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Comparison of Wells Score, D–Dimer and Combination of Wells Score and D–Dimer with Venous Duplex Ultrasonography in Diagnosis of Acute Deep Vein Thrombosis in Lower Extremity

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Abstract

Introduction. Diagnosis of acute deep vein thrombosis (DVT) of lower extremity using available diagnostic tools such as venous duplex ultrasonography (VDUS) encountered problems including cost, time consuming and the operator. A simple and practical tool is required. Thus, we run a study aimed to evaluate the efficacy of Wells score, D–Dimer, or combination of both, compared to VDUS in early detection of acute DVT of lower extremity.

Method. A diagnostic study was run using cross-sectional design in Department of Surgery enrolling all adult subjects of which suspected to acute DVT of lower extremity managed in period of January 2014–December 2015 who met the criteria. The diagnosis was confirmed by VDUS. Those data of medical record were analyzed statistically with diagnostic study to find out the sensitivity and specificity.

Results. The study enrolled of 85 subjects. The prevalence of acute DVT of lower extremity was 65.88%. Sensitivity and the highest negative predictive value of 100.00% were found in score combination of II and IV. While as the highest specificity of 89.66% and the highest positive predictive value of 92.68% were found in score combination of III. The score with balanced diagnostic value (sensitivity of 87.50% and specificity of 72.41%) was found in Wells score 3 level I.

Conclusion. Wells score and VDUS showed comparable efficacy in detection of acute DVT of lower extremity. Thus, a score could be used as a diagnostic tool.

Keywords: *acute DVT of lower extremity, Wells score, D–Dimer, venous duplex ultrasonography*

Introduction

Acute DVT of lower extremity remains a problem both of short term mortality and long term morbidity.¹ Around 60% of DVT represent no manifestation at all and about 50–80% of asymptomatic DVT followed by lung emboli with a death risk of 10–20%. A long term complication known as post thrombotic syndrome (PTS) found in 29–79% cases, referred to the predictor of a poor quality of life.^{2,3} The risk of venous thromboembolism (VTE) in relation to DVT increased up to 150 times in surgical wards and those with acute illness. This medical issue referred to be a serious threat to the problem of patient safety.⁴ Early diagnosis of acute DVT indeed encountered a problem, among others is the early stage represent subclinical symptoms, inaccuracy of diagnosis in more than 50% cases, is believed as the sensitivity and the specificity of individual symptoms is quite low.^{4–6} Available diagnostic test ranged from those with high accuracy but high cost such as contrast venography to clinical evaluation which is low cost but unreliable. The venography is invasive, high cost, time consuming, limited to those with no renal problem, and enfacing the issue of hypersensitivity to a contrast. To date, the venous duplex ultrasonography scanning (VDUS) replaced the venography with the ability to detect the proximal thrombosis reached up to 100% in asymptomatic patient. This, somehow lead to increased up the demand of VDUS with economical consequence of high cost, though such a tool provide the positive predictive value less than 30%.^{5,7} In fact, there were patients in emergency department

with diagnosis of DVT–suspected rather than those with DVT.^{5,8} In the other hand, structured clinical diagnosis showed a higher accuracy than previously expected.¹ Clinical score of pretest probability (PTP) proposed by Wells is calculated from clinical data as well as patient history and classify the patient into categories of low–, moderate– and high risk group. A vary of combination of PTP score with normal D–Dimer, or even solely a normal D–Dimer, is judged to be accurate enough to exclude any VTE. Such a combination referred to the unnecessary to provide a further diagnostic test.^{7,9,10}

There was no study ever run to evaluate the application of this clinical score of Wells yet in management of DVT in Indonesia. Previous studies of Budiwisesa (2007), Hutagalung (2009) and Hartono (2011) in acute DVT did not explicitly apply the score of Wells and D–Dimer.^{11–13} Thus, we believed that a study had to be run to evaluate the correlation between Wells and D–Dimer with VDUS in diagnosis of DVT. Thus, we did try to find out a cut off value that will be a merit in the screening of those with the risk to have DVT, and the patient safety goal would be well maintained with optimal allocation of the budget and manpower in the region.

Method

A diagnostic study using cross-sectional design conducted in Department of Surgery during January to June 2016 enrolling all adult subjects where acute DVT of lower extremity was suspected.

