

Association between modified wells score and D-dimer in malignant lymphoma patients.

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Abstract

Background: Cancer patients have a high risk of new or recurrent venous thromboembolism. Thrombosis decrease 1 year life expectancy of malignant lymphoma patients. In the last 10 years, it has been continuously developed a method to detect early venous thrombosis by combining Modified Wells (MW), D-dimer and Doppler ultrasonography level but only 25% are detected early.

Objective: We analyzed the association between MW score and D-dimer level.

Method: It is an analytic observational study of LNH and LH patients based on clinical and histopathological diagnosis who had never received chemotherapy. The subjects were 35 patients with malignant lymphoma consisting of 30 LNH patients and 5 LH patients. D-dimer was measured using immunochromatography method.

Result: There was a positive linear relationship between MW score and D-dimer level with $p=0.001$ and $r=0.462$. However, there was no association in LH patients ($p=0.215$).

Conclusion: There was a moderate positive correlation between MW scores and D-dimer levels in naive LNH patients.

Keywords: Naive malignant lymphoma, Thrombosis, Modified wells score, D-dimer.

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Introduction

Cancer patients are at high risk of venous thromboembolism, either new or recurrent [1,2]. Cancer patients with venous thromboembolism were more likely to experience recurrent four times compared with non-cancer patients [3]. Patients with hematologic malignancies especially malignant lymphomas and multiple myeloma had relatively high rates of venous thromboembolism. Anticancer treatments such as chemotherapy, anti-angiogenic drugs, hormonal therapy, and surgery also increased the predisposition of venous thromboembolism [4].

The diagnosis of subclinical venous thrombosis is still a problem today. Some studies suggested that in malignant lymphoma patients who had symptoms of Deep Vein Thrombosis (DVT), only 25% of venous thrombosis could be detected with doppler ultrasonography [5].

Thrombosis in malignant lymphoma is a serious complication resulting the greatest mortality if it is not immediately known. In the United States, in 2007 more than 2 million people died each year caused by venous thrombosis. More than 90% of pulmonary embolism cases were derived from the release of thrombus in the popliteal, femoral and iliac veins. Data analysis from Danish Cancer Registries in 2000 reported that the 1-year life expectancy rate of malignant lymphoma patients with venous thromboembolism was 12% while those with no venous thromboembolism were 36% [6]. In addition, venous thromboembolism has an economic impact because Doppler ultrasonography treatment of 110.000 per year in the United

States resulted in the loss of 3 million working hours per year [7-11].

Venous thrombosis diagnosis in malignant lymphoma was still difficult because 50% cases showed no clinical symptoms [12]. In a study that performed an autopsy in 83% of DVT cases, only 19% showed DVT symptoms and were recorded in the medical record. The formation of thrombus in the deep vein system could not be seen clinically due to the large capacity of vein system and the formation of collateral circulation around obstruction [13]. Doppler ultrasonography was one of the diagnostic devices in enforcing thrombosis especially in large superficial and deep veins, whereas venous thrombosis in connective veins was undetectable. In addition, the sensitivity of Doppler ultrasonography would decrease to 73-75% if it was used to diagnose DVT in the distal or calf vein [14]. Doppler ultrasonography could confirm DVT in only 67/177 patients (37.58%) and exclude DVT in only 62.14% of patients. Thus, it needed other non-invasive markers that could detect or predict the presence of venous thrombosis [2].

