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Evaluation of Soluble Fibrin Monomer Complex and D-Dimer as Early Markers for Diagnosis of Deep Venous Thrombosis

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Abstract

Background: Venous thromboembolism (VTE) is the third most frequent vascular disease worldwide; it is a significant preventable cause of in-hospital death. Early screening of DVT in high-risk groups is crucial to prevent the disease & its sequelae, D-dimer has the advantage of excluding venous thromboembolism (VTE) due to its high sensitivity. However, its low specificity is disadvantageous for diagnosing VTE. A method to increase the usefulness of D-dimer in the diagnosis of VTE is warranted.

Aim of Study: Is to examine the possible role of the plasma level of SFMC & D-dimer in the prediction of hypercoagulable state and the subsequent VTE and to assess whether it can be used to indicate anticoagulant therapy.

Patients and Methods: This cross sectional case control study on 85 subjects was performed at a vascular department between July 1, 2021 and December 31, 2021. Subjects were divided as: 60 patients with confirmed DVT positive by Compression ultrasonography (CUS) considered as patients group, and 25 apparently healthy individuals considered as control group with age and sex matched. For both groups levels of D-dimer and SFMC were measured simultaneously. Using ELISA kit supplied by SUNRED BIOTECHNOLOGY COMPANY China.

Results: Compared with the control group, there was a statistically significant difference in levels of both SFMC & D-Dimer in the patient group (higher) than they were in control group.

Conclusion: Monitoring serum DD and SFMC levels enables early detection and treatment intervention of VTE.

Key Words: *DVT – D-dimer – SFMC.*

Introduction

VENOUS thromboembolism (VTE), which is the third most common vascular illness, is a condition that is influenced by various genetic and non-genetic risk factors. The pathogenesis of VT includes Virchow's triad, which is a combination of hypercoagulability, reduced blood flow or stasis, and damage to blood vessels **[1]**.

Venous thromboembolism (VTE) is an important preventable cause of death in the hospital. VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 1,000,000 new cases each year in Europe and the United States combined. Among survivors, VTE is associated with recurrent events, post-thrombotic syndrome, pulmonary hypertension, and bleeding events (due to anticoagulation), all of which contribute to increased mortality, disease burden **[2]**.

It is still difficult to accurately diagnose deep vein thrombosis (DVT) or pulmonary embolism (PE), and confirmation requires a multimodal approach that includes computing a clinical pre-test probability (PTP) score, measuring DD concentrations and other fibrinogen markers, performing serial compression ultrasonographies (CUS), and using computed tomography pulmonary angiograms **[3]**.

D-dimer testing is frequently used for VTE screening. When utilized in high-sensitivity assays for the diagnosis of VTE, D-dimer has the benefit of a high negative predictive value of 97-100 percent and a high sensitivity of 93-100 percent. Circulating D-dimer is also elevated in patients with liver disease, coronary artery disease and other cardiovascular diseases, cancer, trauma, pregnancy, infections, inflammatory diseases, severe renal disease, recent surgical procedures, and advanced age. However, D-dimer has a low positive predictive value and low specificity. D-dimer has mostly been used to rule out VTE; if the screening

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is positive, VTE must then be definitively confirmed using imaging, which is not always accessible [4].

A quantitative approach for measuring the amount of soluble fibrin monomer complex (SFMC) in plasma has been developed. SFMC is a serological marker for activation of the coagulation system. The clinical significance of D-dimer and SFMC differs; SFMC represents the very early stage of a thrombotic event, whereas D-dimer represents secondary fibrinolysis following clot formation. SFM concentration represents thrombin activity, and because its levels can be detected earlier than DD, SFM can be used as an alternative to DD to assess thrombosis [5].

