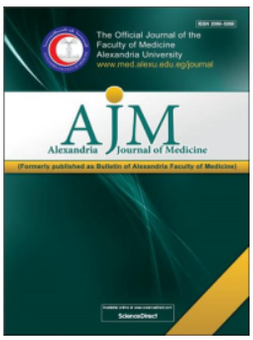

Alexandria Journal of Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tajm20

Evaluation of serum kallistatin level as a predictor of esophageal varices in cirrhotic patients

Osama M. Sobhey, Amal A. Jouda, Ashraf Metwally, Nagwa M. Shawky & Mohammad N. Elkhashab

To cite this article: Osama M. Sobhey, Amal A. Jouda, Ashraf Metwally, Nagwa M. Shawky & Mohammad N. Elkhashab (2020) Evaluation of serum kallistatin level as a predictor of esophageal varices in cirrhotic patients, Alexandria Journal of Medicine, 56:1, 21-26, DOI: 10.1080/20905068.2020.1714191

To link to this article: https://doi.org/10.1080/20905068.2020.1714191

Published online: 27 Jan 2020.

ALEXANDRIA JOURNAL OF MEDICINE
2020, VOL. 56, NO. 1, 21–26
https://doi.org/10.1080/20905068.2020.1714191

Evaluation of serum kallistatin level as a predictor of esophageal varices in cirrhotic patients

Osama M. Sobhey[a], Amal A. Jouda[a], Ashraf Metwally[a], Nagwa M. Shawky[b] and Mohammad N. Elkhashab[a]

[a]Tropical Medicine Department, Faculty of Medicine, Zagazig University and Zagazig University Hospitals, Zagazig, Sharqueya, Egypt; [b]Clinical Pathology Department, Faculty of Medicine, Zagazig University and Zagazig University Hospitals, Zagazig, Sharqueya, Egypt

ABSTRACT

Introduction: The Baveno VI consensus recommended the use of noninvasive predictors to identify patients at high risk of esophageal varices (EV) in whom endoscopic evaluation is most needed. Kallistatin is a protein molecule synthesized by the liver, and its level declines with the deterioration of liver functions. We aim to explore the role of kallistatin as a predictor of esophageal varices.

Methods: This case–control study included 70 cirrhotic patients (35 patients with EV and 35 patients without EV). The laboratory investigations and upper GI endoscopy were performed, and the serum kallistatin level was measured in all patients.

Results: The mean level of serum kallistatin was significantly lower in patients with varices (12.2 ± 5.6 vs 16.9 ± 4.8 µg/ml, p = 0.009). It also shows a significant decline in patients with large varices. Kallistatin can predict the presence of EV and large EV at cut off values of 15.8 and 8.9 µg/ml, respectively, with sensitivity and specificity of 71.4% and 54.3% for EV and 50% and 94.8% for large EV.

Discussion: Kallistatin is a promising marker that can be used to predict the presence of esophageal varices especially when they are large and risky.

ARTICLE HISTORY
Received 14 July 2019
Accepted 7 January 2020

KEYWORDS
Kallistatin; noninvasive; esophageal varices; portal hypertensive gastropathy; Baveno VI

1. Introduction

The prevalence of esophageal varices (EV) among cirrhotic patients ranges from 40% in Child-Pugh class A to 85% in Child-Pugh class C [1,2]. EV are the most serious consequence of portal hypertension. The incidence of variceal bleeding in cirrhotic patients is 5–15% with a mortality rate of more than 20%, despite the advances in management of bleeding [3,4]

Investigating and validating more noninvasive diagnostic markers is recently recommended by Baveno VI consensus; this practice will help save endoscopic diagnosis and intervention to those who need it the most and avoid the hazard of unnecessary endoscopies [5].

Kallistatin is a tissue kallikrein, serine proteinase inhibitor and heparin-binding protein, that is mainly synthesized by the liver [6,7]. Kallistatin is known to have various biological functions. Besides its role as an anti-inflammatory and antioxidant agent, it also acts as a suppressor of angiogenesis and carcinogenesis [8–10]. The kallistatin level was proved to decrease significantly with the deterioration of liver functions [11].