The new approach as a non-invasive thrombosis marker was Modified Wells (MW) Score and D-dimer [15]. MW scores were originally developed by Phillip S Wells to stratify the pre-test probability of DVT, consisting of 9 clinical symptom variables, DVT risk factors, and the presence of potential diagnostic alternatives. A sensitivity of MW score (78.4%), a specificity of 66.1%, with a positive predictive value of 52.3% and a negative predictive value of 86.6% [16]. In line with the increasing D-dimers use, MW scores with D-dimers have been tried to evaluate the possibility of DVT. Venous thrombosis activates the coagulation and fibrinolytic systems thereby

increasing serum fibrin split product levels. In the fibrinolysis process, the fibrin polymer is degraded by plasmin. One of the last products of its process is the D-dimer. Theoretically D-dimers can be used as a marker of venous thromboembolism [17]. D-dimer examination has high sensitivity but not specific. The sensitivity of D-dimer is 73.9%, specificity is 66.1%, positive predictive value is 50.8% and negative predictive value is 84.2% [16]. Therefore, we aimed to identify the relationship between MW scores and D-dimers in malignant lymphoma patients who had never received chemotherapy (naive).

Method

This study was cross-sectional with consecutive sampling technique in all patients with malignant lymphoma which fulfilled inclusion criteria of malign lymphoma patients who treated in the division of Haematology-Medical Oncology Department of Internal Medicine Dr. Soetomo General Hospital, Surabaya and willing to participate in the research. This research started from July 1st, 2014 to September 30th, 2014.

This research used independent variable that was D-dimer. D-dimers are thrombotic markers formed after thrombus formation and are the final product of cross-linked fibrin. D-dimer was done by taking left arm blood vein of subjects and was kept into a 2.7 ml plastic vacutainer containing sodium citrate with 0.109 M levels. Blood samples were then sent to private laboratories without special treatment. Centrifugation was done to obtain a supernatant. The supernatant was kept at a stable temperature of -20°C for a month. Normal reference value was less than 500 µg/l [18]. The method used was ICT principle (Immuno-chromatography) which was the reaction between two monoclonal antibodies toward fibrin degradation product containing element of d-dimer structure [18,19].

Dependent variable in this research was MW score. MW score is a score for estimating thrombosis consisting of 9 detailed questions, those are active cancer (currently in therapy, within the last 6 months or palliative); paralysis or immobilization due to fixation of gyps of the lower leg; lying for 3 days or more, or major surgery within 12 weeks and requiring general or regional anaesthesia; local tenderness in the area of deep venous system; a whole swollen legs; calf swelling with a circumference of at least 3 cm larger than a healthy leg; Pitting edema limited to affected limbs; non-varicose collateral veins; previous DVT history; differential diagnosis leading to DVT [17].

Data collection was performed on malignant lymphoma patients who met the inclusion criteria then further examined and calculated the MW score as described above. Then the data were analyzed by statistical calculation using SPSS 21 software (SPSS, Inc., Chicago, IL.).

Result

Sample size was 35 patients with 30 LNH patients (85.7%) and 5 LH patients (14.3%), the age range of subjects was 17 to 68 years, with average age of 49 years. In this study, normal

distributed variables were BMI, cholesterol and albumin. Meanwhile D-dimers, MW, GDA, TDS and TDD scores were not normally distributed. MW score median of LNH subjects was lower than LH subjects that was 1 vs. 2, D-dimer median of LNH subjects was lower than LH, that was 510 µg/l vs. 1400 µg/l. The details could be seen in table 1.

Table 1. Subject Characteristics.

S. No.	Characteristics	LNH, N=30	LH, N=5
1	Sex	%	%
	Male	18 (60)	4 (80)
	Female	12 (40)	1 (20)
2	Age		
	<50 Years	11 (36.7)	5 (100)
	≥50 Years	19 (63.3)	0
3	Stage		
	I Stage	12 (40)	2 (40)
	II Stage	7 (23.3)	2 (40)
	III Stage	8 (26.7)	1 (20)
	IV Stage	3 (10)	0
4	BMI Average (Standard Deviation)	21.27 (1.69)	20.50 (SD:1.57)
5	Systolic Blood Pressure Median (Range) mmHg	110 (90-125)	110 (90-125)
6	Diastole Blood Pressure Median (Range) mmHg	72.5 (60-85)	75 (60-85)
7	Cholesterol Average (SD) mg/dl	133.60 (41.1)	146.20 (41.1)
8	Albumin Average (SD) g/dl	3.52 (0.25)	3.49 (SD:0.29)9
9	Median of GDA(Range) g/dl	109 (75-160)	96 (80-110)
10	Median of MWS (Range)	1 (1-4)	2 (1-4)
11	Median of D-dimer (Range) µg/l	510 (100-3700)	1400 (580-2100)

