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ORIGINAL RESEARCH ARTICLE

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Diagnosis of portal vein thrombosis in cirrhotic patients with and without hepatocellular carcinoma

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Abstract

Background: The levels of Annexin A5 (Annexin V) were measured in patients with and without HCC who had liver cirrhosis. These patients were followed for 12 months to determine the incidence of PVT and to determine the role of Annexin V in the diagnosis of PVT. Our goal was to look at the value of Annexin A5, platelet count, spleen size, portal flow velocity, portal vein width, Fibrosis 4, and APRI score in these individuals to see if they might be used as PVT markers.

Methods: Between March 2017 and August 2018, ninety-one HCV patients with cirrhosis with and without HCC, as well as a control group of twenty healthy people, were included in this longitudinal study at the NHTMRI. The blood anxA5 level was determined using a commercial Hyphen BioMed immunoassay using Stat Fax 4700's Microstrip Reader l.

Results: Cirrhotic patients with and without HCC who developed PVT had higher Annexin A5 scales (5.75 + 0.18), compared to cirrhotic patients who did not develop PVT (3.63 + 1.08 (*P* 0.001). PVT was 20% in all cirrhotic patients after a year, 15% in cirrhotic patients without HCC, and 25% in cirrhotic patients with HCC. Cirrhotic patients who had PVT throughout the follow-up period had greater AnxA5 serum levels than cirrhotic patients who did not develop PVT.

Conclusions: In all cirrhotic patients, AnxA5 level, platelet count, spleen size, portal flow velocity, portal vein diameter, and Fibrosis 4 score might be employed as markers for PVT development.

Keywords: AnxA5 level, PVT, Portal vein diameter, Portal flow velocity, Thrombocytopenia, FIB-4 score

Background

PVT refers to thrombus-induced portal vein occlusion or thrombus-induced portal vein occlusion [1]. PVT can occur in the presence of liver cirrhosis or cancer, or it can occur in the absence of liver disease [2]. Because of the varied target population and different diagnostic methodologies, the prevalence and incidence of PVT vary between studies [3]. Its prevalence in the general population is one percent, and it is expected to rise as the risk of cirrhosis increases [4]. It is roughly 1% in compensated hepatic cirrhosis, up to 28% in decompensated cirrhosis, and up to 44% when malignancies, particularly HCC, and liver cirrhosis are present [5]. PVT that is severe can result in variceal hemorrhage, intestinal infarction, or death. There are now no favorable sorts in place to manage PVT. Other investigations found that PVT develops in cirrhotic individuals as a result of a hypercoagulable state, endothelial cell injury, cirrhosis sequelae, and a decrease in blood flow velocity; however, the outcomes were inconsistent [6]. PVT's early symptoms are mild, and they can be difficult to detect [7]. The treatment for PVT was

