

D-dimer as a rule-out test for deep venous thrombosis: Gold standards and bias in negative predictive value

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Recent studies of D-dimer as a “rule-out” test for deep venous thrombosis (DVT) frequently have used duplex ultrasound rather than venography as the gold standard.

Because duplex ultrasound has limited ability to image the calf veins, there is potential for ultrasound studies to classify patients with calf DVT as non-diseased, causing bias in test index calculations.

False increases in sensitivity and negative predictive value are particularly likely with ultrasound because false negative calf DVT tests will be counted in error as true negative tests.

A review of six studies using lower-extremity venography in the gold standard, a test capable of imaging both calf and thigh veins, verified that sensitivity and negative predictive value were falsely increased by 3.0 and 3.8 %, respectively, when a thigh-vein-only gold standard

was compared to an overall (thigh and calf) vein gold standard.

To establish the role of D-dimer in DVT diagnosis, researchers must choose carefully the appropriate gold standard, one that is comprehensive enough to avoid underdiagnosis of thromboembolism.

Background

Venous thromboembolism is a disorder that most commonly has two manifestations, thrombosis in the deep veins of the leg (deep venous thrombosis (DVT)) and pulmonary embolism.

In most cases of venous thromboembolism, the thrombus first forms in the leg veins and later can leave the leg, move through the venous system to the lungs and lodge in the pulmonary arteries (pulmonary embolism).

For physicians, determining whether or not a DVT is present in patients with symptoms and signs of DVT is important since a subsequent pulmonary embolism may be fatal and proper treatment requires immediate anticoagulation. In the case of suspected DVT, some diagnostic tests are used to establish a diagnosis, or “rule-in” disease, while other tests are used to exclude a diagnosis, or “rule-out” disease.

The measurement of D-dimer, degradation products of circulating cross-linked fibrin formed during the activation of the coagulation system, is frequently used in clinical practice as a rule-out test for venous thromboembolism.

A good rule-out test is one that, if negative, makes the likelihood of the disease in question sufficiently low that a clinician may exclude it from consideration in the care of the patient.

In the usual approach to diagnostic-testing research, the results of the test being evaluated are compared to the results of a “gold standard” (or “reference standard”) test in an appropriate group of patients suspected of having the disease in question.

The data are then arranged in a two-by-two table (TABLE 1) that allows the indices of test efficacy to be calculated. For a rule-out test, the key issue is that the frequency of patients with DVT having a negative test (“false negative tests”) must be very low.

If this is so, the indices of interest for ruling out disease, sensitivity and negative predictive value (defined in TABLE 1) will be high.

Test	Gold standard test	
	Positive	Negative
Positive	TP	FP
Negative	FN	TN

TABLE 1: The two-by-two table for diagnostic testing research
 TP = true positive tests; FP = false positive tests; FN = false negative tests; TN = true negative tests; NPV = negative predictive value

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

$$\text{NPV} = \frac{\text{TN}}{\text{FN} + \text{TN}}$$

The gold standard test should be an accepted way of determining “the truth” regarding diagnosis. Typical examples of gold standard tests are biopsy results for cancer, coronary arteriography for coronary artery disease and hemoglobin electrophoresis for sickle cell disease.

In the past 25 years, more than 40 studies have been published comparing D-dimer levels with a gold standard for lower-extremity DVT [1, 2]. Until 1995, D-dimer studies usually selected lower-extremity venography as the gold standard for DVT diagnosis [1].

In more recent years, paralleling clinical practice, duplex ultrasonography has assumed a more prominent role as the gold standard. Since March 1995, duplex ultrasound alone was used as the gold standard in nine studies [3].

Despite the fact that clinicians now use duplex ultrasound as the test of choice for the evaluation of patients with suspected lower-extremity DVT [4], it has disadvantages as a gold standard for lower-extremity DVT research.

This is because duplex ultrasound, although it is very accurate in detecting thrombosis in thigh veins, has limited ability to image DVT in the smaller calf veins [5]. In clinical practice, this limitation has been circumvented by a strategy of repeating the ultrasound on subsequent days in order to detect extension of calf DVT to the thigh veins [4].

However, in D-dimer research, the use of a single ultrasound as the gold standard creates the potential for bias. This potential for bias is demonstrated in TABLE 2. A gold standard that images both thigh and calf DVT, such as venography, will enable all patients with

lower-extremity DVT to be properly counted as diseased (TABLE 2 A).

On the other hand, to the extent that a gold standard such as duplex ultrasound fails to fully image the calf veins, diseased patients are counted in the non-diseased category (TABLE 2 B).

This results in biased indices of test efficacy. For example, because the true sensitivity of a D-dimer test for thigh DVT is higher than the sensitivity for calf DVT, the measured sensitivity appears higher than it actually is.

Most importantly for a rule-out test, the negative predictive value appears to be higher than it actually is because false negative calf DVT tests are counted erroneously as true negatives in the calculation of negative predictive value (TABLE 2).

