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ORIGINAL RESEARCH ARTICLE

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Diagnostic validity of serum YKL-40 as a non-invasive diagnostic marker of oesophageal varices in cirrhotic hepatitis C virus patients

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Abstract

Background: Liver cirrhosis is the last phase of chronic hepatitis C virus infection. During the compensated phase, portal pressure is still below the point where varices start to form. On the contrary, decompensated individuals have clinically significant portal hypertension. YKL-40 protein is categorized as an inflammatory protein and is related to various different variables in expressing the severity of hepatic fibrosis, including hepatic venous pressure gradient. The objective of this research was to evaluate the diagnostic validity of serum YKL-40 in cirrhotic hepatitis C virus patients as a predictive non-invasive marker for the diagnosis of oesophageal varices and to compare it to other non-invasive clinical, laboratory, and ultrasonographic parameters, as well as endoscopy with and without treatment modalities.

Results: The present research was done on 80 participants visiting the Tropical Medicine Department at the Main University Hospital in Alexandria; they were divided into four groups, group I ($n=20$) cirrhotic patients with no oesophageal varices, group II ($n=20$) with small varices, group IIIa ($n=20$) with large varices, and group IIIb same patients of group IIIa but after disappearance of varices by band ligation and medical treatment with carvedilol and group IV as apparently healthy control. YKL-40 in serum was evaluated using ELISA. Serum YKL-40 was statistically significantly higher in all cirrhotic patients than healthy controls ($p=<0.001$). Furthermore, it was statistically significantly greater in patients with small varices compared to those without varices ($p=<0.001$) and in large varices rather than no varices or small varices ($p<0.001$) and ($p<0.001$) respectively. However, there was no statistically significant difference between IIIa and IIIb ($p=0.881$). In all tested groups, there was no correlation between serum YKL-40 and FIB-4 or APRI. However, only participants in group I exhibited a significant negative correlation between serum YKL-40 and AST/ALT ratio, whereas subjects in groups II and IIIa exhibited no significant correlation.

Conclusion: Serum YKL-40 could be used as a sensitive non-invasive predictor for diagnosis and grading of oesophageal varices but not for follow up after treatment.

Keywords: Hepatitis C virus, Liver cirrhosis, Portal hypertension, YKL-40

Background

Infection with the hepatitis C virus (HCV) is one of the leading causes of chronic liver disease worldwide [1, 2]. The outcome of HCV infection is very different, ranging from mild necro-inflammatory changes to severe fibrosis

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and cirrhosis, with or without hepatocellular cancer (HCC) [2].

Egypt's HCV prevalence rate is among the highest in the world [1]. So, Egypt launched the biggest illness screening program in history on July 29, 2018 [3], screening more than 60 million Egyptians with a prevalence of less than 5% post direct acting antiviral treatment.

In Egypt, liver cirrhosis is the last stage of numerous liver injuries following HCV infection. It is characterized by persistent necro-inflammatory and fibrogenetic processes, followed by structurally aberrant nodules and thick fibrotic septa [4].

Portal hypertension is by far the most important result of liver cirrhosis. A long-term rise in portal pressure causes collateral development, which changes the way blood flows from portal veins to systemic veins, causing oesophageal varices (OV) [5].

The estimation of the hepatic venous pressure gradient (HVPG) is necessary for the accurate measurement of portal pressure. Although upper gastrointestinal endoscopy (UGIE) is the primary diagnostic method for OV, it is not accepted by all patients and is not available in all facilities [6, 7].

Nonselective beta blockers (NSBBs) should be provided as a primary prophylactic treatment against variceal hemorrhage (VH) in cirrhotic patients with high-risk OV. Moreover, they may be used with endoscopic band ligation (EBL) for secondary prevention of VH. Preventing early bleeding with EBL and NSBB both worked exceptionally well [8].

Due to bleeding EBL-ulcers, EBL is linked with more severe and even life-threatening consequences. Surveillance endoscopies are needed to check for variceal recurrence, which shows that NSBBs are the best treatment overall [8].

Carvedilol has been linked to a higher decrease in portal pressure than the standard NSBB. It decreases resistance inside the liver due to its favorable effect on alpha-1 receptors. However, in decompensated patients, this comes at a higher cost in terms of systemic arterial pressure consequences [9].

Through hepatic vein catheterization and the use of a balloon catheter, the HVPG can be evaluated, and the best way to measure portal pressure is to use a balloon catheter. However, this method has many complications [10].

In addition, the expense and challenges of UGIE urge the search for simpler, non-invasive indicators of OV that might reduce the frequency with which UGIE is done [11]. So, we need to search for a serum non-invasive marker for the diagnosis of portal hypertension.

The glycoprotein YKL-40 (chitinase 3-like 1) belongs to the same non-chitinolytic protein family as human chitinase. Some cells, including macrophages, chondrocytes, and cancer cells, release YKL-40 mRNA, which seems to be elevated in diseases including hepatic fibrosis and malignancy. For the liver, it was shown that hepatocyte macrophages were responsible for its secretion [12].

YKL-40 proteins stimulate chemotaxis, cell adhesion, and migration, which all contribute to endothelial dysfunction. It has been linked to hepatic fibrosis severity indicators such as HVPG and post-sinusoidal resistance [13–15].

The ability of a test to tell the difference between people with and without a certain disorder is called its "diagnostic validity" [16].

Aim of the work

This research aimed to assess the diagnostic validity of serum YKL-40 as a noninvasive diagnostic marker for OV in cirrhotic HCV patients and to compare it with other noninvasive clinical, laboratory, ultrasonographic, and endoscopic findings. In addition, an association between serum YKL-40 and different grades of OV was determined with and without the use of various treatment methods.

Subjects

This prospective controlled research was done on 80 participants visiting the Tropical Medicine Department at the Main University Hospital in Alexandria. Participants were divided into 4 groups. Group I includes 20 patients with liver cirrhosis without OV. Group II contains 20 patients with liver cirrhosis with small OV grade (I, II). Group IIIa contains 20 patients with liver cirrhosis with a large OV grade (III, IV). Group IIIb consists of the same 20 patients as group IIIa but after eradication of OV by band ligation and carvedilol in 3–6 months, and group IV contains 20 healthy subjects as normal controls. The participants' ages varied from 37 to 54 years old.

