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Interleukin-18 Could Serve as a Promising Noninvasive Marker for Esophageal Varices: More than Correlation to Hepatic Dysfunction

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ABSTRACT

Background: Noninvasive screening methods for esophageal varices (EVs) are beneficial to avoid unnecessary esophagogastroduodenoscopy (EGD). This study aimed to determine serum IL-18 levels in liver cirrhosis patients and to assess the association of serum IL-18 levels with EVs.

Method: Case-control research including 54 cirrhotic patients brought on by hepatitis C virus infection and 18 healthy controls. All subjects were subjected to a thorough physical examination, a history assessment, and a set of laboratory tests, including those for alpha-fetoprotein, hepatitis markers, liver function and serum IL-18.

Result: Serum IL-18 was significantly higher in patients with cirrhosis compared with the normal control, as well as in patients with cirrhosis with EVs than in patients without EVs. No significance detected between patients with cirrhosis with and without bleeding EVs. IL-18 was positively correlated with serum bilirubin level, portal vein diameter, spleen diameter, Child–Pugh, and Model for End-Stage Liver Disease scores and negatively correlated with serum albumin, PV velocity, and platelet count. Additionally, IL-18 was significantly correlated with noninvasive scores of liver fibrosis and PH. The univariate logistic regression revealed IL-18, Child–Pugh score, platelet count, serum albumin, PV diameter, SD, and platelet count/SD ratio as potential EV predictors. **Conclusion:**IL-18 yields a significant clinical value for liver cirrhosis and EV development. A cut-off value of >428 pg/ml can predict EV in liver cirrhosis with 66.67% sensitivity and 94.44% specificity but without an apparent role in variceal bleeding prediction.

Keywords: Interleukin-18; Esophageal Varices; Portal Hypertension; Cirrhosis; Hepatitis C Virus**.**

INTRODUCTION

Esophageal varices (EVs), one of the most frequent adverse effects of liver cirrhosis, affect 60% to 80% of those who have the disease. Variceal bleeding from a ruptured EV remained the most fatal side effect of liver cirrhosis with mortality reaching 15%–55% of cases. Therefore, EV screening and prediction are clinically significant in preventing and decreasing bleeding events and associated fatal outcomes in cirrhotic patients. [1].

Esophagogastroduodenoscopy (EGD) is considered the gold standard method for screening EVs. However, this is troublesome in developing countries because of the higher burden of liver cirrhosis and the logistic limitations of using endoscopy [2]. Hence, carefully selecting the population in greatest need of EV screening and reducing the burden of unwarranted endoscopies are critical needs.

The reversal and subsequent regression of liver fibrosis, which holds significant therapeutic effects for chronic liver disease and portal hypertension (PH), have been better understood as a result of the proinflammatory signaling pathway of liver fibrosis that causes extracellular matrix deposition by activating hepatic stellate cells. [3].

Several cells, including macrophages, Kupffer cells, and monocytes, secrete interleukin (IL)-18. It participates in the expression of tumor necrosis

factor and interferon, activation of T cells and vascular endothelial cells, and the generation of nitric oxide and chemokines [4]. Additionally, inflammasomes are multiprotein structures that recognize various exogenous and endogenous danger signals before activating IL-1 and IL-18, which are essential for the onset and progression of chronic liver disease. [5].

Numerous noninvasive indicators for liver cirrhosis and EVs have been studied; however, early detection of inappropriate immune system changes attributed to the pathogenesis of complications from liver cirrhosis, like EV development and variceal bleeding, may be helpful to overcome these complications, delaying disease progression, lowering mortality, and allowing for the development of novel lines of therapy for cirrhosis and PH [3].

The goal of managing patients without EV is to prevent clinical decompensation, whereas the goal of managing patients with EV is to prevent variceal bleeding according to the American Association for the Study of Liver Diseases guidelines 2017 [6].

The Baveno VII consensus recommendations on PH in patients with virus-related compensated advanced chronic liver disease (cACLD) state that a liver stiffness measurement (LSM) value via transient elastography (TE) of >25 kPa is sufficient to rule in CSPH (specificity and positive predictive value of >90%), identifying the patient population at risk for endoscopic PH signs and at higher risk of decompensation. Additionally, in patients with hepatitis C virus (HCV)- and HBV-induced cACLD who achieved persistent virologic response and viral suppression, respectively, LSM of 20 kPa and platelet of >150x10^3/uL are applied to rule out high-risk varices [7].

This study aimed to study the relationship between IL-18 and hepatic dysfunction and as a noninvasive marker for EV detection in patients with cirrhosis. We hope to add IL-18 to LSM, and platelet count to increase diagnosis and avoid unnecessary EGDs.

