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Effect of Circulating Angiotensin Converting Enzyme Level in Portal Hypertension

Ahmed Ahmed El-Shaarawy[1], Eman Ahmed Gawish[1], Ahmed Kamal Khamis[2], Hager Said Hamed Meselhy*[1], Mary Albert Naguib[1]

Departments of [1]Clinical Pathology,

[2]Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Egypt

***Corresponding author:** Hager Said Hamed Meselhy, **Mobile:** (+20)1069774115, **E-Mail:** hagersaid542@gmail.com

ABSTRACT

Background: A common clinical condition, portal hypertension (PHT) is brought on by mesenchymal dysfunction in cirrhotic livers. Esophageal varices (EV), a dangerous complication, demand that patients be watched closely at all times. The zinc metallopeptidase angiotensin-converting enzyme (ACE) is located on the surface of endothelial and epithelial cells. It is an essential part of the renin-angiotensin system (RAS), which controls plasma volume and blood pressure.

Objectives: The present study was designed to assess angiotensin-converting enzyme (ACE) levels in portal hypertension patients and study its association with presence of esophageal varices.

Patients and methods: A total of 105 subjects, including 35 portal hypertension patients with esophageal varices, 35 portal hypertension patients without esophageal varices and 35 healthy controls were selected. ACE level was measured using enzyme-linked immunosorbent assay (ELISA)

Results Serum ACE was significantly increased in PHTN with EV group versus PHTN without EV and healthy groups. A significant association was detected between ACE levels and the size of varices, as higher levels of ACE were found in patients with large varices (p=0.010). In addition, a significant association was found between ACE and blood transfusion (p=0.012) and lower hemoglobin levels (P value < 0.001) in PHTN with EV group. A cutoff values of ≥ 44.15 ng/mL and ≥ 48.75 ng/mL could significantly discriminate PHT patients with EV from healthy controls and PHTN patients without esophageal varices respectively.

Conclusion: It could be concluded that angiotensin-converting enzyme (ACE) could be a potential diagnostic marker for the presence of esophageal varices in portal hypertensive patients and a non- invasive marker for recognizing patients at risk of variceal rupture.

Keywords: Portal hypertension, Esophageal Varices, angiotensin-converting enzyme.

INTRODUCTION

Portal hypertension is a dangerous complication of liver disease caused by increased resistance to portal blood flow into the liver. [(1)]. Due to significant consequences such ascites, bleeding from gastro-esophageal varices, and encephalopathy, cirrhosis has a devastating sequela that increases morbidity and mortality [(2)]. Esophageal varices (EV) are portosystemic collaterals that form in the lower esophageal submucosa preferentially. It is responsible for 10% to 30% of all cases of upper gastrointestinal bleeding. [(3)].

For detecting varices, upper gastrointestinal endoscopy is regarded as the gold standard [(4)]. This procedure, however, is invasive, restrictive, and relatively expensive. As a result, there is an urgent need to identify noninvasive tests that can be repeated during the follow-up of cirrhotic patients at risk of bleeding. [(5)].

The angiotensin-converting enzyme (ACE), a zinc metallopeptidase found on the surface of endothelial and epithelial cells, is an important component of the renin-angiotensin system (RAS). By catalyzing the conversion of angiotensin I to angiotensin II, ACE regulates blood pressure and plasma volume. As a result, ACE raises blood pressure indirectly (by causing blood vessels constriction). Ang II is the primary effector in the regulation of vasoconstriction, sodium homoeostasis, fibrosis, cell proliferation, and the inflammation associated with various diseases, including liver cirrhosis [(6)]. According to earlier studies, the RAS is crucial to the cirrhosis-related development of portal hypertension [(7)]. Furthermore, many experimental and clinical studies have shown that modulating the RAS improves portal pressure in cirrhotic animal models and human patients, implying that this system could be a target in the development of future therapies for cirrhosis-related portal hypertension. [(8)]. So, we aimed to measure angiotensin-converting enzyme (ACE) levels in portal hypertension patients and study its association with presence of esophageal Varices.

