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Research Article

QUANTITATIVE D-DIMER LEVELS BY A LATEX–ENHANCED IMMUNOTURBIDIMETRIC TEST IN EGYPTIAN PATIENTS WITH BUDD-CHIARI SYNDROME

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Abstract- Backgrounds: Budd-Chiari Syndrome (BCS) is a hepatic venous outflow obstruction at any level between the hepatic veins and the right atrium **Objective:** to assess quantitative D-dimer levels in BCS cases and using it as a biomarker in diagnosis of thrombotic events. **Methodology;** Group I included (18) patients with primary BCS. Group II; included (22) patients with primary BCS with newly reported thrombotic event, as well as Control group. For all cases; complete lab, viral markers, thrombophilia work up, D-dimer level assessment as well as radiological evaluation were done. **Results:** Assessment of D-dimer serum levels shows a high statistical difference between the 3 studied groups (P<0.01). D-Dimer equals or more than to 1.65 can predict new thrombosis events with a sensitivity and specificity values (93.8% and 87.5%) respectively. **Conclusion:** D-dimer level was significantly higher in BCS patients on medical treatment who developed new thrombosis than patients without event of new thrombosis.

Key Words- Budd-Chiari Syndrome, D-dimer, vascular thrombosis.

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Introduction

Budd-Chiari syndrome (BCS) is a hepatic venous outflow obstruction at any level with evident thrombosis of the hepatic veins and/or the intrahepatic or suprahepatic inferior vena cava [1]. Hereditary or acquired hyper-coagulable states were diagnosed in 75% of patients; multiple etiologic factors may play a role in 25% of patients [2]. As regards its demographic data; female-to-male ratio was 1.8 and median age was 51 years, however the annual case-fatality rate was 2.8% [3]. Hematological disorders including polycythemia rubra vera, myelopro-liferative disorder (MPD), antiphospholipid antibody syndrome, inherited thrombotic condition [protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden mutation (FVLM)], pregnancy, oral contraceptives, chronic infections, inflammatory diseases, malignancy, membranous webs and idiopathic cases were reported as an etiological disorder [4]. BCS patients may be presented by acute and /or fulminant hepatic failure, subacute liver disease or as chronic liver disease with portal hypertension and cirrhosis [1], however the main complain are abdominal pain, ascites, and hepatomegaly [5]. Radiological evaluation in form of diagnostic imaging (ultrasound with Doppler, computed tomography and/or magnetic resonance imaging) is required to confirm the diagnosis, site of obstruction and recommend the interventional procedure needed for treatment [6]. Also, Ascitic fluid analysis, used as one of the useful clue to diagnose BCS by its high protein concentrations (>2 g/dL), white blood cell count is < 500/µL and Serum/ Ascites albumin gradient is < 1.1 [7].

D-dimer is a fibrin degradation end product of fibrinolysis [8]. It can be measured by an enzyme-linked immunosorbent assay, a latex agglutination assay, enzyme-linked immunofluorescent immunoassays or by the advanced turbidimetric D-dimer test [9]. Latex enhanced immunoassays are quantitative, turbidimetric assays that use latex particles coated with human monoclonal antibody to the D-dimer antigen [10]. A quantitative D-dimer test used to evaluate patients with intermediate or low clinical probability of pulmonary embolism [11]. Also predicts the risk of venous thrombo-embolism recurrence, positive and negative D-dimer values deicide duration of the anticoagulant therapy [12].

Treatment algorithm of BCS; [A] anticoagulation, treatment of underlying condition and symptomatic treatment for complications of portal hypertension in all patients with primary BCS; [B] angioplasty/stenting; or [C] insertion of a transjugular intrahepatic portosystemic shunt (TIPS) [D] liver transplantation in cases not responding to TIPS [13].

Aim of the Work: To assess the quantitative D-dimer levels by a latex–enhanced immune-turbidimetric test in Egyptian patients with BCS and using it as a biomarker in diagnosis of new thrombotic events.

Materials and Methods

This prospective cross-sectional study has been performed in accordance with the ethical standards.

Patients and study design; About 40 cases of BCS patients who presented to the Budd-Chiari Study Group (BCSG) & Egyptian Association for the Study of Vascular Liver Diseases (EASVLD) outpatient clinics were included and divided into Group I; primary BCS (18) patients, Group II: A known case of BCS (22)

patients with newly developed thrombotic event as stent occlusion, as well as Control group that included 24 age & sex matched healthy individuals.

