Master of Medicine

Radiologic approach using Hounsfield unit to access the Pulmonary embolism associated with proximal lower extremity Deep vein thrombosis

The Graduate School
of the University of Ulsan

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ABSTRACT

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Purpose: Proximal lower extremity deep vein thrombosis (pLE-DVT) is a well known condition that can worsen the clinical course of patients with pulmonary embolism (PE). The purpose of this study was to evaluate the feasibility of using Hounsfield units (HFU) for predicting the risk of concurrent PE associated with pLE-DVT.

Methods: PE was evaluated using pulmonary artery CT angiography and lower extremity CT venography to confirm patients with pLE-DVT. The patients were classified into group A (pLE-DVT without PE) and group B (pLE-DVT with PE), and analyzed to clarify clinical risk factors, including HFU ratio, associated with PE in patients with pLE-DVT. Statistical analyses utilized the multivariable logistic

regression model, and receiver operating characteristic (ROC) curve analysis.

Results: We examined 81 patients (age; 59.8 ± 16.9 years, 61.7% male) with pLE-DVT with and without PE. The prevalence of concurrent PE with pLE-DVT was 64.2%. The demographics and clinical characteristics showed no difference between the two groups. Of all the findings, the percentage of neutrophils was negatively associated with PE (neutrophil, p=0.006), and was a condition associated with suspected PE in Wells' score. The HFU ratios were significantly and independently associated with PE (Wells' score, p=0.001; HFU ratio, p=0.003). ROC curve analysis showed that the cut-off value using HFU ratio was 45.5.

Conclusion: HFU ratio can be used as a clinical tool to consider the possibility of PE associated with pLE-DVT.

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Table 1. Patient demographics and VTE characteristics

	Group A (n=29)	**Group B (n=52)**	**Total (n=81)**
Age (years)	59.2 ± 16.7	60.2 ± 17.2	59.8 ± 16.9
Sex (male)	69.0 (20)	57.7 (31)	61.7 (51)
BMI (kg/m^2) *	23.8 ± 3.3	24.9 ± 3.8	24.5 ± 3.6
DVT			
Right leg	6.9 (2)	26.9 (14)	19.8 (16)
Left leg	86.2 (25)	61.5 (32)	70.4 (57)
Both legs	6.9 (2)	11.5 (6)	9.9 (8)
PE			
Symptomatic PE	-	34.6 (18)	22.2 (18)
Right lung	-	32.7 (17)	21.0 (17)
Left lung	-	5.8 (3)	3.7 (3)
Both lungs	-	61.5 (32)	9.5 (32)
Main trunk (any side)	-	21.2 (11)	13.6 (11)

Values are presented as mean ± standard deviation or percentage (number).

Table 2. Clinical risk factors for VTE

	Group A (n=29)	**Group B (n=52)**	***p*-value**
Age (years)	59.2 ± 16.7	60.2 ± 17.2	0.814
Sex (male)	69.0 (20)	57.7 (31)	0.317
BMI (kg/m^2)	23.8 ± 3.3	24.9 ± 3.8	0.184
Hypertension	41.4 (12)	38.5 (21)	0.797
Diabetes mellitus	17.2 (5)	15.4 (8)	0.827
Dyslipidemia	6.9 (2)	9.6 (5)	0.676
Congestive heart failure	3.4 (1)	0.0 (0)	0.178
Coronary artery disease	3.4 (1)	1.9 (1)	0.672
Cerebrovascular disease	10.3 (3)	0.0 (0)	0.018
Chronic renal disease	0.0 (0)	1.9 (1)	0.452
COPD *	0.0 (0)	5.8 (3)	0.187
Cancer (h/o)†	6.9 (2)	13.5 (7)	0.367
Soming‡	34.5 (10)	21.3 (12)	0.269

* COPD, chronic obstructive pulmonary disease

† Cancer (h/o), history of cancer; patients with any cancer that has been diagnosed for more than six months and cured.

‡ Smoking; Patients who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.

