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Appropriate Use of Venous Imaging and Analysis of the D-Dimer/ Clinical Probability Testing Paradigm in the Diagnosis and Location of Deep Venous Thrombosis

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Abstract

Background—The D-dimer (DD) level combined with the pretest Wells criteria probability (WCP) score can safely exclude deep venous thrombosis (DVT). The objective of this study was to examine the correlation between DD results alongside WCP score with findings on venous duplex ultrasound (VDU). The hypothesis is that VDU remains overutilized in low-risk patients with negative DD and that higher DD levels may correlate with thrombus burden and location.

Methods—Patients who presented to a high-volume tertiary care center with lower limb swelling with or without associated pain were retrospectively examined through June and July for 4 consecutive years (2012 to 2015). After calculating WCP, patients were divided into low-, moderate-, and high-risk categories. Electronic DD results utilizing enzyme linked immunosorbent assay, WCP data, and VDU analysis data were merged and analyzed based on receiver operator characteristic curve to determine the DD cutoff point for each WCP. Abnormal DD with an average value 0.6 mg/L fibrinogen equivalent units (FEUs) was correlated to positive DVT to differentiate proximal DVT (above popliteal vein) from distal DVT (below popliteal vein).

Results—Data of 1,909 patients were analyzed, and 239 (12.5%) patients were excluded secondary to serial repeat visits or follow-ups, surveillance screens, and if they had a previous history of DVT. The average age was 62.1 ± 16.3 years with more women (55.7%) and the majority presented with limb pain and edema (87%). DD studies were ordered and completed in 202 patients and correlated with all positive and negative DVT patients (100% sensitivity and negative predictive value, with specificity and positive predictive value of 14.9% and 15.9%, respectively). Twenty-six of 202 patients had DD that were in the normal range 0.1–0.59 mg/L (FEU), all of which were negative for DVT (100% sensitive). Fifty one of 202 patients had DD values of 0.6–1.2 mg/L FEU, of which only 3 DVTs were recorded, and all of them were distal

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DVTs. In addition, 685 patients with WCP <1 and negative DD were sent for VDU. Thus, 762 patients had an unnecessary immediate VDU (Wells = 1 and -DD) study during their initial presentation. Potential charge savings for VDU for all patients are $762 \times \$1,557 = \$1,186,434$ and DD for all patients are $762 \times \$182 = \$138,684$, with total potential savings of \$1,047,750 (USD 2016).

Conclusions—This study suggests that DD is still underutilized, and DD in conjunction with WCP could significantly reduce the number of unnecessary immediate VDUs. Higher value of DD (>1.2 mg/L FEU) may raise concern for proximal DVT. Concern on cost-effectiveness exists and raises the demand for a proposed algorithm to be followed.

INTRODUCTION

D-dimer (DD) is one of the fibrin degradation products^{1,2} produced during activation of both the coagulation system and the fibrinolysis cascade. DD serves clinically as a sensitive marker of acute thrombotic events and may also be elevated in acute aortic syndromes due to the hematologic changes related to blood shear stress.³⁻⁵ A positive DD result may indicate that there is a significant blood clot (thrombus) formation and breakdown in the body, but the test is not specific for location, etiology, or underlying pathology. Although there are numerous conditions associated with elevated DD including pregnancy, recent surgery, and cancer, this procoagulant end degradation product may guide clinicians in diagnosing patients with venous thromboembolism (VTE), hypercoagulable or pro-thrombotic conditions, and arterial dissection.⁵

Multiple studies have reported DD as a sensitive and accurate assay to correlate, not only with the presence but also with the volume of thrombus.⁶ With current advances in biochemical assays and the widespread implementation of enzyme-linked immunosorbent assay (ELISA), the use of DD can approach a negative predictive value of >95%, which can safely allow exclusion of VTE in selected patients.⁷⁻¹² With our in-hospital Siemens Innovance® DD assay, the average turnaround time is 20–30 min. In 2004, an extensive meta-analysis¹³ reported a comparative ranking among contemporary DD assays for sensitivity and negative likelihood ratio to venous duplex ultrasound (VDU). They found that a negative result on quantitative rapid DD ELISA is as diagnostically useful as VDU.

