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Determination of clinical, radiological and laboratory risk factors associated with the development of pulmonary embolism in patients with lower extremity deep vein thrombosis

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ABSTRACT

Aims: This study aimed to determine the clinical, radiological and laboratory risk factors associated with the development of pulmonary embolism (PE) in patients with lower extremity deep vein thrombosis (DVT) and to determine the role of the triglyceride-glucose (TyG) index.

Methods: In this single-center retrospective study, electronic medical records of patients diagnosed with lower extremity DVT confirmed by ultrasonography (USG) were retrospectively reviewed. Among these patients, patients who underwent computed tomography pulmonary angiography (CTPA) imaging within the first 24 hours with suspected PE and developed PE were identified and recorded. Clinical, radiological and laboratory values of these patients were analyzed with statistical methods and the results were compared.

Results: A total of 236 patients who were diagnosed with lower extremity DVT confirmed by USG and met the inclusion criteria were included in this study. PE was detected in 54 (22.9%) of the included patients. In univariate regression analysis, obesity, diabetes, immobility, thrombus location and high TyG index were identified as risk factors ($p<0.05$ for all). In multivariate regression analysis, diabetes and high TyG index were independent risk factors for PE in patients with DVT ($p<0.05$ for all).

Conclusion: Our study findings indicate that diabetes and high TyG index are independent risk factors for PE in patients with DVT. This suggests that the incidence of PE in patients with DVT can be significantly reduced by controlling diabetes and related factors contributing to high TyG index.

Keywords: Ultrasonography, computed tomography, venous thrombosis, pulmonary embolism, triglyceride-glucose index

INTRODUCTION

Deep vein thrombosis (DVT) is an important public health problem that can lead to serious complications, usually seen in lower extremity veins.[1] Three main factors contribute to the basic mechanism predisposing to DVT formation: decreased blood flow, endothelial damage, and hypercoagulability.[2] The most important risk factors for DVT include oral contraceptive use, pregnancy, thrombophilia, infection, malignancy, immobility, surgery, obesity, and advanced age.[3] Pulmonary embolism (PE), the most important complication of DVT, is one of the leading causes of cardiovascular deaths worldwide.[1] Although PE has various clinical symptoms including hemoptysis and dyspnea, the absence of disease-specific clinical symptoms and signs makes diagnosis difficult.[1] PE occurs with a sudden and dramatic onset and may be fatal.[4] Therefore, detection and treatment of these patients is extremely important. Computed tomography pulmonary angiography (CTPA) is the basic imaging method in the diagnosis of PE. However, this imaging method has disadvantages such as allergic reactions, radiation exposure, potential kidney damage and cost.[5] Considering the high mortality rate of patients with undiagnosed PE, early detection and treatment of PE can significantly reduce the complications that may develop.

It is known that the risk of metabolic and cardiovascular diseases (CVD) increases in individuals with insulin resistance (IR) and is even associated with poor prognosis.[6] IR reduces nitric oxide (NO) production in vascular smooth muscle cells, causing inflammation and endothelial dysfunction. It also

activates inflammatory cell cytokine producers that contribute to oxidative stress and increases the release of procoagulant factors, causing platelet aggregation.[7] The triglyceride-glucose (TyG) index is considered a reliable indicator of IR.[8] TyG index has been associated with CVD such as coronary artery disease (CAD), carotid atherosclerosis, hypertension, and coronary artery calcification in several studies.[9-11] In fact, TyG index has been found to be closely related to CVD development and prognosis, independent of traditional risk factors.[10,12,13] However, we did not find any study examining the relationship between PE and TyG index in patients with DVT.

This study aimed to determine the clinical, radiological and laboratory risk factors associated with the development of PE in patients with lower extremity DVT and to determine the role of the TyG index.

METHODS

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee Approval was obtained from the Siirt University Non-invasive Ethics Committee (Date: 05.07.2024, Decision No: 112266).

Study Design and Subjects

In this single-center retrospective study, electronic medical records of patients diagnosed with lower extremity DVT confirmed by ultrasonography (USG) between January 2018 and June 2024 were retrospectively reviewed. Among these patients, those who underwent CTPA imaging within the first 24 hours with suspected PE and in whom PE was detected were identified and recorded.

Patients with a known or detected history of malignancy, those younger than 18 years of age, those with incomplete medical records, those diagnosed with chronic DVT, those diagnosed with upper extremity DVT, those receiving any anticoagulant treatment, those previously diagnosed with PE, and those with arterial or superficial venous thrombosis were excluded from the study.