Table 3. Laboratory findings

	Group A (n=29)	**Group B (n=52)**	***p*-value**
WBC (x10^3/μL)	9.6 ± 3.2	8.4 ± 2.6	0.056
Neutrophil (%)	70.9 ± 9.9	64.9 ± 8.6	0.006
Hemoglobin (g/ μL)	12.7 ± 2.0	13.3 ± 2.3	0.228
Hematocrit (%)	37.9 ± 5.0	39.8 ± 6.3	0.167
Platelet (x10^3/μL)	237.7 ± 81.6	207.7 ± 61.0	0.064
Creatinine (mg/dL)	0.9 ± 0.3	1.0 ± 0.9	0.316
Cholesterol (mg/dL)	174.0 ± 33.5	185.6 ± 37.1	0.166
D-dimer (μg/ml)	8.6 ± 8.0	11.2 ± 9.0	0.196
CRP (mg/dL)	3.1 ± 3.5	2.3 ± 3.3	0.350
HFU *	56.8 ± 16.7	68.0 ± 16.0	0.004
HFU ratio†	43.4 ± 12.1	53.7 ± 12.7	0.001

* HFU, Hounsfield unit

† HFU ratio; HFU ratio was calculated as the ratio of HFU (a) of the most proximal deep vein thrombosis site to the refence HFU (b). (Fig. 3)

Table 4. Findings related with infection and/or inflammation

	Group A (n=29)	**Group B (n=52)**	***p*-value**
WBC (x10^3/μL)	9.6 ± 3.2	8.4 ± 2.6	0.056
Neutrophil (%)	70.9 ± 9.9	64.9 ± 8.6	0.006
CRP (mg/dL)	3.1 ± 3.5	2.3 ± 3.3	0.350
BT (°c) *	36.6 ± 0.5	36.6 ± 0.4	0.903
Pneumonia (%, n)†	6.9 (2)	3.8 (2)	0.544

* BT, body temperature

† Pneumonia; Patients with respiratory symptoms and diagnosed with pneumonia on chest X-ray or CT.

Table 5. Analysis of Wells' score for pulmonary embolism

	Group A (n=29)	**Group B (n=52)**	***p*-value**
Symptomatic PE *	-	34.6 (18)	-
HR >100/min.	13.8 (4)	30.8 (16)	0.089
Recent surgery†	13.8 (4)	11.5 (6)	0.767
Immobilization (>3days)‡	13.8 (4)	26.9 (14)	0.173
Wells' score for PE (>4)§	34.5 (10)	69.2 (36)	0.002

All evaluated patients had confirmed deep vein thrombosis, and those who were treated with previous deep vein thrombosis and/or pulmonary embolism or patients with cancer diagnosed within 6 months, on treatment, or palliative.[17)]

* Symptomatic PE, Symptomatic pulmonary embolism; Patients who had symptoms of unspecified chest pain, dyspnea, cough, hemoptysis, and/or syncope.

† Recent surgery; Patients who underwent major surgery within 4 weeks before diagnosis of deep vein thrombosis.

‡ Immobilization (>3days); Immobilization for more than three days in previous 4 weeks.

§ Wells′ score for PE (>4); Patients corresponding to "pulmonary embolism likely" group exceeding four points on the basis of Wells′ score for pulmonary embolism.

Table 6. Multiple logistic regression analysis

	***P*-value**	**Odd ratio**	**95% CI**
Age (years)	0.268	1.023	0.983 – 1.064
BMI (kg/m^2)	0.788	1.029	0.834 – 1.271
Smoking	0.631	0.685	0.146 – 3.204
D-dimer (μg/ml)	0.233	1.053	0.967 – 1.146
At CIV (most prx DVT) *	0.088	0.216	0.037 – 1.253
Neutrophil (%)	0.004	0.876	0.800 – 0.960
Wells' score for PE (>4)	0.001	23.794	3.823 – 148.108
HFU ratio	0.003	21.423 x10^3	30.448 – 1.410 x10^7

* At CIV (most prx DVT), At common iliac vein (most proximal deep vein thrombosis); The most proximal deep vein thrombosis site located in any side of common iliac vein. (based on the analysis of most proximal deep vein thrombosis site as a risk factor.)

