)	0.575 (0.319-0.665)	^{a}*P= 0.678* ^{b,c}*P< 0.0001*
NLR	2.19 (1.279-3.64)	2.64 (1.377-3.595)	1.227 (0.908-1.46)	^{a}*P= 0.612* ^{b}*P= 0.001* ^{c} *P< 0.0001*
AAR	1.385(1.109-1.763)	1.428 (1.1559-1.759)	1.05 (0.964-1.095)	^{a}*P= 0.548* ^{b,c}*P< 0.0001*
PLR	67.27 (51.8-90.29)	80.95 (61.54-113.39)	88.77 (88.52-132.85)	^{a}*P= 0.233* ^{b}*P= 0.002* ^{c}*P= 0.037*
AFP (ng/mL)	26.0 (4.65-68.5)	3.5.0 (2.395-5.05)	1.95 (0.93-2.0)	^{a,b,c}*P< 0.0001*
GGT (U/L)	38.0 (26.0-68.0)	29.0 (22.0-66.0)	19.0 (14.0-36.0)	^{a}*P= 0.198* ^{b}*P= 0.002* ^{c}*P= 0.038*
HCV infection +HCV Abs/-HCV RNA -HCV Abs/ -HCV RNA	34 /37 (91.9%) 3/37 (8.1%)	18/45 (40%) 27/45 (60%)	20/20 (100%)	*P<0.0001*

^{a,b,c} *represent p<0.05 considered significant in HCC vs. LC, in HCC vs. NDC,in LC vs. NDC control, respectively.*

Data are presented as median (Med) and interquartile range (IQR, 25th-75th)

Abbreviations: HCC-LC: hepatocellular carcinoma, LC: liver cirrhosis, NDC: non disease control, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, INR: international normalized Ratio, AAR: aspartate aminotransferase-to-alanine aminotransferase ratio, APRI: aminotransferase-to-platelet ratio index, FIB-4: Fibrosis-4 score, NLR: neutrophil to lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, CRP: C-reactive protein, *AFP: Alfa-fetoprotein.*

Spearman correlation coefficient of GGT, AST and AFP **(Table 2, Fig 1)** displayed AFP was associated with AST, ALT, Pt and NLR; AST was associated with ALT, AAR, APRI, FIB-4, NLR and PLR. Also, GGT was significantly associated with ALT and, Pt. Regression analysis showed that AFP, ALT, Pt, and INR displayed substantial prediction for tumor development and may be employed as early markers of the onset of HCC (**Table 3**). The diagnostic performance of all biomarkers was studied by ROC curve analysis and only AFP demonstrated excellent accuracy (90.2%) with an AUC of 0.927 (**Table 4, Fig 2**).

Discussion

Clinical indications of liver dysfunction are regularly tested include liver enzyme plasma levels as AST and ALT. Higher risk of HCC and the existence of hepatocellular predominant diseases may be indicated by elevated ALT and AST values **[16].** Li et al**.** found that HCC patients demonstrated higher levels of AST and ALT than chronic hepatitis patients **[17]** and this matched with current results revealed significant difference concerning AST ($p < 0.0001$) in HCC and LC compared to NDC groups but there was no significant difference between HCC and LC groups. Also, there was a significant difference between the three study groups in ALT suggesting that it might be an independent risk factor for the development of HCC in agrees with other reports **[16,18].**

APRI is a novel marker of liver cirrhosis and HCC patients' survival; also it provides additional prognostic insights in assessing the cirrhosis severity. APRI is associated with LC and HCC diagnosis among multiple high-risk populations **[19].** APRI use to differentiate the cirrhotic from non-cirrhotic patients **[20].** These studies support our findings as we found that there was a highly significant elevation of APRI in HCC and LC compared to NDC ***(p<0.0001).***

AAR is a validated diagnostic tool used to evaluate liver fibrosis **[21, 22].** A significant correlation has been found between a high AAR and liver cirrhosis **[23],** particularly in individuals with non-alcoholic liver disease, where an AAR greater than 1.0 suggests the presence of cirrhosis. However, the AAR has not been shown to be a highly effective predictor of HCC **[17]**. In current study, we found that median AAR was 1.385 in HCC group and this was agreed with Li et al, 2019 who found that AAR was 1.43 in HCC group **[17]**; also there was a significant difference between LC and NDC groups **(p<0.0001),** suggesting its potential role in disease severity of the liver.

