International Blood Research & Reviews

Volume 15, Issue 2, Page 1-9, 2024; Article no.IBRR.115053
ISSN: 2321–7219

Interference of Heterophilic Antibody in D-dimer Determination in an Asymptomatic Elderly Woman

Valverde Sara [a], Masiero Elena [a], Seguso Mara [b], Giordano Martina [b], Inglese Margherita [c] and Gessoni Gianluca [d++*]

[a] Laboratory Medicine, Madonna della Navicella Hospital Chioggia, Venice, Italy.
[b] Laboratory Medicine, Dell'Angelo Hospital Mestre, Venice, Italy.
[c] Internal Medicine, Madonna della Navicella Hospital Chioggia, Venice, Italy.
[d] Transfusion Medicine, Dell'Angelo Hospital Mestre, Venice, Italy.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IBRR/2024/v15i2334

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/115053

Original Research Article

Received: 22/01/2024
Accepted: 26/03/2024
Published: 02/04/2024

ABSTRACT

Background: D-Dimer is considered a pivotal biomarker in diagnosis of disseminated intravascular coagulation and in differential diagnosis of thrombosis and pulmonary embolism.
Case Summary: BL, Caucasian woman, 81 years old, was admitted to hospital, in October 2023, for concussive head trauma after an accidental fall. The patient had a "non-assayable D-Dimer due to excess antigen" utilizing Sysmex Innovance D-dimer using a Sysmex CS 5100 analyser. This abnormal result was firstly observed in March 2022. A second Laboratory confirmed the raised D-dimer concentration. The patient had undergone periodic D-dimer checks which had always confirmed the results and had been treated with a direct FXa inhibitor.

[++] Director;
**Corresponding author: E-mail: gianluca.gessoni@aulss3.veneto.it;*

Methods: Patient's samples were tested for D-dimer using different assays and different analysers, moreover sample diluted in phosphate buffer and heterophilic antibodies blocking reagent have been tested.
Results: The Sysmex Innovance D-dimer assay gave us, constantly "non-assayable D-dimer due to excess antigen" results; the HemosIL D-dimer HS assay gave us, constantly a raised D-dimer concentration (four to five higher than upper reference values); the Quidel Triage D-dimer gave us, constantly D-dimer normal concentration. Results obtained from dilution curves confirmed the presence of high concentration high avidity heterophilic antibodies.
Conclusions: Reports regarding the influence of heterophilic antibodies on the measurement of D-dimer are quite uncommon in literature however, they constitute a significant potential risk. Interference from heterophile antibodies often has a different impact using different instruments and methods in the measurement of D-dimer. Using a combination of different assays and analysers, of dilution strategy with heterophilic antibody blockers, and combining laboratory results with clinical examinations and imaging data, we were able to identify the interference and exclude the presence of thrombosis.

Keywords: D-dimer; D-dimer assays; heterophilic antibody; immunoassay; interference.

ABBREVATIONS

FIIa : Activated Factor II
FXa : Activated Factor X
FXIIIa : Activated Factor XIII
aPTT : Activated partial thromboplastin time
aPCR : Activated protein C resistance
AT : Antithrombin
BNP : Brain Natriuretic Perptide
CEA : Carboidratic Embrionary Antigen
Ca15,5, Ca189.9, Ca125 : Carboidratic Antigen 15.3, 19.9, 125
C3 and C4 : Complement Fractions 3 and 4
CMV : Cytomegalovirus
DD : D-Dimer
EBV : Epstein Barr Virus
FVL : Factor V Leiden
FDPs : Fibrin degradation products
HBV : Hepatitis B Virus
HCV : Hepatitis C Virus
HIV : Human Immunodeficiency Virus
PC : Protein C
PS : Protein S
PT : Prothrombin time
TT : Thrombin time

1. INTRODUCTION

The final phase of activation of the blood coagulation process involves the cleavage of fibrinogen into fibrin by FIIa. Thrombin first cleaves two small fragments (fibrinopeptides A and B) from fibrinogen originating the fibrin monomer. Fibrin monomer spontaneously form a polymer through hydrogen bonds. FXIIIa stabilizes the initial fibrin polymer by catalysing the formation of covalent bonds to cross-link adjacent D domains. In a further phase plasmin cleaves fibrin into various fragments (fibrin degradation products - FDPs), D-dimer (DD) are FDPs products, which are composed of two adjacent cross-linked fibrin monomers [1,2]. DD is considered a sensitive, but non-specific indicator to detect deep vein thrombosis (DVT) or pulmonary embolism (PE), and a substantial aid to diagnose or monitor disseminated intravascular coagulation (DIC) [3,4].