Although DD has been clinically utilized in the workup for lower extremity swelling, VDU has been the primary noninvasive test to rule out the possibility of deep venous thrombosis (DVT).¹⁴⁻¹⁶ The sensitivity and specificity of VDU, relative to contrast venography, is estimated to be 86–99%, which has been reported in many studies, including a double-blinded prospective randomized trial.^{17,18} Reports have indicated that the weighted mean sensitivity and specificity of VDU in making a diagnosis of proximal DVT has been estimated to be 97% and 94%, respectively. Recent treatment algorithms, such as the one presented by Streiff et al.,¹⁹ suggest treatment for DVT following a positive VDU. Likewise, they also suggest no treatment if the whole-leg VDU is negative. If a proximal VDU was conducted for patients with moderate or high clinical probability, then they suggest a repeat VDU 1 week after testing. With the high specificity of VDU, some clinicians treat DVT

without any additional testing; however, at the same time, owing to this high sensitivity, some clinicians will withhold treatment if the test is negative.¹⁶

Despite the current evidence-based research findings, many clinicians still precede directly to VDU when a diagnosis of VTE is suggested irrespective of pretest likelihood of disease or DD results. The resultant overutilization of VDU seemingly would be associated with dramatic increases in health-care cost and resource utilization. This added cost creates additional strain on a health-care system that is experiencing unprecedented contraction in reimbursement.

To enhance the appropriate use of DVT testing, other researchers have combined DD with the Wells criteria (see Table I).¹¹ The resultant algorithm utilizing the combination of low Wells criteria probability (WCP) and negative DD has become the current standard for ruling out DVT. The main objective of the present study was to measure the overall appropriateness of VDU testing performed for patients with acute index lower limb pain or swelling and clinical suspicion of DVT in a high-volume tertiary care center. More specifically, it was to measure and assess DD values and apply the WCP to determine the clinical probability of DVT for patients sent for VDU. The secondary objectives include the investigation of (1) the correlation between elevated DD levels and DVT location and (2) age-adjusted DD thresholds to rule out DVT. Thus, the present study was an attempt to examine the effectiveness of proposed DD and WCP models in approaching diagnosis and to determine the location and severity of a possible DVT in a high-volume hospital.

METHODS

The present study was a retrospective review of 1,909 consecutive patients referred for VDU with suspected DVT presenting to a multicenter with high-volume emergency departments (EDs). Owing to the large number of VDU cases and to feasibly perform the electronic chart review, data collection, and analysis over 4 consecutive years from 2012 to 2015, the time period was limited to June and July of each year. This was a retrospective investigation of the clinical assessment made during the initial presentation to determine the appropriateness of the VDU. Clinical probability groups were created based on both Wells criteria and DD. First, trained researchers retrospectively collected the necessary data elements from electronic health records to calculate the Wells score. Any mention of leg swelling was coded as 1. If calf swelling was mentioned whether or not an actual measurement was recorded, it was also coded as 1 (see Table I). The Wells score was not calculated during the data collection process, but later, during the analysis phase, it was electronically calculated by the statistical software package. The Wells score was used to categorized patients into low (<1), moderate (1–2), and high (≥ 3) clinical probability groups (WCP). Likewise, DD values were used to categorize patients into low (0.1–0.59), moderate (0.60–1.2), and high (> 1.3 mg/L FEU) D-dimer clinical probability groups (DCP). In addition, we compared the differences between using our current abnormal DD threshold 0.60 mg/L with an age-adjusted threshold proposed by other researchers (age-adjusted DD cutoff, defined as age × 10 for patients 50 years or older).^{20,21} The formula had to be modified to age × 0.01 for equivalence in mg/L FEU.

