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The Biochemistry and Clinical Significance of D-Dimer

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ABSTRACT: D-dimer, product degradation of fibrin, belongs to the most sensitive and specific markers in the diagnostics of thrombotic disorders, mainly acute PE and DVT. This leads to its measurement because of the high sensitivity in ruling out these conditions, thus reducing unnecessary imaging and improving patient management. The importance of D-dimer has been repeatedly said in various studies, notably during the COVID-19 pandemic, where it has been noted as an essential biomarker in the assessment of thrombotic complications, treatment strategy, and prognostic aspects of the patient. This literature review paper covers basic principles and measurements of D-dimer because of up-to-date knowledge on its clinical applications, limitations, and directions for potential future research.

1. INTRODUCTION

D-dimer is a small protein fragment present in the blood following plasminogen lysis of a blood clot. It has, over time, gained immense attention in clinical practice, especially in regard to thromboembolic disorders comprising venous thromboembolism (VTE), pulmonary embolism (PE), and acute aortic syndromes (AAS). The importance of D-dimer has been emphasized by the most recent studies following the COVID-19 outbreak, where it turned out to be one of the most important biomarkers in the diagnostic assessment of thrombotic complications, guidance on treatment choices, and prediction of outcomes for patients. D-dimer testing does not only have utility in traditional thrombotic disorders; it is also useful in special populations, such as pregnant women and suspected COVID-19 cases. An algorithm was proposed by Pol et al. (2019) to diagnose PE specifically for pregnant patients, which included D-dimer testing, thus overcoming the limitations of the traditional cutoffs based on the demographic uniqueness due to physiological changes. This in turn underlines, in general, the need for very tailored diagnostic approaches that take into account specific patient characteristics.

In the infectious disease domain, the increase in D-dimer levels has been correlated with the increased risk of mortality for COVID-19 patients by Poudel et al. (2021), thereby reinforcing this biomarker's importance in the assessment of severity and decision-making guidelines for treatment. Likewise, according to Berger et al. (2020), elevated D-dimer values among COVID-19 patients hint at bad clinical outcomes; thus, it requires that a close watch be kept and interventions be issued on time. As noted by Kabrhel et al. (2010), though, D-dimer testing is quite specific, whose specificity may be influenced by a series of clinical variables. The presence of comorbidities, recent surgeries, or other such conditions may easily elevate the D-dimer levels, thereby making the test results rather difficult to elicit implications. This is why the necessity has been emphasized for clinicians to focus on the broad clinical view when utilizing the D-dimer in diagnostic decision-making. She et al. (2019) noted that, while D-dimer could work in certain contexts, its role in diagnosing periprosthetic joint infections might not be as effective compared with other inflammatory markers. This shows the need for further research toward identifying more reliable biomarkers for specific conditions.

Problems remain to be resolved in D-dimer testing, reflecting an actual need for future research to home in on reviewing testing protocols pertaining to D-dimer across diverse patient populations as well as clinical scenarios. He offers that further research to determine effectiveness in the diagnosis of thrombotic disorders among patients with recurrent events or complicating factors is necessary. Other authors suggest that in standardizing D-dimer assays and solving questions of preanalytical and postanalytical variables, test outcomes can be made much more reliable. Meanwhile, further research into combining D-dimer tests with emerging clinical prediction models will likely add more diagnostic accuracy in addition to good patient outcomes. Longitudinal research considering prognostic value deserves attention on the use of D-dimers as a biomarker in acute and chronic conditions. The author from above agrees with the idea that the integration of D-dimer testing offers improved diagnostic accuracy in detecting impending disease dynamics from newly developing disease states, but only if this is done in future research, as other arguments show.

More recent research has established a relationship between levels of D-dimers and acute pulmonary embolism in COVID-19 patients, suggesting that elevated D-dimer might be a prognostic factor for worse outcomes. The incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and high D-dimer appears to confirm the relevance of D-dimer determination in the clinician's decision during pandemics. The assessment of D-dimer would enhance diagnostic precision in acute

aortic syndromes with a substantial misdiagnostic risk. Sensitivity is such that, combined with a clinical evaluation, it rules out aortic dissection (Linkins & Lapner, 2017). This could be advantageous on one side but detrimental on the other by not being specific to AAS; this underlines the necessity of a complete diagnostic approach (Linkins & Lapner, 2017; Nazerian et al., 2018).

