Seattle University
ScholarWorks @ SeattleU

Diagnostic Ultrasound Projects | College of Nursing

2024

Systematic Review of Diagnostic Accuracy and Clinical Impact of Ordering Compression Ultrasonography Exams Based on a Positive D-dimer Assay Test

Jacob Nakasone

Follow this and additional works at: https://scholarworks.seattleu.edu/dius-projects

Systematic Review of Diagnostic Accuracy and Clinical Impact of Ordering Compression Ultrasonography Exams Based on a Positive D-dimer Assay Test

Jacob Nakasone, Vascular Ultrasound Student at Seattle University, Seattle, WA, USA

Systematic Review of Diagnostic Accuracy and Clinical Impact of Ordering Compression Ultrasonography Exams Based on a Positive D-dimer Assay Test

Abstract

Purpose: The aim of this literature review was to examine the diagnostic accuracy and clinical impact of medical providers ordering compression ultrasonography (CUS) exams for the lower extremity venous systems based on a patient's positive D-dimer assay test.

Method: A systematic review of the current literature was conducted from September 2023-May 2024 using various search engines without language or date restrictions. From 30 sources inspected, articles were excluded from the research if they did not have statistics relating the positive or negative results of the D-dimer to the pretest clinical probability assessments and results of the following CUS exams. 20 sources met the inclusion criteria for this review.

Results: Across three of the studies with the biggest sample size, it was found that the percentage of patients who had a positive D-dimer and a positive diagnosis of PE, DVT, or VTE were below 25%. It was also found that D-dimer testing still faces ambiguity regarding age-adjusted threshold values, a lack of a universally standardized unit of measure, and differing levels of testing sensitivity and specificity across different commercial brands of D-dimer assays.

Conclusion: Throughout the research done thus far, there is still varying information regarding the effectiveness of D-dimers due to the wide variety of D-dimer assay types that are commercially available. The push for both the standardization of D-dimer threshold values as well as age-adjusted D-dimer threshold values will further optimize this test to reduce the rate of false positives. Most of the literature reflect an overlying theme that D-dimers are most useful in a setting where the test is administered alongside a clinical probability score to determine if a CUS is necessary to further evaluate for DVT, PE, and VTE. This method is most effective once

a medical institution has a firm idea of the threshold values of their D-dimer tests for different age groups.

Keywords: DVT, VTE, PE, D-dimer

Introduction: In the field of vascular ultrasound, one of the most common exams performed are compression ultrasonography (CUS) exams for the lower extremity venous system. This test is often done to evaluate for deep venous thrombosis (DVT), which is when a blood clot forms in one or more of the deep veins in the body.[15] This evaluation is important because without this diagnosis, the formation of these clots could become a life-threatening problem if they break off from the vessel walls and travel proximally to the heart and lungs causing blockages; these events are called a pulmonary embolism (PE) or venous thromboembolism (VTE).[15]

Four of the main indications of possible DVT are pain, leg swelling, heat, and redness in the lower extremities as a result of venous outflow obstruction and venous wall inflammation.[20] Patients may also develop DVT due to other existing medical conditions or factors, such as cancer, pregnancy, trauma, family history of clotting disorders, stasis, or current medications.[9] Due to the wide variety of factors that can contribute to DVT, physicians rely heavily on screening tools and assessments to determine whether further imaging, usually a CUS exam, is required to exclude DVT in a patient's care plan.

One of the most common assessments physicians use when screening for DVT prior to imaging is a clinical probability assessment along with a D-dimer blood assay. The clinical probability assessment screens a patient for the likelihood of DVT or a PE using a questionnaire and will rate the responses on a low-to-high clinical score to determine the likelihood their symptoms may be indicative of DVT, PE, or a VTE.[10,11] Two of the most common clinical score

assessments for PE and DVT are the Wells' score and the Geneva score, both of which are used alongside D-dimer assays in many hospital settings.[9]

The D-dimer assays are commonly used in clinical practice to exclude a diagnosis of DVT or PE.[9] They are also used to help guide patients with VTE when making the decision to continue or stop anticoagulation medicine when an initial treatment is complete.[9] However, literature on the topic of D-dimers reflect that the use of this test has varying results dependent on the method of capture, the instrumentation used, the testing threshold set, the type of assay used, and the patient's demographics.[3,9] Due to these factors, D-dimers can often result in false positives leading to unnecessary CUS exams being ordered. The results of these falsely ordered exams result in the overuse of CUS exams, leading to excessive cost and wasted noninvasive vascular lab time.[15] These factors which have been observed and documented in much of the ongoing D-dimer literature prompted this literature review.