VDU examinations were conducted by registered technicians in a vascular laboratory accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories. The VDU studies were completed using 7-MHz or 10-MHz probes on either Acuson 128xp/10v or Acuson Aspen (Acuson Corporation, Mountain View, CA). Both legs were scanned from the iliac vein to the posterior tibial and peroneal veins, whenever possible. DVT was defined as the visualization of thrombus and/or lack of complete compressibility of the vein. Positive DVT was further differentiated into either proximal (above popliteal vein) or distal DVT (below popliteal vein). Thrombus involving popliteal and/or more proximal veins was classified as proximal DVT. Of the 1,909 patients reviewed for this study, 239 patients (12.5%) were excluded because of serial repeat visits, surveillance screens, or visiting the clinic with a previous history of DVT or pulmonary embolism (PE).

Siemens Innovance[®] DD (Siemens Medical Solutions Diagnostics, Deerfield) for the quantitative determination of cross-linked fibrin degradation products in human plasma was used to provide DD values and thresholds. DD values above 0.60 mg/L fibrinogen equivalent units (FEUs) were considered abnormal according to the current laboratory standards.

The study protocol was approved by our local governing institutional review board, and informed consent was waived for this retrospective review. The study was conducted in accordance with the Health Insurance Portability and Accountability Act requirements and the prevailing ethical principles governing research.

Statistical Analysis

All analyses were performed using SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, version 19.0, IBM Corp, Armonk, NY). Descriptive statistics are expressed in terms of frequencies, percentages, or means \pm one standard deviation. Categorical variables were tested by chi-squared or Fisher's exact tests and continuous variables were tested by Student's *t* test or Mann-Whitney *U* test when deemed appropriate. A "*P*" value of 0.05 or less was considered significant. A receiver operator characteristic curve was used to analyze the ability of DD values to detect DVT. Area under the curve (AUC) was used to measure the performance of the receiver operator characteristic curve analysis. Sensitivity, specificity, and positive and negative predictive values were all used to compare the differences between using our current abnormal DD threshold 0.60 mg/L and an age-adjusted threshold.

RESULTS

The medical records of 1,909 ED patients who presented during the months of June to July from 2012 to 2015 were reviewed. After excluding 239 patients (12.5%) who were seen for other vascular nondiagnostic follow-up, screened for surveillance, or had a previous history of DVT or PE, 1,670 patients were analyzed. The average age was 62.1 ± 16.3 years with more women (931, 55.7%) and the majority reported limb pain and edema.

WCP was calculated for all 1,670 patients, which was then used to divide patients into low-, moderate-, and high-risk groups for DVT. Based on WCP alone, the DVT rate was lower in the low WCP group ($56/839 = 6.7\%$) and significantly higher in the moderate- ($105/752 = 14.0\%$) and high-risk groups ($23/79 = 29.1\%$; $P < 0.001$; see Table II).

Overall, 202 DD tests were performed with a median value of 1.7 mg/L FEU (25th percentile: 0.86 mg/L FEU, 75th percentile: 4.3 mg/L FEU). Based on our laboratory abnormal threshold (0.60 mg/L FEU), the DD identified all patients positive for DVT with 100% sensitivity and negative predictive values, with specificity and positive predictive value of 14.9% and 15.9%, respectively). The AUC to determine the overall accuracy for DD alone to predict DVT was 0.71, 95% confidence interval (CI) 0.63–0.80 (see Fig. 1). Of all DD values in the range of 0.1–0.59 mg/L FEU (low DCP; $n = 26$), there were no recorded DVTs as expected; however, the DVT rate was significantly increased in the moderate (0.6–1.2 mg/L FEU) and high (1.3 mg/L FEU) ranges. For moderate DCP, the DVT rate was 5.9% (3/51), while it was 20.0% (25/125) for high DCP, $P = 0.007$ (see Table III). All DVTs for patients in the moderate DCP range were noted as distal DVT, while there were 18 (18/125 = 14.4%) proximal and 7 (7/125 = 5.6%) distal DVTs for patients in the high DCP range. Thus, overall, the DVT rate was 20% (25/125) for patients with high DCP (i.e., 1.3 mg/L FEU).