SFMC has also been proposed as a marker for VTE, similar to D-dimer. However, the findings of earlier investigations into the efficacy of SFMC for VTE diagnosis are inconsistent. In one study, a sensitivity of 98.5 percent and a specificity of 80.1 percent were obtained by adjusting the cutoff value of SF to 5.9g/mL. According to the authors, SFMC is helpful for VTE diagnosis and exclusion. However, in a different study, reducing the cutoff value of SF to 7.0g/mL resulted in a sensitivity of just 38.9 percent and a specificity of only 64.3 percent, demonstrating that SFMC is not helpful for VTE diagnosis or exclusion [6]. An optimal cutoff level for orthopaedic surgery was 13.9 g/mL, which produced a sensitivity and specificity of 67.9 and 78.2 percent, respectively [7]. Despite the fact that SFMC and D-dimer have not been extensively compared in prior research on VTE, SFMC appears to have a higher specificity than D-dimer [4].

The aim of this study was examine the possible role of the plasma level of SFMC & D-dimer in the prediction of hypercoagulable state and the subsequent VTE and to assess whether it can be used to indicate anticoagulant therapy.

Patients and Methods

This study was a cross sectional case control study and was approved by the Research Ethical Committee. Oral and written consents were obtained from all patients and controls after a full explanation of the study.

This study included eightyfive subjects with their ages & sex matched Subjects were classified into:

1- Control group: Included 25 apparently healthy individuals (not affected by any comorbidity and not treated with any medications at the time of study recruitment) confirmed negative to DVT by Compression ultrasonography (CUS) with matched age and sex.
2- Patient group: Included 60 patients with confirmed positive DVT by Compression ultrasonography (CUS) presented to Al-Azhar Hospitals (Al-Husain and Bab Al-Sharia Hospitals). During the period from July, 2021 to December, 2021.

Inclusion criteria:

- Patients with acute DVT first discovered.
- Age and sex matched.

Exclusion criteria:

- Patients diagnosed with Disseminated Intravascular Coagulation.
- Patients diagnosed with malignancy.
- Patients diagnosed with atrial fibrillation.
- Patients diagnosed with acute myocardial Infarction.

All individuals included in this study were thoroughly clinically assessed, full history, as well as, family history of any symptom or any drug intake that may affect the result were taken & the following data were collected (age, sex, body mass index (BMI), smoking habits, history of contraceptive pills drugs intake, & chronic disease as Diabetes mellitus, hypertension or being bedridden for long time) then both the patient and control group were subjected to the following investigations: Complete blood picture (CBC), Prothrombin Time activated partial thromboplastin time D-dimer & SFMC levels was measured In both control and patient groups, Nine volumes of blood were collected in 1 volume 3.2% trisodium citrate were withdrawn then centrifuged for 10 minutes at 2500g, and the plasme was separated and stored at (–20°c) until assessed for D-dimer & SFMC levels ELISA kit supplied by SUNRED BIOTECHNOLOGY COMPANY China.

Statistical analysis:

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 24. Probability (*p*-value): *p*-value <0.05 was considered significant.

Results

Compared with the control group, there was a statistically significant differences in both SFMC, D-Dimer in the patient group, SFMC in cases group [mean 12.4 SD (±8.6)] while in control group

[mean 2.64 SD (±1.68)] thus at cut off (5.5ug/ml) *p*-value <0.001, Area under curve (AUC) 0.97, Sensitivity 89.7%, Specificity 90%, Positive predictive value (PPV) 90% & (NPV) Negative predictive value 89.7%, and D-dimer in cases group [mean 3.8 SD (±5.1)] while in control group [mean 0.459 SD (±0.23)] thus at cut off (8.5ng/ml) *p*-value <0.001 Are under curve (AUC) 0.89 Sensitivity 84.7% Specificity 95% Positive predictive value (PPV) 94% & (NPV) Negative predictive value 86%.

There was a strong statistically positive correlation of both D-dimer & SFMC results in cases Confirmed of DVT (*p*-value=0.001) positive correlation (*r*=0.734).

Table (1): Diagnostic performance of SFMC & D-dimer in prediction of DVT.