2. Aim of the work

This study aims to investigate the relation between kallistatin level in cirrhotic patients and the grade of EV and explore its role as a noninvasive predictor of EV.

3. Patients and methods

This is a case–control study performed in Tropical Medicine and Clinical Pathology Departments, Zagazig University Hospitals. Seventy cirrhotic patients were included in this study; 40 males and 30 females, age ranging between 34 and 57 years. They were randomly selected from patients admitted to endoscopy unit during the period from August 2017 to January 2018. All patients were previously diagnosed with liver cirrhosis based on clinical examination, biochemical parameters, and radiological evidence. The exclusion criteria were as follows: Patients less than 18 years or more than 60 years, patients who did not give informed consent to participate in the study, patients with intra- or extrahepatic malignancy, diabetic patients with advanced microvascular complications, patients with cardiovascular problems, e.g., hypertension, and patients with renal disease.

On admission, baseline evaluation was performed including detailed medical history and clinical examination. Ultrasound examination of the abdomen and pelvis was performed with specific attention to stigmata of liver cirrhosis, portal hypertension, spleen size, and portal vein diameter (PVD). The spleen was considered enlarged if the splenic axis exceeded 13 cm [12–14]. Ascites was classified according to its amount into three grades; mild (free fluid in the pelvis and in

CONTACT Amal A. Jouda dr.amaljouda@yahoo.com Tropical Medicine, Faculty of Medicine, Zagazig University, Zagazig, Sharqueya, Egypt

the hepatorenal pouch), moderate (free fluid in the flanks), and tense (free fluid in the central part of the abdomen and around the intestine) [15].

Patients included in the study performed all routine laboratory investigations, liver and kidney function tests, complete blood count, coagulation profile, the degree of hepatic decompensation was graded according to Child-Turcotte-Pugh classification [16]. Kallistatin serum level was measured in all patients included in the study by using sandwich enzyme-linked immune-sorbent assay (ELISA) kits.

All patients underwent esophagogastroduodenoscopy to evaluate the presence of esophageal varices, gastric varices, and/or portal hypertensive gastropathy (PHG) using Pentax EG-3490 K diagnostic therapeutic videoscope.

Esophageal varices were graded according to Paquet classification system [17] and PHG was graded according to three grades grading system [18]

Patients were allocated to two groups according to the results of endoscopic evaluation (35 patients in each group); Group I: patients with esophageal varices (test group) and Group II: patients without EV.

3.1. Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 16. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as number and percentage. Independent t-test was used to compare normally distributed numerical data, while Mann–Whitney test was used to compare data that were not normally distributed. The chi-square was used to compare quantitative data. Fisher exact was used as an alternative of chi-square when the sample was small. Spearman's Rho correlation was used to estimate the relation between serum kallistatin level and different patients' parameters. Multivariate logistic regression model was used to test the independent predictors of EV. ROC curve was used to evaluate the clinical performance of kallistatin as a predictor to EV.

4. Results

Demographic, clinical, sonographic, and laboratory data are summarized in Tables 1 and 2. Table 1 shows that there were no significant differences between the studied groups as regards age, gender, viral markers, or history of bilharziasis. There were also no significant differences as regards the frequency of different grades of ascites, different grades of encephalopathy or lower limb edema.

Table 1 shows that group I (EV group) had significantly higher Child's score than group II (7.17 ± 1.96 vs 5.54 ± 0.78, $p < 0.001$), and the frequency of higher Child's grades was significantly higher in group I (42.9% and 14.3% in group I vs 17.1% and 0% in group II successively, $P = 0.001$). The frequency of Child's grade A was significantly higher in group II (82.9% vs 42.9% in group II, $p = 0.001$).

Table 1 also shows that group I had significantly larger mean PVD (14.5 ± 1.2 vs 11.8 ± 0.9 mm in group II, $p < 0.001$). Moreover, group I also had significantly larger mean spleen long axis than group II (20.1 ± 1.9 vs 18.6 ± 1.5 cm, $p = 0.001$).