There was an increase in the DVT rate across all levels of WCP as DCP elevated. Within low WCP, the DVT rate increased from 0.0, 9.7 to 18.8% across low, moderate, and high DCP, respectively. Likewise the same pattern occurred for moderate and high WCP, (0.0, 0.0 to 18.0% and 0.0, 0.0 to 50.0%), respectively. The overall DVT rate for the entire cohort was 11.0% ($n = 183/1,670$) (see Table IV).

We also compared DD cutoff points based on our current laboratory standard of 0.6 mg/L FEU against an age-adjusted threshold ($\text{age} \times 0.01$). Overall, 11 patients were safely excluded (No DVTs) from immediate VDU. For both cut points, the sensitivity and negative predictive values remained 100%, while using the age-adjusted threshold increased the specificity from 14.9% to 21.3% (See Table V).

There were 685 patients with $\text{WCP} < 1$ ($724 - 39 = 685$) without DD testing sent for VDU. This number added to the 51 and 26 with moderate and low DD values, respectively, resulted in a total of 762 patients sent for unnecessary immediate VDU study. Potential charge savings for VDU for all patients are $762 \times \$1,557 = \$1,186,434$ and DD for all patients are $762 \times \$182 = \$138,684$, with total potential savings of \$1,047,750, based on the US 2016 dollar estimates (see Table IV and Fig. 2).

DISCUSSION

Contrast venography used to be considered the gold standard for establishing the diagnosis of deep vein thrombosis. It is invasive and not necessarily without a small risk of an allergic reaction or venous thrombosis. Ultrasound, perhaps the best noninvasive diagnostic method, has been evaluated against venography in many studies, showing an average sensitivity and specificity of 97% for proximal deep vein thrombosis.²² VDU is used to evaluate patients in a similar manner as to that of conventional compression ultrasound. Yet, blood flow characteristics can be evaluated using the pulsed Doppler signal. Normally, blood flow is spontaneous and phasic with respiration. The flow can be augmented by manual compression distal to the ultrasound transducer. If the phasic pattern is absent, then the flow can be defined as continuous and would indicate the presence of venous outflow obstruction.

Duplex ultrasound is thought to be a mandatory and complementary assessment in a physical examination for patients presenting with suspected chronic venous disease. Most authorities agree and current guidelines strongly recommend using VDU as the primary diagnostic test for superficial venous insufficiency, suspected abdominal or pelvic venous pathology, and post-thrombotic syndrome. In addition, VDU is also recommended for the clinical suspicion of other forms of iliac or inferior vena cava obstruction.²³ Normally, an examination of deep veins is thought to be more challenging than for superficial veins. However, VDU may provide very useful information during all stages in the management of chronic venous conditions such as post-thrombotic syndrome.²³

Strong empiric evidence has confirmed that DVT can be ruled out in patients with low WCP and a negative DD. Accordingly, VDU can be safely omitted in those patients.^{11,24,25} In a recent meta-analysis of 10,002 patients, researchers found that patients with a low Wells score (≤ 1) and negative DD had an extremely low probability (1.2%, 95% CI, 0.7–1.8%) of DVT. There were a couple of exceptions to this finding. Patients with cancer had a 2-fold increase in the probability of DVT, and the authors suggested adding an extra point to the Wells score for patients with suspected recurrent events.²⁶ In light of these and other findings, Streiff et al. issued the following guidance statement “We suggest the use of validated pretest probability models in conjunction with DD testing and selective use of objective diagnostic imaging to increase the cost-efficiency and accuracy of VTE diagnosis.” The authors also provided a patient flowchart that depicted the combination of negative DD and low or moderate Wells score as sufficient to rule out DVT.¹⁹ With current constraints of health resources, better utilization of DD as an integral part of diagnostic workup for VTE is imperative. This study aimed to take our utilization of DD one step further by applying age-adjustment thresholds, while directing attention toward the correlation between different levels of DD and location of DVT (i.e., proximal versus distal).

