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Original Article

Plasma soluble CD 163 level as a marker of oesophageal varices in cirrhotic patients

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ABSTRACT

Background: Variceal bleeding (VB), the most common lethal complication of cirrhosis, associated with high mortality. Timely prediction of esophageal varices (EV) represents a real challenge for the medical team. This study evaluated the level of plasma soluble CD 163 as a marker of the presence of EVs and to compare it with other noninvasive clinical, laboratory and ultrasonographic parameters as well as endoscopy.
Methods: This prospective controlled study was conducted on 80 adults. Gp I had no oesophageal varices, gp II had small varices, gp IIIa had large varices, gp IIIb are the same patients of gp IIIa but after eradication of varices and gp IV as healthy controls. Serum samples were assayed for soluble CD 163.
Results: soluble CD163 was statistically significant different between controls and all liver cirrhosis. it showed a statistically significant difference between group I and II ($p = 0.009$) and between group I and IIIa ($p < 0.001$) and between group II and IIIa ($p < 0.001$) but, no difference between group IIIa and IIIb ($p = 0.179$).
Conclusion: Serum soluble CD163 is a good noninvasive predictor for the presence of EVs and it may be used for grading of EVs. Its level does not change after esophageal varices eradication.
Trial registration: IRB No: 00007589 FWA No: 00015712 The Ethics Committee of the faculty of medicine Alexandria University.

1. Background

Cirrhosis is the end stage of every chronic liver disease, resulting in formation of fibrous tissue, dis-organization of liver architecture, and nodule formation, which interferes with liver function and results in portal hypertension. Portal hypertension is associated with development of a hyperdynamic circulation and complications such as ascites, hepatic encephalopathy, and oesophago-gastric varices.[1] Oesophago-gastric varices are the most relevant porto-systemic collaterals because their rupture results in variceal bleeding (VB), the most common lethal complication of cirrhosis, associated with a mortality of at least 20% at 6 weeks.[2]

Timely prediction of esophageal varices (EV) represents a real challenge for the medical team. Nowadays, complete diagnosis of portal hypertension (PHT) requires measurement of the porto-systemic gradient, the parameter that gives the most accurate information about the development of (EV). Although it is safe but it still remains an invasive procedure.[3] The gold standard examination to establish the diagnosis of (EV) is endoscopy but, the available method in rural areas is laboratory examination and ultrasonography. Several studies have been performed to identify predictive factors for esophageal varices.[5]

Current guidelines, recommend that all cirrhotic patients should be screened for varices at diagnosis, with follow up every 2–3 years for patients without varices and 1–2 years for patients with small varices. This guideline causes a significant burden and cost to endoscopy units.[4] The cost and invasive nature of endoscopic screening mean that there is interest in developing noninvasive predictors for EV.[5] Noninvasive predictive variables as platelet count, splenomegaly, Child Pugh, size of right liver lobe, albumin level and portal vein diameter are based on regular laboratory parameters and clinical signs relevant fibrosis, portal hypertension and hypersplenism.[6]

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CD (163) is a macrophage lineage-specific hemoglobin haptoglobin scavenger receptor and a specific marker for macrophage activation.[7,8] CD (163) is shed into the circulation in a soluble form sCD (163) after Toll-like receptor activation by a similar mechanism as TNF-α.[9] Serum concentrations of sCD (163) are accordingly elevated during conditions of macrophage activation and proliferation.[10] Elevated circulating sCD (163) has been demonstrated in viral hepatitis, acute liver failure and cirrhosis.[11–13] Hepatic kupffer cells are activated in cirrhotic patients in parallel with their portal hypertension. sCD (163) is a sensitive marker of macrophages activation that positively correlated with the degree of portal hypertension in cirrhotic patients.[14] In a recent study of highly selected cirrhotic patients setup for treatment with transjugular intrahepatic porto-systemic shunt (TIPS), sCD163 was released from the liver, confirming the activation of Kupffer cells, and its level rose with the portal pressure.[14] This study evaluated the level of plasma soluble CD 163 as a marker of the presence of esophageal varices (EVs) in cirrhotic patients and to compare it with other noninvasive clinical, laboratory and ultrasonographic parameters as well as upper gastrointestinal endoscopic findings.

2. Methods

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria university and the department of tropical medicine, Informed consent was taken from healthy volunteers and the next of kin. This prospective controlled study was conducted on 80 adult subjects (n = 80), they were divided into 5 groups. Group I Contains 20 patients with liver cirrhosis without oesophageal varices. Group II contains 20 patients with liver cirrhosis with small oesophageal varices grade (I, II). Group IIIa contains 20 patients with liver cirrhosis with large oesophageal varices grade (III, IV). Group IIIb are the same 20 patients of group IIIa but after eradication of oesophageal varices. Group IV contains 20 healthy subjects as normal controls.

We classified all patients using upper endoscopy and The varices was classified according to Comar and Sanyal into small or large oesophageal varices. Also, portal hypertensive gastropathy was graded according to McCormack's classification into no, mild (snake skin appearance) and severe (submucosal hemorrhagic spots). Eradication of oesophageal varices was done for group IIIa patients by endoscopic variceal band ligation immediately at time of diagnosis and then other sessions 3 weeks, 6 weeks and 8 weeks later on (one or more sessions was needed with one-month interval until eradication of oesophageal varices was achieved), Banding was done by capturing the targeted varix till complete red out occurs.

We considered all hepatic patients admitted for enrollment in this study but we excluded patients on β-blockers or nitrates or any other pharmacological agents which reduce portal hypertension, patients with hepatocellular carcinoma or acute liver failure, patients with any infectious or inflammatory diseases (such as sepsis, tuberculosis, Rheumatoid arthritis etc.) and patients with diabetes mellitus, hypertension or renal impairment or other comorbid conditions which hinder doing the endoscopic procedure.

All enrolled persons included in this study were subjected to complete history taking including demographic data and clinical data such as abdominal distension, dyspepsia, jaundice, bleeding tendency, weight loss, anemia manifestation, hematemesis and melena. They were clinically examined for liver, spleen, detection of ascites and manifestations of hepatocellular failure. They were subjected to laboratory investigations as complete blood picture (CBC), prothrombin time (PT) and activity, Serum alanine aminotransferase (ALT), Serum aspartate aminotransferase (AST), Serum alkaline phosphatase (ALP), Total and direct serum bilirubin, Blood urea nitrogen (BUN), Serum Creatinine, fasting blood glucose and fasting insulin level. Insulin resistance index "HOMA IR" was calculated as "Blood glucose level mg/dl × insulin/405".

Serum samples from all persons were assayed for our main study marker "Soluble CD 163". Also, it was evaluated at time of eradicated varices for patients of group IIIb. We calculated Child Pugh score and classified all participating patients according to presence of hepatitis C virus antibodies (ELISA), hepatitis B surface antigen (ELISA) and Antischistosomal antibodies (IHAT).

Regarding ultrasonic parameters, we evaluated all enrolled patients using ultrasound assessment of liver and ascites to detect the presence of cirrhosis and/or bilharsial hepatic fibrosis. They were assessed using ultrasound measurement of right liver lobe diameter, splenic bipolar diameter and ultrasound Doppler measurement of the portal vein. We considered all noninvasive clinical, laboratory parameters and predictive Scores such as AST to platelets ratio index(APRI)[15] calculated as [(AST/ULN) × 100]/platelet count 10^9/L (ULN = the upper limit of normal), Index for liver fibrosis FIB4[16] calculated as [age (years) × AST (IU/L)]/[platelet count (109/L) × ALT (IU/L)1/2], Lok score[17] calculated as log odds = −5.56 − 0.0089 × platelet count(103/mm3) + 1.26 × (AST/ALT) + 5.27 × INR; Lok = [exp (log odds)]/[1 + exp(logodds)], Platelet Count 10^9/Spleen Diameter Ratio(mm), AST/ALT Ratio. and Right Lobe Liver Diameter (cm)/Albumin Ratio.