Confirmation was preceded using VDUS. Data were collected from medical record of those managed during January 2014 – December 2015. Those with no data of D–Dimer or VDUS were excluded. In descriptive analytic, subject characteristics which was a categorical were represented in frequency and percentage. Numerical data of normal distribution represented in mean and standard of deviation. In the study, Wells score 2 level (likely, unlikely) and 3 level (high–moderate–, and low risk) were used. Wells score 3 level was further categorized into score 3 level I (high risk, low–moderate) and score 3 level II (high–moderate, low).

Those three scores of Wells (score 2 level, score 3 level I and score 3 level II) was further combined with D–Dimer value. In the study, two kinds of combination applied. First, (extreme positive), a score was positive if both of score of Wells (2 level, 3 level I, and 3 level II) and D–Dimer were positive. While as a negative result of a variable score of Wells or D–Dimer was interpreted as negative. Second, (extreme negative), score was positive if a score of Wells or D–Dimer positive and negative if both of result were negative. Thus, we had six combinations, namely score of combination I (score of Wells likely–unlikely, D–Dimer, extreme positive), score of combination II (score of Wells likely–unlikely, D–Dimer, extreme negative) score of combination III (score of Wells risk high, low–moderate; D–Dimer extreme positive), score of combination IV (score of Wells high risk, low–moderate; D–Dimer extreme negative), score of combination V (score of Wells high–moderate; low; D–Dimer extreme positive) and score of combination VI (score of Wells high–moderate; low; D–Dimer extreme negative). Statistical analysis of diagnostic test was carried out to find out the sensitivity, specificity, negative– and positive predictive value and likelihood ratio of the independent variables score of Wells and D–Dimer as well as combination score of Wells and D–Dimer. The committee of ethics of Faculty of

Medicine Universitas Indonesia approved the study 314/UN2.F1/ETIK/2016 (18 April 2016). Research bureau of dr. Cipto Mangunkusumo General Hospital approved the study LB.02.01/X.2/384/2016 (29 April 2016).

Results

There were 85 subjects met the inclusion criteria enrolled in the study. Out of these subjects, 32 (38%) were male and 53 (62%) were female. Acute DVT of lower extremity found in 56 subjects (66%) where proximal DVT found in 96% subjects. Non–compressibility referred to the criteria of VDUS applied to all subjects (100%). Based on score of Wells, active cancer referred to the most risk factor found (55%) and clinical manifestation mostly found was pitting edema (75%). Wells score in most subjects were likely (87%) and high (67%) with D–Dimer >300 ug/L (65%). Other related risk factor to DVT were diabetes mellitus (21%). The highest sensitivity and negative predictive value of 100%) found in combination score II and IV. Whereas the highest specificity of 89.66% and positive predictive value of 92.68% found in combination score III. The scores with balanced diagnostic value (sensitivity of 87.50%; specificity of 72.41%) found in Wells score 3 level I. Overall results represented in table 1). In the analysis using the procedure of receiver operating characteristics (ROC) in finding out the area under the curve (AUC) and the cutoff point of Wells score and D–Dimer in the predicting acute DVT of lower extremity, we found AUC of Wells score was 81.60% (95% CI, 71.00–92.20%) and the cutoff point of score 2 with sensitivity of 87.50% and specificity of 72.40%. AUC of D–Dimer was 62.30% (95% CI 49.30–75.30%) and the cutoff point of D–Dimer was >550 ug/mL with sensitivity of 75.00% and specificity of 58.60%.

Table 1. Comparison of Wells Score, D–Dimer and combination with VDUS

Combination Score Wells & D–Dimer	Positive Score		Negative Score		Sn (%)	Sp (%)	PPV (%)	NPV (%)	PPR	NPR
	DVT	Non DVT	DVT	Non DVT						
Wells Score 2 level	55	19	1	10	98.21	34.48	74.32	90.91	1.50	0.05
Wells Score 3 level I	49	8	7	21	87.50	72.41	85.96	75.00	3.17	0.17
Wells Score 3 level II	56	26	0	3	100.00	10.34	68.29	100.00	1.12	0
D–Dimer	42	13	14	16	75.00	55.71	76.36	53.33	1.67	0.45
Combination Score 1	41	8	15	21	73.21	72.41	83.67	58.33	2.65	0.37
Combination Score 2	56	21	0	8	100.00	27.59	72.73	100.00	1.38	0
Combination Score 3	38	3	18	26	67.86	89.66	92.68	59.09	6.56	0.36
Combination Score 4	53	18	3	11	94.64	37.93	74.65	78.57	1.52	0.14
Combination Score 5	42	12	14	17	75.00	58.62	77.78	54.84	1.81	0.43
Combination Score 6	56	27	0	2	100.00	6.90	67.47	100.00	1.07	0