MW score result of the subjects

The result of MW score calculation was done by 2 observers, therefore the interclass correlation test was done between them (Table 2). The test results showed a strong and significant correlation ($r=0.761$). In table 3, it was known that most MW scores were less than 2 that was as many as 17/35 subjects or 56.7% in LNH. The percentage of MW score in LH was ≥ 2 .

Table 2. Interclass Test Result of MW Score.

Reliability statistic	
Cronbach's alpha	Cronbach's alpha
	Based on Standardized Items

0.002	0.761
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Based on detailed MW scores, paresis was found in 2/35 subjects (5.7%), immobilization in 4/35 subjects (11.4%), swollen extremities in 2/35 subjects (5.79%), tenderness in 1/35 subjects (2.9%), swelling in 1/35 subjects (2.9%), and calves swelling in 1/35 subjects (2.9%) (Table 4).

Table 3. Calculation Result of MW Score.

Variable	MW Score <2 (%)	MW Score ≥ 2 (%)	MW Score <2 (%)	MW Score ≥ 2 (%)
Total Details		13 (43.3)	1 (20)	4 (80)
I Stage	7 (23.3)	6 (20)	0	1 (20)
II Stage	4 (13.3)	3 (10)	1 (20)	1 (20)
III Stage	4 (13.3)	3 (10)	0	2 (40)
IV Stage	2 (6.7)	1 (3.33)	0	0

Table 4. MW Score Result of Subjects.

Clinical Characteristic	Percentage (%)
Active cancer (currently in therapy, within the last 6 months or palliative)	35 (100)
Paralysis or immobilization due to fixation of gyps of the lower leg	2 (5.7)
Lying for 3 days or more, or major surgery within 12 weeks and requiring general or regional anaesthesia	4 (11.4)
Local tenderness in the area of deep venous system	1 (2.9)
Whole swollen legs	1 (2.9)
Calf swelling with a circumference of at least 3 cm larger than a healthy leg	1 (2.9)
Pitting oedema limited to affected limbs	2 (5.7)
Non-varicose collateral veins	0
Previous DVT history	0
Differential diagnosis leading to DVT	0
Simplified probability score:	
Supports DVT	≥ 2
Does not support DVT	< 2

D-dimer level result of subjects

Table 5. D-dimer level Calculation Result of Subjects.

	D-dimer LNH		D-dimer LH	
	<500 µg/l (%)	≥ 500 µg/l (%)	<500 µg/l (%)	≥ 500 µg/l (%)
Total Stage:	14 (46.7)	16 (53.3)	-	5 (100)

8 (26.7)	4 (133)	-	1 (20)
3 (10)	5 (16.7)	-	1 (20)
2 (6.7)	5 (16.7)	-	3 (60)
1 (3.3)	2 (6.7)	-	

D-dimer examination of subjects was performed using semi quantitative immuno-chromatographic methods. Cut off point of D-dimer level was 500 µg/l. The distribution of both groups based on D-dimer results as followed. (Table 5) The highest level of D-dimer in LNH was ≥ 500 µg/l, those were 16/30 subjects (53.3%) and the highest level of D-dimer in LH ≥ 500 µg/l, those were 5/5 subjects (100%).

Correlation analysis of MW score and D-dimer level of subjects.

Based on table 6, the magnitude of Spearman correlation coefficient on LNH was 0.46 with p=0.001. In LH, p=0.215 and Spearman's correlation was 0.671. In table 6 showed that there was a correlation between MW Score and D-dimer level of LNH subjects. In LH subjects, there was no correlation between MW Score and D-dimer level of LH subjects (p >0.05, Table 6).

Table 6. Analysis Result of Correlation between MW Score and D-dimer Level.