There are 2 main assays for performing DD; namely latex agglutination DD assay and ELISA that is more sensitive. Our laboratory changed from latex agglutination to ELISA long before this present study was conducted. There is little doubt that using a combination of WCP and DD, along with establishing new thresholds or cut points for DD levels by receiver operator characteristic curve analysis, WCP, or age adjustment, can help compensate for the low specificity of DD alone. Therefore, most authorities would agree that there is room for improvement in the current algorithm to diagnose DVT, and perhaps, it will be enhanced even more in the future.

Some researchers have reported on the importance of age-adjusted different levels of DD to magnitude of VTE. One report implemented an algorithm for patients with VTE with different levels of DD from 300 patients with computed tomography pulmonary angiogram (CTPA) scans over 2 years. A higher DD and an age-adjusted DD cutoff were then retrospectively applied to that algorithm. Of the low- and moderate-risk patients who underwent DD testing, the retrospective application of 0.5 mg/L FEU DD cutoff resulted in further 12.1% (95% CI 8.0–17.1%) of patients being excluded from undergoing a CTPA. When combined with an age-adjusted DD cutoff, 27.9% (60/215 95% CIs 22.0–34.3%) were excluded from undergoing a CTPA. The authors concluded that implemented algorithm had maintained risk stratification for PE prevalence and raised the DD threshold by applying

age-adjusted DD cutoffs, which might improve the efficiency of the clinical prediction algorithm in patients aged 50 years and over.²⁷ In addition, using the age-adjusted DD may help to eliminate unneeded CTPA in emergency room for elderly patients with elevated DD.²⁸ Our results were similar. We found that 11 VDUs could have safely been excluded, if an age-adjusted threshold was used. The specificity of DD was increased without any additional DVTs.

The results of our present study also suggest that higher levels of DD (> 1.3 mg/L FEU) were correlated with proximal DVT. First, DD was completed in 202 patients and identified all patients positive for DVT (100% sensitivity and negative predictive value). In 26 of 202 patients, DD values were in the normal range 0.1–0.59 mg/L FEU, all of which were negative for DVT (100% sensitivity); 51 of 202 patients had DD values of 0.6–1.2 mg/L FEU that were in the moderate range with only 3 DVTs recorded and all of which were distal. Other researchers reported that higher level of DD may correlate with the extent of DVT. Jiang et al. reported²⁹ on 339 patients who had completed the analysis. Among them, DVT was confirmed in 28 (8.26%) patients based on ultrasound findings. Multivariate logistic analysis revealed that body mass index was an independent risk factor for developing DVT ($P=0.018$), and DD levels on postoperative days 1 and 7 were independently correlated with the development of DVT ($P=0.019$ and $P<0.001$, respectively). The receiver operating characteristic curve analysis determined that the AUC was largest (0.752) for DD level on postoperative day 7 as diagnostic index. Using a cutoff value of 6.17 $\mu\text{g/mL}$, sensitivity and specificity were reported as 71.4% and 81.7%, respectively. The elevated DD levels followed the same tendency toward a double-peaked distribution with peaks at days 1 and 7 postoperatively. In that study, DD level was a useful screening test to exclude DVT, and the cutoff values of DD determined in this study provide a reference for the absence of DVT to a certain extent.

Cost-effectiveness was an interesting outcome for our study. Potential charge savings were calculated for VDU for all patients ($762 \times \$1,557 = \$1,186,434$)—potential charge savings for DD for all patients are $762 \times \$182 = \$138,684$, with total potential savings of \$1,047,750, based on the US 2016 dollar estimates, which would avoid unnecessary VDU costs to both patients and the hospital. This did not include all other costs of vascular laboratory technicians who are called after hours to perform the duplex study.