Many different D-dimer assays have been developed, which differ in the DD epitope targeted by the antibody, method of capture and detection, instrumentation required, and calibration standard. At present has been reported that there are about twenty different monoclonal antibodies used by almost thirty different DD assays. From a general point of view the majority ok these methods use homogeneous sandwiches of monoclonal antibodies to detect specific epitopes on cross-linked D-dimer fragments. The detection methods for D-dimer in the clinical laboratory mainly include immunoturbidimetry, enzyme immunoassays, immunofluorescence and immunochromatography, with the most widely used being immunoturbidimetry [5-7].

Immunoassays are very sensitive to interference sustained by multivalent antibody binding ligands that can bridge the reagent antibodies. This not specific cross-linking may result in generation of a falsely positive results. The more common cause of such interference was the presence of heterophilic (or human anti mouse) antibodies [8-10].

In this paper we report an observation regarding the finding of a heterophilic antibody related

falsely very high D-Dimer concentration in a wealthy elder woman.

2. MATERIALS AND METHODS

Case History: BL, Caucasian woman, age 81, was admitted, in October 2023, to the medical ward of the "Madonna della Navicella" Hospital in Chioggia because loss of consciousness following concussive head trauma after an accidental fall. During hospitalization, a "non-assayable DD due to excess antigen" was detected utilizing Sysmex Innovance D-dimer using a Sysmex CS 5100 analyser (Siemens). For description of D-Dimes assays see Table 1. The evaluation of BL's health documentation made it possible to detect that the first observation of a "non-assayable D-Dimer due to excess antigen" dated back to March 2022 (random finding during routine checks). Assays were performed in duplicate by diluting the sample with both phosphate buffer and the heterophilic antibody-blocking reagent present in the KIT with comparable results (see Table 2). The sample had been sent to another laboratory for further investigation and a markedly high DD (four times the normal reference value) results was obtained using HemosIL D-dimer HS assay (ACL TOP750). Assays were performed in duplicate by diluting the sample with both phosphate buffer and the heterophilic antibody-blocking reagent present in the KIT with comparable results as reported in Table 2. The patient had undergone periodic DD checks which had always confirmed the results, in the presumption of being in the presence of a subject with active DVT or PE, therapy was started with a direct FXa inhibitor.

At hospital admission a clinical evaluation was performed using the Wells' Criteria for PE and DVT [11,12]. In order to evaluate the head trauma, a skull x-ray and a brain CT scan were performed. In order to evaluate the presence of PE a standard thoracic Rx examination such as computed tomography angiogram of the thorax were performed. To investigate the presence of DVT legs and abdominal ultrasound scans were performed. A comprehensive laboratory evaluation was performed too.

D-Dimer Assays and Comparative Testing: BL plasma samples were simultaneously tested with three different methods: two latex-enhanced immunoturbidimetric immunoassays: Sysmex Innovance D-dimer using a Sysmex CS 5100 analyser and HemosIL D-dimer HS using an ACL TOP750; and a fluorescent based POCT assay (Quidel TriageTrue D-Dimer). For the two latex-enhanced immunoturbidimetric immunoassays, samples were evaluated after treatment with the heterophilic antibody-blocking reagent supplied with the kit. [13,14].

Dilution Tests: BL plasma samples dilutions were tested using our routine laboratory method (Sysmex Innovance D-dimer). Four sets of doubling dilutions (1/10 to 1/320) were set up: in a series the sample was diluted. In two series the sample was diluted using phosphate buffer (I and II); in two series the sample was diluted using the heterophile antibody blocking reagent supplied with the kit (III and IV). Each series was incubated for 60 minutes prior to assays; series I and III were incubated at +22°C and series II and IV were incubated at +37°C. [15,16].

Heterophilic Antibody Blocking Reagent: BL plasma samples were treated with heterophilic blocking tube (HBT, Scantibodies Laboratory Inc) following the manufacturer's instructions. Briefly, the HBT was shaken in an upright position, uncapped and 500 mL of plasma were added, the tube was recapped and mixed by inversion. The tube must be incubated for 60 minutes at room temperature before performing the assay [17,18].