PATIENT AND METHODS

2.1. Study Design and Population

This case-control study was carried out on 54 Egyptian patients with liver cirrhosis caused by HCV infection from the Gastroenterology and Hepatology Intensive Care Unit, endoscopy unit, inpatient wards, and outpatient clinic of the Internal Medicine Department, Zagazig University Hospitals, and 18 healthy people as a control group. Four groups each of 18 participants were picked up:

Group I included age and sex matched healthy subjects as a control group; **Group II** included cirrhotic patients without EV; **Group III** included cirrhotic patients with EV who had never experienced variceal bleeding; **Group IV** included cirrhotic patients with EV and history of variceal bleeding.

Ethical Clearance: The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (No.6018). The study was done according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

2.1.1. Exclusion Criteria

Patients having cirrhosis caused by conditions other than HCV, any inflammatory or infectious conditions (including sepsis, TB, and rheumatoid arthritis), or those who had recently had antibiotic medication were not allowed to participate in the trial. Patients with severe cardiac and chronic kidney diseases, hepatocellular carcinoma (HCC), or other malignancies, as well as those with endoscopic contraindications or who refused to participate in the trial, were all discarded from the study.

2.2. Operational Design

All patients underwent thorough history taking and physical examination.

Laboratory investigations included complete blood count, liver function tests, bleeding profile, renal function tests, alpha-fetoprotein, and hepatitis markers.

Radiological investigations involved abdominal ultrasonography to assess the liver morphology, spleen diameter (SD), PV diameter, PV velocity, splenic vein diameter, ascites, PV thrombosis, and focal lesion. A suspected hepatic focal lesion underwent dynamic computed tomography or magnetic resonance imaging to rule out HCC.

Endoscopy reports of upper gastrointestinal tract endoscopy findings for all cirrhotic cases were included according to **Paquet classification** [8].

Scores for Child-Pugh and MELD (Model for End-Stage Liver Disease) were estimated.

Noninvasive scores for cirrhosis and EVs, such as aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) score, platelet count/SD ratio, and fibrosis-4 (FIB4), were estimated.

2.3. Serum IL-18 Levels

Measuring IL-18, two ml of blood samples in a plain tube without any additives were centrifuged for 10–20 minutes at a speed of 2000–3000 rpm to separate the serum, which was then stored at -80°C The manufacturer's recommendations were followed

while measuring serum IL-18 levels with an enzyme-linked immunosorbent test kit, *(Shanghai Sun red Biological Technology Co.)* (Cat. No. 201-12-0148). A standard curve was used to calculate the IL-18 levels using Pg/mL to interpret the results.

2.4. Statistical Analysis

Statistical Package for the Social Sciences version 24 and National Council for the Social Studies 12, LLC, USA were used to computerize and statistically analyze the collected data. Using the Shapiro-Wilk test, the distribution of the data was checked for normal distribution. Data were represented as frequencies and relative percentages or mean ± standard deviation as indicated. The following tests were used as needed: Kruskal-Wallis, Fisher exact, one-way analysis of variance F-test, and the chi-square test (2). A post hoc test for multiple comparisons was conducted using the least significant difference or Dunn's multiple comparisons. Pearson's and Spearman's correlation tests were used as indicated. To enable the determination of the cut-off value for EV detection, the receiver operating characteristic (ROC) curve was developed. To find the independent factors for EV, univariate and multivariate logistic regression analytic models were applied. At a 95% confidence level, a P-value of 0.05 was found statistically significant.

RESULTS

3.1. Clinico-Demographic, Laboratory, and Endoscopic Data of the Studied Groups

According to age and sex, patients and controls were matched; however, a statistically significant difference was found regarding Child–Pugh score, leukocytic count, hemoglobin level, platelet count, AST, alanine aminotransferase, serum albumin, total bilirubin, direct bilirubin, urea, creatinine, prothrombin time (PT), international normalized ratio (INR), alpha-fetoprotein (AFP), and serum IL-18 between the considered groups, as shown in Table (1) and there was Post-hoc test to indicate which groups were significantly different from each other as shown in supplementary table (7).

3.2. Radiological Variables Among Patients with Liver Cirrhosis

A statically significant difference was observed between cirrhotic patients with EV and cirrhotic patients without EV as regards PV diameter, PV velocity, and SD ($p < 0.001$), but splenic vein diameter was statically nonsignificant. However, the post hoc test showed that these variables cannot differentiate between cirrhotic patients with bleeding EV and cirrhotic patients without bleeding EV ($p > 0.05$), as shown in **Table (2).**

3.3. Noninvasive Scores for Liver Cirrhosis and EV Prediction Among Patients with Cirrhosis

While there was no statistically significant difference between the groups in terms of APRI and FIB4, there was a statistically significant difference in terms of platelet/SD (p 0.001). However, a more thorough study found no statistically significant difference in platelet/SD between cirrhotic patients with bleeding EV and those without bleeding EV ($p > 0.05$), as shown in **Table (3).**

3.4. IL-18 Level in the Considered Populations

According to Table 1, there was a highly statistically significant difference in IL-18 levels between the cirrhotic group and the control group ($p < 0.001$), and this difference was significantly associated with advanced Child's classes B and C in compared to class A (median values for Child's classes A, B, and C were 403, 493, and 687, respectively ($p< 0.001$), as shown in Figure 1.