SUBJECTS AND METHODS

This case-control study was conducted at the National Liver Institute, Menoufia University in Egypt. It included 70 portal hypertensive (PHT) patients; 35 with esophageal varices and 35 without esophageal varices. They were recruited from Departments of Hepatology and Gastroenterology, National Liver Institute. In addition, 35 healthy unrelated individuals who were age- and gender-matched were recruited from Blood Donation Unit of National Liver Institute as a control group.

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All participants were subjected to:

- Full medical history taking and complete clinical examination.
- A liver ultrasound and an upper gastrointestinal endoscopy to evaluate the various esophageal varices grades.
- Fibroscan.
- Routine laboratory investigations including:
  - Complete blood count (Sysmex XT-1800 Automated Hematology Analyzer, Japan).
  - Liver and renal function tests (Cobas-6000 Auto analyser, Roche Diagnostics, Germany).
  - Serology of hepatitis (HBs Ag and HCV Ab) (Cobas e411 immunoassay analyser, Roche diagnostics, Germany).
  - Prothrombin time and international normalized ratio (Coagulometer CA -1500, Siemens, Germany).
- Estimation of serum ACE levels:

Angiotensin converting enzyme levels in serum were assessed by enzyme-linked immunosorbent assay (ELISA), kit for human from Sunred Biotecnology company (Shanghai Sunred Biological Technology company, China). The kit uses double-antibody sandwich technique. Serum was stored at -20 until analyzed according to the manufacturer's directions.

Ethical approval:

The study protocol was accepted and approved by the National Liver Institute's Regional Ethics Council at Menoufia University. Patients and participants in the control group signed informed consent after being aware of the research's goals. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

The statistical analysis for the current study was completed using SPSS version 22.0. (SPSS Inc., Chicago, IL, USA). The information was split into two sections: descriptive and analytical research The odds ratio (OR), confidence interval (CI), Kruskal-Wallis, Fisher's Exact, and Chi-square tests were used. P value less than 0.05 was regarded as significant.

RESULTS

1- Characteristics of the studied subjects

Serum ACE was significantly higher in PHTN patients with EV versus healthy group (P value < 0.001) and PHTN patients without EV (p=0.041).

When compared to PHT patients without EV, PHT patients with EV had significantly higher levels of aspartate aminotransferase (AST), total and direct bilirubin, INR, and significantly lower levels of hemoglobin (Hb), platelets, and albumin.

In addition, both portal hypertensive patients groups showed a highly significant increase of alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), direct bilirubin, INR, urea, creatinine than healthy group **(p <0.001)** and a highly significant lower levels of Albumin, total protein than healthy group **(p< 0.001)** (Table 1).

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Table (1): Biochemical parameters in healthy controls and in portal hypertension without and with esophageal varices groups