D-dimer is known to have prognostic value in thrombotic events, especially in patients with an unprovoked VTE history. Yu et al. have noted that the increase in D-dimer levels post-anticoagulant-therapy discontinuation corresponds with higher recurrence risks. Therefore, the authors commented that D-dimer testing might be useful in guiding the duration of anticoagulation status. As laid out by Douketis et al., the possibility of recurrence greatly depends on the timing and specific cut-off points for D-dimer testing. Besides, D-dimer has been suggested to play a role in pathophysiology in the context of long COVID, with the concept that pulmonary microvascular immuno-thrombosis may present a pathomechanistic explanation of persistent complaints after acute COVID-19 disease (Poudel et al., 2021). Such novel research areas show that D-dimer has potential value in long-term complications as a biomarker, drawing interest from the point of view of its place in patient management.

D-DIMER IN PULMONARY EMBOLISM DIAGNOSIS

D-dimer is of paramount importance in the diagnosis of PE by virtue of his integration into clinical pathways. In their paper, Righini et al. (2014) validated an age-adjusted D-dimer cutoff; hence, according to their recommendation, for patients aged 50 years or more, the threshold has to be the result of multiplying ten by age. That increases the sensitivity of the test among aged patients who are at elevated risk for thromboembolic events compared to the general population, allowing a low rate of failure for missed diagnosis. This kind of fine-tuning in approaches serves to optimize resource utilization, saving from avoidable radiation due to imaging studies.

It has just been further researched and proven by Kearon et al. (2019) that a D-dimer level of less than 1000 ng/mL efficiently excludes PE in patients with low pretest probability while that of less than 500 ng/mL is good enough in those with moderate pretest probability. This just underscores the fact that D-dimer testing additively to clinical assessment can increase diagnostic efficiency so much and in such a way as to improve outcomes for patients.

Raja et al. (2015) have drawn attention to the difficulties of diagnosing PE, especially in low-risk populations, stressing the necessity of validated clinical prediction rules for guiding D-dimer testing. Sensitivity loss for PE and the resultant potential for overdiagnosis and unnecessary imaging among low-risk patients require judicious and appropriate approaches to D-dimer testing, which seem to go against the test's use on the basis of only clinical context. The entire concept has been taken too far in the wrong direction.

D-dimer proves to be an important biomarker in the diagnosis and management of VTE and PE. It is highlighted in the clinic guidelines that D-dimer testing results must be combined with the results of clinical assessment to achieve the highest efficiency of diagnosis in patients with different pretest probabilities of DVT (Bates et al., 2012). For those with a low pretest likelihood, testing D-dimer enables DVT to be ruled out; while those with a moderate probability ought to have a highly sensitive D-dimer test. This shows that the role of D-dimer is noninvasive, cost-effective, in avoiding unnecessary imaging because of the sensitivity and cost of imaging for venous thromboembolism.

Besides, D-dimer levels play a sensitive role in the diagnostic process for PE due to highly prevalent nonspecific symptoms. Applying validated clinical prediction rules for the assessment of the pretest probability before the test with D-dimer and age-related thresholds is recommended for increased specificity. There are many reasons for elevated levels of D-dimers, independent of thrombophilia, and hence, testing approaches should be judicious (Balla et al., 2021)..

D-DIMER IN DEEP VEIN THROMBOSIS

For DVT, Bates et al. 2012, advised D-dimer testing to be based on pretest probability of DVT using highly sensitive assays in low to moderate risk patients. This is in line with the principle of balancing diagnostic accuracy with the cost of healthcare. Kesieme et al. (2011) also stressed the need for combining D-dimer testing with structured algorithms to ensure timely diagnosis and treatment initiation in populations at risk of the disease development, especially among aged individuals.

Another study by Douma et al. (2012) strengthened the concept of age-adjusted D-dimer levels for improving the diagnostic accuracy of DVT, emphasizing that this approach significantly increases the number of patients that can be safely ruled out for DVT and, therefore, imparts a reduction in unnecessary interventions. In spite of D-dimer testing now being widespread in a plethora of clinical scenarios, several knowledge gaps prevail. For example, a marked effect on the clinical utility might be made by the assay characteristics of D-dimer alone, but there lacks any standardization (Raja et al., 2015). The other issue is that there is very little understanding optimal D-dimer cutoff values for definite populations—now, the situation with COVID-19, where D-dimer levels' dynamics could be different from classical thrombotic conditions (Olson, 2015; Poudel et al., 2021).