Exclusion criteria

Patients with sepsis, causes of liver cirrhosis other than HCV, diabetes mellitus, malignancies, rheumatoid arthritis, acute liver failure, and portal vein thrombosis were eliminated from the study.

Methods

All enrolled patients 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 hepatomegaly, splenomegaly, and the detection of ascites and manifestations of hepatocellular failure. They were subjected to laboratory investigations

as complete blood picture (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), blood urea, serum creatinine, fasting blood sugar (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), prothrombin activity (PA), international normalized ratio (INR), serum albumin, bilirubin, and serum alpha fetoprotein (AFP).

Serum samples from all subjects were assayed for our main study marker (YKL-40); also, it was evaluated at the time of eradicated varices for patients of group IIIb by an enzyme-linked immunosorbent assay (ELISA) technique using the Human Chitinase-3-like protein 1 kit (Bioassay Technology Laboratory, China). We calculated the Child Pugh score and performed HCV antibodies (ELISA), hepatitis B surface antigen (ELISA), and anti-schistosomal antibodies (IHAT) for all participating patients.

Regarding ultrasonic parameters, we assessed all parameters; ultrasound evaluation of the liver and ascites was performed on all recruited patients to determine the existence of cirrhosis and/or bilharzial hepatic fibrosis. They were evaluated with ultrasound measurements of right liver lobe diameter, splenic bipolar diameter, and ultrasound Doppler measurements of portal vein diameter. Moreover, portal blood flow volume was calculated as [mean velocity of PV (ml/min) x cross-sectional area of PV (cm^2)] [17].

We took into account all noninvasive clinical, laboratory, and predictive scores, such as the AST to platelet ratio index (APRI) [18] calculated as [(AST/ULN)_100]/platelet count 10^9/L, the index for liver fibrosis FIB4 [18] calculated as [age (years)_AST (IU/L)]/[platelet count (10^9/L) _ ALT (IU/L) 1/2], platelet count to spleen diameter [19], and AST/ALT ratio [20]. In addition, triphasic CT scans were performed on individuals with ultrasound-detected focal hepatic lesions, and UGIE was done for all patients.

Data was entered into the computer and analyzed using version 20.0 of the IBM SPSS software package. Numbers and percentages were used to describe qualitative data. Quantitative data were described by the range (the minimum and maximum), mean, standard deviation, median, and interquartile range (IQR).

Ethical approval

This research was approved by the ethics committee of the Faculty of Medicine at the University of Alexandria. All participants provided their written, informed consent.

Results

This study was conducted on 80 candidates in the Alexandria Main University Hospital, Tropical Medicine Department. Subjects were divided into four groups.

Concerning the demographic information of the analyzed groups, there were no significant variations in age and gender across all groups. As demonstrated in Table 1, females outnumbered males in groups I (60%), group II (55%), and the control group (55%), but males outnumbered females in group IIIa (55%), with mean ages of 44.65 ±3.15 years, 45.70 ± 2.05 years, 45.90 ±4.79 years, and 43.55 ±4.79 years in groups I, II, and IIIa and the control group, respectively.

When it came to patients' symptoms when they were admitted, those with no or small varices (55 and 65%, respectively) were most likely to have dyspepsia. However, Fig. 1 shows that all patients with large varices had abdominal distension and lower limb swelling.

According to the general examination of groups I, II, and IIIa, Fig. 2 shows that pallor and hematemesis were the most common findings in 25% of the people in group I. However, 30% of group II patients had hematemesis, while 60% of patients in group IIIa had palmer erythema.

As shown in Table 1, ascites was found in 30%, 50%, and 100% of the people in groups I, II, and IIIa, respectively, but not in all of the people in group IV, the control group.

Regarding laboratory investigations, CBC findings showed a significant difference in all parameters between liver cirrhosis groups (I, II, and IIIa) and controls. Moreover, a statistically significant difference in platelet count was seen between groups II and IIIa and between groups I and III, but not between groups I and II, as illustrated in Table 1.

All groups had normal kidney function tests, serum AFP level, and FBG level with no significant differences between them. Moreover, all the candidates had a negative CRP with a normal ESR level.

Concerning the liver profile, there were statistically significant differences between all cirrhotic groups and the control group for all measures ($p < 0.001$). As shown in Table 1, serum levels of ALP and total bilirubin were significantly increased in all cirrhotic patients compared to healthy controls.

Table 1 shows that the serum albumin levels of people with both small and large varices were much lower than those of people without varices.

Moreover, serum levels of liver enzymes (AST, ALT) were considerably higher in all cirrhotic groups compared to the control group. Additionally, INR increased considerably in groups I, II, and IIIa relative to the control group. In contrast, PA decreased significantly in groups I, II, and IIIa compared to the control group with a mean of 83.65 ± 14.72, 65.80 ± 11.17, 43.80 ± 8.30, and 94.30 ± 8.41, respectively, as illustrated in Table 1.

All participants in groups I, II, and IIIa had post-viral liver cirrhosis. All were due to chronic HCV infection,

Table 1 Comparison between the three studied groups ($n=80$) according to demographic data and other different parameters