3. RESULTS

At Hospital admission the Well score was 0, therefore BL had less than 1.3% chance of presenting DVT or PE. Furthermore, the ultrasound study of the abdomen and lower limbs did not reveal thrombosis and the thoracic CT study did not reveal pulmonary embolism. It was therefore considered possible to exclude the presence of actual thromboembolic phenomena [11,12].

BL presented a modest monoclonal IgM-K component described four years ago stable in time, asymptomatic and without depression of the other immunoglobulin classes compatible with a diagnosis of MGUS (monoclonal gammopathy of undetermined significance) [19].

Biochemical profile for evaluation of glucose and lipid metabolism, ions, renal function, liver function showed no relevant alterations Blood cells count was normal such as coagulation parameters: prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time

(TT), antithrombin (AT), protein C (PC), protein S (PS), activated protein C resistance (aPCR), genetic test for G1691A FV (FV Leiden) and G20210A FII (Prothrombin G) mutations. Research of lupus anticoagulant was negative such as assays for anti-cardiolipin antibodies (IgG and IgM) and anti-B2-glycoprotein antibodies (IgG and IgM). No infection sustained by HBV, HCV, HIV, Treponema pallidum, CMV, EBV, Mycoplasma pneumoniae was detected. We also investigated the presence of autoimmune-type phenomena finding a positive anti-nucleus autoantibody (ANA titre 1/80, homogeneous pattern), but Autoantibody anti-smooth muscle (ASMA), anti-native DNA, anti-mitochondria antibodies (AMA) were negative, C3 and C4 assays were normal, direct (DAT); and indirect Coombs (IAT) test were negative as well as "*a frigore"* agglutinins and cryoglobulins [20]. No interference was observed with numerous other immunometric assays such as Ferritin CEA, Ca19.9. CA125, CA15.3, Tropoinn T, BNP which always presented values within the normal reference ranges [21-23].

In Table 1 are reported values of DD concentration obtained, from March 2022 to January 2024, with three commercial methods. Sysmex Innovance D-dimer assay and HemosIL D-dimer HS assay, both are immunoturbidimetric immunoassays performed on high throughput automated analysers, samples consist in citrated plasma, the target monoclonal antibody is the so called 8D3 [13-18]. Quidel Triage D-Dimer is an immunofluorescent immunoassay performed using a Triage POCT analyser, samples consist in EDTA whole blood, the target monoclonal antibody is the so called 3B6 [13-18]. As reported in Table 2, when analysing untreated plasma, using the Sysmex Innovance D-dimer assay, we obtained constantly "non-assayable D-Dimer due to excess antigen" results. These results were confirmed using, for sample's dilution, both the standard buffer than the heterophilic antibodies blocking reagent supplied with the kit. While, using the HemosIL D-dimer HS assay, we obtained constantly a raided DD (approximately 4-5 times above the normal reference limit). These results were confirmed using, for sample's dilution, both the standard buffer than the heterophilic antibodies blocking reagent supplied with the kit Using the Quidel Triage D-Dimer assay resulted in an analyte quantification that was within the normal reference range. After sample treatment with Heterophilic Blocking Tube (HBT, Scantibodies Laboratory Inc) we obtain D-dimer normal concentration both with Sysmex Innovance D-dimer assay and HemosIL D-dimer HS assay. These results were comparable to that obtained using POCT instrumentation (Quidel Triage D-Dimer).

In Fig. 1 were reported dilution curves obtained using phosphate buffer solution (INNOVANCE D-Dimer Diluent) and buffer solution with heterophil blocking reagent included in the kit (INNOVANCE D-Dimer Supplement) tested at +22°C (room temperature) and at +37°C. We used the Sysmex Innovance D-dimer kit, the citrated plasma was diluted by twofold (1/1 to 1/320) using both a phosphate buffer solution and a heterophilic antibody blocking reagent of the kit. Each dilution series was incubated for 60 minutes at either +22°C or +37°C prior to analysis. As shown in the Fig. 1 no results (antigen excess alarm) were obtained for dilutions less than 1/40. For dilutions equal to or greater than 1/40 we obtained a quantitative result that was always slightly lower in the series prepared by diluting the sample with heterophilic antibody-blocking reagent than in the series prepared using phosphate buffer. The pre-incubation temperature does not seem to influence the results. In any case the quantification of DD always gave extremely high results despite the attempts made to mitigate the interference from heterophilic antibodies.