Moreover, a statistically significant difference was detected between patients with cirrhosis without EV (median: 382, range: 310–452) and patients with cirrhosis with EV (median: 486, range: 354–763) regarding IL-18 levels ($p < 0.001$). However, no statistically significant difference was detected between patients with cirrhosis with bleeding EV (median: 451, range: 354–684) and patients with cirrhosis without bleeding EV (median: 475, range: 402–763) regarding IL-18 levels ($p = 0.101$), as shown in Figure 2 (A).

IL-18 levels were significantly higher in patients with cirrhosis with EV than in patients with cirrhosis without EV. But its levels were not influenced by the EV grade or the presence of gastric varices, with median (ranges) of 468 (410-513), 482 (354-763), and 462 (397-517) for grades II, III, and IV EV, respectively ($p > 0.05$), as shown in **Figure 2 (B).**

3.5. Correlations Between IL-18, pg/mL Level, and Clinic-Laboratory Variables in Patients with Cirrhosis

Significant direct correlations were found between IL-18 and PV diameter, SD, total bilirubin, direct bilirubin, PT, INR, AFP, APRI, FIB4, Child–Pugh score, and MELD score, whereas a significant negative correlation was noted between IL18 and PV velocity, platelet count, serum albumin, and platelet count/SD, as shown in **Table (4)** and **Figure 3**.

3.6. Validity of IL-18 pg/mL Level as a Diagnostic Marker for EV in Patients with Cirrhosis

As demonstrated in **Figure 4**, using ROC curve analysis, a cut-off points of IL-18 of >428 was able

to detect the presence of EV with 66.67% sensitivity and 94.44% specificity, 96.6% positive predictive value, 58.6% negative predictive value, 0.864 area under the curve, and p-value of <0.001.

3.7. Potential Predictors of EV Among Various Studied Parameters

Child-Pugh score (p 0.01), PC (p 0.002), serum albumin (p = 0.002), IL-18 (p = 0.001), PV diameter (p = 0.001), and platelet count/SD ratio (p = 0.001) were all significant in the univariate analysis and splenic diameter (p = 0.01) as significant potential predictors for EV, as shown in **Table (5).** However, the stepwise multivariate logistic regression only revealed platelet count/SD ratio as a key predictor of EV with 95% CI for odds ratio (OR) of 0.981–0.997 and *p* = 0.008. Additionally, PV diameter was another reliable predictor of EV with a 95% CI for OR of 1.141–17.22 and *p* = 0.031 as shown in **supplementary Table (6).**

Table 1. Clinico-demographic, laboratory, and endoscopic data of the studied groups.

		Group I N = 18	Group II N = 18	Group III N = 18	Group IV N = 18	Test	P
Age (years)		49 ± 5	48 ± 4	51 ± 5	49 ± 4	2.7	0.432
Sex	Female	3 (16.7%)	4 (22.2%)	3 (16.7%)	4 (22.2%)	0.4	0.949
	Male	15 (83.3%)	14 (77.8%)	15 (83.3%)	14 (77.8%)		
Child–Pugh score	A	–	15 (83.3%)	10 (55.6%)	10 (55.6%)	54.1	<0.001
	B	–	3 (16.7%)	5 (27.8%)	5 (27.8%)		
	C	–	0 (0.0%)	3 (16.7%)	3 (16.7%)		
MELD		-	12 (9–17)	14 (7–21)	13 (7–19)	0.8	0.686
Leukocyte's count (10^9/L)		7.7 (6.2-9.6)	6.1 (4.2–9.3)	4.3 (2.8–7.6)	5.2 (3.5–6.8)	32.2	<0.001
Hemoglobin (gm/dl)		13.2 ± 1.0	12.0 ± 1.0	10.6 ± 1.3	10.2 ± 1.5	35.7	<0.001
Platelet (×10^3)		244 ± 63	158 ± 26	119 ± 41	122 ± 28	43.4	<0.001
AST (u/l)		31 (19–38)	63 (43–97)	46 (33–75)	48 (35–77)	43.7	<0.001
ALT (u/l)		21 (16–33)	49 (29–73)	39 (29–83)	37 (26–63)	39.2	<0.001
S. albumin (g/dl)		4.48 (3.80–4.90)	3.80 (3.30–4.20)	3.50 (2.70–4.00)	3.50 (2.70–4.00)	43.7	<0.001
Total bilirubin (mg/dl)		0.82 (0.60–1.00)	1.60 (1.10–2.10)	1.65 (1.00–3.70)	1.60 (0.90–3.30)	38.9	<0.001
D. bilirubin (mg/dl)		0.20 (0.10–0.30)	0.90 (0.70–1.30)	0.90 (0.30–2.40)	0.70 (0.20–1.80)	39.4	<0.001
PT		11.82 ± 0.57	14.59 ± 1.39	15.77 ± 3.45	15.29 ± 2.53	26.5	<0.001
INR		1.02 ± 0.08	1.34 ± 0.20	1.42 ± 0.31	1.38 ± 0.22	27.3	<0.001
AFP (ng/ml)		2.7 (1.6-4.3)	5.2 (2.4–9.5)	5.2 (3.5–16.7)	4.9 (2.9–17.0)	28.4	<0.001
B. urea (mg/dl)		24 (19-29)	28 (17–43)	27 (21–48)	31 (22–69)	12.4	0.006
S. creatinine (mg/dl)		0.9 (0.6-1.1)	1.1 (0.8–1.3)	1.0 (0.7–1.4)	1.0 (0.6–1.3)	9.4	0.025
IL-18 (pg/mL)		249 (191-289)	382 (310–452) **	451 (354–684) **, ***	475 (402–763) **, ***	51.4	<0.001 *
EV grade							
Grade II		-	–	5 (27.8%)	2 (11.1%)	1.7.0	0.424
Grade III		-	–	9 (50.0%)	12 (66.7%)		
Grade IV		-	–	4 (22.2%)	4 (22.2%)		
Gastric varices		-	–	2 (11.1%)	3 (16.7%)	0.22	0.647