Methods and treatment protocol; all the studied cases were further subjected to complete history taking (any thrombotic disorders, use of oral contraceptive or hormonal therapy), thorough clinical evaluation and laboratory investigations including thrombophilia workup (antinuclear antibody, anti-deoxyribonucleic acid (anti DNA), factor V Leiden mutation (FVLM), methylene tetrahydrofolate reductase mutation (MTHFR), Protein C, Protein S, antithrombin levels, Anticardiolipin antibodies, lupus anticoagulant, prothrombin gene mutation (PGM), Jenus tyrosine kinase2 (JAK2) and bone marrow aspirate) to clarify the underlying etiology of BCS. Radiological assessment; Abdominal Duplex US, abdominal Magnetic resonance image, Magnetic resonance venography, multislice Computed tomography scan and/or direct venography were done to evaluate liver parenchyma, show site of obstruction and confirm diagnosis.

Once the diagnosis of BCS was confirmed; all patients were started on anticoagulation therapy; in the form of unfractionated heparin dose or low molecular weight heparin then oral warfarin therapy was added till INR (2-3) then continued on oral therapy alone. All patient treated as regards an algorithm for management of BCS [14] [Fig-1]. Duplex Ultrasound and D-Dimer assay were performed to assess patency at one month, three month and six months post intervention then after one year.

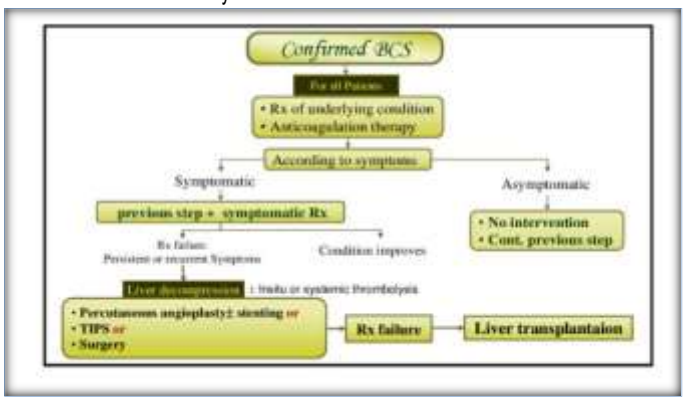

Fig-1 An algorithm for management of BCS. #TIPS: Trans-jagular intrahepatic portosystemic shunt

Both study groups as well as the control group were subjected to D-Dimer assay: Sample collection; a sample of 2 ml venous blood was collected using vacutainer test tubes containing 2 ml trisodium citrate (9 parts blood to 1 part anti-coagulant. Principle; polystyrene particles covalently coated with monoclonal antibody to D-dimer are aggregated when mixed with samples containing D-dimer. Quantitative determination of D-dimer in human plasma is detected by a latex–enhanced immunoturbidimetric test using commercially available kit from Siemens on Sysmex CA-150013. D-dimer results were automatically out by the sysmex analyzers and the results were shown on the screen in mg/dl. Measuring range for D-dimer is 0.17 to 4.40 mg/L.

Statistical Analysis

Analysis of data was performed using SPSS 17 (Statistical Package for Scientific Studies) for Windows. Description of quantitative variables was in the form of mean, standard deviation (SD). Description of qualitative variables was in the form of numbers (No.) and percents (%). Comparison between groups regarding quantitative data was performed using student's t-test. Regarding qualitative data, Chi-square test (X2) was used. Receiver operating characteristic (ROC) curve analysis was used to determine the best cut off values that differentiate between groups. Significance level (P) value was expressed as follows: P > 0.05 = Insignificant. P < 0.05 = Significant. P < 0.01 = High significant.

Results

The studied groups were well-matched regarding age and sex; the mean age of group (I & II) was (29.94 ± 9.02 & 30.50 ± 8.07) respectively and as regards sex (61.1% & 50.0%) were females in group (I & II) respectively.

As shown in [Fig-2], Factor V leiden mutation was the most common etiological factor that occurred in 32.5% of BCS cases; however Anti Phospholipid syndrome and Paroximal nocturnal hemoglobin urea were the least common etiologies. [Fig-3]; illustrated that multiple etiological factors in single patient more common in group (II).