Table 1. D-dimer assays comparison

	Assays description		
Assay	**Sysmex Innovance D-dimer**	**HemosIL D-dimer HS assay**	**Quidel Triage D-Dimer**
Matrix	Citrated Plasma	Citrated Plasma	EDTA whole blood
Reference Values	<800 mcg/L FEU	<700 mcg/L FEU	<600ng/mL
Assay Principle	Immunoturbidimetric	Immunoturbidimetric	Fluorescence immunoassay
Target MoAb	**8D3**	**8D3**	**3B6**

Table 2. D-dimer concentration values obtained using three different commercial methods

	Sysmex Innovance D-dimer		HemosIL D-dimer HS assay		Quidel Triage D-Dimer
	Standard Assay	**KIT Blocking supplement**	**Standard Assay**	**KIT Blocking supplement**	**Standard Assay**
	mcg/L FEU	mcg/L FEU	mcg/L FEU	mcg/L FEU	ng/mL
March 04 22	AE	AE	2907	NT	NT
April 15 22	AE	AE	2974	NT	NT
May 25 22	AE	AE	2942	3300	NT
June 28 22	AE	AE	3003	NT	NT
March 20 23	AE	AE	3014	2900	NT
June 29 2023	AE	AE	3028	3100	NT
September 29 23	AE	AE	3059	NT	NT
October 18 23	AE	AE	3009	2800	390
November 20 23	AE	AE	2848	NT	389
December 28 23	AE	AE	NT	NT	441
January 10 24	458*	NT	658*	NT	452

AE: Antigen Excess, NT: Not Tested

** Results obtained testing undiluted plasma samples treated with heterophilic antibody blocking solution (HBT Heterophilic Blocking Tube, Scantibodies Laboratory INC)*

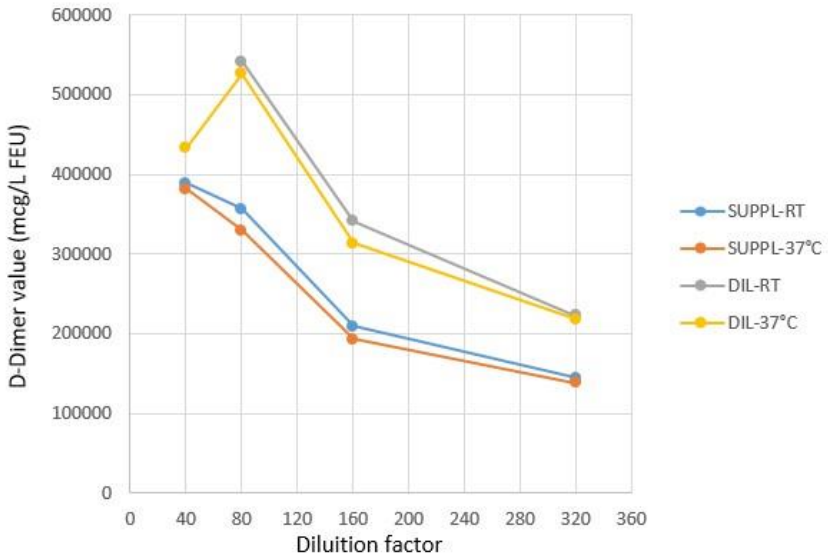

Fig. 1. Effect of dilution with buffer solution and heterophilic antibody blocking solution

Analysis were performed using Sysmex Innovance D-dimer assay with a Sysmex CS 5100 analyser. Four dilution series were set up, In two series plasma samples were diluted using the Kit's suppletive heterophilic antibodies blocking reagent (SUPPL). In two series plasma samples were diluted using the Kit's standard dilution buffer (DIL); each dilution series was incubated for 60 minutes at either room temperature (RT) or +37°C prior to analysis.

4. DISCUSSION

In this elderly patient without symptoms suggestive of possible DVT and/or EP were observed repeatedly elevated (or non-assayable results due to excess antigen) DD values led to extensive unnecessary diagnostic investigations and inappropriate anticoagulant therapy. This resulted in unjustified costs, uncertainty and discomfort for the patient, her parents, and health care providers. in fact the patient underwent repeated tests and was treated with a direct FXa inhibitor [24].