A significant inflammatory burden often characterizes malignant diseases **[24].** FIB-4 is a widely used as non-invasive scoring system helps in liver fibrosis assessment, a key risk factor in HCC as liver fibrosis and cirrhosis are associated with HCC. FIB-4 and liver cirrhosis have been correlated with the incidence of HCC and FIB-4 is known to be a good predictor of fibrosis and cirrhosis **[25-29].** In current study, median FIB-4 in HCC group was 6.257 in agreed with Li et al. (2019) who found that FIB-4 was 6.66 in HCC group **[17]**, also there was a highly significant difference ($p<0.0001$) in FIB-4 between LC and HCC compared to NDC but no significance difference was recorded between LC and HCC.

For inflammatory markers used in HCC diagnosis, we assessed PLR, CRP and NLR, which are commonly assessed through blood tests. These markers act to quantify the systemic inflammatory response linked to HCC and its potential impact on patient outcomes. All of these conditions are associated with inflammation, such as hepatocellular carcinoma **[30].** The platelet-to-lymphocyte ratio (PLR) has been identified as a potential indicator of both malignancy and inflammatory conditions **[31].** PLR is a well-established biomarker that assesses inflammatory and immune responses. It is a known prognostic factor in various malignancies, with elevated PLR values often correlating with unfavorable clinical outcomes in patients with HCC **[32]**, While it is a useful marker, it's not typically used as a distinct diagnostic tool, however, we found that there was a significant difference between HCC and LC compared to NDC **(P<0.05)** but no significant difference between HCC and LC groups, in contrast to Chen et al. (2024) **[33]** who conducted that there was a significant difference in PLR between HCC patients and LC cirrhosis ***(p < 0.0001).***

CRP is acute-phase reactant produced by liver cells in response to inflammation **[34].** Blood CRP levels are increased due to inflammation occurred with the incidence of various cancers, including HCC **[35].** Even though it found in very high values in cirrhotic patients and secreted in the presence of HCC, it isn't a diagnostic marker for HCC **[36,37].** however it is still been noted to have significant prognostic value **[38-40].** Currently, CRP showed highly significant difference in HCC and LC compared to NDC ***(p<0.05).***

The neutrophil to lymphocyte (NLR) ratio in the peripheral blood **[41]** has also been proven to be a valuable indicator of the inflammatory state and a predictor of clinical survival in HCC **[42, 43]** and it has already been proven to be associated with a poor prognosis across a range of tumors **[44].** Currently, we found a highly significant difference in NLR in HCC and LC groups compared to NCD group. However its ability to distinguish HCC from LC is limited. This means that NLR isn't specific enough in HCC diagnosis.

Alfa-fetoprotein (AFP) is a fetal-specific glycoprotein produced by the fetus's liver and its synthesis is suppressed in adult **[10].** Currently, serum AFP expression levels were significantly higher in HCC group compared to LC and NDC group in agree with other reports **[45,46].**

Gamma-glutamyltransferase (GGT) is a cell membrane-bound enzyme secreted in healthy adults by endothelial cell of bile duct and hepatic Kupffer cell and its activity increases in fetal liver and HCC **[47].** Several studies reported that serum GGT was effective diagnostic biomarker of hepatobiliary disease and various tumors **[48,49].** GGT plays a role in the growth and development of HCC **[50,51].** GGT levels abnormally increase in other liver diseases such as a viral hepatitis, alcoholic hepatitis, and liver cirrhosis, so it can't be used as effective indicator for HCC screening **[42].** In current study, GGT showed higher activity in LC and HCC compared to NDC group ***(p<0.05),*** although higher levels of GGT in HCC compared to LC was detected non significant. GGT was associated with ALT and Pt count. Also, AFP was significantly correlated with AST, ALT, Pt and NLR**.** Regression analysis showed AFP, ALT, Pt and INR displayed substantial prediction for tumor development. The diagnostic performance of AFP, ALT, and Pt using ROC curve analysis demonstrated only AFP with excellent accuracy (90.2%) and AUC of 0.972 supporting its clinical applicability.