Methods: A thorough research of a variety of studies surrounding D-dimers and their effectiveness was conducted. A variety of references from various databases spanning research from several countries were included in the research. Sources were found using the four keywords "DVT", "D-dimer", "PE", and "VTE". From 30 sources inspected, articles were excluded from the research if they did not have statistics relating the positive or negative results of the D-dimer to the pretest clinical probability assessments and results of the following CUS exams. 20 sources met the inclusion criteria for this review.

Results: The use of D-dimers and their ability to predict a positive DVT, PE, or VTE in a patient has often been criticized in literature, but the results of this test are much more complex than just a positive or negative result. The majority of the studies conducted and looked at in this review have many overarching themes in research, and only the most common findings will be presented.

Looking at various studies and their results, the three studies with the biggest sample size are compiled to make a greater generalization of the results of D-dimer effectiveness. Results are only drawn from a positive versus negative D-dimer result standpoint, and data related to the low, medium, and high risk pre-test probability assessments is excluded. Shane et al.[15] found in a study that of 292 patients that had a negative D-dimer, ten had a positive ultrasound (3%). In 178 patients who had a positive D-dimer, 113 had a negative ultrasound (38.6%) and 65 had a positive ultrasound (22.2%). In a study performed by Kearon et al.[8], they found that in 408 patients, 99 had a positive D-dimer (24%). From these, venography was performed in 84 of these patients and 19 had DVT (22.6%), while 58 were normal (69%) and seven were nondiagnostic.[8] In a study performed by Vermeer et al.,[18] they found that in a study of 266 patients, 196 had positive D-dimers. There was a positive diagnosis of VTE for 31/229 (13.5%) of patients with suspected PE and 8/45 (17.7%) with suspected DVT.

Another ongoing debate is the correct boundary to set between a positive or negative D-dimer result, which is often referred to as the threshold level. Each D-dimer manufacturer has a different threshold set for their assay. Most thresholds used for a positive test have traditionally been set low to maximize the sensitivity of a D-dimer test to limit the chance of missing a DVT or PE in patients.[9] However, this tradeoff comes at the cost of lowering specificity which in turn reduces the clinical effectiveness of the D-dimer as few patients will have a negative result,

meaning that the majority of patients will have a positive test.[9] Due to the differences in each D-dimer assay, it is highly recommended by various institutions to validate the D-dimer assay and determine the negative value that produces the greatest specificity while maintaining the greatest sensitivity possible before using this assessment tool.[9, 15, 18] The general guideline to safely exclude PE is to have an assay with a sensitivity and negative predictive value approaching 100%, but most assays tend to however around the 95% sensitivity level.[9]

Research of available literature has also shown that the age of a patient may also affect the number of false positive D-dimers. As patients age, their D-dimer levels will naturally increase, therefore the number of false positives increases.[9] A study by Righini et al.[13] found that with an age-adjusted D-dimer threshold and pretest clinical probability assessment, there were a larger number of patients in whom PE could be ruled out. They also found that in patients 75 years or older, the age-adjusted cutoff helped increase 5-fold the proportion of patients in which PE could be ruled out without further imaging due to a negative D-dimer result, further reducing the need for unnecessary imaging.[13] As proposed by Righini et al.[13] and Linkins et al.,[9] the general rule is that the D-dimer threshold for a patient above 50 years of age can be increased by multiplying their age in years by ten (e.g D-dimer threshold for a 70-year old patient should be 700 μg/L instead of the manufacturer's threshold of μg/L).