Table 7. Risk factor analysis, most proximal locations of DVT

	Group A (n=29)	**Group B (n=52)**	***p*-value**
Inferior vena cava	20.7 (6)	25.0 (13)	0.661
Common iliac vein	34.5 (10)	11.5 (6)	0.013
External iliac vein	13.8 (4)	13.5 (7)	0.967
Common femoral vein	6.9 (2)	13.5 (7)	0.367
Superficial femoral vein	20.7 (6)	34.6 (18)	0.188

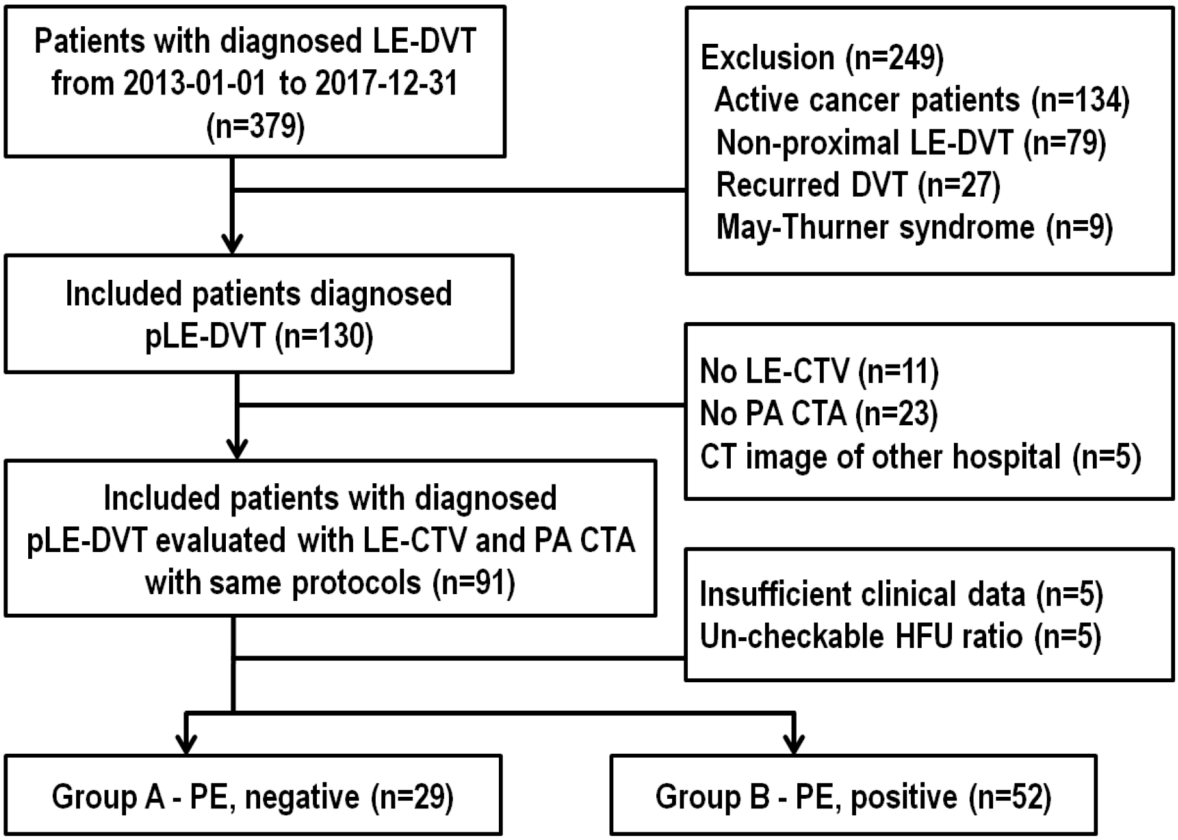

Figure 1. Flow chart of the Study.