Conclusion

Non-invasive inflammatory markers an fibrotic indices are involved in disease severity of the liver. ALT, Pt and INR displayed substantial prediction for tumor development and could be used as early predictors for HCC.

Table (2) Correlation between AFP, GGT and AST with other biomarkers in all patients groups

AFP		
Variable	***Rho***	***P value***
AST	0.253	0.022
ALT	0.350	0.001
NLR	-0.285	0.009
Pt	0.255	0.021
GGT		
ALT	0.311	0.004
Pt	0.229	0.038
AST		
ALT	0.682	<0.0001
AAR	-0.599	<0.0001
APRI	0.680	<0.0001
FIB4	0.457	<0.0001
NLR	-0.350	0.001
PLR	-0.306	0.005
AFP	0.253	0.022

Data was presented by Spearman correlation Coefficient test

Table (3) Regression Analysis of AFP, GGT, ALT, Pt and INR as independent predictors in HCC development

Predictor	B	SE	P value	95% CI	OR
AFP	-0.209	0.048	<0.0001	0.739-0.891	0.812
GGT	-0.005	0.006	0.392	0.983-1.007	0.995
ALT	-0.032	0.015	0.03	0.940-0.097	0.968
Pt	-0.018	0.007	0.014	0.969-0.996	0.982
INR	1.546	0.812	0.057	0.956-23.027	4.693

Table (4) Diagnostic performance of AFP, for discriminating HCC from LC

Variable	AUC	P value	Cut-off	95% CI	Sens.	Spec.	LR+	LR-	PPV	NPV	Accuracy
AFP	0.972	≤0.0001	18.5	0.00-1.0	81.1	95.6	18.43	0.197	93.9	0.877	90.2
ALT	0.673	0.007	21.5	0.557-0.789	83.8	40.0	1.39	0.405	53.4	75.0	59.8
Pt	0.634	0.038	46.0	0.511-0.756	75.7	40.0	1.26	0.607	50.9	66.7	56.1

AUC; Area under ROC curve, PPV; Positive predictive value, NPV; Negative predictive value