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simple, but the key was to catch it early. In the early stages of PVT, there were no symptoms [8]. Biomarkers of thrombosis risk may aid in the selection of patients who will benefit the most from anticoagulant therapy while avoiding the difficulties associated with this treatment in patients with a low risk of thrombosis [9]. Annexin V is a well-defined member of the annexin family that functions as an anticoagulant and antithrombotic protein. AnxA5 is essentially biochemical, including anionic phospholipids binding to Ca2+ [10]. Because it expresses improperly, annexin has been associated to a variety of diseases [11]. AnxA5, a 35-kDa calcium-dependent binding anionic phospholipid protein, is a natural anticoagulant predominantly expressed by placental trophoblasts [12, 13]. Protein I of vascular and placental anticoagulant [14] was one of its many names, reflecting the tissues from which it was isolated and the functions that were recognized. Endothelial cells, smooth muscle cells, and spleen and liver secretory cells have all been found to release AnxA5. AnxA5 can bind to platelets, erythrocytes, and endothelial cells in the plasma [15]. Annexin V is often used to detect apoptosis because of its capacity to bind to phosphatidylserine, particularly in the presence of calcium [16, 17]. Recent research suggests that annexin V may play a key role in the immunomodulatory effects of necrotic (dead) and dying (apoptosis) cells [18]. While annexin's physiologic purpose is unknown, it possesses a number of well-studied features, including coagulation inhibition, phospholipase A2 inhibition, and protein kinase C (intracellular signaling system) suppression [19]. In vitro lyses of organs such as the liver, spleen, kidney, and lung by Schurgers et al. revealed a significant increase in the levels of AnxA5, which is significantly expressed. Because the quantity of anxA5 in peripheral organs was 15,000–31,000 times higher than in blood, he hypothesized that any injury to these organs as a result of congestion would result in a significant increase in Annexin levels [20]. High levels of Annexin V in the blood indicate a high rate of cell death and damage [21]. Guo et al. [22] regard annexin V to be a biomarker for PVT. Higher Annexing V concentrations were also seen in inflammation and increased coagulation abnormalities such as sickle cell disease [23]. PVT has an enigmatic occurrence. The goal of our research was to determine the prevalence of PVT and its risk factors, as well as to determine the utility of two noninvasive procedures in the field of hepatic fibrosis: the AST to platelet ratio index (APRI) and the Fibrosis 4 score as markers for PVT in HCV cirrhotic patients with and without HCC in Egypt, and to determine whether annexin V levels could be used as a marker for the presence of PVT.

Methods

Between March 2017 and August 2018, the NHTMRI received 47 HCV patients with cirrhosis without HCC (27 male patients and 20 female patients), 44 HCV patients with HCC (23 male patients and 21 female patients), and 20 healthy patients (10 male and 10 female) with no indication of liver disease. The formal consent was given by all of the participants in the study. The ethics committee of the National Hepatology and Tropical Medicine Research Institute has approved this study under serial number 15 2016. The study was designed for human subject research in accordance with the Helsinki Declaration on Human Subject Research. The histology of a liver biopsy, unequivocal laboratory changes, and Doppler ultrasound were used to diagnose all of the patients. The severity of liver disease was assessed using the MELD score and the Child-Pugh classification. Hepatitis C impacted by cirrhosis with and without HCC was clinically conformed, with lab and imaging testing performed according to AASLD standards. Patients with antiplatelet, marivan, and other thrombolytic medications, patients with proven PVT at the start of the research, patients with genetic coagulation abnormalities, renal failure patients, splenectomies, and clinically overt hypothyroidism or hyperthyroidism were all excluded. The study lasted a year and was evaluated by CBC, PT, liver function testing, tumor marker (alpha-fetoprotein), serum level Annexin V, and abdominal Doppler US after 12 months. PVT was finally diagnosed using Doppler US (was performed by Toshiba SSA 320A (JUSTVISION 200)), as seen in Fig. 1. At the time of enrolment, a computed tomography (CT) or magnetic resonance imaging (MRI) scan is utilized to provide a prognosis of HCC. Patients with PVT and non-PVT were compared on sex, age, platelet count, INR, PT, serum level AnxA5, US Doppler abdomen findings, and MELD score. Between the PVT and no PVT groups, APRI and Fibrosis 4 scores were calculated. This formula was used to calculate the APRI score: AST of the sample/ULN (upper limit normal) of AST 100/platelets. AST had a ULN of 35 U/L [24]. The Fibrosis 4 score was calculated using the following formula: age AST/platelets (ALT) 12 [25]. The blood anxA5 level was determined using a commercial Hyphen BioMed immunoassay using Stat Fax 4700's Microstrip Reader l.