Biochemical parameters	Healthy controls (n= 35)	PHTN without E.V. (n= 35)	PHTN with E.V. (n= 35)	Kruskal-Wallis test	Pairwise comparisons
ACE (ng/mL)				χ^2= 14.11	p1=0.598 NS
Median (IQR)	37.00 (7.13)	39.97 (12.97)	43.33 (13.04)	P-value =**0.001** HS	**p2<0.001** HS
Range (min-max)	26.00 - 48.80	27.60 - 76.20	30.43 - 133.50		**p3=0.041** S
ALT (U/L)				χ^2= 23.62	**p1<0.001** HS
Median (IQR)	15.00 (5.00)	19.00 (17.00)	21.00 (19.00)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	10.00 - 21.00	12.00 - 108.00	11.00 - 119.00		p3=0.993 NS
AST (U/L)				χ^2= 55.51	**p1<0.001** HS
Median (IQR)	15.00 (6.00)	31.00 (25.00)	47.00 (35.00)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	10.00 - 24.00	13.00 - 140.00	16.00 - 202.00		**p3=0.009** HS
ALP (U/L)				χ^2= 29.7	**p1<0.001** HS
Median (IQR)	59.00 (22.00)	72.00 (57.00)	90.00 (109.00)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	45.00 - 83.00	47.00 - 246.00	46.00 - 320.00		p3=0.137 NS
GGT (U/L)				χ^2= 33.56	**p1<0.001** HS
Median (IQR)	16.00 (8.00)	32.00 (37.00)	52.00 (76.00)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	11.00 - 32.00	13.00 - 175.00	11.00 - 299.00		**p3=0.244** NS
Total bilirubin (mg/dL)				χ^2= 30.9	**p1=0.999** NS
Median (IQR)	0.70 (0.30)	0.70 (0.30)	2.20 (2.40)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	0.40 - 1.20	0.46 - 3.20	0.40 - 6.60		**p3<0.001** HS
Direct bilirubin (mg/dL)				χ^2= 51.02	**p1<0.001** HS
Median (IQR)	0.15 (0.10)	0.21 (0.18)	1.01 (1.37)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	0.05 - 0.25	0.05 - 2.20	0.14 - 3.90		**p3<0.001** HS
Albumin (g/dL)				χ^2= 58.99	**p1<0.001** HS
Median (IQR)	4.00 (0.60)	3.50 (0.80)	2.79 (0.90)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	3.60 - 5.00	2.50 - 4.70	1.44 - 4.20		**p3<0.001** HS
Total protein (g/dL)				χ^2= 34.15	**p1<0.001** HS
Median (IQR)	7.60 (1.00)	6.70 (0.80)	6.30 (1.80)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	6.80 - 8.30	6.10 - 8.20	4.71 - 8.90		**p3=0.124** NS
INR				χ^2= 55.72	**p1<0.001** HS
Median (IQR)	1.05 (0.09)	1.11 (0.11)	1.33 (0.50)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	0.95 - 1.12	0.95 - 1.60	1.05 - 2.10		**p3<0.001** HS
Urea (mg/dL)				χ^2= 52.69	**p1<0.001** HS
Median (IQR)	21.00 (11.00)	50.00 (25.00)	56.00 (53.00)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	12.00 - 35.00	23.00 - 105.00	14.00 - 211.00		**p3=0.718** NS
Creatinine (mg/dL)				χ^2= 30.04	**p1<0.001** HS
Median (IQR)	0.79 (0.27)	1.18 (0.60)	1.20 (0.84)	P-value <**0.001** HS	**p2<0.001** HS
Range (min-max)	13.20 (1.00)	0.60 - 2.30	0.60 - 3.00		**p3=1.000** NS
Hemoglobin (g/dL)					**p1<0.001** HS
Median (IQR)	13.20(1.00)	11.20(1.30)	9.90(3.50)	χ^2= 63.96	**p2<0.001** HS
Range (min-max)	12.00-15.10	8.50-13.50	6.80-13.50	P-value <**0.001** HS	**p3=0.030 S**
WBCs (10^3 cell/µL)					**p1<0.001 HS**
Median (IQR)	6.00(2.60)	7.20(3.00)	7.90(5.90)	χ2= 12.24	**p2=0.070 NS**
Range (min-max)	4.30(9.10)	4.80-14.20	1.90-16.00	P-value =0.002 HS	**p3=0.984 NS**
Platelets count (10^3 cell/µL)					**p1=0.777NS**
Median (IQR)	270.0(90.0)	245.0(120.0)	120.0(101.0)	χ2= 43.82	**p2<0.001HS**
Range (min-max)	188.00-457.00	150.00-400.00	48.00—320.00	P-value <0.001 HS	**p3<0.001 HS**

Median (IQR), Range (min-max): non-parametric test. IQR: Interquartile range (difference between 1st and 3rd quartiles), *: Kruskal-Wallis test; if significant, multiple pairwise comparisons was adjusted by Dunn-Sidak post hoc test. NS : Non significant at p-value ≥ 0.05 S: Significant at p-value < 0.05 HS: Highly significant at p-value < 0.01. p1:-p-value for the difference between Healthy controls and PHTN without E.V. groups , p2: p-value for the difference between Healthy controls and PHTN with E.V. groups, p3: p-value for the difference between PHTN without E.V. and PHTN with E.V. groups.

PHTN with EV group had a highly significant increased Child score than PHTN without EV group (P value < 0.001). Majority of patients in PHTN with EV group were significantly associated with Child B and C (51.4% and 25.7% respectively) while majority of patients in PHTN without EV group were significantly associated with Child A and B (85.7% and 14.3% respectively). The study revealed that 20% of PHTN with EV group had encephalopathy, 34.3% had ascites and 80% had splenomegaly but no patients in PHTN without EV group had encephalopathy, ascites or splenomegaly (Table 2).