	Group I ($n=20$)		Group II ($n=20$)		Group IIIa ($n=20$)		Group IV ($n=20$)		Test of sig.	p
	No.	%	No.	%	No.	%	No.	%		
Gender										
Male	8	40.0	9	45.0	11	55.0	9	45.0	$\chi^2=0.955$	0.812
Female	12	60.0	11	55.0	9	45.0	11	55.0		
Age (years)										
Min.–max.	39.0–49.0		41.0–49.0		39.0–56.0		37.0–54.0		$F=1.605$	0.195
Mean ± SD.	44.65 ± 3.15		45.70 ± 2.05		45.90 ± 4.79		43.55 ± 4.62			
Median (IQR)	45 (42.5–47.0)		45.5 (44–47.5)		46.0 (41.5–49.5)		44.0 (39.5–46.5)			
Hemoglobin										
Min.–Max.	10.0–11.50		10.0–11.30		9.0–11.50		11.50–14.30		$F=68.661$*	< 0.001*
Mean ± SD.	10.91 ± 0.45		10.75 ± 0.39		10.50 ± 0.59		12.86 ± 0.81			
Median (IQR)	10.90 (10.70–11.30)		10.80 (10.55–11.0)		10.70 (10.05–10.95)		13.0 (12.0–13.35)			
p_0	< 0.001*		< 0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.836, p_2=0.127, p_3=0.515$									
WBC(×10^3)										
Min.–max.	4.0–9.0		3.0–8.30	2.70–8.90			5.0–8.0		$F=2.841$*	0.043*
Mean ± SD.	5.85 ± 1.38		5.17 ± 1.46	5.21 ± 1.73			6.26 ± 0.93			
Median (IQR)	5.75 (4.75–7.0)		5.05 (4.0–6.30)	5.15 (3.70–6.40)			6.05 (5.55–7.0)			
p_0	0.793		0.047*	0.091						
Sig.bet.Grps	$p_1=0.418, p_2=0.472, p_3=1.000$									
Platelets (× 10^3)										
Min.–max.	149.0–190.0		130.0–191.0	51.0–168.0			210.0–389.0		$F=80.751$*	< 0.001*
Mean ± SD.	168.95 ± 13.40		157.70 ± 17.68	107.60 ± 37.99			272.80 ± 53.20			
Median (IQR)	168.0 (158.50–178.0)		151.50 (145.0–172.50)	104.0 (77.0–140.0)			268.50 (224.5–309.5)			
p_0	< 0.001*		< 0.001*	< 0.001*						
Sig.bet.Grps	$p_1=0.732, p_2<0.001$*, $p_3<0.001$*									
Total bilirubin										
Min.–max.	0.20–1.0		0.20–1.0		0.60–6.20		0.20–0.90		$H=29.522$*		< 0.001*
Mean ± SD.	0.66 ± 0.27		0.73 ± 0.28		2.74 ± 2.03		0.59 ± 0.22			
Median (IQR)	0.73 (0.45–0.90)		0.80 (0.45–1.0)		2.05 (0.95–4.60)		0.60 (0.45–0.75)			

Table 1 (continued)

	Group I ($n=20$)		Group II ($n=20$)		Group IIIa ($n=20$)		Group IV ($n=20$)		Test of sig.	p
	No.	%	No.	%	No.	%	No.	%		
p_0	0.343		0.074		< 0.001*					
Sig.bet.Grps	$p_1=0.404$, $p_2<0.001$*, $p_3=0.001$*									
Direct bilirubin										
Min.–max.	0.10–0.80		0.10–0.80		0.40–5.30		0.10–0.70		$H=29.094$*	< 0.001*
Mean ± SD.	0.46 ± 0.23		0.51 ± 0.22		2.16 ± 1.68		0.40 ± 0.19			
Median (IQR)	0.50 (0.25–0.70)		0.53 (0.30–0.70)		1.70 (0.70–3.60)		0.35 (0.25–0.60)			
p_0	0.415		0.145		< 0.001*					
Sig.bet.Grps	$p_1=0.520$, $p_2<0.001$*, $p_3=0.001$*									
Albumin										
Min.–max.	3.20–4.60		3.0–4.20		2.30–3.30		3.90–4.50		$F=41.041$*	< 0.001*
Mean ± SD.	3.92 ± 0.48		3.62 ± 0.40		2.99 ± 0.28		4.15 ± 0.16			
Median (IQR)	4.0 (3.35–4.30)		3.60 (3.25–4.0)		3.05 (2.90–3.15)		4.15 (4.0–4.30)			
p_0	0.174		< 0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.042$*, $p_2<0.001$*, $p_3<0.001$*									
ALT										
Min.–max.	10.0–99.0		13.0–81.0		20.0–120.0		12.0–28.0		$H=31.305$*	< 0.001*
Mean ± SD.	38.85 ± 25.97		36.25 ± 18.08		57.80 ± 30.38		19.90 ± 4.62			
Median (IQR)	29.50 (21.0–52.0)		31.0 (24.50–40.50)		47.0 (31.0–83.0)		19.50 (17.0–22.50)			
p_0	0.002*		0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.716$, $p_2=0.014$*, $p_3=0.037$*									
AST										
Min.–max.	42.0–132.0		50.0–121.0		33.0–117.0		7.0–24.0		$F=48.157$*	< 0.001*
Mean ± SD.	75.45 ± 25.18		71.65 ± 17.95		72.90 ± 23.13		13.10 ± 4.45			
Median (IQR)	74.50 (53.5–93.5)		71.0 (55.50–80.0)		68.50 (58.0–89.5)		12.0 10.0–15.50)			
p_0	< 0.001*		< 0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.926$, $p_2=0.976$, $p_3=0.997$									
ALP										
Min.–max.	50.0–135.0		67.0–170.0		59.0–251.0		50.0–111.0		$F=13.208$*	< 0.001*
INR										
Min.–max.	1.0–1.32		1.10–1.50		1.40–2.10		0.90–1.20		$H=61.021$*	< 0.001*
Mean ± SD.	1.13 ± 0.11		1.29 ± 0.11		1.69 ± 0.20		1.05 ± 0.08			
Median (IQR)	1.10 (1.0–1.22)		1.30 (1.20–1.38)		1.61 (1.55–1.80)		1.0 (1.0–1.10)			

Table 1 (continued)

	Group I ($n=20$)		Group II ($n=20$)		Group IIIa ($n=20$)		Group IV ($n=20$)		Test of sig.	p
	No.	%	No.	%	No.	%	No.	%		
p_0	0.103		< 0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.015$*, $p_2<0.001$*, $p_3=0.001$*									
Prothrombin activity										
Min.–max.	60.0–100.0	50.0–92.0		27.0–56.0			79.0–110.0		$H=60.472$*	< 0.001*
Mean ± SD.	83.65 ± 14.72	65.80 ± 11.17		43.80 ± 8.30			94.30 ± 8.41			
Median (IQR)	90.0 (66.50–96.0)	63.0 (58.50–74.0)		45.50 (40.0–51.0)			98.50 (87.5–100.0)			
p_0	0.122	< 0.001*		< 0.001*						
Sig.bet.Grps	$p_1=0.010$*, $p_2<0.001$*, $p_3=0.002$*									
Ascites								$\chi^2=80.984$*		< 0.001*
No	14		10		0		20			
Mild	6		9		0		0			
Moderate	0		1		13		0			
Massive	0		0		7		0			
Child Pugh classification										
A	14		10		0		NA	$\chi^2=32.269$*		^{MC}p < 0.001*
B	6		10		10					
C	0		0		10					
Child Pugh score										
Min.–max.	5.0–7.0		5.0–8.0		7.0–13.0		NA	$H=31.398$*		< 0.001*
Mean ± SD.	5.70 ± 0.92		6.10 ± 1.17		9.55 ± 2.39					
Median (IQR)	5.0 (5.0–7.0)		6.0 (5.0–7.0)		9.50 (7.0–12.0)					
Sig.bet.Grps	$p_1=0.372$, $p_2<0.001$*, $p_3<0.001$*									