Statistical analysis

All statistical analyses were evaluated using SPSS version 19. Quantitative data are listed as mean + SD or median, while qualitative variables are listed as frequencies. To distinguish between the three groups, a one-way analysis of variance (ANOVA) was utilized. A Mann-Whitney *U*-test was used to analyze nonparametric data, and a Student *t*-test was

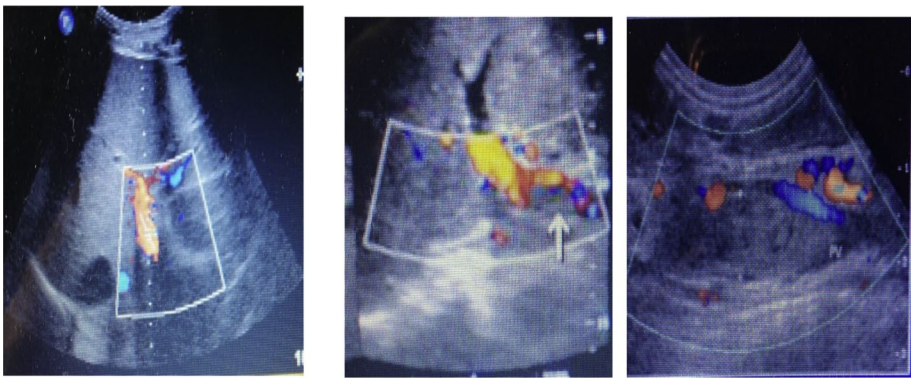

Fig. 1 Normal portal vein (no portal vein thrombosis) and portal vein thrombosis are represented by Doppler US images

used to analyze parametric data, while a categorical 2-test was used. ROC curves were used to determine the ability of independent factors in predicting PVT risk, and area under curve (AUC) for each factor was calculated. A *p* value of less than 0.05 was considered statistically significant.

Results

A total of 91 cirrhotic individuals were included in the study, 44 of whom had HCC and 47 of whom did not. In addition, 20 safe people were enlisted (control group). After 12 months, Table 1 shows the demographic, clinical, and biochemical characteristics of the classes.

The portal flow velocity ROC curve had the highest AUC, 0.941, in the cirrhosis without HCC group, followed by portal vein width, 0.902, serum Annexin V level, 0.882, platelet count, 0.882, spleen size, 0.735, Fibrosis 4 score, 0.706, and APRI score, 0.686. (Table 2, Fig. 2).

The ROC curve of portal vein width exhibited the highest AUC (0.880) in the cirrhosis with the HCC group, followed by Fibrosis 4 score (0.880), serum Annexin V level (0.867), spleen size (0.860), platelet count (0.880), portal flow velocity (0.783), and APRI score (0.773). (Table 3, Fig. 3).

Table 1 The demographic, clinical, biochemical, and radiological characteristics of all cirrhotic patients with and without HCC who had PVT or did not develop PVT after a year

Variables	Group of cirrhosis without HCC ($n=47$)		*P* value	Group cirrhosis with HCC ($n=44$)		*P* value	Total patients of cirrhosis (n=91)		*P* value
	PVT ($n=6$)	No PVT (n =41)		PVT (n =10)	No PVT ($n=34$)		PVT ($n=16$)	No PVT ($n=75$)	
ALT	60.00±8.71	51.00±21.35	0.489 (NS)	59.20±13.16	51.46±20.53	0.444 (NS)	59.50± 10.99	51.21± 20.63	0.283 (NS)
AST	68.33±12.22	65.35±36.99	0.894 (NS)	68.20±17.10	66.67±21.46	0.887 (NS)	68.25± 14.48	65.96± 30.25	0.838 (NS)
ALKP	128.01±56.82	113.76±33.20	0.542 (NS)	110.40±35.87	98.13±49.14	0.616 (NS)	117 ± 41.72	106.43 ± 41.50	0.524 (NS)
GGT	66.33±21.01	55.45±18.89	0.376 (NS)	63.20±9.67	54.40±36.20	0.604 (NS)	64.37 ± 13.50	54.95 ± 27.86	0.362 (NS)
PT	19.27±4.64	18.79±5.91	0.898 (NS)	18.12±3.14	18.11±4.11	0.998(NS)	18.55 ± 3.48	18.47 ± 5.07	0.969 (NS)
INR	1.62±0.49	1.61±0.61	0.985 (NS)	1.53±0.29	1.56±0.43	0.873 (NS)	1.56 ± 0.34	1.59 ± 0.52	0.892 (NS)
Albumin	2.50±0.50	2.25±0.86	0.639 (NS)	2.36±0.75	2.83±0.71	0.221 (NS)	2.41 ± 0.63	2.53 ± 0.84	0.724 (NS)
T. bilirubin	4.13±2.15	3.09±3.78	0.655 (NS)	2.69±1.33	2.99±3.18	0844 (NS)	3.23 ± 1.69	3.06 ± 3.05	0.883 (NS)
Platelet count ($\times 10^3/cm^2$)	73.00±22.00	111.52±33.18	0.041 (S)	85.60±20.03	108.60±16.80	0.021 (S)	80.87 ± 20.25	110.15 ± 26.42	0.006 (HS)
Annexin V (ng/ml)	4.88±2.08	3.5±1.07	0.01 (HS)	6.28±1.78	3.73±1.1	0.001 (HS)	5.75 ±1.96	3.63 ±1.08	<0.001 (HS)
Portal flow velocity (cm/s)	10.33±1.53	18.22±4.14	0.005 (HS)	10.80±1.64	16.53±3.31	0.002 (HS)	10.63 ± 1.50	17.43 ± 3.81	<0.001 (HS)