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	*p*-value
SFMC	>5.5	0.97	89.7%	90%	90%	89.7%	<0.001
D-Dimer	>0.85	0.89	84.6%	95%	94.4%	86.1%	<0.001

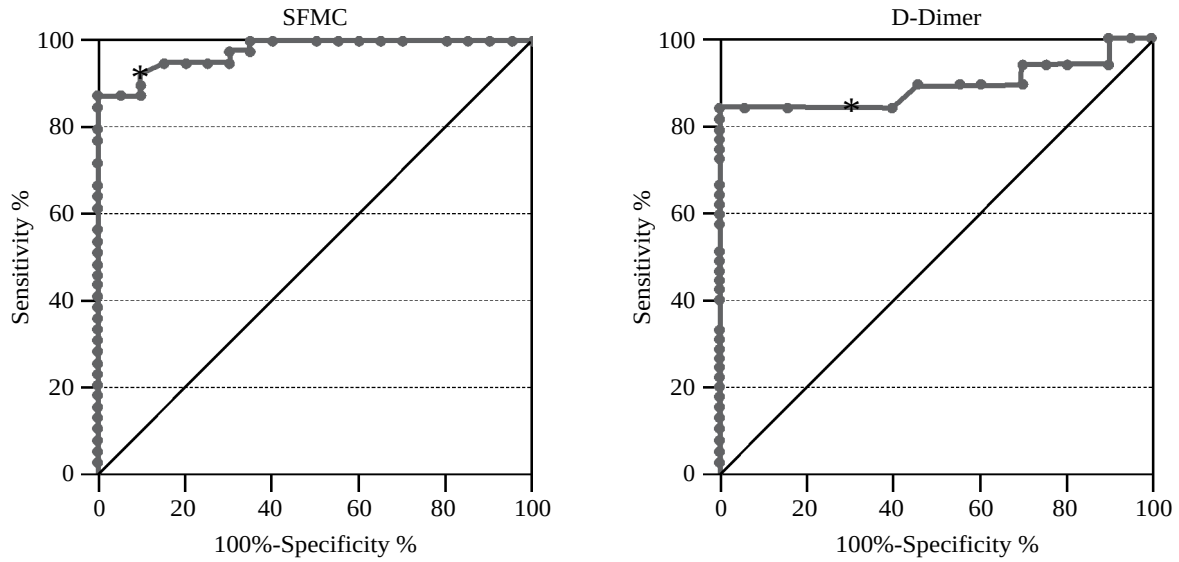

Fig. (1): ROC curve between patients and control as regard SFMC and D-Dimer.

Discussion

Our study results are concordant with Hayashi et al., study 2022 **[8]** that Concluded that Early detection and treatment intervention of VTE following HBP surgery are made possible by monitoring serum DD and SFMC levels.

Our study is in agreement with Imuro, T., & Saito, M. study (2022) **[3]** that concluded that For patients with increased d-dimer levels, lower extremities with a grade 3 MMT (manual muscle test), or DVT positivity, preoperative US DVT screening is advised. Patients who have increased SFMC levels on post-operative day 1 may consider receiving postoperative ultrasound.

Also in keeping with Takeshima, et al., study 2021 **[9]** who found that The diagnosis of VTE in mental patients with positive D-dimer findings was enhanced by SFMC.

Furthermore, The results of current study show agreement with Kochi, et al., study of 123 patients in 2017 That found that Compared to clinical risk factors and other fibrin related indicators, the SFMC on Post-operative Day 1 strongly predicted the hypercoagulable condition after gastroenterological surgery.

Our results also are in keeping with Nakagawa, et al., study 2016 **[10]** that found that DD and SFMC measurements can be used to assess the pathophysiology of PE and DVT.

Consistent with our findings,Mitani, et al., study in 2015 **[11]** a retrospective study of 50 patients concluded that An efficient hemostatic marker for DVT early identification is SFMC concentration. The relevance of D-dimer concentration alone as a hemostatic marker for DVT early diagnosis is limited. A more accurate diagnostic tool than SFMC

concentration alone may include the measurement of D-dimer and SFMC concentrations.

On the other hand, other studies found that SFMC or D-dimer was not always useful to detect VTE development.

In contrast with our results Yoshimura, et al. study in 2018 **[12]** discovered that sometimes it was difficult to detect the onset of VTE using SFMC or D-dimer.

Also, in study conducted by Yano S, et al., 2019 **[6]** they found that Measurement of DD but not SF was suggested to be helpful for incident VTE screening, particularly in non-operative inpatients.