Table 2 represents a comparison between the studied groups as regards the routine laboratory parameters. It shows that there were no significant differences between the studied groups as regards hemoglobin concentration, WBCs count, bilirubin, liver enzymes, creatinine, or urea. On the other hand, Table 2 shows that group I had significantly lower platelet count than group II (105.4 ± 25.3 vs

Table 1. Comparison of demographic, clinical, and sonographic data in the studied groups.

		Group I No=35	Group II No=35	Test	p-value
Age (years) (mean ±SD)		49.3 ± 4.3	48.9 ± 3.1	T= 0.477	0.635 (NS)
Gender No (%)	Males	18 (51.4%)	22 (62.9%)	X^2= 0.933	0.334 (NS)
	Female	17 (48.6%)	13 (37.1%)		
Viral markers	HBV	4 (11.4%)	2 (5.7%)	X^2= 0.731	0.694 (NS)
	HCV	30 (85.7%)	32 (91.4%)		
	Both	1 (2.9%)	1 (2.9%)		
History of bilharziasis		6 (17.1%)	6 (17.1%)	X^2 =1	1.00 (NS)
Hepatomegaly		13 (37.1%)	12 (34.3%)	0.062	0.803 (NS)
Ascites	No ascites	25 (71.4%)	29 (82.9%)	5.387	0.146 (NS)
	Mild	5 (14.3%)	6 (17.1%)		
	Moderate	3 (8.6%)	0 (%)		
	Tense	2 (5.7%)	0 (%)		
Lower limb edema		8 (22.9%)	6 (17.1%)	0.357	0.55 (NS)
Encephalopathy		4 (11.4%)	0 (%)	4.242 ^{F}	0.114(NS)
Child's grade No (%)	A	15 (42.9%)	29 (82.9%)	X^2= 13.312	0.001 (S)
	B	15 (42.9%)	6 (17.1%)		
	C	5 (14.3%)	0 (0%)		
Child's score (points)		7.17 ± 1.96	5.54 ± 0.78	Z=-4.34	<0.001 (HS)
Portal vein diameter (mm)		14.5 ± 1.2	11.8 ± 0.9	Z=-6.968	<0.001 (HS)
Spleen diameter (cm)		20.1 ± 1.9	18.6 ± 1.5	T=3.523	0.001 (S)

SD, standard deviation; NS, non-significant; HS, highly significant; S, significant; ^{F}, fisher exact; Z, Mann–Whitney test; T, student test; X^2, chi-square.

Table 2. Comparison of laboratory parameters in the studied groups.

	Group I No = 35	Group II No = 35	test	p-value (sig.)
Hemoglobin(g/dl)	12.2 ± 0.9	12.4 ± 1.1	T = −1.102	0.274 (NS)
WBC's(x10^3/ml)	5.7 ± 1.4	6.2 ± 2.1	T = −1.232	0.222 (NS)
Platelet count (x10^3/ml)	105.4 ± 25.3	145.3 ± 32.3	T = −5.749	<0.001 (HS)
Bilirubin (mg/dl)	1.77 ± 0.71	1.38 ± 0.36	Z = −1.898	0.058 (NS)
Albumin(g/dl)	3.16 ± 0.36	3.62 ± 0.33	T = −5.699	<0.001 (HS)
ALT(IU/L)	44.5 ± 13.7	41.6 ± 14.2	Z = −1.129	0.259 (NS)
AST(IU/L)	49.5 ± 15	46.0 ± 12.2	Z = −1.005	0.315 (NS)
INR	1.49 ± 0.28	1.22 ± 0.18	Z = −4.598	<0.001 (HS)
Urea(mg/dl)	20.0 ± 4.1	22.5 ± 9.9	Z = −0.124	0.901 (NS)
Creatinine (mg/dl)	0.98 ± 0.19	0.91 ± 0.18	Z = −1.453	0.146 (NS)
Kallistatin (µg/ml)	12.21 ± 5.65	16.99 ± 4.87	Z = −2.596	0.009
Median	14.9	15.9		(S)
Range	1.8–17.8	10.3–32.5		

WBCs, white blood cells; ALT, alanine transaminase; AST, aspartate transaminase; PT, prothrombin time; INR, international normalizing ratio; T, student test; Z, Mann–Whitney test; SD, standard deviation; NS, non-significant; HS, highly significant; S, significant.