P value for comparing between all groups. Values are expressed as mean ± SD, median (IQR), or *n* (%)

*: statistically significant at $p < 0.05$

Table 2 Validity of portal flow velocity, portal vein diameter, spleen size, platelet count, Annexin V level, APRI score, and Fibrosis 4 score as PVT markers in cirrhotic patients without HCC

	Group of cirrhosis without HCC						
	Portal flow velocity	**Portal vein diameter**	**Spleen size**	**Annexin V level**	**Platelet count**	**APRI score**	**Fibrosis 4 score**
Cut-off	≤15 (cm/s)	>13 (mm)	>17 (cm)	<4.61 (ng/ml)	≤75 ($\times 10^3/cm^2$)	>1.956	>4.74
Sens.	100%	66.67%	66.67%	66.67%	66.67%	66.67%	100%
Spec.	82.35%	88.24%	88.24%	82.35%	94.12%	64.71%	52.94%
+PV	50%	50%	50%	40%	66.7%	25%	27.3%
−PV	100%	93.7%	93.7%	93.3%	94.1%	91.7%	100%
AUC	0.941	0.902	0.735	0.882	0.882	0.686	0.706

Discussion

Coagulation assays such as PT, INR, and platelet counts are common. Patients with cirrhosis have a greater PT/INR and a lower PLT. As a result, they have a greater risk of bleeding [26]. However, the long-held belief that people with CLD had a tendency to bleed has been disproved [27]. This is usually true in gastrointestinal spontaneous bleeding; however, we now know that this is due to portal hypertension, not a drop in plasma factors initiating the coagulation cascade, as previously thought [28]. In some recent research, patients with CLD are demonstrated to be in a state of "rebalanced hemostasis," in which a shortfall in prohemostatic drivers is offset by corresponding improvements in antihemostatic drivers [29]. As a result, CLD's overall influence on hemostasis is complex, and patients with CLD might suffer from both bleeding and thrombotic problems [30]. In our study, the 1-year incidence of PVT was 15% in HCC-free cirrhotic patients and 25% in cirrhotic HCC patients. Our findings are in line with those of Ogren et al., who found that PVT was highest in individuals with both cirrhosis and HCC [4].. According to Zanetto et al., prothrombotic circumstances in cirrhotic individuals with HCC increase the risk of PVT [31]. The ability of tumor cells to activate the coagulation system, which