χ^2 chi square test

H: *H* for Kruskal-Wallis test, pairwise comparison between each 2 groups was done using post hoc test (Dunn's for multiple comparisons test)

F: *F* for ANOVA test, pairwise comparison between each 2 groups was done using post hoc test (Tukey)

p: *p* value for comparing between the studied groups

p_0: *p* value for comparing between group IV and each other group

p_1: *p* value for comparing between groups I and II

p_2: *p* value for comparing between groups I and III

p_3: *p* value for comparing between groups II and III

*Statistically significant at $p \leq 0.05$

IQR interquartile range, *SD* standard deviation

Group I: cirrhosis without varices

Group II: cirrhosis with small varices (I, II)

Group IIIa: cirrhosis with large varices (III, IV)

Group IV: control

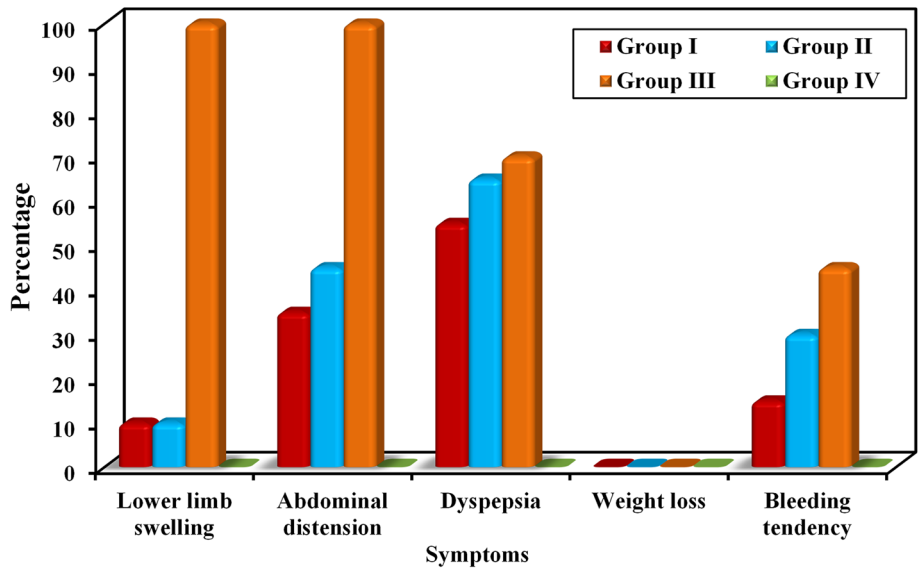

Fig. 1 Comparison between the different studied groups according to symptoms

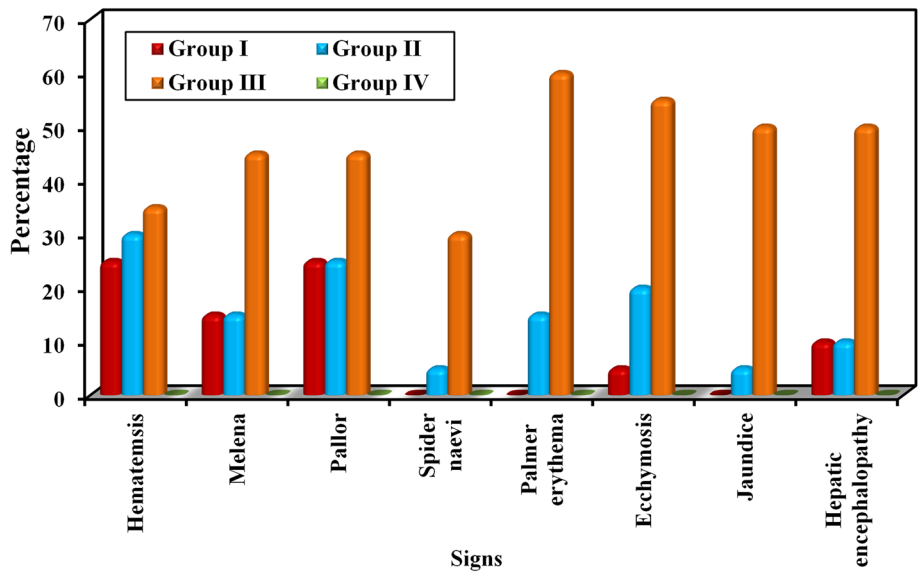

Fig. 2 Comparison between the different studied groups according to signs

and all of them received treatment for HCV and had a negative polymerase chain reaction for HCV. Furthermore, they were negative for the hepatitis B virus (HBV) and the autoimmune hepatitis marker. Table 1 displays the Child-Pugh score and classification of all cases.

In terms of ultrasonography, all participants in groups I, II, and IIIa were cirrhotic, while those in group IV had normal livers. In addition, individuals with large varices had statistically significantly larger spleens than patients without varices or small varices, as illustrated in Table 1.

Also, Table 2 shows that *Schistosoma* caused mixed cirrhosis with periportal hepatic fibrosis in 10% of the people in group I, 15% of the people in group II, and 30% of the people in group IIIa.