145.3 ± 32.3, p < 0.001), Group I also had significantly lower albumin level, and significantly higher INR than group II as well (3.16 ± 0.36 gm/dl and 1.49 ± 0.28 vs 3.62 ± 0.33 and 1.22 ± 0.18, p < 0.001).

Table 2 shows also a comparison between the studied groups as regards serum kallistatin. It shows that kallistatin level ranged between 1.8 and 17.8 µg/ml in the cirrhotic patients with EV and between 10.3 and 32.5 µg/ml in cirrhotic patients without EV. Serum kallistatin mean level was significantly lower in cirrhotic patients with varices (12.21 ± 5.65 vs 16.99 ± 4.87 µg/ml, Z = −2.596, P = 0.009).

Table 3 represents a comparison of mean kallistatin level in different Child's grades, EV grades, and PHG grades. Mean kallistatin level was significantly lower in patients with Child grade C than A and B (4.35 ± 4.95 vs 15.53 ± 4.07 and 15.1 ± 6.75 µg/ml, respectively, KW = 11.676, P = 0.003). Mean kallistatin level was significantly lower in patients with grade IV and gastric varices than in other patients (8.93 ± 6.45 and 2.25 ± 0.18, respectively, vs 13.46 ± 3.99 in grade I, 14.44 ± 4.22 in grade II, and 16.43 ± 1.35µg/ml in grade III, KW = 18.745, P = 0.002). Mean kallistatin level was significantly lower in patients with severe portal hypertensive gastropathy than in other patients (8.48 ± 6.7 vs 15.92 ± 3.98 in patients without PHG, 16.62 ± 6.65 in mild PHG, and 14.69 ± 4.27 µg/ml in moderate PHG) (Table 3).

Table 4 shows the correlation between kallistatin level and different patients' parameters. It shows that kallistatin level has significant negative correlation to WBC count, hemoglobin concentration, INR, and creatinine (r = −0.24, −0.25, −0.28, −0.27 in succession, P < 0.05). There was also a significant negative correlation between kallistatin and PVD (r = −0.23, P = 0.049) and grade of esophageal varices (r = −0.28, p = 0.02) as well as a significant negative correlation to Child's score (r = −0.4, p = 0.002).

The parameters that were found significantly different between the studied groups were used to build a multivariate regression model to investigate their role as independent predictors of the presence and the grade of esophageal varices. Table 5 shows that only PVD and kallistatin level were found to be significant independent predictors of EV (regression coefficient = 0.583, P < 0.001 for PVD and −0.014, P = 0.048 for kallistatin level).

On blotting ROC curve, it revealed that at a cut-off value of 15.8 µg/ml kallistatin level can predict the presence of EV with sensitivity and specificity of 71.4% and 54.3%, respectively [AUC = 0.68]. It can also predict the presence of large EV (grade III, IV, and gastric) at a cut-off value of 8.9 µg/ml with

Table 3. Comparison of kallistatin level in different child, esophageal varices, and portal hypertensive gastropathy grades in both groups.

		Kallistatin level Mean ±SD	Kruskal–Wallis test	P
Child's grade	A	15.53 ± 4.07	11.676	0.003
	B	15.1 ± 6.75		(S)
	C	4.35 ± 4.95		
Esophageal varices	0	16.99 ± 4.87	18.745	0.002
	I	13.46 ± 3.99		(S)
	II	14.44 ± 4.22		
	III	16.43 ± 1.35		
	IV	8.93 ± 6.45		
	Gastric	2.25 ± 0.18		
PHG	Non	15.92 ± 3.98	10.276	0.016
	I	16.62 ± 6.65		(S)
	II	14.69 ± 4.27		
	III	8.48 ± 6.7		

PHG, portal hypertensive gastropathy; SD, standard deviation; S, significant.

Table 4. Correlation between kallistatin level and different patients' parameters in the studied population.