CONCLUSION

D-dimer measurement has come to be an essential part of the triage and workup of thrombotic disorders, especially suspected PE and DVT. The use of age-adjusted cutoffs in this manner, with further refinement of specific algorithms based on the likely prevalence of disease by age group and taking into account pretest probability, can really make D-dimer testing useful. Sensitivity

aside, and given the view for more impact, the individual must take this into account with the community approach to diagnostic decision-making. With changing patterns within clinical practice, D-dimer holds prevalence as a frontline biomarker; therefore, there is a continued rationale for ongoing research and optimization for clinical value in improving patient care outcomes. Standardizing D-dimer assays for age-adjusted thresholds in different populations with long-term sequelae from postinfection sustained elevated levels would, therefore, be the line of future research allowing definite recommendations in decision rules. This would therefore greatly improve patient outcomes by specifically developing clinical pathways for management if the long-term implications were elevated D-dimer levels post-COVID-19 infection due to thrombotic complications.

REFERENCES

1) Álvarez-Pérez, F. J.., Castelo-Branco, M.., & Álvarez-Sabín, J.. (2011). Usefulness of measurement of fibrinogen, D-dimer, D-dimer/fibrinogen ratio, C reactive protein and erythrocyte sedimentation rate to assess the pathophysiology and mechanism of ischaemic stroke. Journal of Neurology, Neurosurgery & Psychiatry , 82 , 986 – 992. http://doi.org/10.1136/jnnp.2010.230870
2) Balla, Evangelia D.., Daniilidis, Vasileios., Karlioti, Georgia., Kalamas, Theocharis., Stefanidou, Myrika., Bikiaris, Nikolaos D.., Vlachopoulos, Antonios., Koumentakou, Ioanna., & Bikiaris, D.. (2021). Poly(lactic Acid): A Versatile Biobased Polymer for the Future with Multifunctional Properties—From Monomer Synthesis, Polymerization Techniques and Molecular Weight Increase to PLA Applications. Polymers , 13 . http://doi.org/10.3390/polym13111822
3) Bates, S.., Jaeschke, Roman., Stevens, S.., Goodacre, S.., Wells, P.., Stevenson, M.., Kearon, C.., Schunemann, H.., Crowther, M.., Pauker, S.., Makdissi, R.., & Guyatt, G.. (2012). Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.. Chest , 141 2 Suppl , e351S-e418S . http://doi.org/10.1378/chest.11-2299
4) Berger, J.., Kunichoff, Dennis., Adhikari, S.., Ahuja, T.., Amoroso, N.., Aphinyanaphongs, Y.., Cao, Meng., Goldenberg, R.., Hindenburg, A.., Horowitz, J.., Parnia, S.., Petrilli, C.., Reynolds, H.., Simon, Emma., Slater, J.., Yaghi, S.., Yuriditsky, E.., Hochman, J.., & Horwitz, Leora I.. (2020). Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. Arteriosclerosis, Thrombosis, and Vascular Biology , 40 , 2539 – 2547. http://doi.org/10.1161/ATVBAHA.120.314872
5) Demelo-Rodríguez, P.., Cervilla-Muñoz, E.., Ordieres-Ortega, L.., Parra-Virto, A.., Toledano-Macías, M.., Toledo-Samaniego, N.., García-García, Alejandra., García-Fernández-Bravo, Irene., Ji, Z.., de-Miguel-Diez, J.., Alvarez-Sala-Walther, L.., del-Toro-Cervera, J.., Galeano-Valle, Francisco., & Galeano-Valle, Francisco. (2020). Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thrombosis Research , 192 , 23 - 26 . http://doi.org/10.1016/j.thromres.2020.05.018
6) Dessap, A. Mekontso., Deux, J.., Abidi, N.., Lavenu-Bombled, C.., Melica, G.., Renaud, B.., Godeau, B.., Adnot, S.., Brochard, L.., Brun-Buisson, C.., Galactéros, F.., Rahmouni, A.., Habibi, A.., & Maître, B.. (2011). Pulmonary artery thrombosis during acute chest syndrome in sickle cell disease.. American journal of respiratory and critical care medicine , 184 9 , 1022-9 . http://doi.org/10.1164/rccm.201105-0783OC
7) Douketis, J.., Tosetto, A.., Marcucci, M.., Baglin, T.., Cushman, M.., Eichinger, S.., Palareti, G.., Poli, D.., Tait, R.., & Iorio, A.. (2010). Patient-Level Meta-analysis: Effect of Measurement Timing, Threshold, and Patient Age on Ability of d-Dimer Testing to Assess Recurrence Risk After Unprovoked Venous Thromboembolism. Annals of Internal Medicine , 153 , 523 - 531 . http://doi.org/10.7326/0003-4819-153-8-201010190-00009
8) Douma, R.., Tan, M.., Schutgens, R.., Bates, S.., Perrier, A.., Legnani, C.., Biesma, D.., Ginsberg, Jeffrey S.., Bounameaux, H.., Palareti, G.., Carrier, M.., Mol, G.., Gal, G. Le., Kamphuisen, P.., & Righini, M.. (2012). Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. Haematologica , 97 , 1507 - 1513 . http://doi.org/10.3324/haematol.2011.060657
9) Favresse, J.., Lippi, G.., Roy, P.., Châtelain, B.., Jacqmin, H.., Cate, H. ten., & Mullier, F.. (2018). D-dimer: Preanalytical, analytical, postanalytical variables, and clinical applications. Critical Reviews in Clinical Laboratory Sciences , 55 , 548 - 577 . http://doi.org/10.1080/10408363.2018.1529734
10) Gibson, C.., Spyropoulos, A.., Cohen, A.., Hull, R.., Goldhaber, S.., Yusen, R.., Hernandez, Adrian F.., Korjian, Serge.., Daaboul, Y.., Gold, A.., Harrington, R.., & Chi, G.. (2017). The IMPROVEDD VTE Risk Score: Incorporation of D-Dimer into the IMPROVE Score to Improve Venous Thromboembolism Risk Stratification. TH Open: Companion Journal to Thrombosis and Haemostasis , 1 , e56 - e65 . http://doi.org/10.1055/s-0037-1603929
11) Kabrhel, C.., Courtney, D. Mark., Camargo, C.., Plewa, M.., Nordenholz, K.., Moore, C.., Richman, P.., Smithline, H.., Beam, D.., & Kline, J.. (2010). Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism.. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine , 17 6 , 589-97 . http://doi.org/10.1111/j.1553-2712.2010.00765.x