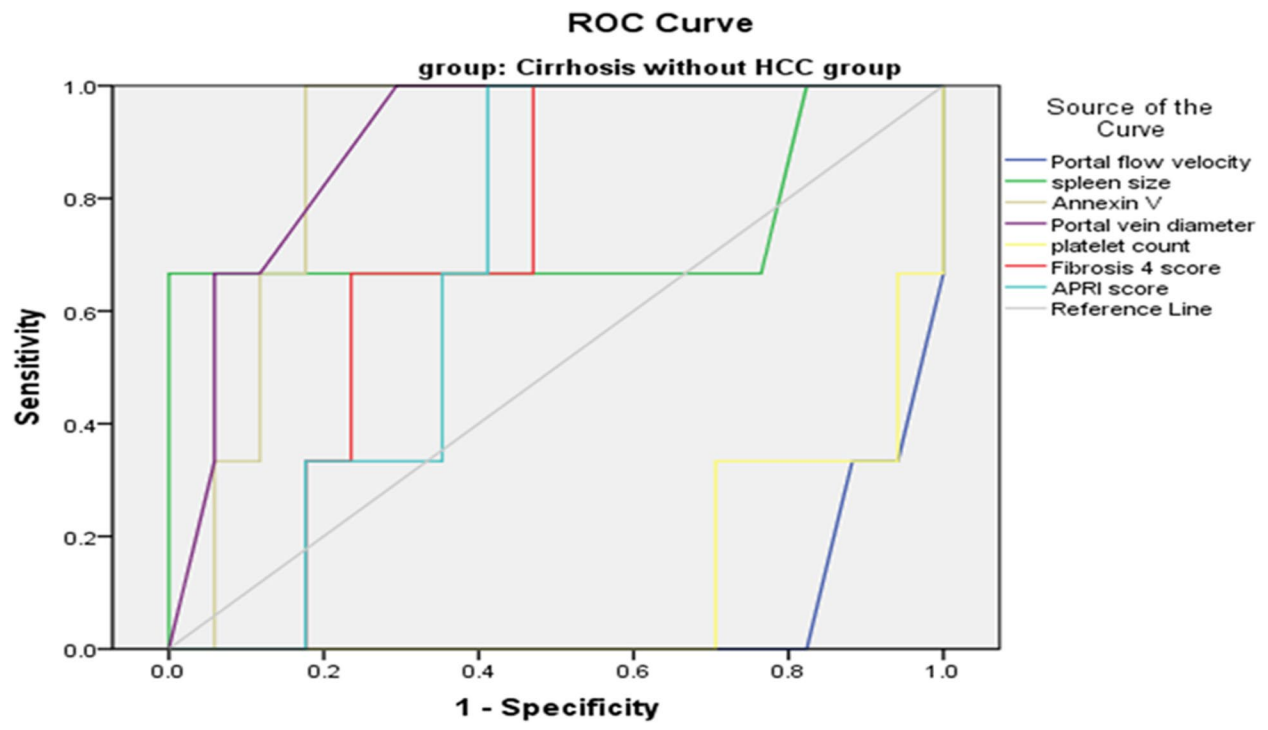

Fig. 2 ROC for the group of cirrhosis without HCC

Table 3 Validity of portal flow velocity, portal vein diameter, spleen size, platelet count, Annexin V level, APRI score, and Fibrosis 4 score as PVT markers in cirrhotic with HCC patients

	Group of cirrhosis with HCC						
	Portal flow velocity	**Portal vein diameter**	**Spleen size**	**Annexin V level**	**Platelet count**	**APRI score**	**Fibrosis 4 score**
Cut-off	≤15 (cm/s)	>12 (mm)	>17 (cm)	>4.61 (ng/ml)	≤89 ($\times 10^3/cm^2$)	>2.01	>5.79
Sens.	80%	80.00%	80.00%	80.00%	80.00%	60.00%	100%
Spec.	66.67%	86.67%	93.33%	80.00%	80.33%	80.00%	80%
+PV	44.4%	66.7%	66.7%	57.1%	60.0%	50.00%	62.5%
−PV	90.9%	92.9%	92.9%	92.3%	86.7%	85.7%	100%
AUC	0.783	0.880	0.860	0.867	0.800	0.773	0.880