	Kallistatin	
Variables	R	P-Value
Bilirubin	−0.11	0.3(NS)
Albumin	0.11	0.3(NS)
WBC's	0.24	0.04(S)
Hemoglobin	0.25	0.03(S)
Platelet count	0.09	0.4(NS)
Creatinine	−0.27	0.019(S)
INR	−0.28	0.15(S)
PVD	−0.23	0.049(S)
Spleen size	−0.18	0.13(NS)
EV grade	−0.283	0.02 (S)
Child score	−0.478	0.002 (S)

WBCs: white blood cells, INR: international normalizing ration, PVD: portal vein diameter, EV: esophageal varices, S: significant, NS: non-significant.

Table 5. Multivariate regression analysis of significant independent predictors of presence of esophageal varices.

variables	coefficient	SE	P
INR	0.00710849	0.638871	0.99(NS)
Platelet count	−0.00316456	0.00469364	0.5(NS)
Kallistatin level	−0.0141504	0.00702236	0.048 (S)
Child's score	0.0567011	0.115648	0.62(NS)
PVD	0.583626	0.116040	<0.001(HS)
Spleen size	0.0567011	0.115648	0.82(NS)

$r^2 = 0.681$.
ANOVA < 0.001.
Albumin was excluded from the model,
PVD: portal vein diameter, INR: international normalizing ratio, WBCs: white blood cells, S: significant, NS: non-significant.

sensitivity and specificity of 50% and 94.6%, respectively, [AUC = 0.712]. Kallistatin level can predict the presence of PHG at a cut-off value of 15.4 µg/ml with sensitivity and specificity of 60% and 62.9%, respectively [AUC = 0.587]. The presence of severe PHG can be predicted by serum kallistatin level at a cut-off value of 8.9 µg/ml with sensitivity and specificity of 58.3% and 94.8%, respectively [AUC = 0.794] (Table 6).

5. Discussion

In the present study, we tried to demonstrate the correlation between serum Kallistatin level and the presence and grade of EV in patients with liver cirrhosis as well as its clinical performance as a noninvasive predictor of EV. Regarding age, gender, and viral markers, there were no significant differences between both groups. This agrees with Tafarel et al. [19], who found that the presence of esophageal varices is not affected by age, gender, or type of chronic viral hepatitis. This also agrees with Eltoukhy and Issa [20], who found that the presence of varices is not affected by the type of viral hepatitis or the history of bilharziasis. This also agrees with AbdelMaksoud et al. [21], who found that there were no significant differences as regards age, gender, viral hepatitis, or bilharziasis between cirrhotic patients with and without varices.

There were no statistically significant differences between both groups, regarding lower limb edema, ascites, or encephalopathy; these findings agree with that reported by Madhotra et al. [12], except that ascites in the latter study were more frequent and severe in patients with EV. This may be because most of the patients with EV in the latter study were Child B grade. These findings also agree with AbdelMaksoud et al. [21], who found that there was not any clinical sign of liver disease that can be specifically linked to the presence of esophageal varices.

The comparison between the studied groups as regards laboratory data revealed that there were highly significant differences between the studied groups as regards mean levels of albumin, INR, and platelet count, these findings are in agreement with the results of Emam et al. [22], who found that albumin and platelet count were significantly lower in patients with varices and prothrombin time was significantly higher indicating that the presence of EV is associated with decreased liver synesthetic functions and thrombocytopenia. Regarding mean serum bilirubin, there was no significant difference between the studied groups and that finding is against Emam et al. [22] and Madhotra et al. [12]. The other laboratory parameters as hemoglobin, WBCs, ALT, AST, creatinine, and urea showed no significant differences between the studied groups and that finding agrees with Kraja et al. [23].

In our study, we found that there was a significant difference between the studied groups as regards mean PVD and mean spleen long axis. Both parameters were significantly higher among patients with EV. This finding agrees with Emam et al. [22] and Mandal et al. [24], who found that the mean PVD and spleen long axis were significantly higher in patients with varices. This also agrees with Kedar et al. [25], who found that spleen size is a good indicator of portal hypertension and its sequelae.

Comparison of kallistatin level in different Child-Pugh grades showed that kallistatin serum level decreases significantly in grade C indicating that kallistatin level may be a marker of the severity of liver dysfunction. This finding comes in agreement with Cheng et al. [11], who found that the level of kallistatin decreases with deterioration of liver functions in advanced cirrhosis.