Our study reaffirms, supports, and agrees with others^{30,31} that the best cost-effective strategy is to combine the Wells criteria (i.e., pretest clinical probability; WCP) with DD to rule out patients at low risk for VTE. Crippa et al. performed a cost-effective analysis and indicated that a diagnostic algorithm utilizing DD and VDU selectively would result in a cost saving of up to 55% in patients with low WCP.³² Hull et al.³³ performed a cost-effectiveness analysis on 516 patients with clinically suspected DVT. Unfortunately, this study focused only on clinical diagnosis, venogram, and the combination of impedance plethysmography and leg scanning. This analysis indicated that a clinical diagnosis is cost ineffective and venogram is cost-effective, especially when applied as an outpatient investigation, and impedance plethysmography plus leg scanning is a practical, less invasive alternative to outpatient venography. An inpatient diagnosis is likely to remain the major cost; thus, emphasis for patients with DVT should be placed on outpatient diagnostic procedures.

The present study has many limitations, first and foremost is its retrospective design. We did not assign but rather selected patients based on the hospital services that they received. The number of cases from a high-volume tertiary care center was exceedingly high and accordingly we limited our data collection. The decision to limit data collection to 2 months for each of the 4 years may have resulted in selection bias. We began with a group of patients who were screened for DVT by VDU and worked backwards to determine if the referral for a VDU was appropriate. From our data, we do not have patients for which the Wells criteria and DD might have been used appropriately and not referred to VDU. We were more interested in trying to determine the appropriateness of the ones who were sent for VDU. We had no control over which patients received which test. We also applied the Wells criteria in a retrospective way. That is, in most cases, the Wells criteria score was not calculated at the time of the visit but later during the data collection process. The Wells criteria was not recorded in our electronic medical records and that information, if existed, may or may not have been used in physicians' decision-making processes. Somewhat expectedly, we found no DVT in the low WCP groups; however, other studies have reported a small percentage of DVT in this group.^{24–27} It is possible that DD was used to rule in instead of rule out DVT. It was not abundantly clear why the DD and VDU were ordered for these low clinical probability patients. However, it is possible that clinical suspicion existed beyond the data elements that we collected from the electronic health records. For example, the VDUs may have been conducted to obtain a broad understanding of the general status of a patient's venous, superficial, or deep venous system as a baseline evaluation.

It is our belief that our results will improve the appropriate use of VDU in our hospital in the future. This belief is based on the results of a study that demonstrated that having the referral dependent on the use of DD and Wells criteria irrespective of values decreased VDUs.³⁴

The authors found that the rate of VDUs based on total in-patient admissions was significantly reduced after implementation of the new referral request (0.84–0.63%, $P=0.009$). The following are our future perspectives: with the current understanding and demand to generate a cost-effective practice, we are collecting more data to improve the validity of current findings and we also plan to share our results with the ED staff to see if a more formal protocol (please refer to our suggested algorithm, Fig. 3) can be established and to monitor the appropriateness of VDU referrals, while assessing the progress and effectiveness of the change.

CONCLUSIONS

This study suggests that DD is still underutilized and along with WCP can reduce the significant number of unneeded VDUs. Higher values of DD (>1.2 mg/L FEU) may raise a concern for proximal DVT. Concern on cost-effectiveness exists and raises the demand for a proposed algorithm to be followed.

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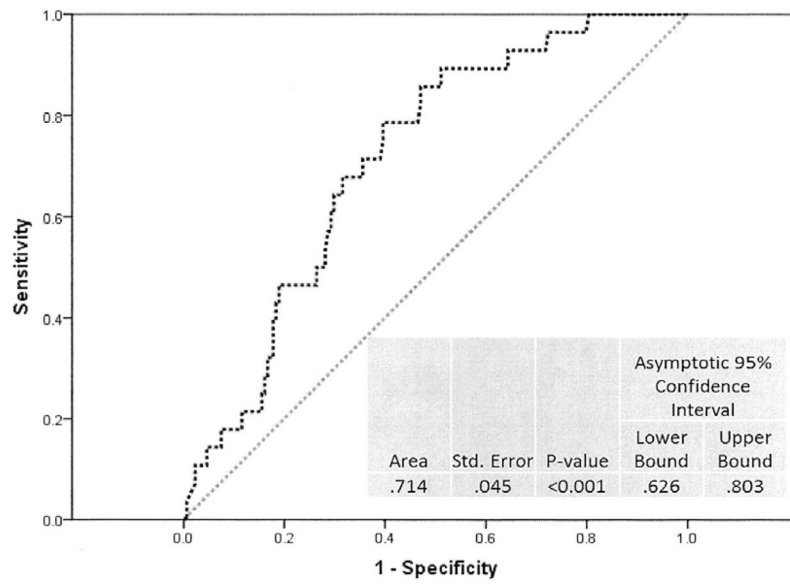