2.1. Statistical methods

Data entry and analysis were done using SPSS software v24. Continuous values were described by mean and standard deviation. Categorical values were described by counts and proportions. Univariate analysis for determining the association of various clinical and laboratory variables with the stage of liver fibrosis and the presence or absence of EV was performed using Student's *t*-test for continuous variables and χ^2 test for categorical variables. Differences were considered statistically significant if *p*-value was less than 0.05. To determine the clinical utility and the diagnostic performance of markers, 2 receiver operating characteristic (ROC) curves were constructed for each of the non-invasive scoring systems that appeared significant in the univariate analysis. Performance of the non-invasive markers was expressed as sensitivity, specificity, positive and negative predictive values (PPV and NPV) and test accuracy.

3. Results

Regarding the demographic data of the studied groups, there were no any significant differences between the studied groups in age and sex. Males predominated females (55% in group I, 60% in group II, 85% in group III and 60% in control group|), while the mean age was 52.0 years, 54.45 years, 52.55 years and 50.59 years in group I, II, III and control group respectively. There was no any significant difference between the studied groups as regard body mass index (BMI) (Table 1).

Regarding symptoms of patients at admission, the most common symptoms in group (I) was abdominal distension (55%) followed by dyspepsia (40%) while jaundice and weight loss were present in (30%) of patients. However, 80% of group II patients complained of a dyspepsia, 75% suffered from abdominal distension and 65% of this group had bleeding tendency. In group IIIa, 90% had dyspepsia, 85% had anemia manifestations and 60% had abdominal distention and bleeding tendency while melena was present in 65% of this group.

Regarding the etiology of liver cirrhosis, Group I was mainly HCV positive patients, only one patient with HBV and he was enrolled in group IIIa, all patients in group II were HCV positive,

Table 1
Comparison between the different studied groups according to demographic data.

	Group I (n = 20)		Group II (n = 20)		Group IIIa (n = 20)		IV (Control) (n = 20)		Test of sig.	p
	No.	%	No.	%	No.	%	No.	%		
Sex										
Female	9	45.0	8	40.0	3	15.0	8	40.0	χ^2 = 4.835	0.184*
Male	11	55.0	12	60.0	17	85.0	12	60.0		
Age										
Min.–Max.	35.0–73.0		46.0–71.0		45.0–65.0		40.0–61.0		F = 0.969	0.412*
Mean ± SD.	52.0 ± 7.89		54.45 ± 6.29		52.55 ± 5.29		50.95 ± 6.93			
BMI (kg/m^2)										
Min.–Max	22.0–28.10		24.0–30.70		23.0–31.90		22.0–27.0		F = 2.287	0.085*
Mean ± SD.	26.01 ± 1.95		27.17 ± 2.30		27.40 ± 2.49		26.15 ± 1.42			

χ^2: Chi square test, F: ANOVA test, p: p value for comparing between the four groups.
* Statistically significant at $p \leq 0.05$.

group IIIa was mainly formed of patients with positive shistosomal antibodies titer (Table 2). Regarding local abdominal examination of liver, there was no a statistically significant difference between groups I, II and IIIa in liver enlargement. But, there were significant differences between them in spleen enlargement and clinically detected ascites. (Table 3) The Child-Pugh score of all patients is showed in (Table 4)

Regarding lab investigations, CBC results showed significant differences between liver cirrhosis groups (I, II and IIIa) and control group IV in all parameters. Within the liver cirrhosis groups, hemoglobin level showed a statistically significant difference between group I and IIIa ($p_2 < 0.001$) and between group II and III ($p_3 < 0.001$) but no significant difference was found between group I and II ($p_1 = 0.960$). Platelets count showed statistically significant differences between group I and II ($p_1 = 0.037$) and between group I and III (p_2=0.003) but no significant difference was found between group II and III ($p_3 = 0.797$). There was a significant difference between group I, II and IIIa in comparison to control as regard fasting insulin level ($p < 0.001$) and HOMA IR ($p < 0.001$) with no statistically significant difference in fasting blood glucose level ($p = 0.924$). While HOMA IR showed a statistically significant difference between group I and III ($p_2 = 0.003$) only. (Table 5) All groups showed a normal renal functions tests with no significant differences between them.

Table 2
Comparison between the three studied groups according to etiology of liver cirrhosis and fibrosis.

	Group I (n = 20)		Group II (n = 20)		Group IIIa (n = 20)		Control (n = 20)		χ^2	p
	No.	%	No.	%	No.	%	No.	%		
HCV anti bodies										
Negative	1	5.0	0	0.0	2	10.0	20	100.0	66.575	<0.001*
Positive	19	95.0	20	100.0	18	90.0	0	0.0		
HBS antigen										
Negative	20	100.0	20	100.0	19	95.0	20	100.0	2.842	^{MC}p = 1.000
Positive	0	0.0	0	0.0	1	5.0	0	0.0		
Schistosomal anti bodies titer										
Negative	9	45.0	12	60.0	8	40.0	20	100	80.0	<0.001*
Positive	11	55.0	8	40.0	12	60.0	0	0.0		

χ^2: Chi square test, MC: Monte Carlo for Chi square test, p: p value for comparing between the four groups,
* Statistically significant at $p \leq 0.05$.

Table 3
Comparison between the three studied groups according to Local abdominal examination.

Local abdominal examination	Group I (n = 20)		Group II (n = 20)		Group IIIa (n = 20)		χ^2	p
	No.	%	No.	%	No.	%		
Liver								
Not enlarged	19	95.0	13	65.0	14	70.0	6.204	$^{MC}p = 0.062$
Enlarged	1	5.0	7	35.0	6	30.0		
Spleen								
Not enlarged	19	95.0	8	40.0	0	0.0	36.768*	<0.001*
Enlarged	1	5.0	12	60.0	20	100.0		
Clinically detected ascites								
Absent	16	80.0	6	30.0	5	25.0	14.949*	0.001*
Present	4	20.0	14	70.0	15	75.0		

χ^2: Chi square test, MC: Monte Carlo for Chi square test, p value.
* Statistically significant at $p \leq 0.05$.

Table 4
Comparison between the different studied groups according to Child-Pugh classification.

Child-Pugh	Group I (n = 20)		Group II (n = 20)		Group III (n = 20)		Test of sig.	p
	No.	%	No.	%	No.	%		
Classes								
A	11	55.0	0	0.0	2	10.0	χ^2 = 27.972*	^{MC}p < 0.001*
B	7	35.0	17	85.0	7	35.0		
C	2	10.0	3	15.0	11	55.0		
Scores								
Mean ± SD.	6.70 ± 2.0		8.60 ± 1.54		9.60 ± 2.26		F = 11.358	<0.001*
Sig. bet. grps	p_1 = 0.003*, p2 < 0.001*, p_3 = 0.111							

χ^2: Chi square test, MC: Monte Carlo for Chi square test, F: ANOVA test, Sig. bet. grps was done using test (LSD) for ANOVA.
p: p value for comparing between the three groups.
p_1: p value for comparing between group I and group II.
p_2: p value for comparing between group I and group III.
p_3: p value for comparing between group II and group III.
* Statistically significant at $p \leq 0.05$.

Table 5
Comparison between the different studied groups according to lab investigations.