After repeated DD evaluations with pathological / undeterminable values without explanation and without attempts to investigate the causes of these abnormal results, we approached the

problem by assuming the presence of an analytical interference. Interference from hyperbilirubinemia, hemolysis and hyperlipemia, sometimes reported in literature, were excluded because appearance of the specimen and the results of biochemical tests [6-8,25,26]. We therefore considered the presence of an interference sustained by heterophilic antibodies [27,28]. The first approach to the problem, which had already, partially, been carried out prior to our observation, was to repeat the DD determination using different methods and different instrumentations. In a first time, assays were performed in duplicate with the Sysmex Innovance D-dimer kit using a Sysmex CS 5100 analyser and the HemosIL D-dimer HS kit using an ACL TOP750 analyser. This approach did not solve the problem, probably because, the two methods are extremely similar: the same sample (citrated plasma), the same assay principle (turbidimetric immunoassay) and the same monoclonal antibody used to bind the analyte (8D3). Both these assays include the availability of an additional reagent to mitigate interference from heterophilc antibodies. For both methods, the D-Dimer assay was performed by diluting the patient's plasma using the reagent blocking heterophile antibodies. In this case these measures did not appreciably modify the obtained results.

We therefore considered to perform the DD determination using a third method using the Triage instrumentation and the Quidel Triage D-Dimer kit, this method uses a different sample (EDTA whole blood), a different detection system (immunofluorescent immunoassay) and a different monoclonal antibody used to bind the analyte (3B6) [13-18]. Using the Sysmex Innovance D-dimer assay D-Dimer was always “non-determinable due to excess antigen” even using the kit’s suppletive reagent to mitigation of heterophilic antibodies interference. Using the HemosIL D-dimer HS assay D-Dimer was consistently high (about 4-5 times above the upper reference values) even using the kit’s suppletive reagent to mitigation of heterophilic antibodies interference. Using the Quidel-Triage assay we obtained a D-Dimer quantification within normal limits. It was therefore possible to confirm that the patient did not present an increase in DD and that the anomalous results obtained were, probably, attributable to analytical interference from heterophilic antibodies [29-31].

Four samples’ series have been set-up and tested using the Sysmex Innovance D-dimer assay. Pre assay incubation temperature Incubation temperature did not demonstrate any influence on the results, demonstrating that it was in the presence of a heterophilic antibody with a wide thermal range of activity (from +22°C to +37°C). Moreover, the dilution of the sample with the suppletive reagent for the mitigation of interference from heterophilic antibodies supplied with the Kit was not able to resolve the problem. This observation led us to hypothesize the presence of a heterophilic antibody with high concentration and high avidity [27-29]. Furthermore, the observation that the heterophile antibody did not seem to interfere with other immunometric assays carried out with the EIA method (e.g. tumor markers) or D-Dimer quantification performed using an immunofluorescent based assay, seemed to suggest a fair specificity for the immuno turbidimetric assay [30-32].

Normal D-dimer concentration was obtained using heterophilic blocking tube (HBT, Scantibodies Laboratory Inc) both with Sysmex Innovance D-dimer assay and HemosIL D-dimer HS assay; for this kind of heterophilic antibodies contained in the plasma sample, HBT has proven to be more effective than the suppletive blocking reagent included both in the kit of the Sysmex Innovance D-dimer assay and HemosIL D-dimer HS assay. HBT contains a unique blocking reagent composed of specific binders which inactivate heterophilic antibodies. Once the specific binders have bound to the heterophilic antibodies, the antibodies are no longer able to cause immunoassay interference arising a normal D-dimer concentration [31,32].

5. CONCLUSIONS

Analytical interference in antibody-based tests is a well-known phenomenon in laboratory medicine. Immunoassays, including assays for human chorionic gonadotropin, troponin, or thyroid hormones, are known to be sensitive to interference from heterophilic antibodies [32,33]. These are naturally occurring polyreactive antibodies, autoantibodies, human anti–animal antibodies, or rheumatoid factor [8-10]. Published reports on antibody interference in D-dimer assays quite uncommon. In literature were reported cases both in women and men of different ages. Interestingly, the great majority of described cases showed interference on latex enhanced immunoturbidimetric D-dimer assays and occurred with monoclonal antibodies of different manufacturers, different antibody

epitopes, and in reagents with different blocking agents [28-30]. Determination of the origin of heterophilic antibodies is challenging. The occurrence of antibody interference and the lack of a clearly definable cause for this interference makes considering the pretest probability of DVT and PE in the context of D-dimer analysis even more important because D-dimer testing is sensitive but not specific.