Continuous variables are described as mean ± SD for normally disturbed variables and compared using the one-way ANOVA test and median (range) for nonnormally disturbed variables and compared using the Kruskal–Wallis test, whereas qualitative variables were expressed as numbers and percentages and compared using the Chi-square X^2 test.

* Significant P-value when comparing between all groups.

** Significant P-value when comparing patients with cirrhosis with control.

*** Significant P-value when comparing patients with EV with patients without EV.

- 83.3% of group II were child A compared with group III, IV were 55.6% and it was highly significance difference.

-Post-hoc analysis for Child Paugh score: Group II Vs. III,Group II Vs. IV and Group III Vs. IV *were* 0.012, 0.019 and 0.847 respectively

Table 2. Radiological variables among patients with liver cirrhosis.

	Group II N = 18	Group III N = 18	Group IV N = 18	KW test	P
PV diameter	12 (10–14)	14 (11–16) **,***	14 (12–16) **,***	19.6	<0.001*
PV VELOCITY	25 (17–37)	14 (10–19) **,***	14 (9–25) **,***	29.1	<0.001*
Splenic V diameter	9 (8–12)	10 (8–13)	11 (7–13)	4.2	0.121
Spleen diameter cm	12.6 ± 1.1	15.6 ± 1.1**,***	15.9 ± 1.0**,***	34.4	<0.001*

* Significant p-value (<0.05) between three groups.
** Significant p-value (<0.001) when compared with group II.
*** Nonsignificant p-value (>0.05) when comparing group III with IV.

Table 3. Noninvasive scores for liver cirrhosis and EV among patients with liver cirrhosis.

	Group II N = 18	Group III N = 18	Group IV N = 18	KW test	P
APRI	1.0 (0.6–1.8)	1.1 (0.5–2.0)	1.1 (0.6–2.0)	0.27	0.873
Plat/spleen diameter	1260.92 ± 259.61	752.82 ± 214.13**,***	774.28 ± 183.41**,***	54.1	<0.001 *
FIB4	2.97 (1.95–4.39)	3.29 (1.35–5.96)	3.35 (1.79–5.40)	2.4	0.287

* Significant p-value (<0.05) between three groups.
** Significant p-value (<0.001) when compared with group II.
*** Nonsignificant p-value (>0.05) when comparing group III with IV.
Post-hoc analysis for Plt/Spleen Diameter: Group II Vs. III, Group II Vs. IV, and Group III Vs. IV were P <0.001, <0.001 and 0.772 respectively

Table 4. Correlations between IL-18 level and various variables in the cirrhotic group [II, III, and IV].

Cirrhotic group	IL-18, pg/mL	
	R	*P*-value
Age	0.234	0.089
PV diameter	0.532	<0.001*
PV velocity	−0.464	<0.001*
Splenic V diameter	0.254	0.064
SD cm	0.386	0.004*
Platelet count	−0.618	<0.001*
AST	−0.142	0.306
ALT	−0.011	0.934
S. albumin	−0.818	<0.001*
Total bilirubin	0.637	<0.001*
D. bilirubin	0.390	0.004*
PT	0.591	<0.001*
INR	0.613	<0.001*
AFP	0.283	0.038
Child–Pugh score	0.811	<0.001*
APRI	0.374	0.005*
MELD	0.668	<0.001*
PC/SD	−0.655	<0.001*
FIB4	0.488	<0.001*

* Significant *p*-value (<0.05).

Table 5. Univariate logistic regression of potential EV predictors.