	Group I	Group II (n = 20)	Group IIIa (n = 20)	IV Control (n = 20)	Test of Sig.	p
HB(g/dl)						
Mean ± SD.	12.06 ± 1.91	11.83 ± 1.63	9.57 ± 1.17	14.27 ± 1.03	F = 33.714*	<0.001*
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	p_1 = 0.960, p_2 < 0.001*,p_3 < 0.001*					
RBCs						
Mean ± SD.	3.96 ± 0.82	4.14 ± 0.71	3.45 ± 0.67	4.31 ± 0.39	F = 6.228*	0.001*
$p_{Cont.}$	0.350	0.846	0.001*			
Sig. bet. grps	p_1 = 0.831, p_2 = 0.082, p_3 = 0.009*					
WBCs						
Mean ± SD.	5.14 ± 1.68	5.21 ± 1.81	4.45 ± 1.55	7.43 ± 1.78	H = 24.813*	<0.001*
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	p_1 = 0.860, p_2 = 0.140, p_3 = 0.074					
Platelets						
Mean ± SD.	135.10 ± 53.74	97.30 ± 48.65	89.25 ± 33.57	327.85 ± 70.72	H = 48.823	<0.001*
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	p_1 = 0.037*, p_2 = 0.003*, p_3 = 0.797					
Fasting insulin level						
Mean ± SD.	11.63 ± 2.12	18.14 ± 1.55	22.92 ± 3.72	7.94 ± 2.10	F = 141.752	<0.001*
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	p_1 < 0.001*,p_2 < 0.001*, p_3 < 0.001*					
FBS g/dl						
Mean ± SD.	88.37 ± 13.73	89.27 ± 11.46	91.12 ± 13.40	90.27 ± 14.84	F = 0.159	0.924
HOMA IR						
Mean ± SD.	2.49 ± 0.37	3.03 ± 0.81	3.64 ± 1.20	1.82 ± 0.70	17.636	<0.001*
$p_{Cont.}$	0.059	<0.001*	<0.001*			
Sig. bet. grps	p_1 = 0.173,p_2 < 0.001*,p_3 = 0.098					

F: ANOVA test, Sig. bet. grps was done using test (Tukey) for ANOVA.
H: Kruskal Wallis test, Sig. bet. grps was done using Mann Whitney test.
p: p value for comparing between the four groups.
$p_{Cont.}$: p value for comparing between control and each other periods.
p_1: p value for comparing between group I and group II.
p_2: p value for comparing between group I and group III.
p_3: p value for comparing between group II and group III.
* Statistically significant at $p \leq 0.05$.

Regarding liver profile, there were statistically significant differences between each group of patients and group IV of controls in all parameters ($p < 0.001$). The mean of Serum aspartate aminotransferase (AST) of group I was higher than group II with a statistically significant difference ($p_1 = 0.010$). The mean of serum albumin level showed significant differences between all groups. (Table 6) The results of coagulation profiles of all groups are showed in (Table 7).

Regarding ultrasonography, all subjects were cirrhotic except in control group and 60% of subjects in group I and 40% of subjects in group II and IIIa group showed mixed cirrhosis with Schistosomal periportal hepatic fibrosis. Within group I, II and IIIa ascites was not present in 80% of subjects of group I while it was found as mild ascites in 50% of patients of group II and moderate ascites in 35% of patients of group IIIa. Direction of portal blood flow was hepatopetal in 100% of subjects in control and group I while it was non hepatopetal (hepatofugal) in 50% and 65% of subjects of group II and III respectively. Significant difference was found as regard portal blood volume between control group and liver cirrhosis group with median 1241.0 in group of controls. Moreover, within liver cirrhosis

Table 6
Comparison between the different studied groups according to liver profiles.

Liver function	Group I (n = 20)	Group II (n = 20)	Group IIIa (n = 20)	IV Control (n = 20)	Test of sig.	p
ALT(U/L)					H = 27.516	<0.001*
Mean ± SD.	55.95 ± 21.48	53.55 ± 26.35	44.20 ± 25.53	26.50 ± 7.58		
$p_{Cont.}$	<0.001*	<0.001*	0.001*			
Sig. bet. grps	$p_1 = 0.379, p_2 = 0.025^*, p_3 = 0.099$					
AST(U/L)					H = 30.470	<0.001*
Mean ± SD.	47.70 ± 23.04	71.45 ± 43.32	58.60 ± 32.77	29.75 ± 7.68		
$p_{Cont.}$	0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.010^*, p_2 = 0.343, p_3 = 0.168$					
Albumin (g/dl)					F = 39.465	<0.001*
Mean ± SD.	3.30 ± 0.52	2.67 ± 0.41	2.47 ± 0.78	4.12 ± 0.26		
$p_{Cont.}$	<0.001*	0.627	<0.001*			
Sig. bet. grps	$p_1 = 0.002^*, p_2 < 0.001^*, p_3 = 0.002^*$					
Total bilirubin (mg/dl)					H = 24.375	<0.001*
Mean ± SD.	1.63 ± 0.80	1.82 ± 0.99	2.58 ± 1.56	0.93 ± 0.12		
$p_{Cont.}$	0.005*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.440, p_2 = 0.032^*, p_3 = 0.129$					
Direct bilirubin (mg/dl)					H = 33.656	<0.001*
Mean ± SD.	0.68 ± 0.42	0.91 ± 0.58	1.29 ± 1.16	0.19 ± 0.05		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.328, p_2 = 0.131, p_3 = 0.684$					
Alkaline phosphatase (u/l)					25.261	<0.001*
Mean ± SD.	146.20 ± 34.68	141.06 ± 27.31	157.93 ± 38.23	81.60 ± 16.75		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.950, p_2 = 0.616, p_3 = 0.303$					

F: ANOVA test, Sig. bet. grps was done using test (Tukey) for ANOVA.
H: Kruskal Wallis test, Sig. bet. grps was done using Mann Whitney test.
p: p value for comparing between the four groups.
$p_{Cont.}$: p value for comparing between control and each other periods.
p_1: p value for comparing between group I and group II.
p_2: p value for comparing between group I and group III.
p_3: p value for comparing between group II and group III.
* Statistically significant at $p \leq 0.05$.

Table 7
Comparison between the different studied groups according to prothrombin activity, prothrombin time and INR.

Prothrombin	Group I (n = 20)	Group II (n = 20)	Group IIIa (n = 20)	IV Control (n = 20)	F	p
Activity (%)					45.312*	<0.001*
Mean ± SD.	69.13 ± 15.69	52.62 ± 9.10	59.64 ± 14.97	93.94 ± 4.72		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 < 0.001^*, p_2 = 0.068, p_3 = 0.258$					
Time (sec.)					10.423*	<0.001*
Mean ± SD.	14.91 ± 3.27	17.42 ± 6.69	16.0 ± 2.84	10.60 ± 1.67		
$p_{Cont.}$	0.007*	0.689	<0.001*			
Sig. bet. grps	$p_1 = 0.216, p_2 = 0.832, p_4 = 0.216$					
INR					20.847*	<0.001*
Mean ± SD.	1.46 ± 0.34	1.55 ± 0.19	1.65 ± 0.40	0.99 ± 0.14		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.736, p_2 = 0.178, p_3 = 0.733$					

F: ANOVA test, Sig. bet. grps was done using test (Tukey) for ANOVA, p: p value for comparing between the four groups.
$p_{Cont.}$: p value for comparing between control and each other periods.
p_1: p value for comparing between group I and group II.
p_2: p value for comparing between group I and group III.
p_3: p value for comparing between group II and group III.
* Statistically significant at $p \leq 0.05$.

groups significant difference was found between group I and II and between group I and III but no significant difference was found between group II and III. In terms of portal vein diameter, statistically significant differences were found between group I and III ($p_2 < 0.001$) and between group II and III ($p_3 < 0.001$) but not between group I and II ($p_1 = 0.549$). (Table 8) (Appendix A)

Regarding the classic predictive scores, APRI was higher in group II than group I with a statistically significant difference (P < 0.001). FIB4 was higher in group II than group I with a statistically significant difference (P < 0.001). There was no significant difference between group II and III in their lok score ($p_3 = 0.909$). AST/ALT Ratio and Right lobe liver diameter (cm)/albumin ratio was evaluated also as predictive scores (Table 9).

All patients assigned to the groups using upper GI endoscopy and during it, portal hypertensive gastropathy grading was done and revealed that 55% of patients of group I had no PHG and 55% of patients of group II had mild PHG while 35% of subjects of group III had severe PHG. oesophageal variceal band ligation sessions

Table 8
Comparison between the studied groups according to ultra-sonographic data.