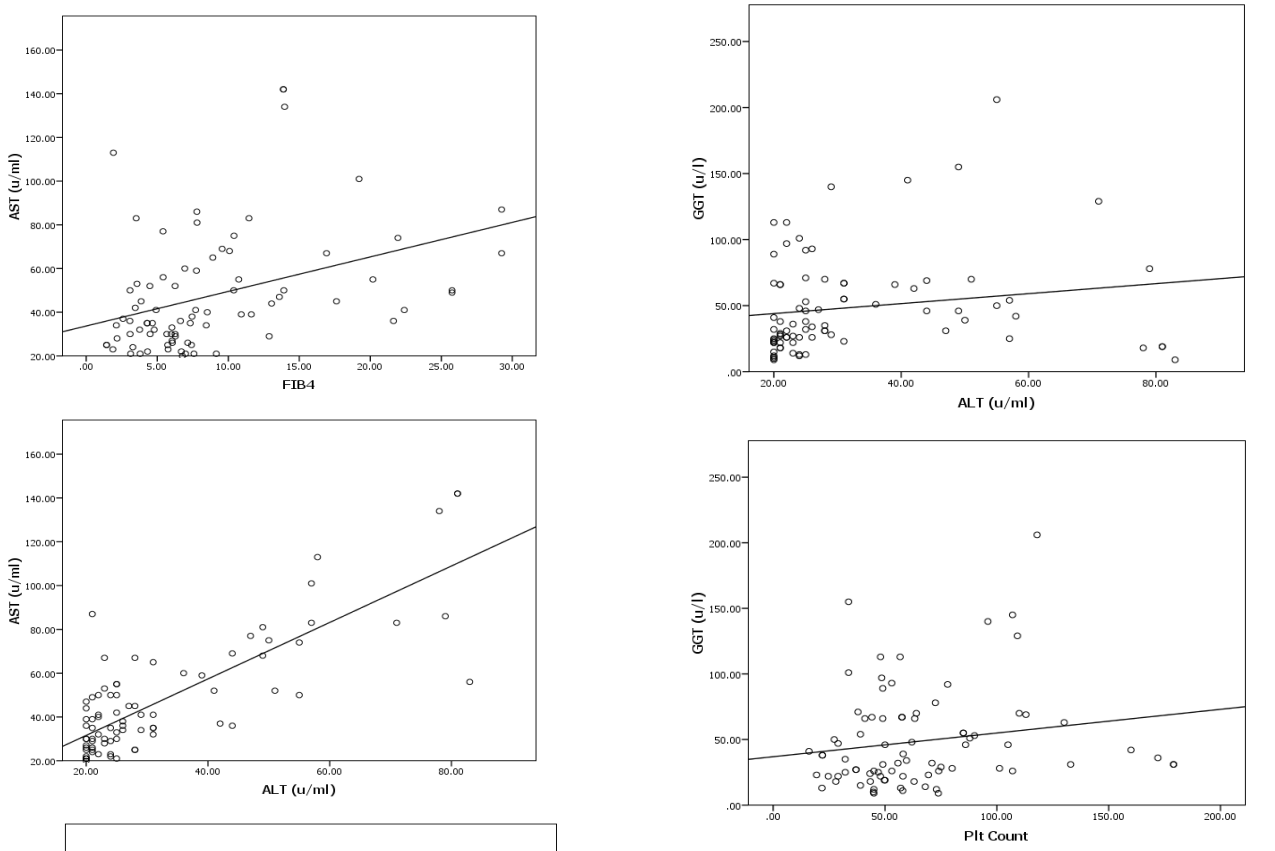
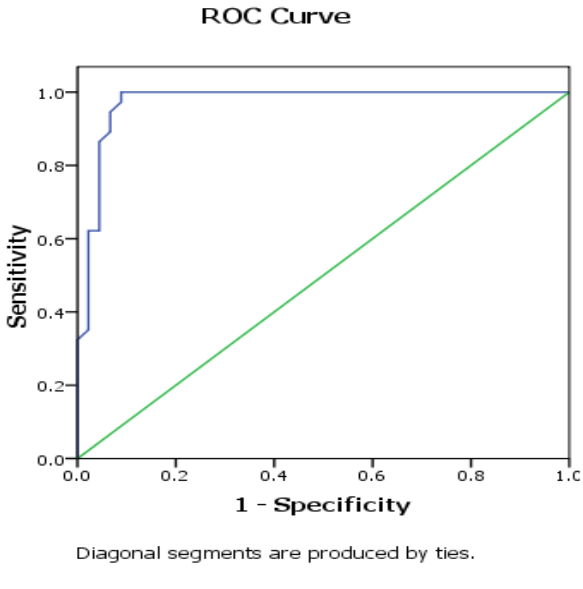
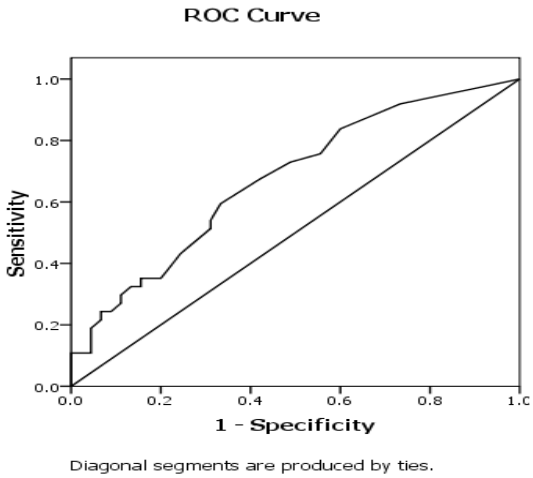


Figure (1) Spearman correlation of GGT with ALT and Pt and of AST with ALT, AAR, APRI and FIB4



AFP



ALT

Figure (2) ROC curve of AFP, ALT

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