Fig. 1. Area under the curve (AUC) results using receiver operating curve (ROC) analysis to predict DVT based on D-dimer values.

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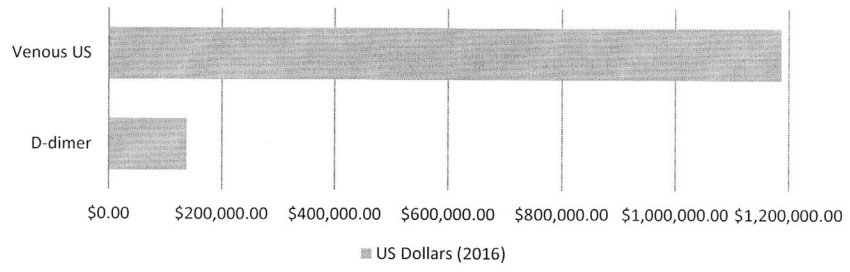


Fig. 2.
Cost of D-dimer and venous ultrasound testing for 762 patients.

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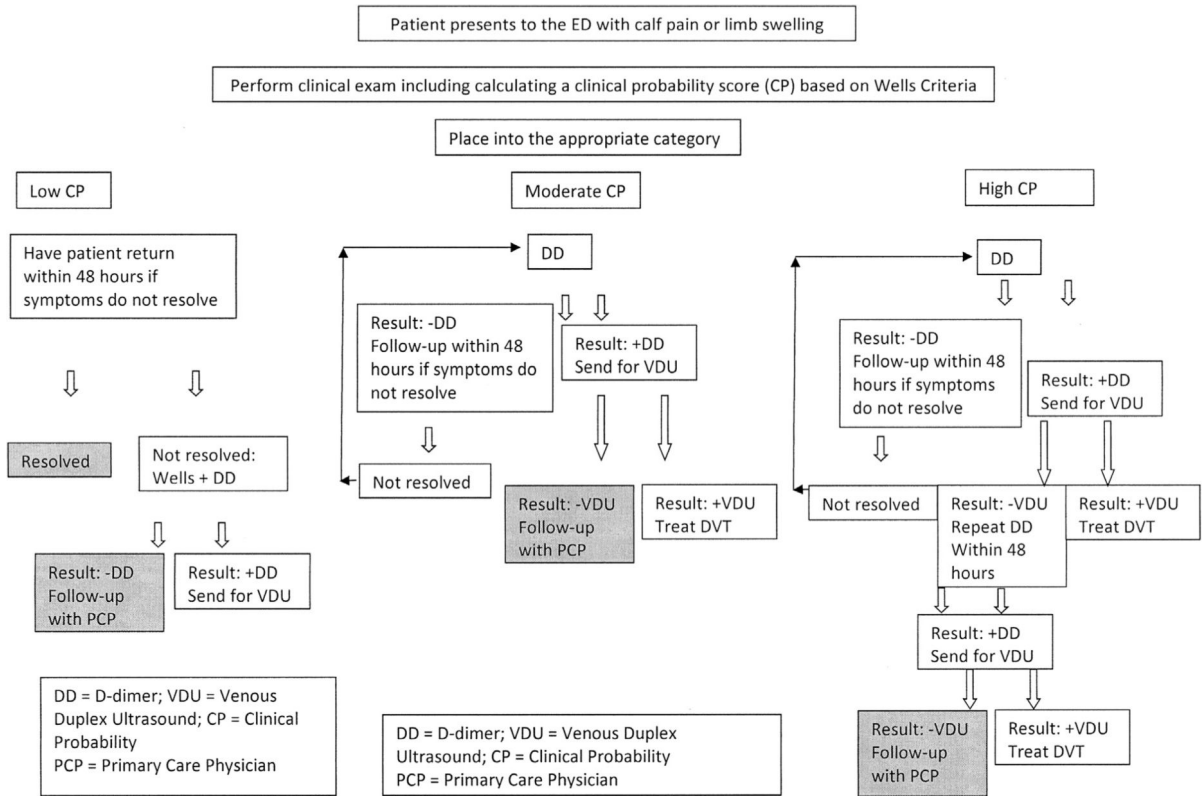