Ultra Sonographic data	Group I (n = 20)		Group II (n = 20)		Group IIIa (n = 20)		IV Control (n = 20)		Test of sig.	p
	No.	%	No.	%	No.	%	No.	%		
No liver cirrhosis	0	0.0	0	0.0	0	0.0	20	100.0	χ^2= 80.0	<0.001*
Liver cirrhosis	20	100.0	20	100.0	20	100.0	0	0.0		
No SHF	8	40.0	12	60.0	8	40.0	20	100.0	χ^2= 20.000	<0.001*
SHF	12	60.0	8	40.0	12	60.0	0	0.0		
Ascites										
No	16	80.0	6	30.0	6	30.0	20	100.0	χ^2= 38.546	MCp < 0.001*
Mild	4	20.0	10	50.0	6	30.0	0	0.0		
Moderate	0	0.0	4	20.0	7	35.0	0	0.0		
Tense	0.0	0	0	0.0	1	5.0	0	0.0		
Direction of portal blood flow										
Hepatopetal	20	100.0	10	50.0	7	35.0	20	100.0	χ^2= 33.379	<0.001*
Non hepatopetal	0	0.0	10	50.0	13	65.0	0	0.0		
Portal blood volume										
Mean ± SD.	843.75 ± 182.40		672.65 ± 185.32		559.75 ± 97.75		1222.70 ± 66.75		F = 82.356	<0.001*
$p_{Cont.}$	<0.001*		<0.001*		<0.001*					
Sig. bet. grps	p_1 = 0.002*, p_2 < 0.001*, p_3 = 0.068									
Liver right lobe diameter(cm)										
Mean ± SD.	13.56 ± 0.78		12.83 ± 0.84		10.87 ± 1.02		15.01 ± 0.82		F = 77.888	<0.001*
$p_{Cont.}$	<0.001*		<0.001*		<0.001*					
Sig. bet. grps	p_1 = 0.047*, p_2 < 0.001*, p_3 < 0.001*									
Spleen bipolar diameter (cm)										
Mean ± SD.	13.84 ± 1.23		15.44 ± 1.37		19.59 ± 2.09		10.30 ± 1.29		F = 125.746	<0.001*
$p_{Cont.}$	<0.001*		<0.001*		<0.001*					
Sig. bet. grps	p_1 = 0.008*, p_2 < 0.001* p_3 < 0.001*									
Portal vein diameter (mm)										
Mean ± SD.	12.71 ± 0.93		13.35 ± 1.90		16.38 ± 1.76		9.84 ± 1.34		F = 61.668	<0.001*
$p_{Cont.}$	<0.001*		<0.001*		<0.001*					
Sig. bet. grps	p_1 = 0.549, p_2 < 0.001* p_3 < 0.001*									

F: ANOVA test, Sig. bet. grps was done using test (Tukey) for ANOVA.
χ^2: Chi square test.
p: p value for comparing between the four groups.
$p_{Cont.}$: p value for comparing between control and each other periods.
p_1: p value for comparing between group I and group II.
p_2: p value for comparing between group I and group III.
p_3: p value for comparing between group II and group III.
* Statistically significant at $p \leq 0.05$.

required for eradication of the large oesophageal varices in group IIIa with mean of 3.0 (±1.45) sessions and duration mean 6.50 (±3.0) weeks. (Appendix B)

Regarding our main study marker, "soluble CD163" was statistically significant different between control and liver cirrhosis groups with a mean 69.03 (ng/ml) in control and 151.52 (ng/ml), 183.75 (ng/ml) and 209.52 (ng/ml) in group I, II and IIIa respectively. Moreover, within group I, II and IIIa it showed a statistically significant difference between group I and II (p = 0.009) and between group I and IIIa (p < 0.001) and between group II and IIIa (p < 0.001). There was no difference between group IIIa and IIIb (p = 0.179). (Fig. 1)

Regarding the presence of EV, serum soluble CD163 level, HOMA and platelets count are good predictors for presence of oesophageal varices with cut off value > 191.71 for soluble CD163 with 77.50% sensitivity and 77.0% specificity. Soluble CD163, HOMA IR and Platelets to predict presence of EV between (Group II + Group IIIa) vs Group I showed the best sensitivity and specificity 90% and 80% respectively and 90% PPV and 80% NPV. (Fig. 2) APRI, FIB4, Lok score, platelets count to spleen diameter ratio and AST/ALT ratio are good predictors. All new variables sensitivity and specificity are showed in (Table 10). Moreover, ability of the studied marker soluble CD163 to differentiate between small varices and large varices with cut off value 199.19 with 85.0 % sensitivity and 90.0% specificity. (Table 11), (Fig. 3)

4. Discussion

Several non-invasive methods have emerged in recent years, assessing the potential of various laboratory, clinical, and ultrasonographic parameters, linked directly or indirectly to portal hypertension including: Thrombocytopenia, splenomegaly[18]. AST/ALT ratio,[19] AST to platelets ratio index (APRI).[20] platelets count to spleen diameter ratio,[21] The right liver lobe diameter/albumin index,[22] Transient elastography,[23] Forns Index,[24] Lok score[25] and Insulin resistance.[26]

Insulin resistance which is firstly introduced by Cammà et al. study, which stated that Insulin resistance measured by HOMA-IR, regardless of the presence of diabetes, significantly predicts the presence of EV[26].Studies in chronic liver diseases have shown a strong and independent pathogenic link between Insulin resistance (IR) and HCV infection and between IR and the severity of hepatic fibrosis.[27] Cammà et al.[26] studied 104 patients of Child A HCV induced cirrhosis conclude that HOMA-IR score of greater than 3.5 is the cut-off value with the best sensitivity 61% and specificity 76% for predicting EV presence and HOMA score less than 3.5 (if non-diabetic) could be useful to identify patients at low risk of EV.[26] Eslam et al.,[28] also concluded that in patients with cirrhosis, the presence of esophageal varices was independently associated with lower platelet count and raised HOMA score with HOMA score correlates with HVPG and independently predict clinical

Table 9
Comparison between the different studied groups according to predictive scores.

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Control (n = 20)	Test of Sig.	p
AST to platelets ratio index (APRI)					H = 50.971	<0.001*
Mean ± SD.	1.11 ± 0.72	2.47 ± 1.75	1.93 ± 0.92	0.24 ± 0.09		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.003^*, p_2 = 0.004^*, p_3 = 0.525$					
FIB4					H = 54.983	<0.001*
Mean ± SD.	2.77 ± 1.31	6.88 ± 4.04	5.49 ± 2.05	0.95 ± 0.33		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 < 0.001^*, p_2 < 0.001^*, p_3 = 0.482$					
Lok score					F = 157.928	<0.001*
Mean ± SD.	0.78 ± 0.23	0.96 ± 0.04	0.93 ± 0.10	0.15 ± 0.08		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 < 0.001^*, p_2 = 0.002^*, p_3 = 0.909$					
Platelet count /spleen diameter (mm) ratio					H = 54.992	<0.001*
Mean ± SD.	997.65 ± 436.48	647.03 ± 349.53	462.80 ± 181.91	3233.10 ± 838.74		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig. bet. grps	$p_1 = 0.009^*, p_2 < 0.001^*, p_3 = 0.144$					
AST/ALT Ratio					H = 18.246	<0.001*
Mean ± SD.	0.94 ± 0.53	1.36 ± 0.54	1.40 ± 0.55	1.10 ± 0.11		
$p_{Cont.}$	=0.004*	0.045*	0.007*			
Sig. bet. grps	$p_1 = 0.001^*, p_2 = 0.003^*, p_3 = 0.957$					
Right lobe liver diameter (cm)/albumin ratio					F = 7.855	<0.001*
Mean ± SD.	4.17 ± 0.73	4.94 ± 1.03	4.76 ± 1.36	3.65 ± 0.29		
$p_{Cont.}$	0.309	<0.001*	0.002*			
Sig. bet. grps	$p_1 = 0.052, p_2 = 0.201, p_3 = 0.924$					

H: Kruskal Wallis test, Sig. bet. grps was done using Mann Whitney test.
F: ANOVA test, Sig. bet. grps was done using test (Tukey) for ANOVA.
p: p value for comparing between the four groups.
$p_{Cont.}$: p value for comparing between control and each other periods.
p_1: p value for comparing between group I and group II.
p_2: p value for comparing between group I and group III.
p_3: p value for comparing between group II and group III.
* Statistically significant at $p \leq 0.05$.