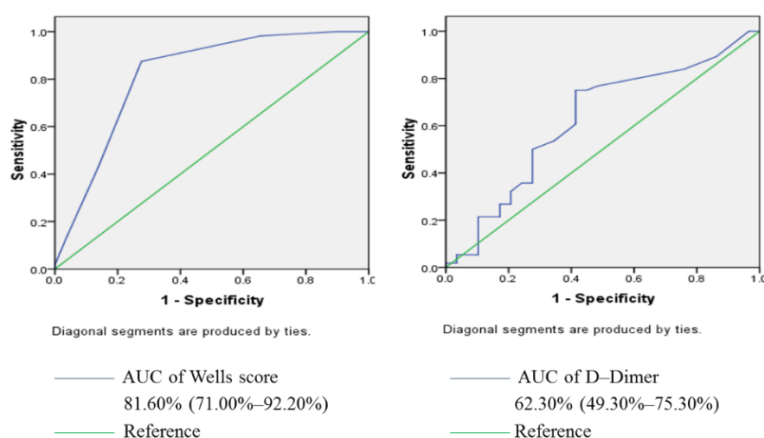


Figure 1. The curve of receiving operator characteristics (ROC) Wells score and D–Dimer with area under the curve (AUC) and 95% confidence of interval.

Discussion

Out of 129 subjects where acute DVT of lower extremity was suspected in period of January 2014 – December 2015, 85 subjects were confirmed to DVT by VDUS. Thus, the prevalence of DVT

was 65.88%. Meanwhile, per Lennox et al detection value of DVT was 30%.⁵ This might be found in training hospital with high awareness let the presented cases were those with acute DVT of lower extremity is suspected. We found mean age was 47 years old, which is somehow different to studies found mostly up to 50–60

years old. Mostly (62%) subjects were female, paralleled to the findings in other studies. Our data showed that the consults from obstetrics and gynecology department was as that high, rather than the other department.

The diagnostic criteria of VDUS in all subjects was a non-compressibility of the deep vein as a single criterion which has a sensitivity of 97% and specificity 94% in detection of a proximal DVT.¹ Increased a venous diameter up (>9 mm for femoral veins and >8 mm for popliteal veins) found in 25 subjects. Studies of Sharifian and Gharekhanloo showed that acute DVT is suspected if the diameter of femoral vein $>9-9.5$ mm and/or popliteal vein $>8-8.5$, whereas highly suspected as the absolute diameter of femoral vein >9.5 mm and/or popliteal vein >8.5 mm.¹⁴

In the recent study we found 54 of DVT were in proximal (96%) and 4 in distal part (5%). Most thrombus starts in low flow veins area of lower extremity, some underwent spontaneous resolution and in fact, those with involvement of the veins in the lower trunk are seldom involves the proximals.^{1,15} In those with symptomatic DVT episode, thrombus in the proximal were common, and of 99% subjects were associated with thrombus in the distal. The VDUS sensitivity in detection of proximal DVT was 97%, but the VDUS sensitivity for distal DVT decreased to 63.5%. This was found to be the limitation of duplex USG.¹

We found the sensitivity and negative predictive value of Wells score is quite high (sensitivity of 87.50–100% and negative predictive value of 75–100%), while as for its specificity (10.34–72.41%) and negative predictive value was found in vary (68.29–85.96%). Wells score 3 level I has an optimal diagnostic value (sensitivity of 87.50%; specificity of 72.41%; positive predictive value 85.96%; negative predictive value 75%) with the cutoff point of 2.