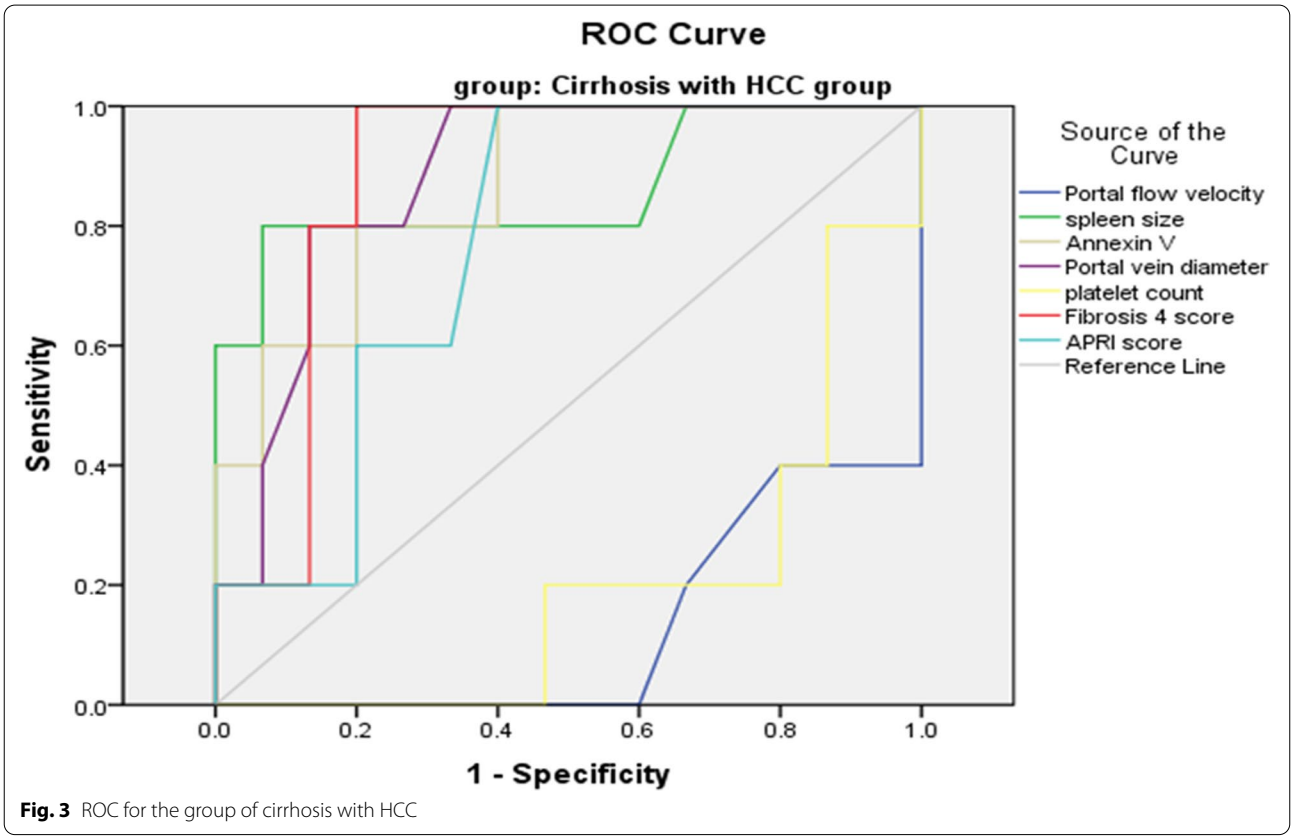

Fig. 3 ROC for the group of cirrhosis with HCC

is the origin of the hypercoagulable or prothrombotic condition of malignancy, may explain why cirrhotic individuals with HCC have a higher prevalence of PVT. [32]. Until far, the prognostic significance of portal flow velocity for cirrhotic patients with PVT has been hotly debated. Lower portal flow velocity was found to be substantially associated with PVT in this study when compared to non-PVT, suggesting that lower portal vein velocity may be an independent risk factor for PVT development. Stine et al. found that PV flow below 15 cm/s is more sensitive to prospective PVT risk projections [33], which is consistent with our findings. However, according to another study [34], the P.F velocities in both groups (with and without PVT) were not significantly different. The bigger diameter of the P.V. was significantly correlated with the group of PVT against the group of non-PVT in our investigation, which is consistent with Lin's conclusion that a high D-dimer level and a large diameter of the main portal vein are factors independent of the risk of developing PVT [35]. The increased splenic thickness was significantly associated with the PVT group in this