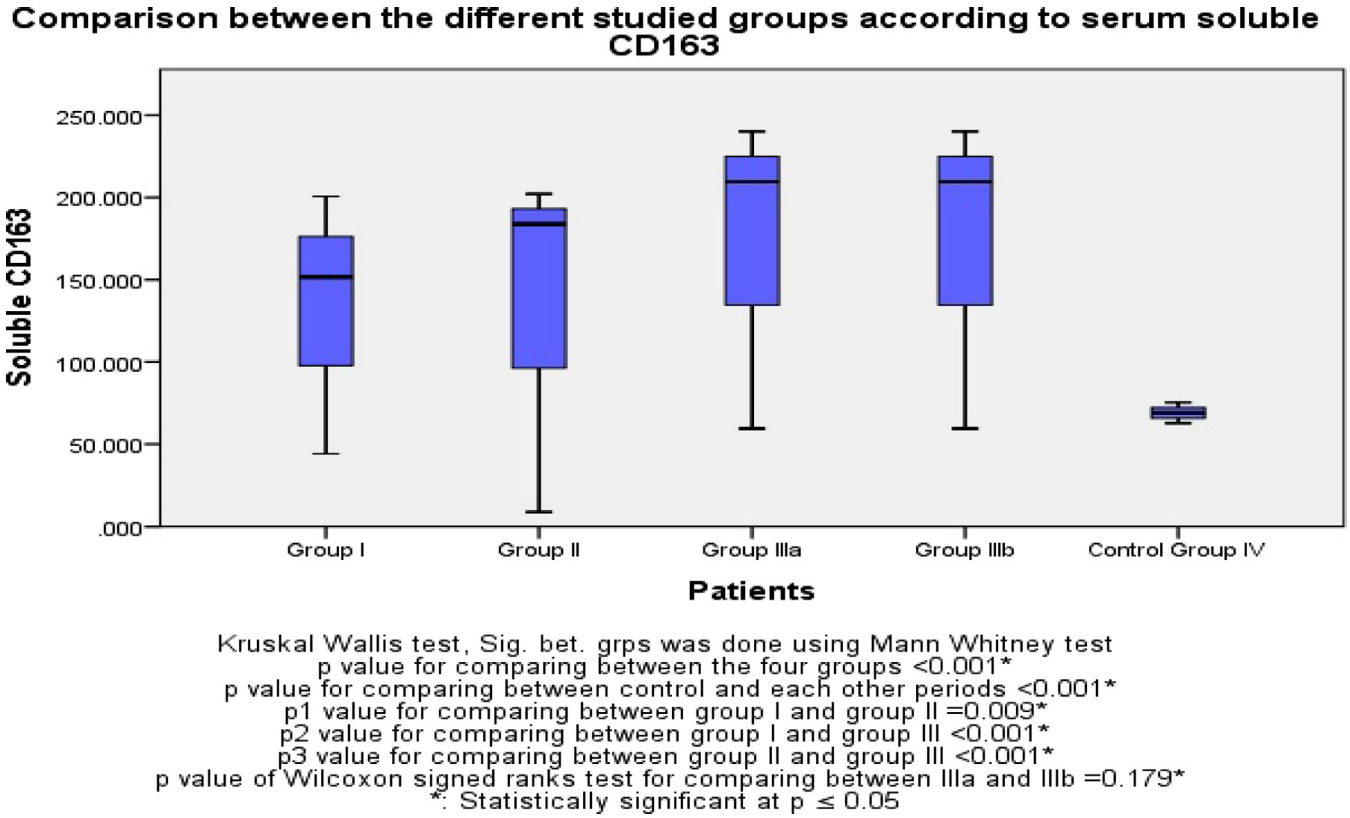

Fig. 1. Comparison between the different studied groups according to serum soluble CD163.

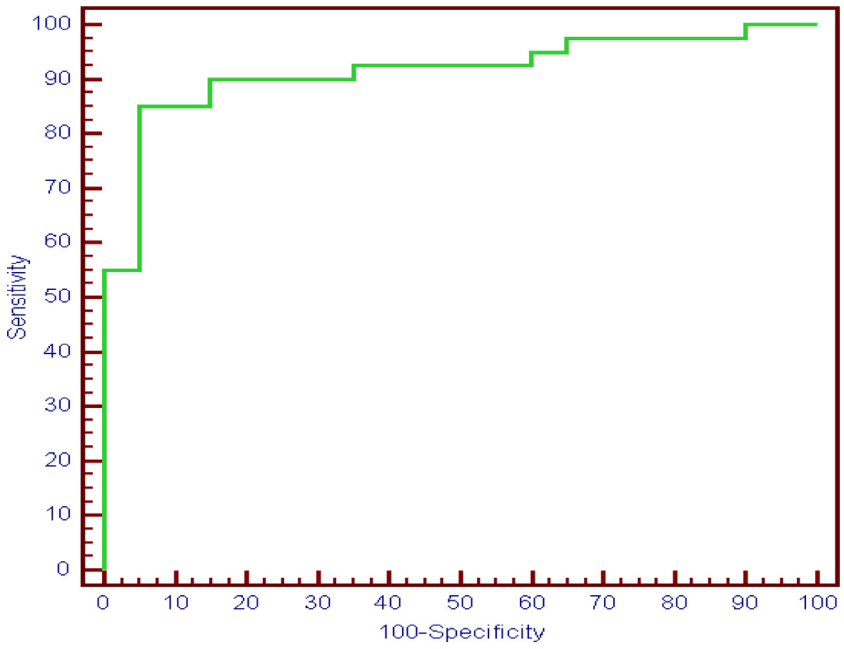

Fig. 2. ROC curve for Soluble CD163, HOMA IR and Platelets to predict presence of oesophageal varices between (Group II + Group IIIa) vs Group I.

Table 10
Agreement (sensitivity, specificity and accuracy) for different parameters to predict presence of oesophageal varices between (Group II + Group III) vs Group I.

(Group II + Group III) vs Group I	AUROC	p	Cut off	Sensitivity	Specificity	PPV	NPV
Soluble CD163	0.820*	<0.001*	>191.71	77.50	75.0	86.1	62.5
HOMA IR	0.763*	0.001*	>2.83	67.50	90.0	93.1	58.1
Platelets count	0.734*	0.003*	≤93	62.50	80.0	86.2	51.6
Soluble CD163 and HOMA IR	0.863*	<0.001*		87.50	45.0	76.09	64.29
Soluble CD163 and Platelets	0.845*	<0.001*		85.0	65.0	82.93	68.42
Soluble CD163, HOMA IR and Platelets	0.915*	<0.001*		90.0	80.0	90.0	80.0
Soluble CD163, platelet count /spleen diameter (mm) and FIB4	0.910*	<0.001*		90.0	85.0	92.31	80.95
Soluble CD163, AST ALT ratio and ABRI	0.892*	<0.001*		90.0	70.0	85.71	77.78
Soluble CD163, Lok score and PLT	0.882*	<0.001*		92.50	75.0	88.10	83.33
Platelet count /spleen diameter (mm)	0.822*	<0.001*	≤643	75.0	85.0	90.9	63.0
FIB4	0.862*	<0.001*	>4.01	77.50	90.0	93.9	66.7
AST/ALT Ratio	0.785*	<0.001*	>0.9	77.50	75.0	86.1	62.5
AST to platelets ratio index (APRI)	0.770*	<0.001*	>1.54	67.50	95.0	96.4	59.4
Lok score	0.735*	0.003*	>0.85	87.50	55.0	79.5	68.8

Table 11
Agreement (sensitivity, specificity and accuracy) for soluble CD163 to differentiate small oesophageal varices from large oesophageal varices (Group IIIa vs Group II).