Covariate	P	OR	95% CI for OR
Child–Pugh score	0.017	1.93	1.13–3.31
MELD	0.488	1.06	0.90–1.24
Platelet	0.002	0.96	0.94–0.99
S. albumin	0.002	0.02	0.00–0.24
Total bilirubin	0.108	2.52	0.82–7.75
D. bilirubin	0.983	0.99	0.28–3.48
INR	0.338	3.23	0.29–35.52
AFP	0.152	1.17	0.94–1.45

Covariate	P	OR	95% CI for OR
S. creatinine	0.461	0.33	0.02–6.24
IL-18, pg/ml	0.001	1.03	1.01–1.05
PV diameter	0.001	3.43	1.70–6.89
Splenic V diameter	0.050	1.54	1.00–2.38
APRI	0.752	1.29	0.27–6.24
PC/SD ratio	0.001	0.99	0.98–1.00
SD cm	0.016	130.90	2.52–6806.22
FIB4	0.078	1.73	0.94–3.17

OR: odds ratio; 95% CI: 95% confidence interval, $p < 0.05$ is significant.

Supplementary table:

Table 6. Stepwise multivariate logistic regression of potential predictors of OV

Covariate	P	OR	95%CI for OR
Plt/Spleen Diameter	0.008	0.989	0.981-0.997
P.v diameter	0.031	4.434	1.141-17.22

OR: odds ratio; 95%CI: 95% confidence interval, p< 0.05 is significant.

Plt/Spleen Diameter and P.v diameter were independent predictors for OV.

Table 7. Post-hoc test, to indicate which groups were significantly different from each other

	Group I Vs. II	Group I Vs. III	Group I Vs. IV	Group II Vs. III	Group II Vs. IV	Group III Vs. IV
Leukocyte's count	0.003	<0.001	<0.001	0.001	0.003	0.659
Hemoglobin	0.005	<0.001	<0.001	0.001	<0.001	0.324
Platelet	<0.001	<0.001	<0.001	0.008	0.015	0.835
AST	<0.001	<0.001	<0.001	<0.001	<0.001	0.846
ALT	<0.001	<0.001	<0.001	0.139	0.01	0.255
S. Albumin	<0.001	<0.001	<0.001	<0.001	0.001	0.965
total bilirubin	<0.001	<0.001	<0.001	0.073	0.131	0.77
D. bilirubin	<0.001	<0.001	<0.001	0.677	0.647	0.383
PT	<0.001	<0.001	<0.001	0.124	0.354	0.536
INR	<0.001	<0.001	<0.001	0.239	0.502	0.609
AFP	0.024	<0.001	0.001	0.065	0.269	0.448
B. urea	0.16	0.119	<0.001	0.877	0.016	0.024
s. creatinine	0.004	0.024	0.019	0.48	0.536	0.929
IL-18, pg/mL	<0.001	<0.001	<0.001	0.001	<0.001	0.101
P.V diameter	-	-	-	<0.001	<0.001	0.709
P.V VELOCITY	-	-	-	<0.001	<0.001	0.854
Spleen Diameter cm	-	-	-	<0.001	<0.001	0.532

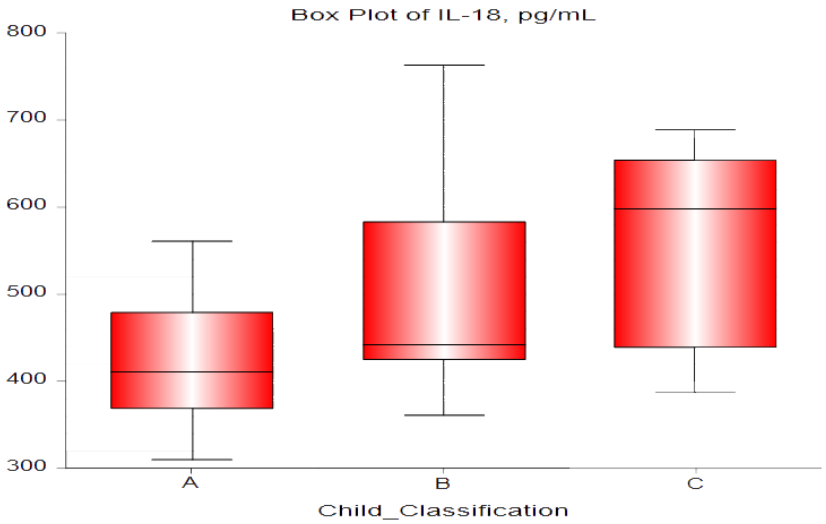
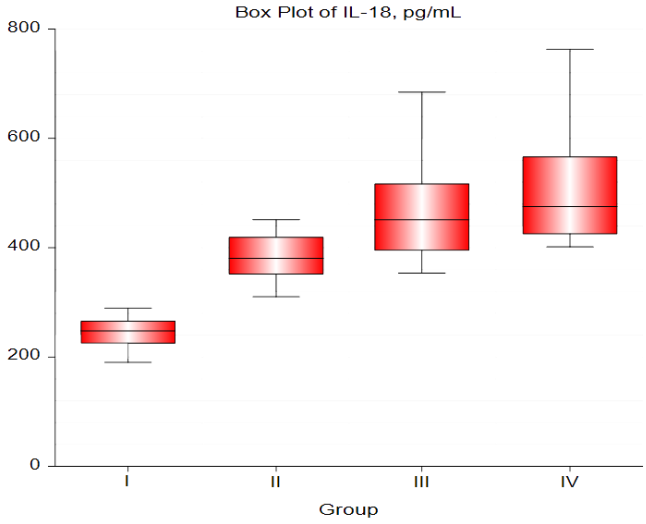


Figure 1. The range of IL-18, pg/mL, in different Child's classes.