A. Results with gold standard that images both thigh and calf veins

D-dimer test	Deep venous thrombosis	
	Present	Absent
Positive	TP _{Thigh} + TP _{Calf}	FP
Negative	FN _{Thigh} + FN _{Calf}	TN

$$NPV_{\text{Thigh and calf}} = \frac{TN}{\text{All negative D-dimer tests}}$$

B. Results with gold standard that images thigh veins only

D-dimer test	Deep venous thrombosis	
	Thigh	Calf or Absent
Positive	TP _{Thigh} + TP _{Calf}	FP
Negative	FN _{Thigh} + FN _{Calf}	TN

$$NPV_{\text{Thigh}} = \frac{FN_{\text{Calf}} + TN}{\text{All negative D-dimer tests}}$$

TABLE 2: Effect of different gold standards on content of two-by-two table cells.

TP = true positive tests; FP = false positive tests; FN = false negative tests; TN = true negative tests; NPV = negative predictive value

Effect of the choice of gold standard on negative predictive value

The presence and magnitude of this bias have been demonstrated [3] and are summarized in TABLE 3. Six studies [6-11] were identified that utilized venography to verify the presence or absence of thigh and calf DVT in all subjects.

Four studies evaluated more than one D-dimer assay [7-9, 11]. In the six studies, the mean overall prevalence of DVT was 43 % while the thigh-only prevalence was 37 %.

As expected, when thigh DVT alone was used as the gold standard, sensitivity was 3.0 % greater than when overall (thigh and calf) DVT was used. Also as expected, when thigh DVT was used as the gold standard, negative predictive value was 3.8 % greater than when overall (thigh and calf) DVT was used.

In the six studies, overall negative predictive value averaged 93.8 % and was less than 95 % in three studies.

Reference	N	Assays	Prevalence (%)		Sensitivity (mean)		Specificity (mean)		Negative predictive value				
			Overall	Thigh	Overall	Thigh	Δ	Overall	Thigh	Δ			
Knecht [6]	113	1	52	46	98.3	100	1.7	44.4	41.0	-3.4	96.0	100	4.0
Legnani [7]	81	7	52	46	95.5	97.3	1.8	60.4	55.5	-4.9	92.3	95.9	3.6
Legnani [8]	99	3	39	34	97.4	99.0	1.6	75.4	70.5	-4.9	97.8	99.1	1.3
Lindahl [9]	155	2	39	30	92.5	96.8	4.3	54.2	50.5	-3.7	92.2	97.4	5.2
Wells [10]	214	1	25	20	88.7	93.0	4.3	77.0	74.3	-2.7	95.4	97.7	2.3
Van der Graaf [11]	99	12	51	44	90.4	94.7	4.3	62.0	59.5	-2.5	89.2	95.3	6.1
Mean			43	37			3.0			-3.7			3.8

TABLE 3: Overall and thigh test indices

Discussion

D-dimer is an easily performed blood test that has advantages over other diagnostic tests for lower-extremity DVT. The alternatives, venography and ultrasonography, are radiologic imaging tests that require the availability of someone with the skills to perform and interpret the tests.

In addition, venography carries the risks of radiologic contrast (allergic reactions and renal damage) and also of causing a DVT. Because D-dimer assays are positive in a variety of common conditions including some with signs and symptoms of DVT (e.g. surgery on hip or knee, trauma, cellulitis or malignancy), they are not

appropriate for use as rule-in tests where a low false positive rate is needed.

On the other hand, while studies of D-dimer as a rule-out test have shown promise, care must be taken in interpreting results of the studies that have used ultrasound as the gold standard.

To the extent that ultrasound misses isolated calf DVT, the important test index of negative predictive value will appear to be higher than its true value. The potential magnitude of this bias is large enough to be of clinical significance.

It is possible in ultrasound studies that the actual magnitude of this bias is less than reported here, since ultrasonographers often extend their evaluation to the trifurcation of the popliteal vein, or even more distal, and report the presence of calf DVT when found.

In evaluating D-dimer studies using ultrasound as the gold standard, careful reading of the ultrasound methods will provide the necessary information to determine how well the calf veins have been evaluated.

It is also possible that the true differences are even larger than shown here. Venous thromboembolism frequently is not limited to the deep veins of the legs. Silent pulmonary embolism occurs in 40-50 % of patients with thigh DVT [12].

It is thus possible that there are additional patients with undetected pulmonary emboli counted in the non-diseased column along with the patients with undetected calf DVT.

Venous thromboembolism diagnostic-testing research presents particular challenges because the best gold standards, venography of the legs and pulmonary angiography, are invasive, expensive and potentially risky.

In addition, unlike radiologic imaging tests, the D-dimer test has the important advantage of potentially being used to rule out venous thromboembolism in all locations including calf, thigh, pelvis, upper extremity and lungs.

However, to establish this role for D-dimer, researchers must choose carefully the appropriate gold standard, one that is comprehensive and not prone to underdiagnosis. This would be one that includes complete testing for both DVT (e.g. venography) and pulmonary embolism (e.g. spiral computed tomography or pulmonary arteriography) [2].

Because of cost and risk, studies of this design are difficult to carry out. An alternative approach is the use of management studies, where patients are evaluated using diagnostic algorithms with outcome assessment to determine safety and cost-effectiveness.

Most management trials have combined a probability assessment of DVT with D-dimer results, with the results determining whether further testing would be performed [13, 14].

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