Gp IIIa vs Gp II	AUROC	p	Cut off	Sensitivity	Specificity	PPV	NPV
Soluble CD163	0.863*	<0.001*	>199.19	85.0	90.0	89.5	85.7

outcomes in these patients. In this study, analysis of the area under the ROC curve (AUROC) revealed that the cut-off value for HOMA-IR score of greater than 2.83 was the optimal value for accurate prediction of EVs with a resulting 67.50% sensitivity, 90% specificity. The differences between the best cut-off values, sensitivity and specificity in this study and Cammà et al.[26] study may be attributed to the different ethnic group of the patients, all patients in this study were non-diabetic and non-obese. Where in Cammà et al. study 27 patients were diabetic and 11 patients were obese, and may be due to different genotype of HCV in studied groups where genotype 1 predominate Cammà et al. study and genotype 4 mostly predominate this study.

Fib-4 had been examined for the prediction of EV in patients with cirrhosis, having an AUROC of 0.64 for the prediction of EV at a cutoff value of 3.5, while for the diagnosis of LEV the AUROC was 0.63 and the cutoff value 4.3.[29] In another study, for predicting EV, they used a cutoff value of 3.98 and the AUROC was 0.624; for the diagnosis of LEV they used a cutoff value of 6.75.[30] Moreover, Eman et al.[31] proposed a very low cutoff (2.8) for predicting EV which showed sensitivity 76%, specificity 80%, PPV 92.7% and

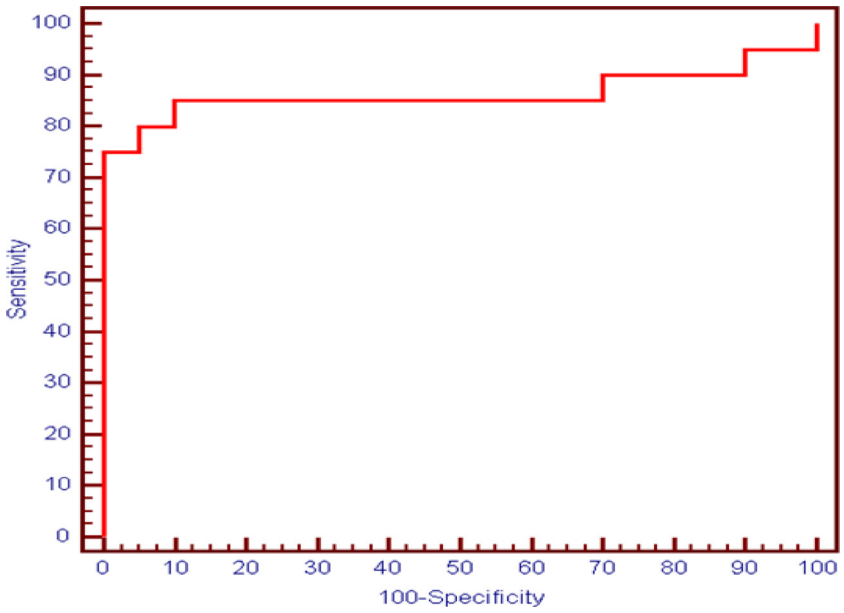

Fig. 3. ROC curve for Soluble CD163 to differentiate small oesophageal varices from large oesophageal varices (Group IIIa vs Group II).

NPV 50%. However, in this study Fib-4 couldn't differentiate between small EV in group II and large EV in group III and there was no statistically significant difference. While Sebastiani et al.[29] and Stefanescu et al.[30] proposed a cutoff value 4.3 and 6.75 respectively.

Lok Score had been considered a very satisfactory predictor of EV. At a cutoff value of 0.9, the Lok Score had an AUROC of 0.77 for the diagnosis of EV, while for a cutoff value of 1.5, the AUROC was 0.69 for the prediction of LEV.[29] In another prospective study, the best cutoff value for the diagnosis of LEV was 0.8, with an AUROC of 0.731 and a NPV of 86.4%.[30] While Eman et al.[31] proposed a cutoff value of 0.63 for diagnosis of EV. At this cutoff, the sensitivity was 60%, specificity was 80%, PPV was 78%, NPV was 42.9% and the overall accuracy was 79%. Also, Eman et al.[31] proposed a cutoff of 0.72 for the diagnosis of LEV at which sensitivity was 87.5%, specificity was 55.5% and the overall accuracy was 76%. AUROC was 0.72. In the current study, we proposed a cutoff 0.85 which showed sensitivity 87.5%, specificity 55%, PPV 79.5% and NPV 68.8%. However, in this present study Lok Score couldn't differentiate between small EV in group II and large EV in group III with no statistical significant difference. While Sebastiani et al.[29] and Eman et al.[31] proposed a cutoff value 1.5 and 0.72 respectively.

Mona et al.[32] proposed APRI at a cutoff greater than 1.26 could predict the presence of EV (AUROC 0.695) with PPV of 81.42% and APRI at a cutoff greater than 1.47 could predict LEV (AUROC 0.734). These findings are in agreement with the studies by Castéra et al.[33], Tafarel et al.[34], and Adami et al.[35] who proposed APRI at a cutoff 1.3, 1.64, and greater than 1.4, respectively, for prediction of EV. In addition, Sebastiani et al.[29] reported APRI at a cutoff of 1.4 for prediction of EV and at a cutoff of 1.5 for detection of LEV. However, Stefanescu et al.[30] suggested APRI at a cutoff more than 2.201 with AUROC 0.538 for detection of LEV and Galal et al.[36] suggested a cutoff greater than 0.16 for detection of EV and LEV. These different cutoff results indicate the need for further studies in large-scaled studies.

The AST/ALT ratio has been used to predict cirrhosis, and by natural extension studies have been performed to assess its usefulness in predicting oesophageal varices. In a retrospective study by Neblom et al.[37], significantly higher AST/ALT ratio were seen in patients with varices compared to those without (ratio: 1.8 versus 1.0, $P < 0.0001$). In our study ratio was 1.11 in group I without EV and 2.47 in group II and 1.93 in group III. Treeptrasertsuk G et al.[38] found an AST/ALT ratio >1.12 to be significantly associated with the presence of varices at initial endoscopy (OR 3.9, $P = 0.02$ 95% CI 1.3–11.8). This cutoff gave a sensitivity of 47.8%, specificity of 87%, PPV 42.3%, and NPV 89.2%, and an AUROC of 0.69. Castéra et al.[33] proposed a cutoff of $\geq$1.0 which demonstrated a sensitivity of 68%, specificity of 89%, PPV 77%, and NPV 83%, with an AUROC 0.83 (0.72–0.94) for predicting the presence of oesophageal varices. In our study, we proposed a cutoff 0.9 which showed sensitivity 77.5%, specificity 75%, PPV 86.1% and NPV 62.5%. Also, in this present study AST/ALT ratio couldn't differentiate between small EV in group II and large EV in group III and there was no a statistically significant difference.

Giannini et al.[39] introduced the use of the platelet count/spleen diameter ratio as a tool to predict oesophageal varices. This ratio links thrombocytopenia to splenomegaly to introduce a variable that takes into consideration that thrombocytopenia is mainly due to hypersplenism secondary to portal hypertension. In that study, when a cut-off value of 909 used, the sensitivity was 100%, and the specificity was 93% this agree with Agha et al.[40] Cammà et al.[26] studied 104 newly diagnosed patients with Child A HCV cirrhosis, identified a value of 792 as the best cutoff for the presence of EVs and ratio greater than 792 Could be useful to identify patients at low risk of EV. And stated these, different results are perhaps related to differences in etiology and class of disease between the two populations as regard Giannini et al. study[39]. In one study on Egyptian patients Esmat et al.[41] concluded that a cut-off value of 1326.58 for the platelet count/spleen diameter ratio was used with a resulting 96.34% sensitivity, 83.33% specificity and 94% accuracy. In another study also in Egyptian patients Abu El Makarem et al.[42] concluded that a cut-off value of 939.7 for the platelet count/spleen diameter ratio was used with a resulting 100% sensitivity, 86.3% specificity and 96.5% accuracy. Monkez et al.[43] proposed a cut-off of the platelet count/spleen diameter ratio 750 for accurate prediction of EVs with a resulting 81% sensitivity, 81% specificity and 81% accuracy. In the current study, we proposed a cutoff 643 which showed sensitivity 75%, specificity 85%, PPV 90.9% and NPV 63%. Also, in this present study platelet count/spleen diameter ratio couldn't differentiate between

small EV in group II and large EV in group III and there was no statistically significant difference. The difference in the cutoff values between these studies and that of the present work can be explained by their patient sample that included only cirrhotic patients, and none of their patients had evidence of bilharziasis, whereas most of the patients included in the present study had mixed disease etiology: bilharzial and post viral hepatitis C cirrhosis. Both had their insult on the platelets, besides bilharziasis that specifically produces larger even huge spleen. None of these studies included these types of patients that are characteristically prevalent in the Delta region of Egypt. In addition, the absence of interobserver agreement between the sonographers and endoscopists of the different studies which can affect the results. Hence, it is sure to have our different and specific cutoff that needs further larger scale studies in Egypt.