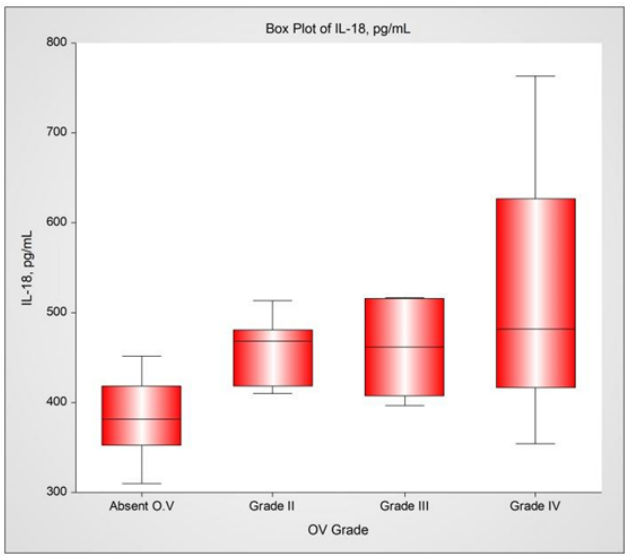


Figure 2. (A)The range of IL-18, pg/mL, in different groups.
(B) The range of IL-18, pg/mL, in different EV grades

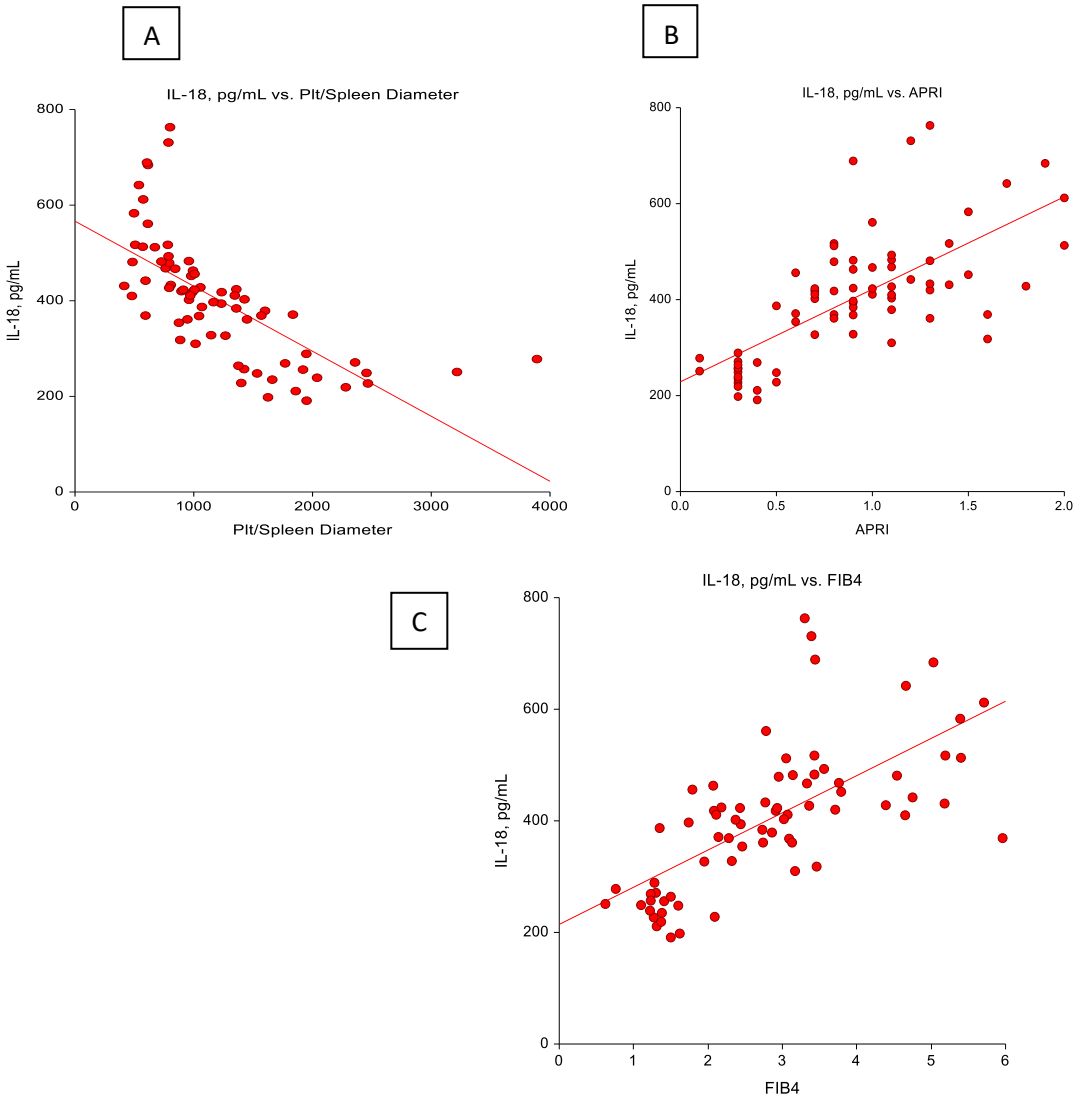


Figure 3. Correlation of IL-18 with (A) platelet count to splenic diameter ratio, (B) APRI score, and (C) FIB4.