Table (2): Clinical parameters in portal hypertension without and with esophageal varices groups

Clinical parameters	PHTN without E.V. (n= 35)	PHTN with E.V. (n= 35)	Significance test	P-value
Child score			z= 5.57 [a]	**<0.001** [HS]
Median (IQR)	6.00 (1.00)	9.00 (3.00)		
Range (min-max)	5.00 - 9.00	5.00 - 12.00		
Child classification [n (%)]			χ^2= 30.45 [b]	**<0.001** [HS]
A	30 (85.7)	8 (22.9)		
B	5 (14.3)	18 (51.4)		
C	0 (0.0)	9 (25.7)		
Encephalopathy [n (%)]			χ^2= 7.78 [b]	**0.011** [S]
No	35 (100.0)	28 (80.0)		
Yes	0 (0.0)	7 (20.0)		
Ascites [n (%)]			χ^2=14.48 [c]	**<0.001** [HS]
No	35 (100.0)	23 (65.7)		
Yes	0 (0.0)	12 (34.3)		
Splenomegaly [n (%)]			χ^2= 46.67 [c]	**<0.001** [HS]
No	35 (100.0)	7 (20.0)		
Yes	0 (0.0)	28 (80.0)		
Blood transfusion [n (%)]			χ^2= 1.20 [c]	0.274 [NS]
No	28 (80.0)	24 (68.6)		
Yes	7 (20.0)	11 (31.4)		
DM/HTN [n (%)]			χ^2= 0.92 [c]	0.337 [NS]
No	21 (60.0)	17 (48.6)		
Yes	14 (40.0)	18 (51.4)		
Smoking [n (%)]			χ^2= 0.70 [c]	0.403 [NS]
No	28 (80.0)	25 (71.4)		
Yes	7 (20.0)	10 (28.6)		

PHTN: portal hypertension DM: Diabetes Mellitus HTN :Hypertension, IQR: Interquartile range (difference between 1st and 3rd quartiles), a: Mann-Whitney test b: Fisher's Exact test c:Pearson chi-square test. NS : Non significant at p-value ≥ 0.05 S: Significant at p-value < 0.05, HS: Highly significant at p-value < 0.01

2- Studying ACE levels and its correlation with different parameters

Serum ACE was significantly higher in PHTN patients with EV versus healthy group (P value < 0.001) and PHTN patients without EV (p=0.041). However, there was a non- significant increase of ACE levels in PHTN patients without EV compared to healthy controls (Table 1). Serum ACE levels in PHTN patients with EV showed high significant associated with lower hemoglobin levels (P value < 0.001) (Table 3). Also, we found that serum ACE was significantly higher in PHTN patients with large varices and in patients with blood transfusion (p=0.010 and 0.012 respectively) (Table 4)

Otherwise, there was no significant association between ACE and other clinical parameters in PHTN with EV group (p≥ 0.05) (Table 4).

Table (3): Correlation between ACE (ng/mL) and various parameters in groups of portal hypertension without and with esophageal varices.

Correlated parameters	ACE (ng/mL)			
	PHTN without E.V.		PHTN with E.V.	
	r_s	P-value	r_s	P-value
Age (years)	0.20	0.241 NS	0.05	0.776 NS
ALT (U/L)	-0.03	0.885 NS	-0.27	0.111 NS
AST (U/L)	-0.08	0.664 NS	-0.32	0.064 NS
ALP (U/L)	-0.23	0.177 NS	0.21	0.225 NS
GGT (U/L)	-0.07	0.702 NS	-0.06	0.715 NS
Total bilirubin (mg/dL)	0.11	0.528 NS	-0.15	0.395 NS
Direct bilirubin (mg/dL)	0.08	0.648 NS	0.01	0.978 NS
Albumin (g/dL)	-0.09	0.612 NS	-0.01	0.936 NS
Total protein (g/dL)	-0.18	0.296 NS	-0.27	0.112 NS
INR	0.15	0.402 NS	-0.09	0.604 NS
Urea (mg/dL)	-0.06	0.750 NS	0.14	0.416 NS
Creatinine (mg/dL)	-0.29	0.088 NS	0.19	0.268 NS
Hemoglobin (g/dL)	-0.29	0.090 NS	-0.63	**<0.001 HS**
WBCs (10^3 cell/µL)	-0.12	0.508 NS	-0.02	0.915 NS
Platelets (10^3 cell/µL)	0.25	0.141 NS	-0.15	0.406 NS
Child score	0.30	0.077 NS	-0.12	0.498 NS