Regarding the right liver lobe diameter /serum albumin ratio Alempijevic et al.[44] had counted an original ratio. For the first time they reported the value of the right liver lobe diameter/serum albumin concentration in assessment of portal hypertension. They used serum albumin concentration as a parameter of liver function in combination with right liver lobe size and used this ratio as a non-invasive predictor of oesophageal varices with at a cut-off value of 4.425, the sensitivity was 83.1%, and the specificity was 73.9%. In another study on Egyptian patients Esmat et al.[41] concluded that a cut-off value of 4.422 for the right liver lobe diameter/albumin concentration ratio gave sensitivity 91.46%, and the specificity 77.78%. Monkez et al.[43] proposed a cut-off value for the right liver lobe diameter/albumin concentration ratio 3.5 for accurate prediction of EVs with a resulting 78.5% sensitivity, 57.1% specificity, and 74% accuracy. On the other hand, El Ray et al.[45] found that right liver lobe diameter/serum albumin had no role in prediction of EV presence that agrees with our study. The differences between the best cut-off values, sensitivity, specificity, and accuracy in these studies may be attributed to the different group of patient where all patients in this study were child A, B and C. In the other studies, the patients were child A, also patients were had a different ethnic origin. In addition, the differences between the sonographers of different studies, which can affect the results. This suggests the need for further multicenter studies including a large number of patients with different ethnic background for determining the best cut-off, value for that ratio.

Recent researches has highlighted the important role of liver macrophages (Kupffer cells) in the fibrotic process.[46] Macrophage-specific markers may, therefore, prove to be useful for the monitoring of fibrosis development like serum soluble CD163.[47,48] These endocytic macrophage surface receptors are shed from activated macrophages during inflammation.[49,50] Rødgaard-Hansen et al.[48] was the first to indicate that macrophage-related sCD163 may serve as biomarkers for fibrosis. This marker are readily measurable in serum and reflect monocyte/macrophage activation. In the current study, soluble CD163 showed a statistically significant difference between control and liver cirrhosis groups and this agrees with Ying-Ying et al.[51] and Gronaek et al.[52]When applying ROC curves of serum soluble CD163 level, it was a significantly good predictors for presence of oesophageal varices between group I (no EV) and other both groups II and III (those of EV) with cut off value >191.71 ng/ml with 77.50% sensitivity and 77.0% specificity. This agrees with Ying-Ying et al.[51] and Waidmann et al.[53]

An interesting new finding is the ability of the studied marker soluble CD163 to differentiate between small varices and large varices with cut off value 199.19 with 85.0 % sensitivity and 90.0% specificity. This is the first study to correlate sCD163 with grading of EV as noninvasive predictor. No previous studies had correlated this marker after eradication of EV. However, Peter Holland-fischer et al.[14] proposed That normalization of the portal hypertension by the TIPS procedure did not normalize sCD163, which remained increased.

After searching the literature, no studies were found to show a relation between bilharsiasis and sCD163.In this study, No significant difference between sCD163 level in group I patients with or without hepatic schistosomiasis with median sCD163 level 100.60 ng/ml in patients without schistosomiasis and 175.61 ng/ml in patients with schistosomiasis. Moreover, No significant difference between sCD163 level in group II patients with or without hepatic schistosomiasis with median SCD163 level 194.15 ng/ml in patients without schistosomiasis and 194.76 ng/ml in patients with schistosomiasis. Also, in group III. We found a model combining serum Soluble CD163, HOMA IR and Platelets to predict presence of oesophageal varices had an area under the curve (AUC) of 0.915 with sensitivity and specificity 90% and 80% respectively. While, ROC curve for Soluble CD163, platelet count /spleen diameter (mm) and FIB4, had sensitivity and specificity 90% and 85% respectively with AUC 0.910.

5. Conclusion

From our results, Serum soluble CD163 is a good noninvasive predictor for the presence of esophageal varices EVs and it may be used for grading of EVs. Serum soluble CD163 level does not change after esophageal varices eradication and it does not be effected by presence or absence of bilharsiasis. Insulin resistance measured by HOMA-IR, Fib-4, Lok Score, APRI, AST/ALT ratio and platelet count/spleen diameter ratio, are good predictors for the presence of EV but not for grading of esophageal varices. Right liver lobe diameter/ serum albumin had no role in prediction of EV presence. Combining of different noninvasive parameters can increase area under the curve AUC for prediction of EVs. A model combining serum Soluble CD163, HOMA IR and Platelets to predict presence of oesophageal varices had the best AUC. Our recommendations are studying serum soluble CD163 on larger sample size, CD163 and risk for variceal bleeding and its correlations with different etiologies of liver cirrhosis, acute liver failure and staging of liver fibrosis.

Acknowledgements

Not applicable.

Ethics

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria university and the department of critical care, Informed consents for participating and publishing were taken from the next of kin of patients after approval by critical care department committee.

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Availability of data and materials

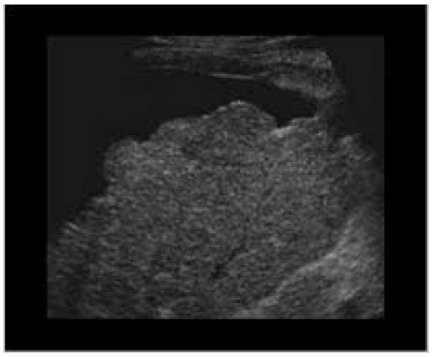
Please contact author for any data requests.

Competing interests

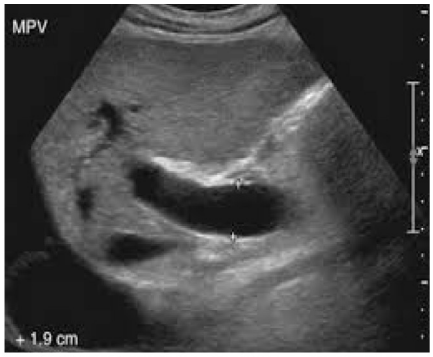
The authors declare that they have no competing interests.