Analysis: From the three studies compiled earlier in the results, research shows that a D-dimer is not a perfect assessment. Across the three studies from Shane et al.,[15] Kratom et al.,[8] and Vermeer et al.,[18] the percentage of patients who had a positive D-dimer and a positive diagnosis of PE, DVT, or VTE were 22.2%, 22.6%, and 13.5%, respectively. This shows that even with a positive D-dimer, the chances of a patient being positive for DVT, PE, or VTE are still usually

less than 25%. While a D-dimer is a good assessment for the chances of these diagnoses, it cannot be fully sufficient on its own.

Across the majority of the literature reviewed, the most common theme is the suggestion that a combination of D-dimer testing alongside a clinical probability score provides the most effective method to determine if a CUS is necessary to further evaluate for DVT, PE, and VTE. Before implementing the use of a D-dimer assay, the institution should have a clear understanding of the threshold, sensitivity, and specificity in order to properly test patients and minimize false positives and negatives.[9, 18] This also includes finding an appropriate threshold that can be adjusted based on patient's age, as this can affect the result of a D-dimer dramatically.[9]

Another aspect of D-dimers that still limits the clinical effectiveness of D-dimer testing is its threshold values and lack of a standardized unit of measure. A study done in 2017 found that with a range of over 30 different commercially available D-dimer assays using 20 different monoclonal antibodies, the variance in testing sensitivity, specificity, and different testing units makes standardization much more difficult.[9] D-dimers use two different units: purified D-dimer units (DDUs) or fibrinogen equivalent units (FEUs). With these two different units, different laboratories report different D-dimer concentrations based on the units they use.[9] Without a universal calibrator, it becomes tough to have proper standardization of D-dimer concentrations across the various assay types.[9]

Regarding methods in place for D-dimer testing, one study conducted in Japan looked at the use of an algorithm to reduce unnecessary off hour CUS exams.[20] They found that with effective training, emergency department physicians could accurately classify patients into high, moderate, and low probability scores and use that in conjunction with a D-dimer assay to exclude

the diagnosis of DVT in patients with low probability scores.[20] If a patient was suspected to have DVT, a low molecular weight heparin could be given to them as they waited to have the CUS done the next routine working hours to avoid overworking the physician performing the ultrasound.[20] This study shows an effective method of reducing unnecessary workload on the sonographer, and this method can similarly be applied to many institutions to help avoid overworking sonographers.

Conclusion: Throughout the research done thus far, there is still varying information regarding the effectiveness of D-dimers due to the wide variety of D-dimer assay types that are commercially available. The push for both the standardization of D-dimer threshold values as well as age-adjusted D-dimer threshold values will further optimize this test to reduce the rate of false positives. By achieving this, institutions will be able to prevent overuse of CUS exams, thus reducing the loss of time, money, and resources for both the sonographer and the patient. Most of the literature reflect an overlying theme that D-dimers are most useful in a setting where the test is administered alongside a clinical probability score to determine if a CUS is necessary to further evaluate for DVT, PE, and VTE. This method is most effective once a medical institution has a firm idea of the threshold values of their D-dimer tests for different age groups.

References

1. Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for evaluating suspected venous thromboembolism. Thromb Haemost. 2007;97(2):195-201.
2. Brill-Edwards P, Lee A. D-dimer testing in the diagnosis of acute venous thromboembolism. Thromb Haemost. 1999;82(2):688-694.