In the present study, mean kallistatin level was significantly lower in patients with EV in comparison to patients without EV. Comparison of mean kallistatin level in patients with different EV grades shows that kallistatin level decreases significantly with the increase in the size of EV with the lowest mean level found in patients with gastric varices suggesting that kallistatin level may reflect the size and severity of varices. We also found that kallistatin level may reflect

Table 6. Clinical performance of the kallistatin as predictor of the presence of EV, large EV, PHG, and severe PHG.

	Cutoff value(µg/ml)	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	p-value
EV	≤ 15.8	0.68	71.4	54.3	62.9	61	65.5	0.009(S)
Large EV	≤ 8.9	0.712	50	94.6	85.7	70	88.3	0.015(S)
PHG	≤ 15.4	0.587	60	62.9	61.4	61.8	61.1	0.21(NS)
Severe PHG	≤ 8.9	0.794	58.3	94.8	88.6	70	91.7	.001(HS)

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; EV, esophageal varices; PHG, portal hypertensive gastropathy; NS, non-significant; HS, highly significant; S, significant.

the severity of PHG as there was a significant decrease in kallistatin level with severe PHG. Cheng et al. [11] stated that kallistatin level declines with the progression of the fibrosis and cirrhosis process inside the liver parenchyma, the process that progressively leads to more rise in the portal pressure and appearance of more collateral vessels. The decline in the kallistatin level itself, being a mediator with antiangiogenic function, may even contribute to the appearance of collateral vessels like EV.

Another finding that supports the relation of kallistatin level to the severity of portal hypertension is that there was a significant correlation between kallistatin level and PVD which is also considered a predictor of esophageal varices by Mandal et al. [24].

Multivariate regression model was done and all the possible predictors of the presence of EV were represented in it. We found that the only independent predictors of EV in our study were PVD and kallistatin level. This means that the relation between kallistatin level and EV was independent and not affected by any of these possible confounding variables. This agrees with Cheng et al. [11], who confirmed that although kallistatin was correlated to the liver function tests in cirrhotic patients, its relation to the severity of liver cirrhosis in those patients was independent and not affected by the other variables in the study.

Using Receiver Operating Characteristic (ROC) curve showed that at level of 15.8 μg/mL or less, kallistatin can predict the presence of EV with sensitivity of 71.4%, specificity of 54.3%, and accuracy 62.9%, while at level of 8.9 μg/ml or less, it can predict presence of large EV with sensitivity of 50%, specificity of 94.6%, and accuracy 85.7%. This clarifies that kallistatin better detects the presence of large varices. At a level of 8.9 μg/mL, kallistatin can also predict the presence of severe PHG with sensitivity of 58.3%, specificity of 94.8% and accuracy 88.6%.

6. Conclusions

Serum kallistatin levels decrease significantly with higher grades of EV. Kallistatin serum level is independently correlated to the presence and grade of varices. Serum kalllistatin level is a promising marker that can be used as a predictor of large EV and severe PHG.

Ethical regulations

The study design was reviewed and approved by the institutional review board.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Osama M. Sobhey, Master degree in tropical medicine, resident of gastroenterology and hepatology in AlAhrar eductional hospital in Zagazig, specialist of gastroenetrology and hepatology.

Amal A. Jouda, PhD in tropical medicine, assistant professor of tropical medicine, faculty of medicine, Zagazig University, consultant of gastroenterology and hepatology, member of the Egyptian society of study of endoscopy and hepatogastroenterology.

Ashraf Metwally, PhD in tropical medicine, assistant professor of tropical medicine Faculty of medicine Zagazig University, diploma in hospital management from Sadat Academy of Management Sciences, consultant of gastroenetrology and hepatology, member of the Egyptian society of study of endoscopyn and heptogastroenetrology.

Nagwa M. Shawky, PhD in clinical pathology, professor and former head of clinical pathology department Faculty of medicine Zagazig University, consultant of clinical pathology in zagazig University hospitals.

Mohammad N. Elkhashab, PhD in tropical medicine, professor and former head of tropical medicine department, Faculty of medicine zagazig University, member of the Egyptian society of study of endoscopy and hepatogastroenetrology, consultant of gastroeneterology and hepatology, editor in chief of the afro-Egyptian journal of infectious and endemic diseases.