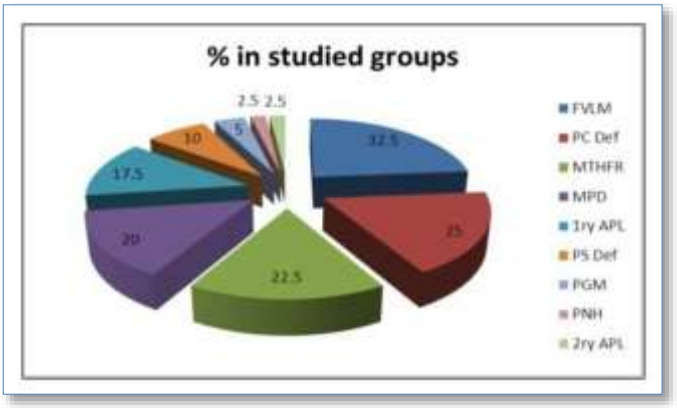

Fig-2 The etiology of BCS in the studied patients

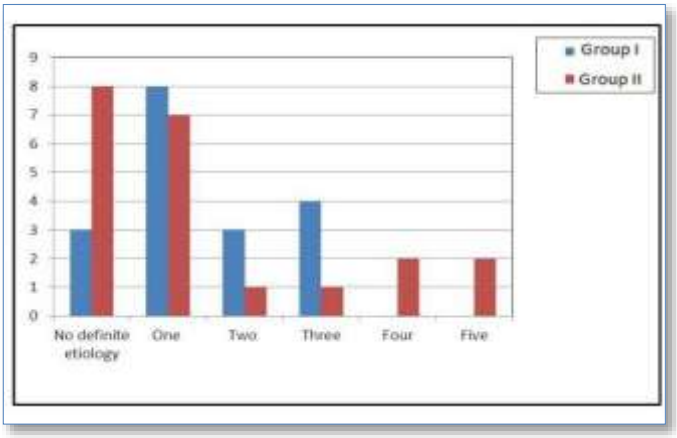

Fig-3 Comparison between the 2 studied groups regarding the frequency of etiological factors in a single patient

[Table-1], revealed the status of hepatic veins within studied groups (I & II) that was assessed by different imaging modalities (Doppler Ultrasound, Computed tomography & Magnetic resonance image, there were 3 cases with 2 HV occluded and 15 cases with 3 HV occluded in group (I), while all cases had 3 HV occluded in group (II), with a statistically significant difference (P<0.05), however no statistically significant difference between the studied groups as regards the type of BCS-related therapeutic options (P>0.05).

Table-1 *Status of hepatic veins assessed by different imaging modalities (Doppler ultrasound, computed tomography & Magnetic resonance image) and therapeutic options within studied groups (I & II)*

Variables		Group (I) (N=18)	Group (II) (N=22)	Total No.	Total %	X^2	P
Number of HVs* Occluded	2	3	0	3	7.5	**3.96**	**0.05 (S)**
	3	15	22	37	92.5		
IVC#	Occluded	2	1	3	7.5	3.08	0.21 (NS)
	Patent	16	18	34	85		
	Attenuated	0	3	3	7.5		
Therapeutic Options	TIPSS§	13	15	28	70	1.09	5.81**(NS)**
	Angioplasty	2	1	3	7.5		
	Medical treatment	3	6	9	22.5		

Chi-Square Test NS: non-significant

*Hepatic viens, # Inferior vena cava, § Transarterial intrahepatic portosystemic shunts

The assessment of D-dimer serum levels in the studied groups shows that there was a high statistical significant difference (P<0.01) between the 3 studied groups as shown in [Table-2].

Table-2 *D-dimer serum levels in the studied groups*

Variable	Group (I) (N=18)	Group (II) (N=22)	Control Group (N=24)	F	P (Sig.)
D dimer level *(≤0.5 mcg/mL)*	0.47± 0.26	2.85 ± 1.72	0.25 ± 0.09	**43.93**	**0.00 (HS)**

Chi-Square Test HS: high significant

Using Receiver operating characteristic (ROC) analysis in this study, revealed that the value of D-Dimer is more than or equals to 1.65, it can used as diagnostic biomarker in primary BCS cases and predict new thrombosis in controlled BCS cases with a sensitivity value of 93.8% and a specificity value of 87.5% [Fig-4].