r_s: Spearman correlation coefficient
NS : Non significant at p-value ≥ 0.05 HS: Highly significant at p-value < 0.01

Table (4): Relation between ACE and clinical parameters in the group of portal hypertension with esophageal varices

Clinical parameters	ACE (ng/mL)		P-value [a]
	no of cases (%)	Median (IQR)	
Gender			0.887 NS
Male	24 (68.6)	42.055 (17.19)	
Female	11 (31.4)	44.28 (12.08)	
Liver cirrhosis			0.641 NS
No	4 (11.4)	40.105 (42.00)	
Yes	31 (88.6)	44.28 (13.04)	
Child Pugh classification			0.751 NS
A	8 (22.9)	45.39 (16.09)	
B	18 (51.4)	44.39 (12.06)	
C	9 (25.7)	40.72 (17.37)	
Splenomegaly			0.483 NS
No	7 (20.0)	39.39 (19.94)	
Yes	28 (80.0)	43.805 (12.78)	
Ascites			0.466 NS
No	23 (65.7)	44.28 (14.60)	
Yes	12 (34.3)	41.915 (17.08)	
Varices			**0.010** S
Small	17 (48.6)	40.12 (9.66)	
Large	18 (51.4)	50.925 (24.56)	
Encephalopathy			0.174 NS
No	28 (80.0)	42.055 (12.86)	
Yes	7 (20.0)	51.1 (57.34)	
Smoking			0.688 NS
No	25 (71.4)	43.33 (12.71)	
Yes	10 (28.6)	41.945 (19.77)	
Blood transfusion			**0.012** S
No	24 (68.6)	40.77 (12.49)	
Yes	11 (31.4)	51.87 (11.48)	
DM or HTN comorbidity			0.575 NS
No	17 (48.6)	44.5 (15.22)	
Yes	18 (51.4)	41.915 (13.96)	

IQR: Interquartile range (difference between 1st and 3rd quartiles)
a : Mann-Whitney test
S: Significant at p-value < 0.05

3- ACE as diagnostic marker:

Using ROC curve analysis revealed that ACE cutoff value of 44.15 ng/mL or more could distinguish PHTN patients with EV from healthy controls with sensitivity 48.6 %, specificity 94.3 %, accuracy 71.5 % and area under the curve (AUC) was 0.758 (P < 0.001). Also, cutoff value

of 48.75 ng/mL or more could discriminate between PHTN with EV and PHTN without EV groups with sensitivity 40 %, specificity 88.6 % , accuracy 64.3 % and area under the curve (AUC) 0.670 (P-value =0.014) (Table 5).

Table (5): Diagnostic performance of ACE for discrimination between portal hypertension with esophageal varices group, portal hypertension without esophageal varices group and healthy controls

Test characteristics	PHTN with E.V. vs. healthy controls	PHTN with E.V. vs. PHTN without E.V.	PHTN without E.V. vs. Healthy controls
	ACE (ng/mL)	ACE (ng/mL)	ACE (ng/mL)
Best cutoff value	≥ 44.15	≥ 48.75	≥ 41.77
AUC	0.758	0.670	0.578
P-value	**<0.001** **HS**	**0.014** **S**	0.262 NS
Sensitivity %	48.6	40.0	42.9
Specificity %	94.3	88.6	82.9
PPV %	89.5	77.8	71.5
NPV %	64.7	59.6	59.2
Accuracy %	71.5	64.3	62.9

PPV: Positive predictive value NPV: Negative predictive value
Non-significant at p-value ≥ 0.05
HS: Highly significant at p-value < 0.01
S: Significant at p-value < 0.05**.**

DISCUSSION

One of the most severe side effects of portal hypertension in liver cirrhosis is esophageal varices. Variceal rupture may increase mortality. Additionally, patients are vulnerable to consequences such as hepatorenal syndrome, ascites, hepatic encephalopathy, and others [(9)]. Due to the reported role of renin angiotensin system in the pathogenesis of portal hypertension, we studied ACE levels in portal hypertension patients with and without esophageal varices

As far as we are aware, this is the first study to assess the ability of ACE level in detecting esophageal varices in portal hypertensive patients.