The differences in experimental design, sample size, patient selection criteria, geographic differences, racial differences, and ethnic differences may have contributed to the discrepant results between our study and earlier research.

Due to the study's design, it's possible that the current study has certain limitations. First, a case-control study conducted at a hospital made it difficult to rule out potential selection bias. Second, the statistical power may have been limited by the sample size, which could have resulted in the chance occurrence of statistical deviations and the missed detection of weak associations.

References

1- WANG X., YANG Y.Q., LIU S.H., HONG X.Y., SUN X.F. and SHI J.H.: Comparing different venous thromboembolism risk assessment machine learning models in Chinese patients. J. Eval. Clin. Pract., 26: 26-34, 2019.

2- BIKDELI B., JIMENEZ D., HAWKINS M., ORTÍZ S., PRANDONI P., BRENNER B. and RIETE Investigators: Rationale, design and methodology of the computerized registry of patients with venous thromboembolism (RIETE). Thrombosis and haemostasis, 118 (01): 214-224, 2018.

3- IMURO T. and SAITO M.: Preoperative Lower Extremity Motor Weakness Affects Deep Vein Thrombosis During the Perioperative Period of Lumbar Surgery. Spine, 47 (3): E116-E123, 2022.

4- REFAAI M. A., RILEY P., MARDOVINA T. and BELL P.D.: The clinical significance of fibrin monomers. Thrombosis and haemostasis, 118 (11): 1856-1866, 2018.

5- MITANI G., TAKAGAKI T., HAMAHASHI K., SERIGANO K., NAKAMURA Y., SATO M. and MOCHIDA J.: Associations between venous thromboembolism onset, D-dimer, and soluble fibrin monomer complex after total knee arthroplasty. Journal of Orthopaedic Surgery and Research, 10 (1): 1-8, 2015.

6- YANO S., YOSHIDA Y., NOTSU Y., FUKUMA A., NITTA E., MISHIMA S. and NAGAI A.: Significance of D-dimer and soluble fibrin testing in screening of incident venous thromboembolism. Vascular Failure, 3 (1): 26-30, 2019.

7- HASEGAWA M., WADA H., WAKABAYASHI H., et al.: The relationships among hemostatic markers, the withdrawal of fondaparinux due to a reduction in hemoglobin and deep vein thrombosis in Japanese patients undergoing major orthopedic surgery. Clin. Chim. Acta., 425: 109-113, 2013. doi:10.1016/j.cca.2013.07.009

8- HAYASHI H., SHIMIZU A., KUBOTA K., NOTAKE T., SUGENOYA S., MASUO H. and SOEJIMA Y.: Asymptomatic Venous Thromboembolism After Hepatobiliary-Pancreatic Surgery: Early Detection Using D-dimer and Soluble Fibrin Monomer Complex Levels. Annals of Gastroenterological Surgery, 6 (1): 109-118, 2022.

9- TAKESHIMA M., ISHIKAWA H., OGASAWARA M., KOMATSU M., FUJIWARA D., ITOH Y. and MISHIMA K.: The Usefulness of the Combination of D-Dimer and Soluble Fibrin Monomer Complex for Diagnosis of Venous Thromboembolism in Psychiatric Practice: A Prospective Study. Vascular Health and Risk Management, 17: 239, 2021.

10- NAKAGAWA I., MURAKAMI S., HIDAKA S., OKADA Y. and KUWAHARA Y.: Fibrin-related markers in acute phase of pulmonary embolism and deep venous thrombosis. Masui. The Japanese Journal of Anesthesiology, 65 (6): 578-582, 2016.

11- MITANI G., TAKAGAKI T., HAMAHASHI K., SERIGANO K., NAKAMURA Y., SATO M. and MOCHIDA J.: Associations between venous thromboembolism onset, D-dimer, and soluble fibrin monomer complex after total knee Migita K, Bito S, Nakamura M, Miyata S., Saito M., Kakizaki H., et al.: Venous thromboembolism after total joint arthroplasty: Results from a Japanese multicenter cohort study. Arthritis Res. Ther., 16 (4): R154, 2015. doi: 10.1186/ar4616.