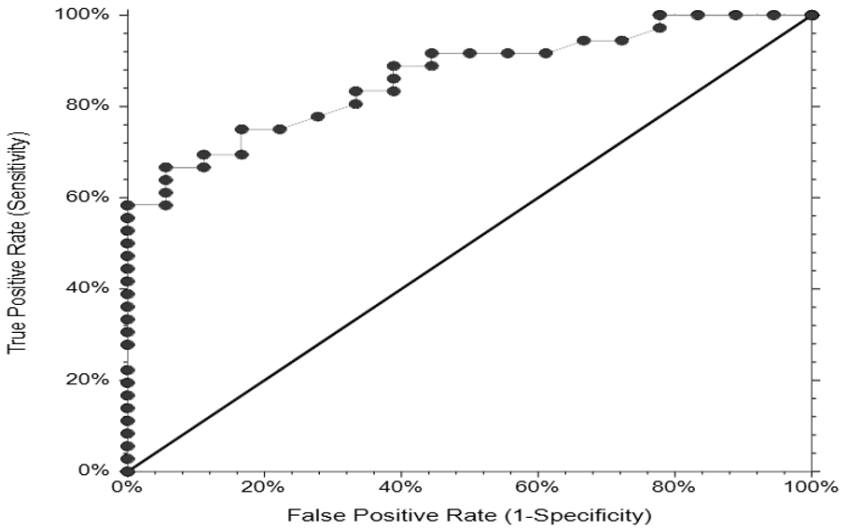


Figure 4. The ROC curve for diagnostic performance of IL-18, pg/mL, as a noninvasive marker for EV in patients with cirrhosis.

DISCUSSION

Many patients with liver cirrhosis were discovered in the past ten years at an early stage due to advancements in noninvasive diagnostic techniques. Due to the extremely low prevalence of high-risk varices (HRV) in individuals with early liver cirrhosis, most screening gastroscopies result in negative results. However, gastroscopy is a costly, invasive technique. However, none of these techniques, either separately or in combination, have been shown to be accurate enough to take the role of upper GI endoscopic examinations in the diagnosis or exclusion of EV or HRV [9].

Numerous cells, such as macrophages, Kupffer cells, and monocytes release IL-18, which can be extremely important in the onset and progression of chronic liver disease. Patients with chronic hepatitis C have higher levels of IL-18 than in healthy individuals. The fact that its level increases significantly as the disease progresses histologically and fibrosis progresses indicates the role of IL-18 in liver injury. IL-18 could therefore be employed as another noninvasive marker for assessing the level of liver fibrosis in patients with chronic hepatitis C [10].

The present study aimed to assess IL-18 serum levels in cirrhotic patients with and without EVs and correlate its level with standard EGD findings, as well as assess IL-18 as a noninvasive marker for EV prediction in cirrhotic patients to overcome the unnecessary EGD that needs special centers and expertise.

The current study found that individuals with cirrhosis had statistically significantly higher levels of IL-18 than did controls and deep analysis revealed an increasingly significant difference between various groups of study as regards IL-18 with a median range of 249, 382, and 468 for the control (I), cirrhosis without EV (II), and cirrhosis with EV (III and IV) groups, respectively.

Our findings corroborated earlier research by Swidnicka-Siergiejko et al. [11], who found that median IL-18 levels were significantly higher in cirrhotic patients than in healthy controls. (506.25 vs 242.10). Additionally, a study conducted by Anton Komala et al. revealed a statistically significant higher IL-18 level in liver cirrhosis (688 ± 674.3 pg/ml) compared with control (163.9 ± 100 pg/ml) [12]. Another study conducted by Ludwiczek et al. reported similar results [13].

This is revealed by markedly elevated IL-18 mRNA levels in chronic HCV-infected patients, and IL-18 continues to have a proinflammatory function in HCV infection that can exacerbate hepatic damage [14]. Furthermore, Vecchiet et al. and Sharma et al. found a correlation between elevated IL-18 levels in HCV-infected patients and the severity of the disease, confirming that the disease progresses along with an increase in IL-18 levels and strongly supporting the involvement of IL-18 in causing liver injury [15,16]. Furthermore, this theory is strongly supported by a substantial drop in serum IL-18 levels following treatment [17].