The influence of heterophilic antibodies on the measurements of D-dimer remains a relevant challenge. Heterophilic antibodies should be considered when an elevated D-Dimer value is not in conformity with the clinical evidence and imaging data; the use of different methods and reagent that inactivate the heterophilic antibodies could be a strategy to obtain a reliable result [32,33].

6. STUDY LIMITATIONS

This is a short paper reporting an evaluation about interference in D-Dimer quantification sustained by presence of high concentration high avidity heterophilic antibodies. The main limitation of this study, in our opinion, lies in the fact that it was only possible to compare three different commercial methods for the determination of D-Dimer.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Weitz JI, Fredenburgh JC, Eikelboom JW. A test in contest: D-dimer. J Am Coll Cardiol. 2017;70:2411–20.
   DOI: 10.1016/j.jacc.2017.09.024
2. Brotman DJ. Higher D-dimer thresholds for excluding pulmonary embolism: No free lunch? Ann Intern Med. 2022;175:295-296.
   DOI: 10.7326/M21-4295
3. Udovenko A, Makogonenko Y, Korolova D, et al. Formation and elimination of soluble fibrin and D-dimer in the bloodstream. Croat Med J. 2023;64:421-429.
   DOI: 10.3325/cmj.2023.64.421
4. Riley RS, Gilbert AR, Dalton JB, et al. Widely used types and clinical applications of D-dimer assay. Lab Med. 2016;47: 90–102.
   DOI: 10.1093/labmed/lmw001
5. Talon L, Fourneyron V, Trapani A, et al. Analytical performance of a new immune turbidimetric D-dimer assay and comparison with available assays. Res Pract Thromb Haemost. 2022;6:e12660.
   DOI: 10.1002/rth2.12660.
6. Favresse J, Lippi G, Roy PM, et al. D-dimer: Preanalytical, analytical, postanalytical variables, and clinical applications. Crit Rev Clin Lab Sci. 2018; 55:548-577.
   DOI: 10.1080/10408363.2018.1529734
7. Mastella AK, de Carvalho JAM, Stein CS, et al. Interference of icterus on plasma D-dimer levels measured using immunoturbidimetric assays. Blood Coagul Fibrinolysis. 2021;32:162-163.
   DOI: 10.1097/MBC.0000000000001004
8. Tate J, Ward G. Interferences in immunoassay. Clin Biochem Rev. 2004; 25:105–20.
9. Cheng X, Guo X, Chai X, et al. Heterophilic antibody interference with TSH measurement on different immunoassay platforms. Clin Chim Acta. 2021;512:63-65.
   DOI: 10.1016/j.cca.2020.11.018
10. Zhang XY, Zhang XX, Xu JL, et al. Identification of and solution for false D-dimer results. J Clin Lab Anal. 2020;34: e23216.
    DOI: 10.1002/jcla.23216
11. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the Simpli RED D-dimer. Thromb Haemost. 2000;83:416–20.
    DOI: 10.1055/s-0037-1613830
12. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;350(9094): 1795–8.
    DOI: 10.1016/S0140-6736(97)08140-3
13. Adriaansen MJ, Morison IM, Perry HE. Discrepancies between two D-dimer

assays and impact on clinical decisions; a retrospective analysis of samples tested in community and hospital-based laboratories in Auckland. N Z Med J. 2024;137: 12-19.
DOI: 10.26635/6965.6302