Appendix A

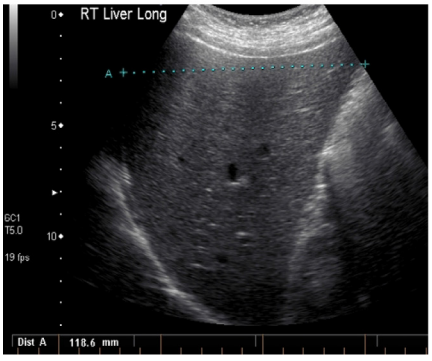
Ultrasound imaging



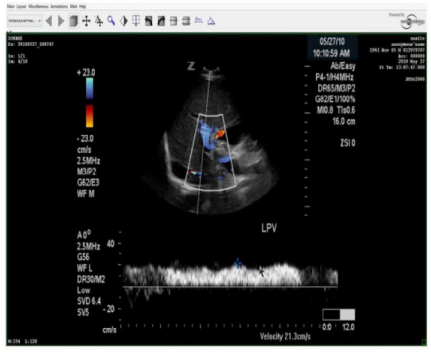
Liver cirrhosis with ascites



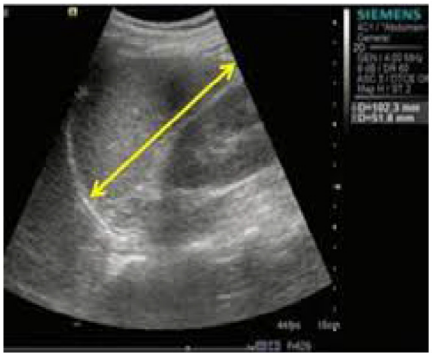
Portal vein diameter



Right lobe liver diameter



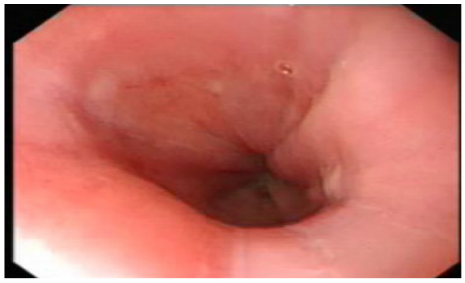
Portal blood flow volume and direction



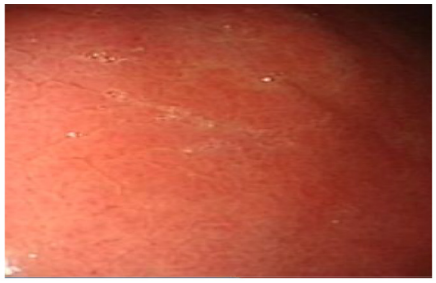
Spleen bipolar diameter

Appendix B

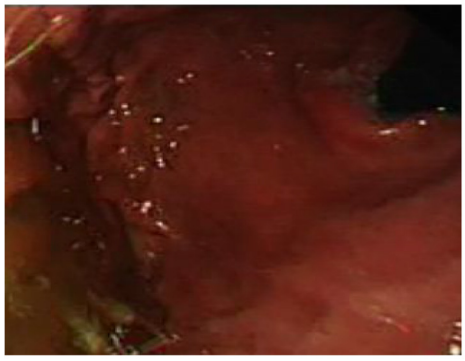
Upper GI endoscopy and band ligation



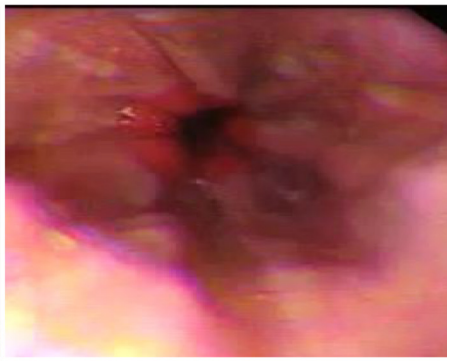
No oesophageal varices



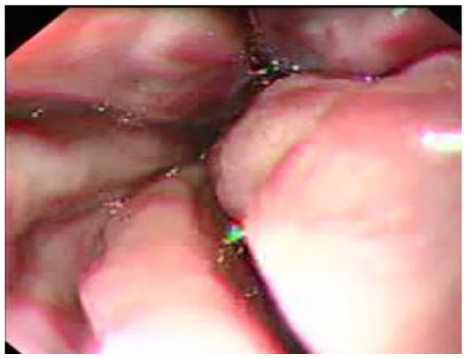
mild portal hypertensive gastropathy



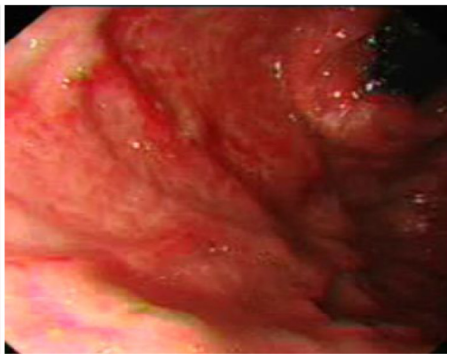
Retroflection with no gastric varices



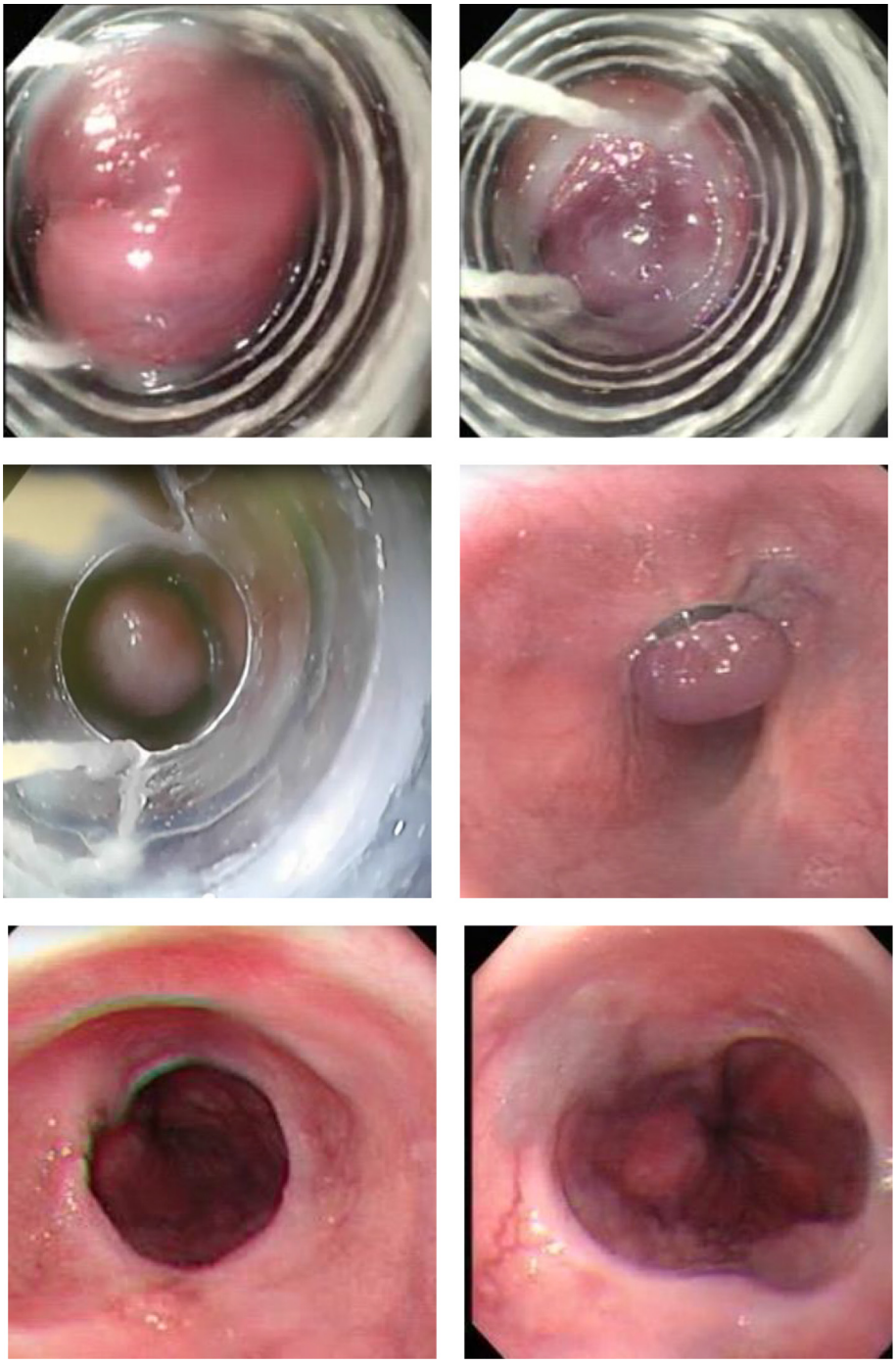
Small oesophageal varices (grade II)



Large oesophageal varices (grade IV)



Severe portal hypertensive gastropathy



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