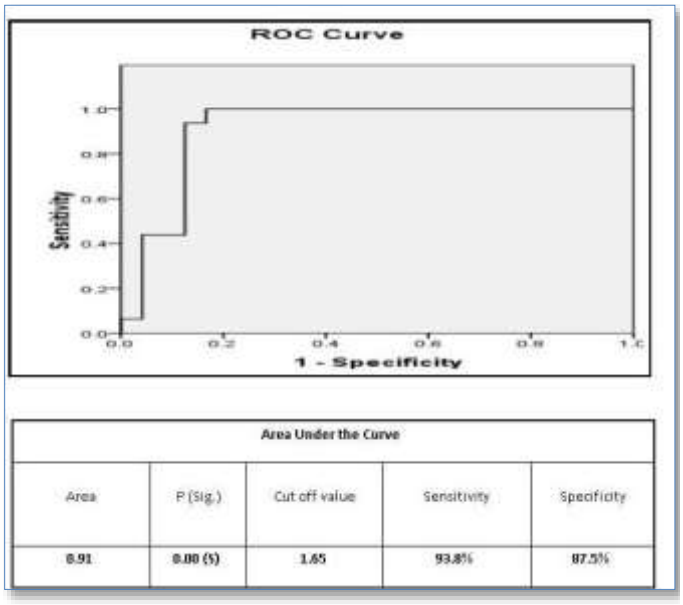

Fig-4 Receiver operating characteristic (ROC) curve for D-Dimer as a predictor for new thrombosis in BCS

Discussion

As regards demographic data in BCS patients, female patients were more predominant than male patients and represented (61.1% and 50.0%) in groups I & II respectively, this agree with both of Valla [15] and Roy [7] who reported that BCS patients slightly predominant in females. However, Murad et al. [16] stated that mean age was about 45 years, and Roy [7] concluded that was usually at the third or fourth decades of life that agree with our study as mean age was 29.94 ± 9.02 in group I and 30.50 ± 8.07 in group II. Regarding the etiology of BCS, among the inherited procoagulative disorders FVLM was the most common disorder (32.5%) which is nearly the same as Sakr, *et al.* [17] & Mohanty et al. [18] who stated that FVLM was the most common risk factor with percentages 53.1% and 26% of BCS patients respectively. However, among the acquired procoagulative disorders, primary MPD were the most common cause in the current study about 20%. These results in agreement with Sakr, *et al.* [17] who stated that MPD was found in 29% of patients. Uskudar, *et al.* [19] in Turkey, reported that 2 etiological factors in 18.6% and 3 factors in 1.3% of patients, which is in a harmony with our study as multiple etiological factors in a single patient were detected, also our results were matched with Denninger, *et al.* [2] who stated that combined etiology was found in at least 25% of the patients.Concerning Status of liver related veins as shown by Doppler ultrasound and computed tomography, it was found that (3 and 15) cases with (2 and 3) HV occluded respectively in group (I), while in group (II) all cases had 3 HV occluded. This is in consistent with Bargallo, *et al.* [20] who stated that involvement of HVs occlusion to diagnose BCS is also necessary. D-dimer levels were significantly higher in BCS patients who developed new thrombosis (Group II) than others, so D-dimer serum level is a significant predictor for presence of thrombosis. Stein et al. [21] explained this elevated D-dimer level in a new thrombotic event by massive activation of the coagulation system, generation of thrombin that turns the soluble fibrinogen into fibrin which by the action of plasmin on it, cleaved into high molecular weight fragments and finally fragmented into D-dimers. However, Schrecengost, *et al.* [22] concluded that anticoagulation therapy prevents thrombus extension so producing lower D-dimer concentrations. D-dimer can be used as a predictor for new thrombosis with a sensitivity of 93.8% and a specificity of 87.5%, this finding was supported by Righini, *et al.*, 2008 [23] and Lukaschek, *et al.*, 2001 [24], D-dimer assay can exclude VTE with a sensitivity (> 95% and 92%) respectively.

Conclusions

- BCS in the studied cohort of Egyptian patients commonly occurs during the third decade of life and is more predominant in females.
- D-dimer level was significantly higher in BCS patients on medical treatment who developed new thrombosis than patients without event of new thrombosis
- D-dimer cut-off point at 1.65 is a significant predictor for the presence of new thrombosis in the studied cases with Budd-Chiari syndrome with a sensitivity of 93.8% and a specificity of 87.5%.

Application of research:

- D-dimer can be used as a predictor for new thrombosis
- D-dimer can be used as a non imaging method in routine follow up for the stent patency.

Abbreviations

BCS: Budd Chiari syndrome
HV: Hepatic Viens
MPD: myeloproliferative disorders
FVLM:factor V Leiden mutation
TIPS: transjugular intrahepatic portosystemic shunt

Research Category: Biomarker in diagnosis

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Author Contributions: All author equally contributed

Author statement: All authors read, reviewed, agree and approved the final manuscript

Conflict of Interest: None declared

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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