References

[1] Garcia–Tsao G, Friedman S, Iredale J, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology. 2010;51(4):1445–1449.

[2] Groszmann R, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353 (21):2254–2261.

[3] Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38(3):266–272.

[4] D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther. 2014;39(10):1180–1193.

[5] De Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–752.

[6] Chen V, Chao L, Pimenta D, et al. Identification of a major heparin-binding site in kallistatin. J Biol Chem. 2001;276(2):1276–1284.

[7] Chao J, Schmaier A, Chen L, et al. Kallistatin, a novel human tissue kallikrein inhibitor: levels in body fluids, blood cells, and tissues in health and disease. J Lab Clin Med. 1996;S*127*(6):612–620.

[8] Miao R, Agata J, Chao L, et al. Kallistatin is a new inhibitor of angiogenesis and tumor growth. Blood. 2002;100:3245–3252.

[9] Chao J, Bledsoe G, Chao L. Protective role of kallistatin in vascular and organ injury. Hypertension. 2016;68(3):533–541.

[10] Shen B, Hagiwara M, Yao Y, et al. Salutary effect of kallistatin in salt-induced renal injury, inflammation, and fibrosis via antioxidative stress. Hypertension. 2008;51:1358–1365.
[11] Cheng Z, Lv Y, Pang S, et al. Kallistatin, a new and reliable biomarker for the diagnosis of liver cirrhosis. Acta Pharm Sin. 2015;B 5:194–200.
[12] Madhotra R, Mulcahy H, Willner I, et al. Prediction of esophageal varices in patients with cirrhosis. J Clin Gastroenterol. 2002;34(1):81–85.
[13] Cales P, Oberti F, Bernard-Chabert B, et al. Evaluation of Baveno recommendations for grading esophageal varices. J Hepatol. 2003;39 (4):658–659.
[14] Loftus W, Chow L, Metreweli C. Sonographic measurement of splenic length: correlation with measurement at autopsy. J Clin Ultrasound. 1999;27(2):71–74.
[15] Runyon BA, Commitee APG. Management of adult patients with ascites. AASLD PRACTICE GUIDELINE due to cirrhosis: update 2012., revised and updated guideline based on the previously published version. Hepatology. 2009;49:2087–2107.
[16] CG C, Turcotte JG. Surgery and portal hypertension. The liver and portal hypertension. Philadelphia: Saunders; 1964.
[17] Paquet K. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices - a prospective controlled randomized trial. Endoscopy. 1982;14 (1):4–5.
[18] Pungpapong S, Keaveny A, Raimondo M, et al. Accuracy and interobserver agreement of small-caliber vs. Conventional esophagogastroduodenoscopy for evaluating esophageal varices. Endoscopy. 2007;39(08):673–680.
[19] Tafarel J, Tolentino L, Correa L, et al. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. Eur J Gastroenterol Hepatol. 2011;23 (9):754–758.
[20] El Toukhy N. Issa H: predictive and prognostic vale of von Willebrand factor in patients with cirrhosis and esophageal varices. Afro-Egypt J Infect Endem Dis. 2019;9(1):67–73.
[21] AbdelMaksoud MA, Jouda A, Fathy T, et al. Role of plasma von willebrand factor-antigen in predicting the presence of esophageal varices and occurrence of its bleeding in cirrhotic patient. Afro-Egypt J Infect Endem Dis. 2019;9(2):139–149.
[22] Emam E, Ramadan A, Badway M, et al. Prediction of oesophageal varices in patients with compensated cirrhosis: A novel scoring system. Arab J Gastroenterol. 2009;10(4):129–134.
[23] Kraja B, Mone I, Akshija I, et al. Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients. World J Gastroenterol. 2017;23 (26):4806.
[24] Mandal L, Mandal S, Bandyopadhyay D, et al. Correlation of portal vein diameter and splenic size with gastro-oesophageal varices in cirrhosis of liver. J Indian Acad Clin Med. 2011;12(4):266–270.
[25] Kedar RP, Merchant SA, Malde HH, et al. Multiple reflective channels in the spleen: A sonographic sign of portal hypertension. Abdom Imaging. 1994;19:453–458.