12- YOSHIMURA Y., IKEGAMI S., AOKI K., ISOBE K.I. and KITO M.: Incidence, diagnosis, and risk factors of venous thromboembolism after surgery for malignant bone and soft tissue tumour of lower extremity. International Journal of Physical Medicine & Rehabilitation, 6 (1), 2018.

تقييم الفيبرين الذائب والدى دايمر فى الكشف المبكر عن التخثر الوريدى العميق

خلفية البحث : بالرغم من كون تخثر الأوردة العميقة ممكن الوقاية منه إلا يعتبر سبب رئيسى للوفيات والمضاعفات المرضية فى جميع أنحاء العالم حيث يتسبب تخثر الزوردة العميقة ومضاعتها من الإنسداد الرئوى فى وفاة ٦٠.٠٠٠ إلى ١٠٠.٠٠٠ سنوياً فى الولايات المتحدة.

يمكن الو قاية من التخثر الوريدى العميق عن طريق معالجة الاسباب المؤدية إليه والتشخيص المبكر للمرض للحماية من المضاعفات التى قد تنتج عنه.

بالرغم من كون الدى دايمر يعتبر حجر الزاوية فى تشخيص تكون الجلطات ومتابعتها إلا أن مستويات الدى دايمر تكون عالية فى كثير من الأمراض الأخرى بدون تكوين جلطات مما يقلل من كفائته كمؤشر أساسى لتكوين الجلطة.

يعتبر وحدات الفيبرين الذائب من أهم نواتج تنشيط الفيبرين أثناء مراحل تكوين الجلطة ويعتقد بعض العلماء أنه قد يكون مؤشراً جيداً لتشخيص الجلطات مع الدى الدايمر بينما يرى أخرون أنه أقل منه كفاءة.

الهدف من البحث : هو فحص الدور المحتمل لمستوى البلازما لـ SFMC & D-dimer فى التنبؤ بحالة فرط التخثر وبالتالى إمكانية حدوث التخثر الوريدى العميق وتقييم ما إذا كان يمكن استخدامه للإشارة للبدء بالعلاج المضاد للتخثر.

المرضى وطرق البحث : تم دراسة عدد من الحالات التى كانت تردد على عيادة الأوعية الدموية بمستشفيات جامعة الزهر فى سنة ٢٠٢١. من عدد ٨٥ حالة تمت دراستهم ثبت باستخدام أشعة السونارالضاغطة أن حالة يعانون بالفعل من تخثر وريدى عميق فى الجزء السفلى من الجسم (تم اعتبارهم الحالات المصابة) بينما تأكد باستخدام السونار الضاغط لعدد ٦٠حالة عدم وجود أى تخثر وريدى عميق (تم اعتبارهم المجموعة الحاكمة).

لكل من المجموعتين تم أخذ التاريخ المرضى وتم سؤالهم عن عاداتهم من تدخين ونحوه والأدوية التى يتناولونها وعن إجرائهم لأى عمليات جراحية تستلزم إقامة بالسرير بعدها كما تم قياس الوزن لحساب الـ Body Mass Index وتم عمل بعض التحاليل لهم (صورة دم كاملة وعوامل التجلط PT & PTT وتم قياس مستويات الدى دايمر ومستويات وحدات الفيبرين الذائب لكل من المجموعتين).

النتائج : تم معالجة النتائج إحصائياً وتبين التالى :

هناك فارق إحصائى بين المجموعتين فى نتائج كلا من مستويات الدى دايمر ووحدات الفيبرين الذائب والسن والهيمو جلبين ونتائج الـINR، كما يوجد توافق إحصائى بين زيادة وحدات الفيبرين الذائب وكل من زيادة مستويات الدى دايمر ونقص الهيموجلوبين وزيادة معدلات الـ INR.

الاستنتاج : يعتبر كل من وحدات الفيبرين الذائب والدى دايمر من المؤشرات القوية للتجلط وينصح بإستخدامهما للتشخيص المبكر لحالات التخثر الوريدى العميق.