3. Curtin N, Highe G, Harris M, Braunstein A, Demattia F, Coss L. Extensive evaluation of the instrumentation laboratory IL test D-Dimer immunoturbidimetric assay on the ACL 9000 determines the D-Dimer cutoff value for reliable exclusion of venous thromboembolism. Lab Hematol. 2004;10(2):88-94.
4. Elf JL, Strandberg K, Nilsson C, Svensson PJ. Clinical probability assessment and D-dimer determination in patients with suspected deep vein thrombosis, a prospective multicenter management study. Thromb Res. 2009;123(4):612-616. doi:10.1016/j.thromres.2008.04.007
5. Gaitini D. Multimodality imaging of the peripheral venous system. Int J Biomed Imaging. 2007;2007:54616. doi:10.1155/2007/54616
6. Ignatyev IM. Method of Preventive Ultrasound Diagnosis of Venous Thrombosis. Journal for Vascular Ultrasound. 2019;43(2):69-75. doi:10.1177/1544316719839536
7. Janssen MC, Wollersheim H, Verbruggen B, Nováková IR. Rapid D-dimer assays to exclude deep venous thrombosis and pulmonary embolism: current status and new developments. Semin Thromb Hemost. 1998;24(4):393-400. doi:10.1055/s-2007-996028
8. Kearon C, Ginsberg JS, Douketis J, Crowther MA, al e. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. Ann Intern Med. 2005/04/05/;142(7):490-6. http://login.proxy.seattleu.edu/login?url=https://www.proquest.com/scholarly-journals/randomized-trial-diagnostic-strategies-after/docview/222200905/se-2.
9. Linkins LA, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. Int J Lab Hematol. 2017;39 Suppl 1:98-103. doi:10.1111/ijlh.12665

10. Michiels JJ, Gadisseur A, Van Der Planken M, et al. A critical appraisal of non-invasive diagnosis and exclusion of deep vein thrombosis and pulmonary embolism in outpatients with suspected deep vein thrombosis or pulmonary embolism: how many tests do we need?. Int Angiol. 2005;24(1):27-39.
11. Michiels JJ, Gadisseur A, van der Planken M, et al. Different accuracies of rapid enzyme-linked immunosorbent, turbidimetric, and agglutination D-dimer assays for thrombosis exclusion: impact on diagnostic work-ups of outpatients with suspected deep vein thrombosis and pulmonary embolism. Semin Thromb Hemost. 2006;32(7):678-693. doi:10.1055/s-2006-951296
12. Michiels JJ, Gadisseur A, van der Planken M, et al. Screening for deep vein thrombosis and pulmonary embolism in outpatients with suspected DVT or PE by the sequential use of clinical score: a sensitive quantitative D-dimer test and noninvasive diagnostic tools. Semin Vasc Med. 2005;5(4):351-364. doi:10.1055/s-2005-922480
13. Righini M, Van Es J, Den Exter PL, et al. Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism: The ADJUST-PE Study. JAMA. 2014;311(11):1117–1124. doi:10.1001/jama.2014.2135
14. Schutgens RE, Haas FJ, Biesma DH. Reduced efficacy of clinical probability score and D-dimer assay in elderly subjects suspected of having deep vein thrombosis. Br J Haematol. 2005;129(5):653-657. doi:10.1111/j.1365-2141.2005.05515.x
15. Shane RA, Scott J. D-Dimer as a Screening Tool for Ultrasound Examination for Diagnosis of Deep Vein Thrombosis. Journal for Vascular Ultrasound. 2004;28(2):77-79. doi:10.1177/154431670402800203

16. Siragusa S, Anastasio R, Porta C, et al. Deferment of objective assessment of deep vein thrombosis and pulmonary embolism without increased risk of thrombosis: a practical approach based on the pretest clinical model, D-dimer testing, and the use of low-molecular-weight heparins. Arch Intern Med. 2004;164(22):2477-2482. doi:10.1001/archinte.164.22.2477
17. Tardy B, Tardy-Poncet B, Viallon A, et al. Evaluation of D-dimer ELISA test in elderly patients with suspected pulmonary embolism. Thromb Haemost. 1998;79(1):38-41.
18. Vermeer HJ, Ypma P, van Strijen MJ, et al. Exclusion of venous thromboembolism: evaluation of D-Dimer PLUS for the quantitative determination of D-dimer. Thromb Res. 2005;115(5):381-386. doi:10.1016/j.thromres.2004.09.005
19. Wells PS, Anderson DR, Ginsberg J. Assessment of deep vein thrombosis or pulmonary embolism by the combined use of clinical model and noninvasive diagnostic tests. Semin Thromb Hemost. 2000;26(6):643-656. doi:10.1055/s-2000-13219
20. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Prospective evaluation of a screening protocol to exclude deep vein thrombosis on the basis of a combination of quantitative D-dimer testing and pretest clinical probability score. J Am Coll Surg. 2005;201(5):701-709. doi:10.1016/j.jamcollsurg.2005.06.267