12) Kearon, C.., Wit, K. de., Parpia, S.., Schulman, S.., Afilalo, M.., Hirsch, A.., Spencer, F.., Sharma, Sangita., D'Aragon, F.., Deshaies, J.., Gal, G. Le., Lazo-Langner, A.., Wu, Cynthia., Rudd-Scott, L.., Bates, S.., & Julian, J.. (2019). Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability.. The New England journal of medicine , 381 22 , 2125-2134 . http://doi.org/10.1056/NEJMoa1909159
13) Kesieme, E.., Kesieme, C.., Jebbin, Nze J.., Irekpita, E.., & Dongo, A.. (2011). Deep vein thrombosis: a clinical review. Journal of blood medicine , 2 , 59 - 69 . http://doi.org/10.2147/JBM.S19009
14) Leonard-Lorant, I.., Delabranche, X.., Séverac, F.., Helms, J.., Pauzet, Coralie., Collange, O.., Schneider, F.., Labani, A.., Bilbault, P.., Molière, S.., Leyendecker, P.., Roy, C.., & Ohana, M.. (2020). Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. Radiology . http://doi.org/10.1148/radiol.2020201561
15) Li, Rui., Shao, H.., Hao, L.., Yu, Baozhan., Qu, P.., Zhou, Yixin., & Chen, Jiying. (2019). Plasma Fibrinogen Exhibits Better Performance Than Plasma D-Dimer in the Diagnosis of Periprosthetic Joint Infection: A Multicenter Retrospective Study. The Journal of Bone and Joint Surgery , 101 , 613–619 . http://doi.org/10.2106/JBJS.18.00624
16) Linkins, L.., & Lapner, S. Takach. (2017). Review of D-dimer testing: Good, Bad, and Ugly. International Journal of Laboratory Hematology , 39 , 103 - 98 . http://doi.org/10.1111/ijlh.12665
17) Nazerian, P.., Mueller, C.., Soeiro, A.., Leidel, B. A.., Salvadeo, S.., Giachino, F.., Vanni, S.., Grimm, Karin., Oliveira, M.., Pivetta, E.., Lupia, E.., Grifoni, S.., Morello, F.., Capretti, Elisa., Castelli, M.., Gualtieri, S.., Trausi, F.., Battista, S.., Bima, Paolo., Carbone, F.., Tizzani, M.., Veglio, M. G.., Badertscher, P.., Boeddinghaus, J.., Nestelberger, T.., & Twerenbold, R.. (2018). Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes: The ADvISED Prospective Multicenter Study. Circulation, 137, 250–258. http://doi.org/10.1161/CIRCULATIONAHA.117.029457
18) Olson, J.. (2015). D-dimer: An Overview of Hemostasis and Fibrinolysis, Assays, and Clinical Applications.. Advances in clinical chemistry , 69 , 1-46 . http://doi.org/10.1016/bs.acc.2014.12.001
19) Pol, L. M. van der., Tromeur, C.., Bistervels, I.., Áinle, F. N. Ní., Bemmel, T. van., Bertoletti, L.., Couturaud, F.., Dooren, Yordi van., Elias, A.., Faber, L.., Hofstee, H.., Hulle, T. van der., Kruip, M.., Maignan, M.., Mairuhu, A.., Middeldorp, S.., Nijkeuter, M.., Roy, P.., Sanchez, O.., Schmidt, Jeannot., Wolde, M. ten., Klok, F.., & Huisman, M.. (2019). Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. Obstetrical & Gynecological Survey . http://doi.org/10.1097/01.ogx.0000577816.58861.db