	LNH	LH
Correlation	Spearman 0.462	Spearman 0.671
P value (2 tails)	0.001	0.215

Discussion

In this study, the number of LNH subjects was more than LH subjects. LNH subjects were 30 patients (85.7%) and LH subjects were 5 patients (14.3%). LNH subjects was male dominated (51.4%). This result was consistent with the Shankland study that reported the incidence of LNH in males was 67.7%. The result of this study was also similar to the study in Pakistan that the incidence of LNH in men was more than women, those were 5.3/100.00 vs. 4.1/100.000 [20,21]. The results of this study were in accordance with the research of Birmann and Hoffbrand who mentioned that in LH the ratio of men was more compared to women that were 1.4:1 [22]. Most of LNH subjects >50 years old were more comparing to <50 years (63.3% vs. 36.7%). Most of LH patients <50 years was less than patients >50 years (100% vs. 0%). This result was similar to a study by Thomas et al., who reported that most of LH patients was <50 years [23].

In this study, the median MW score of LH subjects was higher than LNH subjects. This was due to several variables such as embolization that was the most variable (11.4%), paresis found in 2 patients (5.7%), swollen on the extremity in 1 patient (2.9%). These results were different from Mozafar in Iran who found that swelling was the most variable (108/177.61%), paresis was found in 20/177 (11%), immobilized in 24/177 (13.5%) patients [24]. Different results were also presented by

Geersing who reported that tenderness was the most variable (51%), followed by edema of 47%, paresis of 6.1%; immobilization of 11.1%.

Table 7. MW Score Result of Subjects and other Studies.

Clinical Characteristic	Study Result (%)	Kearon (%)	Bates (%)	Mozafar (%)	Geersing (%)	Owaidah (%)
Active cancer (currently in therapy, within the last 6 months or palliative)	35 (100)	47 (11)	50 (9.1)	38 (40.1)	65 (56)	43 (76)
Paralysis or immobilization due to fixation of gyms of the lower leg	2 (5.7)	12 (2.8)	12 (2.2)	11	6.1	3
Lying for 3 days or more, or major surgery within 12 weeks and requiring general or regional anesthesia	4 (11.4)	25 (5.8)	39 (7.1)	13.5	11.1	7
Local tenderness in the area of deep venous system	1 (2.9)	203 (47.3)	176 (32)	6	9	26.2
Whole swollen legs	1 (2.9)	30 (7.0)	83 (15.1)	61	47	78.5
Calf swelling with a circumference of at least 3 cm larger than a healthy leg	1 (2.9)	96 (22.4)	114 (20.7)	15	20	32
Pitting edema limited to affected limbs	2 (5.7)	87 (20.3)	251 (45.6)	43	31	23
Non-varicose collateral veins	0	33 (7.7)	28 (5.1)	4	3.7	4.1
Previous DVT history	0					
Previous DVT history	0	176 (41)	245 (44.6)	2.1	3	3.8

From table 7 it was known that this study reported different results with the study by Kearon, Bates, Mozafar, Geersing and Owaidah. The most variables were immobilization whereas in other studies the most variables were tenderness, total swelling of one leg, calf swelling and pitting edema. Based on Geersing's study, the risk of DVT increased in line with the MW score. Thus theoretically, LH subjects who was at risk of DVT was 26.6% meanwhile in LNH was 19%. According to study, in patients with an MW score <2 and D-dimer <500 µg/l, DVT could be excluded [17].