Data Collection

Data on clinical and demographic characteristics of all patients including gender, age, smoking and presence of major cardiovascular risk factors (diabetes, hypertension, smoking, dyslipidaemia) were collected and recorded. The inclusion criteria for diabetes mellitus, hypertension and hyperlipidaemia were defined as being diagnosed and/or receiving medication for these diseases. At least 10 cigarettes a day for at least 1 year was determined as a criterion for smoking. Fasting blood glucose, total cholesterol (TC), triglycerides (TG), low density lipoprotein-C (LDL-C), high density lipoprotein-C (HDL-C), serum albumin, total protein, sedimentation (ESR), C-reactive protein (CRP) and haematological parameters (Hg, neutrophil, lymphocyte, platelet and leukocyte levels) were analysed and recorded in the laboratory information system. Patients with fasting triglyceride and glucose measurements within 24 hours after diagnosis were included in the study. TyG index was calculated as follows: TyG=Ln [fasting TG (mg/dl)xfasting glucose (mg/dl)/2].[14]

The Sonographic Procedure

USG reports of all patients were accessed from the electronic medical record system and data on radiological imaging features of the disease were obtained. Patients without an USG report in the system were excluded from the study. In USG reports, the presence of a non-compressible venous segment in the lower extremity veins, the presence of thrombus in the lumen, or the absence of colored flow were defined as DVT. The location of the thrombus was classified as proximal type if it was in the popliteal vein or above, as distal type if it was below the popliteal vein, and as mixed type if it was in both distal and proximal veins.

CT Protocol and Analysis

CTPA images of all patients diagnosed with PE were retrospectively re-evaluated via picture archiving and communication system (PACS). The presence of thrombus causing a complete or partial filling defect in the pulmonary arteries was accepted as PE (**Figure 1**).

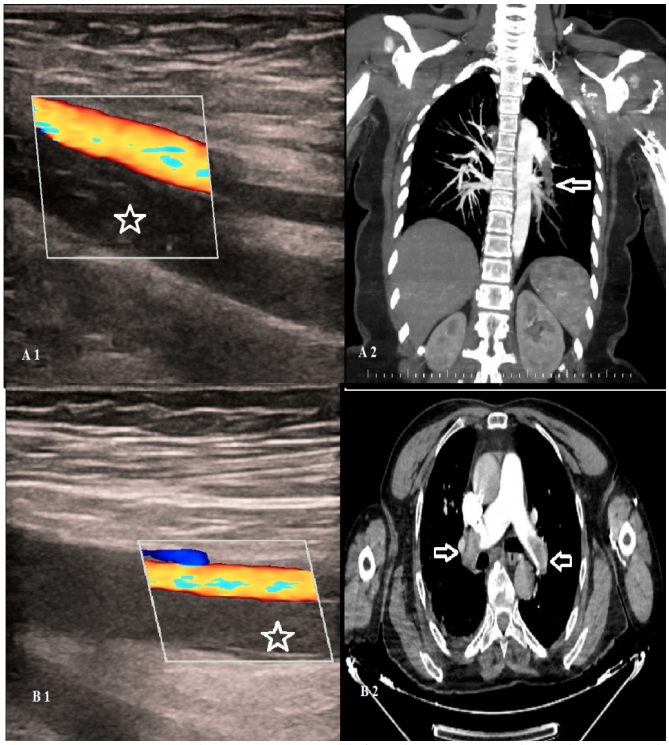

Figure 1. Case examples. A 32-year-old female patient with no known risk factors and a Tyg index of 8.95 is shown to have acute DVT in the right superficial femoral vein on USG Doppler examination (A1) and embolism findings in the left pulmonary artery lumen on CTPA images of the same patient (A2). A 72-year-old male patient with a TyG index of 9.40, known to have diabetes, hypertension and smoking history, shows a DVT in the right superficial femoral vein that does not allow flow on USG Doppler examination (B1) and bilateral pulmonary artery embolism findings on CTPA images (B2).

Statistical Analysis

SPSS 20.0 software (Statistical Package for the Social Sciences, Chicago, IL) was used for data analysis. Qualitative data were expressed as number (n) and percentage (%) and quantitative data were expressed as mean±standard deviation (SD).

During data analysis, Student's t test was used for variables showing normal distribution and Mann-Whitney U test was used for variables not showing normal distribution in comparisons between groups. Chi-square test or Fisher's exact test was applied to analyze the relationship between categorical data depending on the sample size. Univariate and Multivariate Binary Logistic Regression analyses were used to determine risk factors for PE. ROC (receiver operating characteristic) curve analysis was used to determine whether the TyG index is a prognostic indicator for predicting the risk of PE and to determine the optimum cut-off values. The significance level for statistical results was accepted as $p<0.05$.

RESULTS

A total of 236 patients with USG-confirmed DVT who fulfilled the inclusion criteria were included in this study. PE was detected in 54 (22.9%) of the included patients. The mean age at diagnosis of patients with PE was 62.5±10.8 years and the mean age of patients without PE was 63.7±9.6 years. Of the patients with PE, 21 (38.8%) were male and 33 (61.2%) were female. There were no statistically significant differences between patients with and without PE in age, gender, smoking history, HT and CAD (p>0.05 for all). Body-mass index was 27.8±4.3 kg/m^2 in patients with PE and 26.4±3.8 kg/m^2 in patients without PE (p=0.024, **Figure 1**). The presence of immobilisation and diabetes were statistically higher in the group of patients with PE (p=0.039, p<0.001, respectively). The most common thrombus location in patients with PE was found to be proximal type with 40.7% (p=0.026). When laboratory parameters were compared, no statistically significant difference was found between the two groups in laboratory parameters such as ESR, CRP, fasting glucose, LDL, TC, HDL and D-dimer and haematological values (WBC, neutrophil, lymphocyte, platelet and leukocyte levels) (p>0.05 for all). However, triglyceride value was statistically higher in patients with PE (p= 0.037). TyG index was significantly higher in patients with PE than in patients without PE (p<0.001, **Figure 2**). The basic clinical and laboratory data of the patients included in the study are presented in **Table 1**.