20) Poudel, A.., Poudel, Yashasa., Adhikari, A.., Aryal, B.., Dangol, D.., Bajracharya, T.., Maharjan, Anil., & Gautam, R.. (2021). D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS ONE , 16. http://doi.org/10.1371/journal.pone.0256744
21) Raja, A.., Greenberg, J.., Qaseem, A.., Denberg, Thomas D.., Fitterman, N.., & Schuur, J.. (2015). Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians.. Annals of internal medicine , 163 9 , 701-11 . http://doi.org/10.7326/M14-1772
22) Righini, M.., Es, J. van., Exter, P. D. den., Roy, P.., Verschuren, F.., Ghuysen, A.., Rutschmann, O.., Sanchez, O.., Jaffrelot, M.., Trinh-Duc, A.., Gall, C. le., Moustafa, F.., Principe, A.., Houten, A. V. van., Wolde, M. ten., Douma, R.., Hazelaar, Germa., Erkens, P.., Kralingen, K. V. van., Grootenboers, M.., Durian, M.., Cheung, Y. W.., Meyer, G.., Bounameaux, H.., Huisman, M.., Kamphuisen, P.., & Gal, G. Le. (2014). Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study.. JAMA , 311 11 , 1117-24 . http://doi.org/10.1001/jama.2014.2135
23) Riley, R.., Gilbert, Andrea R.., Dalton, Justin B.., Pai, Sheela S.., & Mcpherson, R.. (2016). Widely Used Types and Clinical Applications of D-Dimer Assay.. Laboratory medicine , 47 2 , 90-102 . http://doi.org/10.1093/labmed/lmw001
24) Townsend, L.., Fogarty, Helen., Dyer, A.., Martín-Loeches, I.., Bannan, C.., Nadarajan, P.., Bergin, C.., 'farrelly, Cliona O., Conlon, N.., Bourke, N.., Ward, Soracha E.., Byrne, M.., Ryan, K.., Connell, Niamh M O'., Sullivan, Jamie M O'., Cheallaigh, C. Ní., & Donnell, James S O'. (2021). Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. Journal of Thrombosis and Haemostasis , 19 , 1064 - 1070 . http://doi.org/10.1111/jth.15267
25) Tripodi, A.. (2011). D-dimer testing in laboratory practice.. Clinical chemistry , 57 9 , 1256-62. http://doi.org/10.1373/clinchem.2011.166249
26) Venkatesh, Arjun K.., Kline, Jeffrey A.., Courtney, D.., Camargo, Carlos A.., Plewa, Michael C.., Nordenholz, K.., Moore, Christopher L.., Richman, Peter B.., Smithline, Howard A.., Beam, D.., & Kabrhel, C.. (2012). Evaluation of pulmonary embolism in the emergency department and consistency with a national quality measure: quantifying the opportunity for improvement.. Archives of internal medicine , 172 13 , 1028-32 . http://doi.org/10.1001/archinternmed.2012.1804
27) Yu, Bilian., Li, Xin., Chen, Jin., Ouyang, M.., Zhang, Hong., Zhao, Xinge., Tang, L.., Luo, Qin., Xu, Mingjing., Yang, Lizhen., Huang, Guxiang., Liu, Xianling., & Tang, Jianjun. (2020). Evaluation of variation in D-dimer levels among

COVID-19 and bacterial pneumonia: a retrospective analysis. Journal of Thrombosis and Thrombolysis , 50 , 548 - 557 . http://doi.org/10.1007/s11239-020-02171-y

28) Zhang, Litao., Yan, Xinsheng., Fan, Q.., Liu, Haiyan., Liu, Xintian., Liu, Zejin., & Zhang, Zhenlu. (2020). D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of Thrombosis and Haemostasis , 18 , 1324 - 1329 . http://doi.org/10.1111/jth.14859