Fig. 3.
Proposed VTE screening algorithm for our center.

Table I

Wells criteria

Criteria	Points
Active cancer	1
Paralysis or recent plaster immobilization of lower extremities	1
Recently bedridden	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling more than 3 cm compared with asymptomatic leg	1
Pitting edema (greater than asymptomatic leg)	1
Previous DVT documented	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of DVT	-2

Low risk = Wells score <1; moderate risk = Wells score 1–2; high risk = Wells score 3.

Table II

Wells clinical probability category table

Categories	Total	DVT	D-dimer
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Low	839 (50.2)	55 (6.6)	115 (13.7)
Moderate	752 (45.0)	105 (14.0)	79 (10.5)
High	79 (4.7)	23 (29.1)	8 (10.1)
<i>P</i> value		<0.001	0.127
Total	1,670	183	202

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Table III

D-dimer value and location table

D-dimer categories	DVT location				Total
	No DVT		Any DVT		
	n (%)	n (%)	n (%)	n (%)	
0.1–0.59 (mg/L)	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	26
0.60–1.2 (mg/L)	48 (94.1)	0 (0.0)	3 (5.9)	3 (5.9)	51
1.3 (mg/L)	100 (80.0)	18 (14.4)	7 (5.6)	25 (20.0)	125
Total	174 (86.1)	18 (8.9)	10 (5.0)	28 (13.9)	202

P = 0.007.

Table IV

DVT rate by D-dimer level by Wells criteria

D-dimer level	Wells <1		Wells 1-2		Wells 3			
	Total	DVT	Total	DVT	Total	DVT		
No D-dimer (mg/L FEU), n (%)	724 ^a	39 ^a (5.4)	673	96 (14.3)	71	20 (28.2)	1,468	155 (10.6)
0.1-0.59, n (%)	15	0 (0)	11	0 (0)	0	0 (0)	26 ^a	0 (0)
0.60-1.2, n (%)	31	3 (9.7)	18	0 (0)	2	0 (0)	51 ^a	3 (5.9)
1.3, n (%)	69	13 (18.8)	50	9 (18.0)	6	3 (50.0)	125	25 (20.0)
Total, n (%)	115	16 (23.2)	79	9 (13.0)	8	3 (4.3)	202	28 (22.4)
Grand total, n (%)	839	55 (6.6)	752	105 (14.0)	79	23 (29.1)	1,670	183 (11.0)

^a(724-39] = 685 + 51 + 26) identifies patients with low Wells score without D-dimer or with low or moderate D-dimer levels that would not require immediate VDU.

Table V

Sensitivity and specificity of D-dimer cutoff levels

Cutoff point	TP	FP	TN	FN	Sen	Spec	PPV	NPV
Laboratory set 0.59	28	148	26	0	100.0	14.9	15.9	100.0
Age adjusted	28	137	37	0	100.0	21.3	17.0	100.0

Lab set 0.59 = values 0.6 mg/L fibrinogen equivalent units (FEUs) were considered abnormal.

Age adjusted = for patients above 50 years old, values greater than age \times 0.01 were considered abnormal.

TP, true positive; FP, false positive; TN, true negative; FN, false negative; Sen, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.