All participants in the control and group I had hepatopetal portal blood flow, whereas 45% and 70% of patients

Table 2 Comparison between the different studied groups according to different ultrasonographic parameters

	Group I ($n=20$)		Group II ($n=20$)		Group IIIa ($n=20$)		Group IV ($n=20$)		Test of sig.	p
	No.	%	No.	%	No.	%	No.	%		
Liver cirrhosis	20	100.0	20	100.0	20	100.0	0	0.0	$\chi^2=80.0$*	< 0.001*
Liver rt lobe size (cm)										
Min.–max.	10.50–15.0		11.0–15.0		8.50–13.0		12.0–15.0		$F=11.706$*	< 0.001*
Mean ± SD.	13.51 ± 1.33		13.40 ± 1.39		11.58 ± 1.66		13.90 ± 0.94			
Median (IQR)	13.75 (12.5–14.75)		13.75 (12.50–14.75)		12.25 (10.0–13.0)		14.0 (13.25–14.75)			
p_0	0.793		0.649		< 0.001*					
Sig.bet.Grps	$p_1=0.995, p_2<0.001$*, $p_3<0.001$*									
Hepatomegaly	0	0.0	0	0.0	0	0.0	0	0.0	-	-
Splenomegaly	20	100.0	20	100.0	20	100.0	0	0.0	$\chi^2=80.0$*	< 0.001*
Spleen size (cm)										
Min.–max.	14.0–16.0		14.0–16.0		16.0–19.0		10.0–12.0		$F=156.679$*	< 0.001*
Mean ± SD.	14.65 ± 0.67		15.50 ± 0.69		17.0 ± 1.21		11.40 ± 0.68			
Median (IQR)	15.0 (14.0–15.0)		16.0 (15.0–16.0)		16.50 (16.0–18.0)		11.50 (11.0–12.0)			
p_0	< 0.001*		< 0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.011$*, $p_2<0.001$*, $p_3<0.001$*									
Bilharzial hepatic fibrosis	2	10.0	3	15.0	6	30.0	0	0.0	$\chi^2=7.540$	$^{MC}p=0.051$
Portal vien thrombosis										
No	–	100.0	20	100.0	20	100.0	20	100.0	–	–
Yes	0	0.0	0	0.0	0	0.0	0	0.0		
Portal vien diameter (mm)										
Min.–max.	14.0–15.0		15.0–17.0		17.0–19.0		8.0–12.0		$H=72.658$*	< 0.001*
Mean ± SD.	14.30 ± 0.47		15.60 ± 0.68		17.58 ± 0.63		9.75 ± 1.21			
Median (IQR)	14.0 (14.0–15.0)		15.50 (15.0–16.0)		17.50 (17.0–18.0)		10.0 (9.0–11.0)			
p_0	0.003*		< 0.001,*		< 0.001*					
Sig.bet.Grps	$p_1=0.016$*, $p_2<0.001$*, $p_3=0.005$*									
Portal blood volume										
Min.–max.	610.0–1499.0		501.0–1411.0		570.0–1377.0		1213.0–1521.0		$H=37.254$*	< 0.001*
Mean ± SD.	1140.75 ± 243.69		880.60 ± 300.73		891.15 ± 324.92		1393.65 ± 71.90			
Median (IQR)	1174.0 (993.50–1321.0)		880.50 (590.50–1155.50)		734.50 (600.0–1239.0)		1400.0 (1371.50–1435.0)			
p_0	0.002*		< 0.001*		< 0.001*					
Sig.bet.Grps	$p_1=0.021$*, $p_2=0.044$*, $p_3=0.762$									

Table 2 (continued)

	Group I ($n = 20$)		Group II ($n = 20$)		Group IIIa ($n = 20$)		Group IV ($n = 20$)		Test of sig.	p
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
Portal blood flow (hepatopetal)										
No	0	0.0	9	45.0	14	70.0	0	0.0	$\chi^2 = 35.332$*	< 0.001*
Yes	20	100.0	11	55.0	6	30.0	20	100.0		

χ^2 chi-square test

H: *H* for Kruskal-Wallis test, pairwise comparison between each 2 groups was done using post hoc test (Dunn's for multiple comparisons test)

F: *F* for ANOVA test, pairwise comparison between each 2 groups was done using post hoc test (Tukey)

p: *p* value for comparing between the studied groups

p_0: *p* value for comparing between group IV and each other group

p_1: *p* value for comparing between groups I and II

p_2: *p* value for comparing between groups I and III

p_3: *p* value for comparing between groups II and III

*Statistically significant at $p \leq 0.05$

IQR interquartile range, *SD* standard deviation

I: cirrhosis without varices

Group II: cirrhosis with small varices (I, II)

Group IIIa: cirrhosis with large varices (III, IV)

Group IV: control

in groups II and IIIa had hepatofugal portal blood flow, respectively. Between the control group and the group with liver cirrhosis, there was a substantial difference in portal blood volume, with the control group having a median of 1400.0. In addition, among the liver cirrhosis groups, substantial differences were seen between groups I and II and between groups I and IIIa, but not between groups II and IIIa. There were statistically significant variations in portal vein diameter between groups I and II ($p1 < 0.016$), between groups I and IIIa ($p2 < 0.001$), and between groups II and IIIa ($p3 = 0.005$), as shown in Table 2.

Regarding the classic predictive scores, APRI [18], FIB4 [18], the AST/ALT ratio, and the ratio of platelet count to spleen diameter [19] all demonstrated statistically significant differences between the control and cirrhotic groups. Within all cirrhotic groups, there was a statistically significant difference between groups I and IIIa and between groups II and IIIa, but not between groups I and II, in all predicted scores, as shown in Table 3.

Table 3 Comparison between the different studied groups according to predictive non-invasive liver cirrhosis scores