LE-DVT, Lower extremity deep vein thrombosis; pLE-DVT, proximal lower extremity deep vein thrombosis; LE-CTV, Lower extremity computed tomographic venography; PA CTA, pulmonary artery computed tomographic angiography; HFU, Hounsfield unit; PE, pulmonary embolism

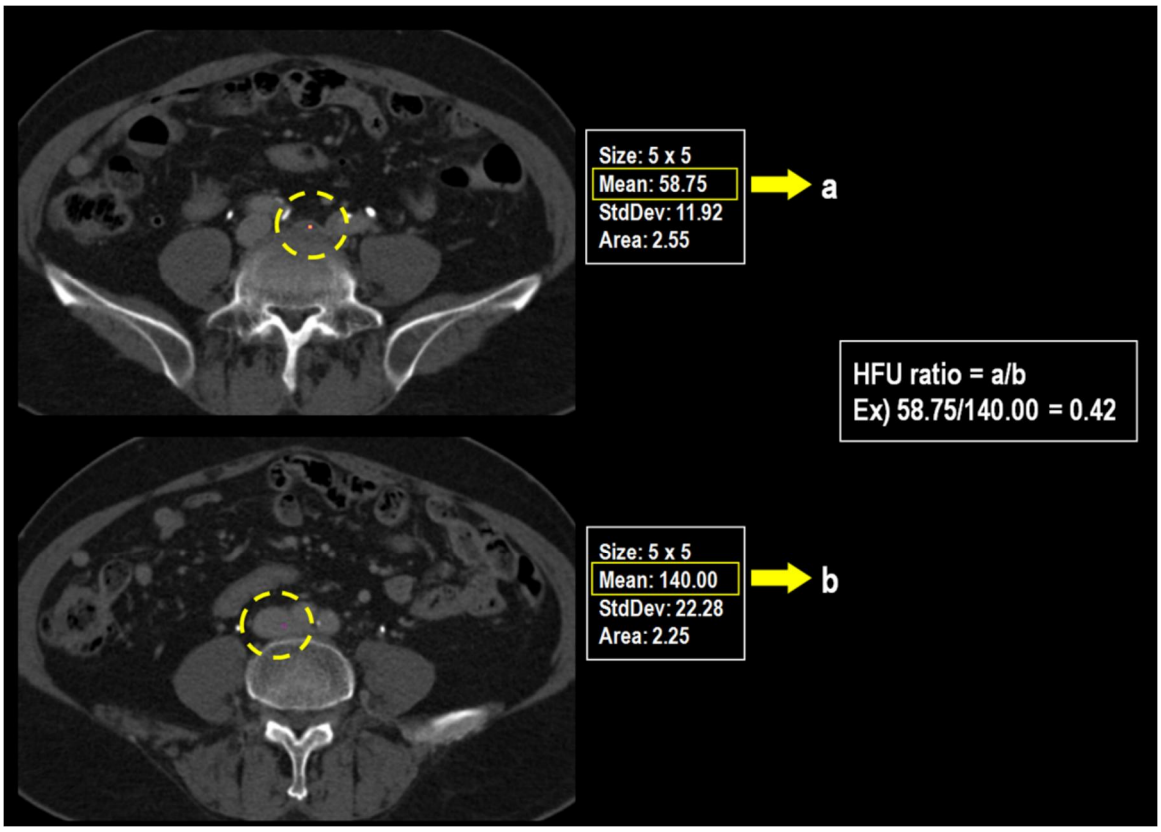

Figure 2. Hounsfield unit (HFU) ratio calculation.

HFU (a) at the most proximal deep vein thrombosis, reference HFU (b) at the site of 3 or 4 cuts above the checked HFU site. (HFU ratio = a/b)

HFU _ratio	Sensitivity (%)	Specificity (%)
42.5	82.7	58.6
44.0	80.8	62.1
45.5	**78.8**	**69.0**
46.5	76.9	69.0
47.5	75.0	69.0