14. Ma H, Chen CH, Li YM, Wang JJ, Hu ZD. Falsely elevated D-dimer partially caused by heterophilic antibodies: A case report. Clin Chim Acta. 2022; 535(1):40-142.
DOI: 10.1016/j.cca.2022.08.011
15. Zhang L, Bao G, Zheng Z. Two cases of pseudoelevation of plasma D-dimer levels. Clin Lab. 2021;67(9).
DOI: 10.7754/Clin.Lab.2021.210203
16. Chen L, Chen Y. Performance Evaluation of the Sysmex CS-5100 Automated Coagulation Analyzer. Clin Lab. 2015; 61:653-60.
DOI: 10.7754/clin.lab.2014.141124
17. Favaloro EJ, Mohammed S, Vong R, et al. Verification of the ACL Top 50 Family (350, 550, and 750) for harmonization of routine coagulation assays in a large network of 60 laboratories. Am J Clin Pathol. 2021; 156:661-678.
DOI: 10.1093/ajcp/aqab004.
18. Ghys T, Achtergael W, Verschraegen I,et al. Diagnostic accuracy of the Triage D-dimer test for exclusion of venous thromboembolism in outpatients. Thromb Res. 2008;121:735-41.
DOI: 10.1016/j.thromres.2007.07.012
19. Anderson LD Jr, Bladé J, Kyle RA. A case of benign immunoglobulin D monoclonal gammopathy of undetermined significance with 26 years of follow-up. E J Haem. 2024;5:235-237.
DOI: 10.1002/jha2.846
20. Sun L, Wang N, Feng Y, et al. The distribution of heterophilic antigens and their relationship with autoimmune diseases. Front Immunol. 2023;14: 12756-58.
DOI :10.3389/fimmu.2023.1275658
21. Aliberti L, Gagliardi I, Dorizzi RM, et al. Hypeprolactinemia: Still an insidious diagnosis. Endocrine. 2021;72:928-931.
DOi: 10.1007/s12020-020-02497-w
22. Hammarsten O, Becker C, Engberg AE. Methods for analyzing positive cardiac troponin assay interference. Clin Biochem. 2023;116:24-30.
DOI: 10.1016/j.clinbiochem.2023.03.004
23. Zhao W, Duan L, Fang L, et al. Persistent increase of carbohydrate antigen 19-9 with an unknown reason: A seven-year follow-up case. J Clin Lab Anal. 2022;36:e24792.
DOI: 10.1002/jcla.24792
24. Carter-Brzezinski L, Houston S, Thachil J. D-dimers: A most misunderstood test. Br J Hosp Med (Lond). 2021;82:1-5.
DOI: 10.12968/hmed.2021.0279
25. Lippi G, Avanzini P, Zobbi V, Ippolito L. Influence of mechanical hemolysis of blood on two D-dimer immunoassays. Blood Coagul Fibrinolysis. 2012;23:461-3.
DOI: 10.1097/MBC.0b013e3283549696
26. Negrini D, Bernardi D, Antonelli G, Plebani M. Interference of lipemia in samples for routine coagulation testing using a Sysmex CS-5100 coagulometer. Int J Lab Hematol. 2019;41:772-777.
DOI: 10.1111/ijlh.13108
27. Robier C, Edler E, Klescher D, Neubauer M. False-positive D-dimer result in a latex-enhanced immunoassay caused by interfering human anti-mouse antibodies. Clin Chem Lab Med. 2014;52:253-5.
DOI: 10.1515/cclm-2014-0496
28. Wu Y, Xiao YX, Huang TY, et al. What makes D-dimer assays suspicious-heterophilic antibodies? J Clin Lab Anal. 2019;33:e22687.
DOI: 10.1002/jcla.22687.
29. Ozbalci D, Doguc DK, Yilmaz G, et al. Interference of D-dimer levels from heterophilic antibody in Covid-19: A serious concern in treatment and follow-up of patients. Int J Lab Hematol. 2022;44:e13-e16.
DOI: 10.1111/ijlh.13654
30. Lippi G, Ippolito L, Tondelli MT, Favaloro EJ. Interference from heterophilic antibodies in D-dimer assessment. A case report. Blood Coagul Fibrinolysis. 2014;25:277-9.
DOI: 10.1097/MBC.0000000000000017
31. Favaloro EJ, Dean E. Variability in D-dimer reporting revisited. Pathology. 2021;53:538-540.
DOI: 10.1016/j.pathol.2020.08.010.
32. Sun HX, Ge H, Xu ZQ, Sheng HM. Clinical laboratory investigation of a patient with an extremely high D-dimer level: A case report. World J Clin Cases. 2020;8:3560-3566.
DOI: 10.12998/wjcc.v8.i16.3560

33. Lippi G, Aloe R, Meschi T, ei al. Interference from heterophilic antibodies in troponin testing. Case report and systematic review of the literature. Clin Chim Acta. 2013;426:79-84.
DOI: 10.1016/j.cca.2013.09.004

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/115053