	Group I ($n = 20$)	Group II ($n = 20$)	Group IIIa ($n = 20$)	Group IV ($n = 20$)	Test of sig.	*p*
FIB-4						
Min.–max.	3.16–4.15	3.17–4.48	3.34–11.53	0.22–0.83	$H = 62.963$*	< 0.001*
Mean ± SD.	3.37 ± 0.22	3.52 ± 0.39	5.58 ± 2.04	0.42 ± 0.15		
Median (IQR)	3.29 (3.25–3.47)	3.37 (3.30–3.51)	4.90 (4.14–6.92)	0.42 (0.31–0.48)		
p_0	< 0.001*	< 0.001*	< 0.001*			
Sig.bet.Grps	$p_1 = 0.317$, $p_2 < 0.001$*, $p_3 < 0.001$*					
APRI						
Min.–max.	0.74–2.34	1.03–1.77	1.14–6.75	0.06–0.30	$H = 53.436$*	< 0.001*
Mean ± SD.	1.32 ± 0.45	1.30 ± 0.25	2.25 ± 1.32	0.15 ± 0.06		
Median (IQR)	1.23 (1.03–1.64)	1.19 (1.10–1.52)	1.81 (1.37–2.83)	0.14 (0.11–0.16)		
p_0	< 0.001*	< 0.001*	< 0.001*			
Sig.bet.Grps	$p_1 = 0.814$, $p_2 = 0.007$*, $p_3 = 0.014$*					
PLT/spleen diameter						
Min.–max.	931.20–1357.10	812.50–1364.20	268.40–1050.0	1758.30–3536.3	$F = 126.160$*	< 0.001*
Mean ± SD.	1158.92 ± 139.22	1023.83 ± 160.86	645.83 ± 253.64	2404.40±508.86		
Median (IQR)	1119.95 (1056.6–1271.4)	946.85 (906.2–1149.95)	607.88 (442.60–853.10)	2349.95 (1987.5–2813.3)		
p_0	< 0.001*	< 0.001*	< 0.001*			
Sig.bet.Grps	$p_1 = 0.499$, $p_2 < 0.001$*, $p_3 = 0.001$*					
AST/ALT ratio						
Min.–max.	1.26–4.50	1.27–3.84	0.77–3.25	0.37–0.95	$F = 37.712$*	< 0.001*
Mean ± SD.	2.40 ± 0.87	2.20 ± 0.61	1.46 ± 0.63	0.65 ± 0.14		
Median (IQR)	2.19 (1.78–2.99)	2.26 (1.91–2.41)	1.21 (1.12–1.57)	0.63 (0.57–0.74)		
p_0	< 0.001*	< 0.001*	0.001*			
Sig.bet.Grps	$p_1 = 0.499$, $p_2 < 0.001$*, $p_3 < 0.001$*					

H: *H* for Kruskal-Wallis test, pairwise comparison between each 2 groups was done using post hoc test (Dunn's for multiple comparisons test)

F: *F* for ANOVA test, pairwise comparison between each 2 groups was done using post hoc test (Tukey)

p: *p* value for comparing between the studied groups

p_0: *p* value for comparing between groups IV and each other group

p_1: *p* value for comparing between groups I and II

p_2: *p* value for comparing between groups I and III

p_3: *p* value for comparing between groups II and III

*Statistically significant at $p \leq 0.05$

IQR interquartile range, *SD* standard deviation

Group I: cirrhosis without varices

Group II: cirrhosis with small varices (I, II)

Group IIIa: cirrhosis with large varices (III, IV)

Group IV: control

All patients were graded for portal hypertensive gastropathy (PHG) using UGIE, finding that 80% of patients in group I had no PHG, 25% and 35% of patients in group II had mild and moderate PHG, respectively, and 35% of people in group IIIa had severe PHG.

The number of OV band ligation procedures necessary to eradicate the large OV in group IIIa varied from 2 to 5 sessions over a period of 12 to 24 weeks.

Regarding our primary study marker, serum YKL-40 is significantly different between the control and liver cirrhosis groups, with a mean of 46.04 ± 9.11 ng/ml in the control group and 70.95 ± 13.11 ng/ml, 99.11 ± 15.46 ng/ml, and 146.89 ± 29.18 ng/ml in groups I, II, and IIIa, respectively. In addition, among groups I, II, and IIIa, statistically significant differences were discovered between I and II, I and IIIa, and between groups II and IIIa. However, there was no difference between the IIIa and IIIb groups, as illustrated in Figs. 3 and 4.

Moreover, a cutoff value of > 80.3 (ng/ml) for serum YKL-40 was a very good predictor of the presence of OV, with 90% sensitivity and 75% specificity, as shown in Table 4 and Fig. 5.