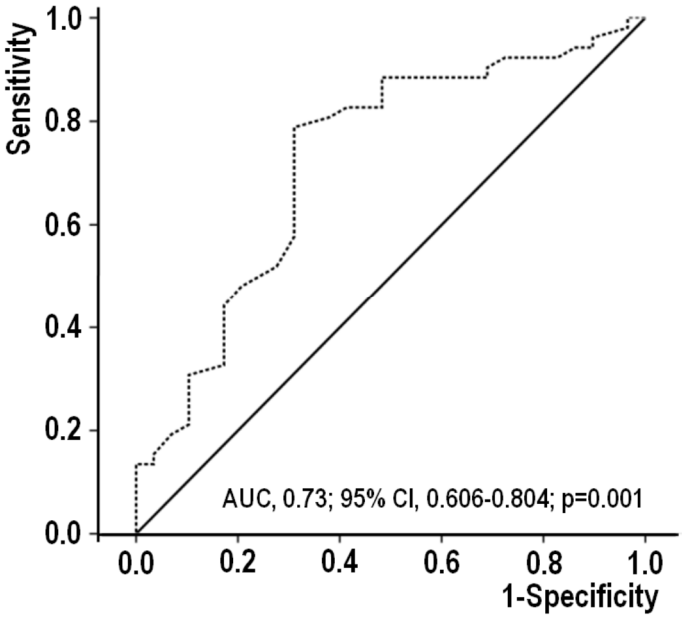

Figure 3. Receiver operating characteristics (ROC) curve analysis using HFU ratio.

HFU ratio exceeding 45.5 was the best value to predict the pulmonary embolism in patients with proximal lower extremity deep vein thrombosis.

Introduction

Venous thromboembolism (VTE) is a disease entity that includes deep vein thrombosis (DVT) and pulmonary embolism (PE), and DVT is a condition that accompanies PE and can potentially lead to patient death.[1-3] The prevalence of VTE is increasing and affects the overall mortality of the affected disease group.[3, 4] In particular, proximal lower extremity DVT (pLE-DVT) is considered to be an important risk factor for PE.[5, 6]

The Hounsfield unit (HFU) scale is defined as the value specified by the linear transformation of the original linear attenuation after CT image reconstruction. The scale defines the radiodensity of water as 0 HFU and the radiodensity of air as -1,000 HFU at standard pressure and temperature.[7, 8] In the VTE field, HFU is used to study the prognosis of thrombolysis because it represents the density of the thrombus by representing the blood cell components contained in the thrombus.[9]

The purpose of this study was to evaluate whether PE can be assessed using lower extremity CT venography HFU used for the diagnosis of DVT.

Methods

In this single center, retrospective, observational study, we analyzed data extracted from subjects' medical records. The study protocol was approved by the institutional review board of the Asan Medical Center. A review was performed of patients with LE-DVT with or without PE. LE-DVT was diagnosed with lower extremity CT venography, and PE was evaluated with pulmonary artery CT angiography.

We recruited subjects from among those aged >20 years who were diagnosed with LE-DVT between January 2013 and December 2017. The exclusion criteria were non-proximal LE-DVT, recurrent DVT, May-Thurner syndrome, patients with cancer diagnosed within the past six months or having untreated cancer.

Patients were excluded who were diagnosed with DVT through techniques other than lower extremity CT venography or pulmonary artery CT angiography, because of the need for lower extremity CT venography HFU. Lower extremity CT venography performed at other hospitals was also excluded in order to include only similarly-performed CT scanning. Eighty one patients were enrolled, except for patients who were not able to check for HFU in the proximal DVT site and those who lacked clinical data at the time of initial diagnosis (Fig 1).

We collected clinical risk factors including baseline characteristics such as age, sex, body mass index (BMI), hypertension, diabetes, dyslipidemia, smoking, pneumonia, and treatment or diagnosis of congestive heart failure, coronary artery disease, cerebrovascular disease, chronic renal disease, chronic obstructive pulmonary disease, and cancer. The baseline laboratory data were analyzed to determine the white blood cell count, percentage of neutrophil, hemoglobin, hematocrit, platelet count, creatinine, cholesterol, D-dimer, and CRP.

The HFU ratio was calculated by checking the HFU in the most proximal DVT site and checking the reference HFU in the vein where the intact flow was above 3 or 4 cuts of checked HFU of DVT at the transverse view of CT (HFU ratio = HFU of DVT / reference HFU) (Fig. 2).