ROC curve impressed that Wells score has a good diagnostic value as the curve far beyond 50% and reached up to 100%. AUC value found was 81.60% (ranged of 71–92.20% based on confidence of interval), which is meant should the Wells score applied in diagnosing acute DVT of the lower extremity on 100 subjects, then the accuracy of conclusion will be found in 81 subjects. Both of clinically and statistically, diagnostic value of Wells score met the satisfaction as it found the minimal expected AUC of 70%. The benefit relatively better should it be addressed for a screening purpose (where the highest sensitivity and specificity is required).

The diagnostic analysis of D-Dimer showed the sensitivity of 75%; specificity of 55.17%; negative predictive value of 76.36% and positive predictive value of 53.33%. these findings were found paralleled to those in reports (sensitivity of 60–90%). We found the specificity of DVT is quite low as it found related to many factors other than DVT lead the D-Dimer increased up; this include of active cancer, surgery and pregnancy.¹ The cutoff point of D-Dimer in recent study was 0.55; paralleled to those in reports where >0.5 ug/mL is positive.^{1,6,9,17}

However, this laboratory finding should be adjusted to a local standard (in this case, department of clinical pathology Cipto Mangunkusumo Hospital) whereas the criteria of positive met if its value of >0.3 ug/mL. ROC curve impressed that D-Dimer had unsatisfactory diagnostic value as its curve approaching 50%. AUC found from ROC was 62.30% (based on confidence of interval ranged of 49.30–75.30%), means that accuracy found in 62 out of 100 subjects where acute DVT of lower extremity is suspected. This was found did not meet the minimal criteria of expected AUC of 70%; thus, both of clinically and statistically, the diagnostic value of D-Dimer is insufficient.

The highest sensitivity and negative predictive value of 100% found in combination score II (Wells score 2 level [likely and unlikely] and D-Dimer) and combination score VI (combination Wells score 3 level II [risk moderate–high and low] and D-Dimer). In combination score II and VI group, DVT was negative if the Wells score and D-Dimer is negative. Moreover, in combination score VI, negative was set if Wells score <1 . This was found to extent the scope of DVT let a more subjects screened as DVT, with consequence of a low specificity (27.59% and 6.9%). Combination of Wells score low risk and negative D-Dimer with sensitivity and negative predictive value reached up to 100% were described in the reference.^{1,8,9,20} The highest specificity of 89.66% and negative predictive value of 92.68% found in combination score III. In combination score III (Wells score 3 level I and D-Dimer; high risk group and low–moderate) positive results found if high risk (score >2) with high D-Dimer. This combination would let the false positive decreased in those scores where DVT was diagnosed, results in the increased up both specificity and negative predictive value. In accordance with this, the number of subjects with true positive is lower let the sensitivity (67.86%) and negative predictive value (59.09%) in the combination is quite low.

Recent study was the first one run in dr. Cipto Mangunkusumo General Hospital that aimed to evaluate Wells score and D-Dimer as well as the combination applied to constitute the diagnosis of acute DVT of lower extremity. Wells score as a simple and practical tool might be applied in all health facilities, which is independent to high-tech facilities such as VDUS. Meanwhile D-Dimer test commonly found in B or C type hospital is available. Necessarily, validation test in population of a primary health care which has a different characteristic to those in tertiary should be provided prior to its implication.

Somehow, there were limitations to recent study. First, a study was retrospective one, let the required data unavailable. Second, USG findings in the study solely based on venous non-compressibility. Records data of distal veins found in four subjects only. VDUS using the same device but different operator (it was realized that USG interpretation is operator-dependent). Third, the enrolled subjects were all symptomatic while as the asymptomatic of 60% were not involved in the study and we found it not representing all DVT population in the center. This is explained for the reliability of a study.

Conclusion

The incidence of acute DVT of lower extremity in our center is 65.88%. The highest sensitivity and negative predictive value of 100% found in combination score II and IV. The highest specificity of 89.66% and positive predictive value of 92.68% found in combination score III. The scores with balanced diagnostic value (sensitivity of 87.50%; specificity of 72.41%) found in Wells score 3 level I. Wells score showed efficacy comparable to VDUS in detection of acute DVT of lower extremity. It is necessarily to run validation of such a score in population of a primary health care.

Conflict of interest

Author disclose no conflict of interest.

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