We found that serum ACE was significantly increased in PHTN with EV group versus PHTN without EV and healthy groups. Also, serum ACE was increased in PHTN without EV compared to healthy group, however, this difference couldn`t attain the significant levels. Our results came in agreement with **Lubel and his colleagues** [(10)] who found a significant increased level of ACE in patients with advanced cirrhosis.

Previous research found that serum ACE levels were higher in patients with chronic liver disease. Possible causes include decreased inactivation of this enzyme due to cirrhosis-related decreased lung function, ACE hyperproduction in the spleen, hypoxia, and electrolyte imbalance due to hemodynamic changes. Furthermore, these patients have higher levels of histamine, a substance that causes blood vessel endothelial cells to secrete more ACE [(11)].

Zhan and colleagues [(12)] stated that ACE levels were significantly higher in patients with liver cirrhosis and were positively related to portal vein pressure, implying that ACE played a role in the pathogenesis of portal hypertension. They stated that ACE can constrict hepatic stellate cells and promote vascular smooth muscle hyperplasia, resulting in vascular lumen stricture and increased portal pressure.

Purnak and colleagues[(13)] stated that patients with chronic hepatitis B (CHB) have elevated circulating ACE levels. This finding was more prevalent in patients with advanced liver fibrosis. **Miranda and Silva**[(14)] also discovered a significantly higher level of ACE in CHB patients with advanced fibrosis and cirrhosis than in CHB patients in the early stages of fibrosis, concluding that serum levels of ACE may represent an accurate, non-invasive, widely available, and simple method to evaluate fibrosis related to CHB.

Efe and his colleagues [(15)] demonstrated a correlation between elevated circulating ACE levels and fibrosis score and came to the conclusion that serum ACE provides a quick, reliable, and affordable noninvasive method for differentiating between significant and nonsignificant liver fibrosis in autoimmune hepatitis (AIH).

It is worth noting that variceal rupture is the most common fatal cirrhosis complication; the larger the varix, the greater the risk of rupture. Child classification also increases the risk of hemorrhage, which could cause drop of hemoglobin level [(16)].

Interestingly, our results revealed significant association between ACE levels and the size of varices, as higher levels of ACE were found in patients with large varices (p=0.010),in addition to the significant association between ACE and blood transfusion (p=0.012). Furthermore, ACE levels in PHTN patients with EV was highly significant associated with lower hemoglobin (P value < 0.001). This shows that ACE levels could be used as reliable marker for recognizing patients with risk of variceal rupture.

However, in both groups of PHTN patients, there was no statistically significant association between ACE levels and Child-Pugh score. This lack of association may be caused by certain patients' ascites and degree of hepatic encephalopathy being under- or over-scored [(17)].

The ROC curve analysis revealed that ACE cutoff values of ≥ 44.15 ng/mL and ≥ 48.75 ng/mL could significantly discriminate PHT patients with EV from healthy controls and PHTN patients without EV with sensitivity 48.6 % and 40 % respectively, specificity 94.3 % and 88.6 % respectively and accuracy 71.5 % and 64.3 % respectively.

On the other hand, we found that ACE levels could not significantly differentiate between portal hypertension without esophageal varices group and healthy controls. This was going in hand with our findings that there was no significant correlation between ACE and different laboratory parameters which may reveal that serum ACE could not reflect the progression of different liver functions.

CONCLUSION

It could be concluded that angiotensin-converting enzyme (ACE) could be a potential diagnostic marker for the presence of esophageal varices in portal hypertensive patients and a non- invasive marker for recognizing patients at risk of variceal rupture.

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