Statistical analyses were performed with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Independent t-test, chi-square test, multiple logistic regression model, and receiver operating characteristics (ROCs) curve were used to evaluate the clinical risk factors and HFU ratio. All p-values were considered significant if $p<0.005$

Results

We collected the data from eighty-one patients with pLE-DVT. Twenty-nine cases did not have co-existing PE (group A), and fifty-two cases had co-existing PE (group B). Table 1 shows the patient baseline demographics and VTE

characteristics. The mean age of patients (51 females) was 57.8 ± 16.9 years. The mean BMI was 24.5 ± 3.6 kg/m^2. PE was detected in 52 patients on pulmonary artery CT angiography and 11 patients had PE involving the main trunk of the pulmonary artery.

Statistical analysis of patient demographics and characteristics were similar in both groups (Table 2). Initial laboratory findings and analysis of HFU are shown in Table 3. The percentage of neutrophils was higher in group A (p=0.006), and the other factors were similar in the two groups. The HFU of the most proximal DVT was higher in group B (p=0.004), and the HFU ratio was also higher in group B (p=0.001).

The factors associated with infection are shown in Table 4. As mentioned in table 3, the percentage of neutrophils was significantly lower in group B. However, other factors, including pneumonia, showed no significant difference between the two groups.

Wells' score for PE and related factors are summarized in table 5. In Wells' score for PE, the distribution for the group with high PE probability (>4) was significantly higher in group B.

Multiple logistic regression analysis data shown in Table 6 revealed that the percentage of neutrophils, Wells' score for PE, and HFU ratio were associated with the risk of statistically significant co-existing PE.

The mean value for the HFU ratio in group A and group B was 43.4 ± 12.1 and 53.7 ± 12.7. An independent t-test identified that the HFU ratio was significantly higher in the group with PE (group B; P=0.001). Subsequently, the HFU ratio at which the risk of PE increases was determined using ROC curve analysis to be 45.5 (sensitivity, 78.8%; specificity, 69.0%; area under the curve=0.73) (Fig. 3).

Discussion

This study demonstrates that the HFU ratio in the CT used to diagnose pLE-DVT was higher in the PE group, indicating a high risk of thrombi migrating into the pulmonary circulation. The use of the Wells' score for PE was successful in predicting the associated PE status, and the percentage of neurtophils was inversely related to the PE accompanying status.

Thrombus density reflects the freshness of clots. Studies on the relationship between thrombus density and HFU have been performed mainly in the area of thromboembolic stroke. Thrombus density can be assessed as a result of treatment applications. As reported in previous studies, the composition of the thrombus influences the success of mechanical and pharmacological clot disruption as well as recanalization. In addition, the lower HFU of thrombi results in less effective pharmacological thrombolysis and mechanical thrombectomy, reflecting lower thrombus density.[9-12] Previous studies have shown that the mean

percentage of erythrocytes is high in the thrombus evaluated at a high density on CT.[10, 11] Platelet-rich thrombi have a lower HFU than erythrocyte-rich thrombi because HFU has a linear correlation with hemoglobin. Platelet, atheromas, and cellular debris are all known to decrease thrombus HFU in reconstructed CT images.[9, 13] Because the HFU ratio is data based on the HFU value from the normal flow vein of the patient relative to the absolute HFU value, it can be expressed as the relative density of the thrombus. This information is considered useful related to individual patients.

In this study, only a small number of patients had infections. There were four pneumonia patients (two in each group) and no other specific infections. Infections have been reported to be associated with the VTE development. Infections can affect thrombosis, because inflammatory processes, coagulation and fibrinolytic processes share a common pathway.[14, 15] However a more recent study about the risk of PE associated with DVT is unclear which factors relative to

the influence of infection and/or inflammation are most important on the formation of PE when considering clinical conditions and recent surgery associated with pLE-DVT.[5)]

Neutrophils are elevated in association with bacterial infection. During venous thrombosis formation, Neutrophil Extracellular Traps (NETs) are formed and are involved in thrombus formation.[16)] In the case of the study group without the specified infection status, the consumption of neutrophil by the formation of NETs in venous thrombus formation process may show a relatively decreased neutrophil level. In this study, the percentage of neutrophil showed a statistically significant decrease in group B with more aggressive thrombus formation.