At the current study, on top of that statistically significant correlation between IL-18 and Child-Pugh score was found. This agrees with Sharma et al. findings that the Child-Pugh score significantly predicted the degree of liver dysfunction and the course of the disease [16]. Like this, Swidnicka-Siergiejko et al. found that individuals with liver cirrhosis grade C had statistically significantly higher levels of IL-18 than those with Child-Pugh grades B or A [11].

Those with cirrhosis with EV had significantly higher levels of IL-18 than patients with cirrhosis without EV. To the best of our knowledge, this is the first study to investigate the correlation between elevated IL-18 levels and the establishment of PH complications such EVs.

According to Volin and Koch, IL-18 has both direct and indirect effects on angiogenesis by generating angiogenic mediators, including vascular endothelial growth factor, which is important for the establishment of portal-systemic collaterals and sinusoidal remodeling in PH [18–20]. Because it promotes inflammation, endothelial dysfunction, and angiogenesis, IL-18 has a significant impact on how PH and EVs develop.

Despite those patients with cirrhosis with EV bleeding having higher IL-18 levels than cirrhotic patients without EV bleeding, this was nonsignificant, and this was following Swidnicka-Siergiejko et al., who experienced a nonsignificant difference between bleeding and nonbleeding variceal groups with p-values of 0.73 [11].

Additionally, IL-18 levels were significantly unrelated to EV grade or the presence of gastric varices in patients with cirrhosis with EV compared to individuals with cirrhosis without EV. This was also in line with the findings of Swidnicka-Siergiejko et al., who found no discernible variations in median IL-18 concentration when varices size was considered [11].

We noted a significant direct correlation between IL-18 and PV diameter, SD, Child–Pugh score, and MELD score, and a negative correlation between IL-18 with PV velocity and platelet count for each. Similar results were noted by Swidnicka-Siergieko et al. [11], who discovered a substantial direct association between IL-18 and the Child-Pugh score and MELD score as well as a significant inverse correlation between IL-18 and the platelet count and PV velocity. [11], our results for PV diameter and SD were inconsistent. This might be because of the different etiology and severity of liver cirrhosis in our study.

Additionally, in individuals with cirrhosis, IL-18 was inversely correlated with serum albumin and positive correlated with INR level and serum bilirubin. This was in line with the findings of Swidnicka-Siergiejko et al. and El-Hendawy et al., who found a statistically significant negative correlation between IL-18 and serum an albumin and significant positive correlation between IL-18 and INR level and serum bilirubin and who explained that this was because IL-18 serum levels may reflect the severity of liver disease in which decrease in liver synthetic capacity [11,21].

In addition, we found a strong relationship between IL-18 and noninvasive measures of PH and liver fibrosis in cirrhosis patients, including APRI, PC/SD, and FIB-4. This is the first study that, to our knowledge, links serum IL-18 levels with noninvasive measures of liver fibrosis. However, El-Amin et al. observed that serum IL-18 is markedly elevated and is associated with TE-staged liver fibrosis. Therefore, in individuals with chronic hepatitis C, IL-18 can be employed as a noninvasive proinflammatory marker to assess the severity and chronicity of liver fibrosis [22]. Equally, Selim et al. and Said et al. found that there was a statistically significant direct link between IL-18 plasma level and the severity of liver disease as measured by METAVIR necro-inflammatory grade (A) and fibrosis stage (F) [10,23].

Our univariate logistic regression analysis for potential predictors of EV revealed that serum IL-18 levels served as a potential predictor of EV, as well as other variables, such as Child–Pugh score, platelet count, serum albumin, PV diameter, platelet count/SD ratio, and SD ($p < 0.05$). We represent the first study to investigate IL-18 as an independent predictor of EVs. Therefore, we conclude that IL-18 may serve as a recent promising predictor for the noninvasive diagnosis of cirrhosis and EV besides other previously investigated variables although the multivariate logistic regression analysis revealed only platelet count/SD and PV diameter as the key predictors of EV.

Additionally, we investigated the most accurate cut-off point for IL-18 to distinguish between cirrhosis patients with EV and cirrhosis patients without EV, and we discovered that a cut-off value >428 pg/ml significantly detect EV with 66.67% sensitivity, 94.44% specificity, and a p-value of <0.001.

CONCLUSION

IL-18 yields a significant clinical value for liver cirrhosis progression, as well as PH and EV development. A cut-off value of >428 was able to predict EV in liver cirrhosis but did not

demonstrate an apparent role in the prediction of variceal bleeding. Therefore, IL-18 may be used as a noninvasive predictor for EVs to help prompt intervention and avoid unnecessary EGDs.

LIMITATIONS AND RECOMMENDATIONS

Due to the present study's small sample size and inclusion of only patients from one institution, additional multicenter studies with a bigger sample size are required to validate the findings.

The role of IL-18 in EVs in patients with cirrhosis needs to be further examined in larger research, particularly regarding the severity of PH and HVPG.

In the near future, research needs to be done to determine how IL-18 antagonists affect liver cirrhosis and PH progression.

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