study compared to the non-PVT group. This observation is similar to Chen et al.'s [26] findings, which suggested that PVT was caused by splenic thickness. Splenomegaly has been connected to portal hypertension and larger splenic enlargement, both of which have been linked to a worsening of portal hypertension [36]. In our study, thrombocytopenia was significantly associated with the PVT group as well as the non-PVT group. This was discovered by Ushitora et al., [33], who discovered a relationship between low platelet counts and PVT. HCV appears to be the cause of bone marrow suppression and, eventually, thrombocytopenia in chronically infected hepatitis C patients [37–40]. In cirrhotic individuals, a low platelet count is very prevalent, and it is usually interpreted as a symptom of increased portal pressure [41]. The APRI score was insignificant as a marker of PVT development in all cirrhotic patients in our investigation; however, the Fibrosis 4 score could be useful as a marker of PVT development in those patients. Verma et al., on the other hand, suggested that an APRI score of 1.09 is accurate in predicting portal hypertension [42]. The inability of the APRI score to be a PVT marker in our study could be related to the close link between liver fibrosis, portal hypertension, and the development of PVT. Our research found that cirrhotic patients with and without HCC who developed PVT during the follow-up procedure had higher serum levels of annexin V than cirrhotic patients with and without HCC who did not develop PVT. According to Nomura et al., AnxA5 is produced early in the circulation as a defense mechanism to prevent the development of microparticles (MPs were first connected to thrombotic disorders because they contain procoagulant phospholipids) [43]. AnnexinA5's capacity to bind ionized calcium and PS inhibits microparticle production, according to Van Genderen, H.O. et al. [44]. This study is similar to the findings that found AnxA5 MP and endothelial-derived MP levels in patients with HCC and cirrhosis who formed the PVT were significantly greater than those in patients with HCC and cirrhosis who did not [45, 46]. Higher AnxA5 levels have been found in treated hypertension patients as a protective mechanism due to its anti-inflammatory and anticoagulant properties [17, 47]. It has also been associated to inflammation and enhanced coagulation states such as sickle cell disease [23] and systemic lupus erythematosus [48]. Furthermore, AnxA5 is linked to thrombotic illness via the Antiphospholipid (APL) syndrome, where it appears to be a target for autoantibodies, implying a thrombotic susceptibility perception in these patients [14].

Conclusions

Serum Annexin V level, reduced portal flow velocity, wider portal vein, larger spleen size, thrombocytopenia, and higher Fibrosis 4 score could be markers for the development of PVT but APRI score showed non-significant performance.

Limitation of study

In our study, the control group's sample size is relatively small compared to the disease groups. Finally, it would have been more appropriate if the number of people in the control group had been at least equal to the number of people in the diseased group.

Recommendation

This result should be validated using a large sample size.

Abbreviations

PVT: Portal vein thrombosis; MELD: Model for End-stage Liver Disease; AASLD: American Association for the Study of Liver Diseases; CLD: Chronic liver diseases; APA: Antiphospholipid antibody; PT: Prothrombin time; APRI score: AST to Platelet Ratio Index; M: Male; F: Female; AnxA5: Annexin V; ULN: Upper limit normal; AUC: Area under curve; APL: Antiphospholipid.

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Authors' contributions

The practical section, data analysis, and manuscript preparation were all handled by WS. BE was in charge of sample selection and classification, as well as manuscript revision. All contributors read and approved the final manuscript.

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Availability of data and materials

The published article [and its supplementary information files] contains all the data produced or analyzed during this research.

Declarations

Ethics approval and consent to participate

The formal consent was given by everyone in the study. The ethics committee of the National Hepatology and Tropical Medicine Research Institute has approved this study, which has the serial number 15-2016. The study was designed to comply with the Helsinki Declaration on Human Subjects Research.

Competing interests

There are no conflicts of interest declared by the authors.

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