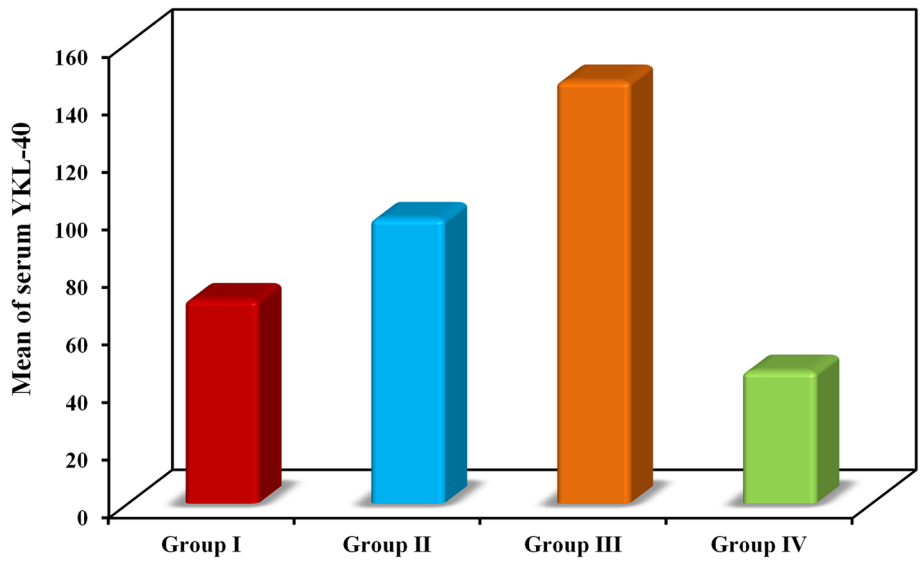

Fig. 3 Comparison of the several investigated groups based on serum YKL-40

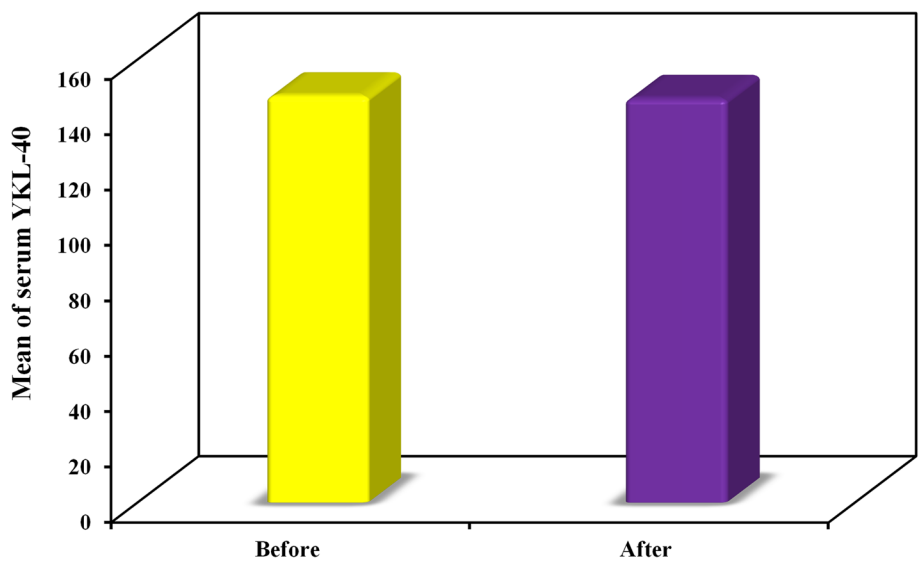

Fig. 4 Serum YKL-40 in group IIIa and group IIIb after oesophageal varices elimination

Also, with a cutoff value of > 111.1 (ng/ml) and a sensitivity of 80% and a specificity of 75%, serum YKL-40 could tell the difference between small varices and large varices. This is shown in Table 5 and Fig. 6.

There was no correlation between serum YKL-40 and the Child Pugh score, FIB-4, or APRI in any of the examined groups.

Discussion

Recent studies have revealed that liver macrophages (Kupffer cells) play an important role in the fibrotic process [21]. Macrophage specific indicators may, therefore, prove to be valuable for the monitoring of fibrosis progression, such as serum YKL-40.

In addition, YKL-40 serum levels correlate strongly with the degree of liver fibrosis resulting from nonalcoholic fatty liver disease, HCV, and HBV [22].

YKL-40 may be considered an inflammatory protein as it enhances chemotaxis, cell adhesion, and migration in response to endothelium damage. Several studies suggest an association between elevated blood levels of YKL-40 and endothelial damage, liver injury, and fibrosis [12].

Thrombocytopenia, splenomegaly, AST/ALT ratio [20], APRI [18], and platelet count to spleen diameter ratio [19] are all non-invasive ways that have been developed recently to evaluate the value of different laboratory, clinical, and ultrasonographic parameters that are linked to portal hypertension.

In this study, serum YKL-40 was evaluated as a potential noninvasive diagnostic marker for OV, and statistically significant differences were seen between the control and liver cirrhosis groups. In addition, statistically significant differences were found among groups I, II, and IIIa; between groups I and II; between groups

Table 4 Validity (AUC, sensitivity, specificity) for serum YKL-40 to discriminate group II ($n = 20$) from group I ($n = 20$)

	AUC	*p*	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Serum YKL-40	0.919	< 0.001*	0.835–1.0	> 80.3	90.0	75.0	78.3	88.2

AUC area under a curve, *p value* probability value, *CI* confidence intervals, *NPV* negative predictive value, *PPV* positive predictive value

*Statistically significant at $p \leq 0.05$

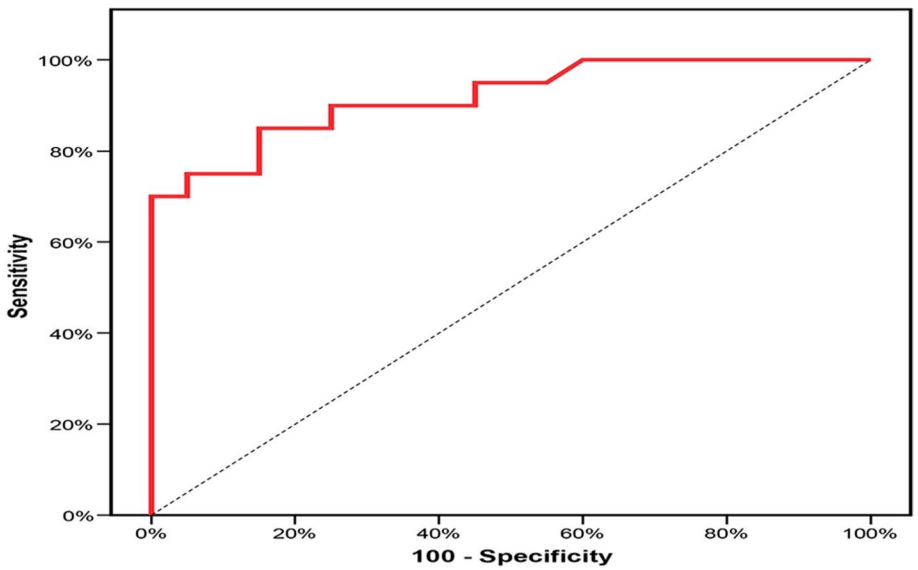

Fig. 5 ROC curve for serum YKL-40 to discriminate group II ($n = 20$) from group I ($n = 20$)

Table 5 Validity (AUC, sensitivity, specificity) for serum YKL-40 to discriminate group III ($n = 20$) from group II ($n = 20$)

	AUC	*p*	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Serum YKL-40	0.893	< 0.001*	0.794–0.991	> 111.1	80.0	75.0	76.2	78.9

AUC area under a curve, *p value* probability value, *CI* confidence intervals, *NPV* negative predictive value, *PPV* positive predictive value