D-dimer is a thrombosis marker that increases rapidly in blood circulation in line with thrombosis process. Righini reported that D-dimer examination could be applied to patients under the age of 79 years. In LH subjects, D-dimer median was 1400 µg/l with a range of 580-2100 µg/l. Meanwhile LNH D-dimer median was lower than LH which was 510 µg/l with a range of 100-3700 µg/l. D-dimer levels are influenced by several factors, how many thrombus formed before followed by fibrinolysis response, thrombus age, blood clot position, and heparin use. D-dimer level decreased to normal after a month since the formation of venous thrombus [25]. Thus, the lower levels of D-dimer in LNH could also be assumed that within a month to 42 days after blood sampling there was no venous thrombus formation or had already formed venous but had experienced spontaneous resolution. In this study, all LH patients (5/5.100%) were under 50 years old but had D-dimer levels >500 µg/l. Meanwhile in LNH, patients under 50 years old were 6/30 patients (20%) having D-dimer levels <500 µg/l and 5/30 patients (16.6%) having D-dimer levels ≥ 500 µg/l. In patients >50 years old, 11/30 patients (36.6%) had a D-dimer level of ≥ 500 µg/l, and 8/30 patients (26.6%) had D-dimer levels <500 µg/l. D-dimer levels were also affected by age [26].

In this study, MW scores and D-dimer levels in LH were higher than LNH. It is similar to other studies that the incidence of venous thrombosis in LH was more frequently than low grade LNH (7.2% vs. 5.8%) [27] and a higher incidence of venous thromboembolism in LNH compared to LH (51/641; 8%) vs. LH (3/45; 6.7%) [28]. Thus it was known that in prospective design, the incidence of venous thrombosis in LH was higher whereas in retrospective design studies the incidence of venous thrombosis in LNH patients was higher than in LH patients [11].

LH was at greater risk of venous thrombosis compared to LNH marked with MW scores and higher D-dimer levels. In LH subjects there was a patient having an MW <2 but D-dimer >500 µg/l. Meanwhile 4 other subjects had MW score ≥ 2 with D-dimer ≥ 500 µg/l. Increased MW scores indicated by LH subjects showed a risk of thrombosis. This result also conformed the study by Lacombe et al., that reported the incidence of distal vein thrombosis in the low risk group (MW score <2) was 0.6%. The study by Engelberger et al., mentioned the prevalence of venous thrombosis in low risk group was 7-8%, whereas in high risk group was 36-37% [29].

Increased levels of D-dimer above 500 µg/l found in LH subjects showed the high risk and recurrence of venous thrombosis. D-dimer levels increased up to 100 times under acute venous thrombosis [30]. D-dimer tests had high sensitivity, and normal results could be used to rule out venous thrombosis [30]. In this study, D-dimer levels were not comparable with BMI. BMI in LNH was higher than in LH. The association of body weight with risk of venous thrombosis had been demonstrated by experts including research in Austria with a sample of 1107, studies in Sweden with a sample size of 855, and a study in Italy with a sample size of 15.180 patients [31-33]. In this study, although MW scores and D-dimer levels were high but the incidence of venous thrombosis was low, it

was caused by the highest MW score variables that was immobilization as listed in Table 7.

Theoretically, it was assumed that the risk of venous thromboembolism was higher in LH than in LNH. In a study with splenectomy experimental animal samples given B cells *via* infusion, it was shown that B cells played a role in the resolution of thrombus but this process continued that caused unstable venous thrombus and triggered venous thrombosis at other sites and increased the risk of recurrent thrombosis [34]. In addition, Reed Stenberg cells also produced TNF- α which further inhibited the formation of thrombomodulin and inhibited C protein, which led to the formation of venous thrombosis [35].

Demographic factors including ethnicity, age and gender also affected venous thrombosis. The highest incidence of venous thrombosis was in blacks and the lowest was in Asian. In addition, the risk of venous thrombosis increased in line with age up to 90 times from <15 years to >80 years due to endothelial dysfunction [36]. This study was different from other study in which the high D-dimer level was found in younger subject. Patients with high blood glucose levels due to diabetes mellitus and hyperglycaemia were at greater risk of venous thrombosis [37]. D-dimer result was also affected by the method used. Patients with MW score <2 were recommended to use ELISA and immunoturbidimetry while patients with MW score ≥ 2 were recommended to use SimpliRED method due to its sensitivity (88%) [38].

Conclusion

There was a moderate positive correlation between MW scores and D-dimer levels in naive LNH patients.

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