To address the potential of PE in patients with DVT, two scoring systems can be used: the Wells' score[17)] and the revised Geneva score[18)]. The Wells' score for PE is more widely used in patients with DVT. Hendriksen JM, et al. reported that the clinical use of the Wells' score for PE with D-dimer could be useful for clinical

prediction of PE below the failure rate of 2.0%.[19] The results of this study showed that the probability of predicting PE by the use of the Wells' score for PE was statistically significant, indicating that this study is a proper way to possibly predict PE in DVT patients. In the same way, it demonstrated the validity of applying the Wells' score for PE.

This study has several limitations. Due to the retrospective study design, difficulties concerning accessibility of information and its accuracy were encountered. In addition, this study had a number of exclusion criteria and therefore a number of exclusion groups. In the case of cancer patients, active cancer is an important risk factor for VTE[3,4], but it is included in the exclusion criteria because it can cause tumor thrombosis and anatomically cause venous compression and other factors besides the density of primary venous thrombosis. It was the same reason that the May-Thurner syndrome was included in the exclusion criteria. There was a lack of basic data on inherited VTE risk factors,

including antiphopholipid syndrome, protein C, and protein S deficiency.[3, 4] As a retrospective study, there was no intervention for initial screening and an evaluation of risk factors that could genetically induce VTE was not performed. Studies on anatomical risk factors have been carried out in the evaluation of PE risk related to DVT.[20, 21] In this study, anatomical factors providing additional risks or may providing protective effects were excluded or not considered, in order to focus on the association with thrombus density.

Conclusion

The HFU ratio, obtained by lower extremity CT venography for evaluation of DVT, can be used as a tool to consider the possibility of PE associated with pLE-DVT. Our results should be further investigated in larger prospective studies.

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국문 요약

근위부 하지 심부 정맥 혈전증과 동반된 폐색전증 추정을 위한 하운스필드 단위를 이용한 방사선학적 접근.

연구목적

근위부 하지 심부 정맥 혈전증은 폐색전증을 동반하여 환자의 임상 경과를 악화시킬 수 있는 질환으로 잘 알려져 있다. 이 연구를 통해 근위부 하지 심부 정맥 혈전증과 동반된 폐색전증의 위험을 예측하기 위한 Hounsfield unit의 활용의 타당성을 평가하고자 한다.

연구 방법

하지 CT 정맥 조영술을 통해 근위부 하지 정맥 혈전증을 진단받은 환자를 대상으로 폐동맥 CT 조영술의 결과를 통해 폐색전증 동반 여부를 확인하였다. 환자는 폐색전증 동반이 없는 A군과 폐색전증이 동반된 B군으로 분류하여 Hounsfield unit ratio를 포함한 근위부 하지 심부 정맥 혈전증 환자에서 폐색전증과 연관된 임상적 위험 인자를 확인하기 위해 분석하였다. 통계 분석은 다변량 로지스틱 회귀 모델과 Receiver operating

characteristic curve (ROC 곡선) 분석을 활용하였다.

결과

폐색전증 동반이 있거나 없는 근위부 하지 심부 정맥 혈전증 환자 81명 (나이 59 ± 16.9 세, 남성 61.7%) 을 대상으로 하였다. 폐색전증이 동반된 경우가 64.2% 였다. 인구 통계학적 및 임상적 특성은 두 군간에 차이가 없었다. 모든 결과 중 호중구의 백분율은 폐색전증 동반군에서 역의 상관관계를 보였고 (p=0.006), 폐색전증 동반 여부 판단을 위한 Wells' score 기준에서 폐색전증 동반이 의심되는 경우와 Hounsfield unit ratio는 폐색전증 동반과 통계적으로 유의미한 연관을 보였다. (Wells' score, p=0.001, Hounsfield unit, p=0.003). ROC 곡선 분석 결과, Hounsfield unit ratio를 활용한 cut-off value의 값은 45.5 의 결과를 보였다.

결론

근위부 하지 심부 정맥 혈전증 진단을 위한 하지 CT 정맥 조영술에서의 Hounsfield unit 을 활용하여, 근위부 하지 심부정맥 혈전증과 동반된 폐색전증의 가능성을 평가하여 임상적으로 활용할 수 있을 것으로 고려된다.