*Statistically significant at $p \leq 0.05$

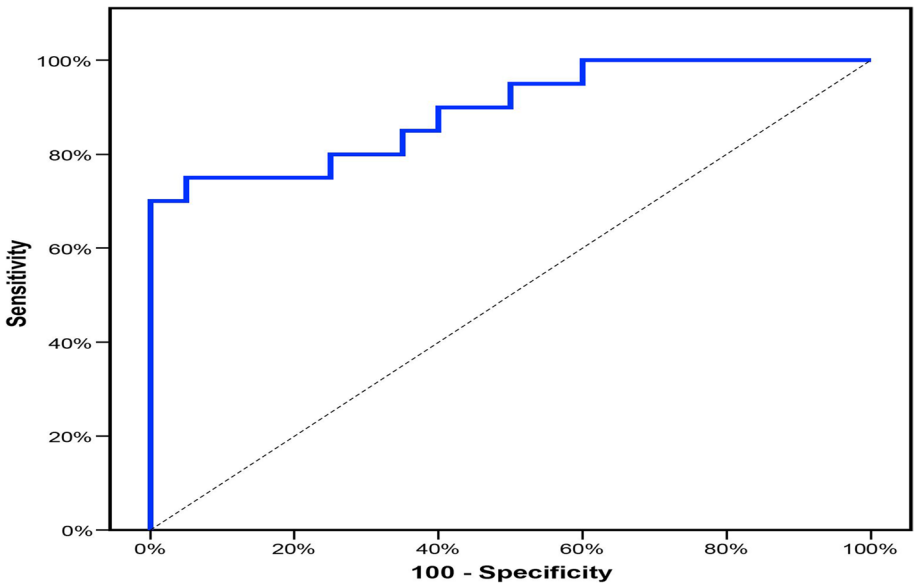

Fig. 6 ROC curve for serum YKL-40to discriminate group III ($n = 20$) from group II ($n = 20$)

I and IIIa; and between groups II and IIIa. This matches the findings of Sumanth et al. (2018) [23].

However, there was no statistically significant difference between group IIIa and group IIIb in terms of serum YKL-40 following eradication of OV by combined band ligation and carvedilol, which diminishes its prognostic value. However, additional larger randomized studies are required to confirm this finding.

This was in line with what Sira et al. (2016) [24] found. They concluded that YKL-40 serum levels are linked with more advanced stages of liver fibrosis and can distinguish those with significant fibrosis efficiently. Also, the levels of YKL-40 in the blood of people with cirrhosis and hepatic schistosomiasis were statistically significantly higher than those without schistosomiasis.

This was consistent with the findings of Johansen et al. [15]. Individuals with alcoholic cirrhosis had the highest median blood YKL-40 levels (532 μg/L). Serum YKL-40 levels were also linked to the severity of liver fibrosis ($p = 0.001$), as they were higher in patients with moderate fibrosis (270 μg/L) than in those without fibrosis ($p = 0.018$).

The discrepancy in blood levels between our research and that of Johansen et al. [15] may be attributed to a larger sample size, different etiological causes of cirrhosis, such as alcoholism, the existence of additional confounding variables, or the use of different serological kits.

Moreover, Wang et al. [25] observed an increase in immunohistochemistry YKL-40 expression in the spleen of individuals with portal hypertension. This was also consistent with the findings of Abruzzi et al. (2015) [26], who mentioned that co-infection with HCV and schistosoma reduces the capacity to spontaneously cure the viral infection and often leads to rapid fibrosis and greater mortality, which is explained by the synergistic interaction between schistosoma-HCV and hepatic fibrosis.

In the present research, we additionally correlated serum YKL-40 with other non-invasive cirrhosis indicators in each group, and found that there was no significant correlation between serum YKL-40 and FIB-4 or APRI in any of the examined groups.

This matched the findings of Yan et al. [27], who mentioned that serum YKL-40 was a viable biomarker of liver fibrosis in individuals with chronic HBV. In addition, the YKL-40 model proved better than the APRI, FIB-4, Forns' index, and Hui model for diagnosing severe fibrosis in individuals with normal or modestly increased ALT levels.

Meanwhile, in our research, a significant negative association between serum YKL-40 and AST/ALT ratio was discovered only in group I, but there was no significant correlation in groups II and III.

Also, Ruizhao Qi et al. [28] found that the levels of YKL-40 in the blood of people with cirrhosis were significantly higher and were linked to the Child–Pugh score and HBV infection. Moreover, patients with HBV-related cirrhotic portal hypertension had higher YKL-40 levels than those with HCV infection, who had a higher serum YKL-40 level than in our study, possibly due to the effect of HBV infection, the difference in study participant number or the use of different kits. This is mostly owing to the persistence of

HBV infection inside the hepatocyte, which makes the necro-inflammation last longer than it does in HCV-infected people.

The highest acceptable dosage of carvedilol utilized in our research to achieve a 25% drop in pulse rate but not below 60 beats per minute varied from 6.25 to 12 mg per day. This dose is identical to the one used in the trial by Tripathi et al. [29].

In our research, following full eradication of OV with EBL and carvedilol, there was also a statistically significant improvement in PHG among group IIIb. This was consistent with Abbasi et al. [30], who said that the severity of PHG was related to the severity of OV, which suggests that the two conditions have similar causes.

Conclusions

YKL-40 is an effective noninvasive predictor for the presence of OV and may be used to grade OV, according to our findings. The serum YKL-40 level does not change after OV eradication. However, the serum YKL-40 level increases dramatically in the presence of bilharziasis.

Abbreviations

HCV: Hepatitis C virus; HCC: Hepatocellular cancer; OV: Oesophageal varices; HVPG: Hepatic venous pressure gradient; UGIE: Upper gastrointestinal endoscopy; NSBBs: Nonselective beta blockers; VH: Variceal hemorrhage; EBL: Endoscopic band ligation; CBC: Complete blood count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; FBG: Fasting blood sugar; AST: Aspartate transferase; ALT: Alanine transferase; ALP: Alkaline phosphatase; PA: Prothrombin activity; INR: International normalized ratio; AFP: Alpha fetoprotein; APRI: AST to platelet ratio index; ELISA: Enzyme-linked immunosorbent assays; HBV: Hepatitis B virus; PHG: Portal hypertensive gastropathy; ULN: Upper limit of normal.

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Authors' contributions

MA was in charge of the practical section, data analysis, and manuscript preparation. All authors provided critical feedback and helped shape and revise the research, the analysis, and the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The article contains the information utilized to support the conclusions of this study.

Declarations

Ethics approval and consent to participate

This research was conducted in line with ethical principles. Before beginning the research, the Faculty of Medicine, Alexandria University Ethical Committee granted clearance on July 16, 2020, and the study protocol adheres to the ethical principles outlined in the 1975 Declaration of Helsinki. Each participant's consent was acquired in advance. The Committee's serial number is 0201368, and the reference number is FWA NO: 00018699.

Consent for publication

Both patients and the control group provided written informed consent. Patients participating in this research consent to data publication.

Competing interests

The authors declare that they have no competing interests.

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