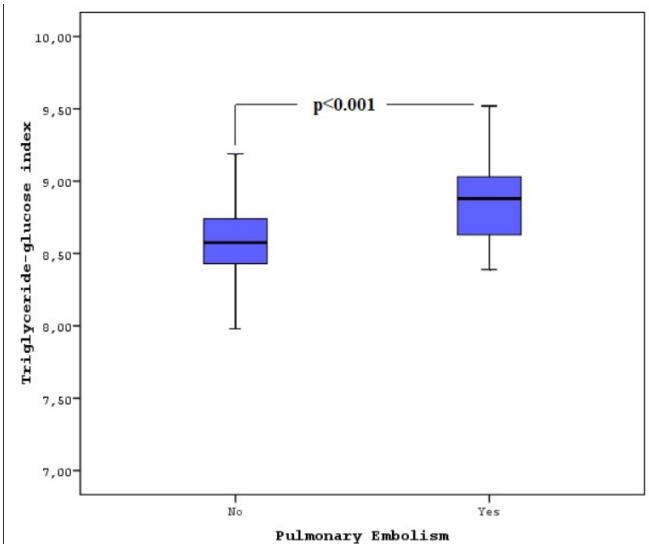

Figure 2. Box plot of the distribution of TyG index values in patients with DVT with and without PE. The horizontal lines within each box represent the mean values, and the lower and upper rows of each box represent the minimum and maximum values, respectively.

In the ROC curve analysis test of the TyG index, the AUC values were determined as 0.746 (0.668-0.823), respectively, at a 95% confidence interval and were therefore considered statistically significant (p<0.001, **Figure 3**). Accordingly, when the cut-off value of the TyG index was taken as ≥8.75 in determining the risk of PE in patients with DVT, the sensitivity was determined as 70.4% and the specificity as 76.9%.

Regression analysis was used to determine the risk of PE in patients diagnosed with DVT. In univariate regression analysis, obesity (yes or no), diabetes (yes or no), immobility (yes or no), thrombus location (proximal type versus distal and mixed type) and high TyG index (≥8.75) were identified as risk factors. In multivariate regression analysis, diabetes (p=0.001, OR: 3.65; 95% confidence interval (CI), 1.68-7.92) and TyG index cut-off value above 8.75 (p=0.005, OR: 11.2; 95% confidence interval (CI), 5-24.9) were independent risk factors for PE in patients with DVT (**Table 2**).

DISCUSSION

It has been reported that PE is seen in 50-60% of DVT patients, while DVT is seen in 13-93% of PE patients.[15] The clinical diagnosis of PE is nonspecific and the screening test D-dimer has a very low specificity despite its high sensitivity. Although CTPA is the most commonly used imaging method in patients with suspected PE, radiation exposure is its most important disadvantage.[15] Determining and identifying risk factors that are effective in the development of PE is very important in preventing serious complications such as mortality and morbidity. In this study, we analyzed clinical, radiological and laboratory risk factors associated with PE and found that the TyG index may be an important factor in the development of PE in patients with DVT.

TyG index has been reported to be a highly sensitive and reliable marker used in determining IR.[16] In recent years, the relationship between the TyG index and many cardiovascular and cerebrovascular events has attracted increasing attention. It has been reported that high TyG index is an important risk factor for CAD and is associated with the number of stenotic coronary arteries and the degree of stenosis.[10,17] Cerebrovascular disease with a high TyG index has been associated with more rapid neurological deterioration and increased mortality.[18,19] Recent studies suggest that venous thromboembolism is part of a "pan-cardiovascular syndrome" because they all result from the same pathophysiological processes, including hypercoagulability, endothelial damage, and inflammation.[20] To our knowledge, this current study is the first to investigate the relationship between TyG index and PE in patients with DVT. Our findings revealed that DVT patients with high TyG index had a higher risk of PE, and even high TyG index was an independent risk factor for PE in patients with DVT in multivariate logistic regression analysis.

It seems possible that the relationship between TyG index and PE may be mediated by several mechanisms. It is known that IR causes endothelial dysfunction and increases platelet activation.[21-24] Blood levels of fibrinolysis inhibitors such as plasminogen activator inhibitors are increased in patients with high IR.[25] In addition, IR may cause the thrombus to become more dense and become more resistant to lysis.[26] These events may explain the pulmunary thromboembolism that develops in DVT patients with high IR.

There are studies reporting that long-term immobilization is a clinical risk factor for PE.[27,28] Being bedridden for a long time can cause blood flow to slow down and small thrombi to coalesce to form larger thrombi.[29,30] Obesity is one of the leading causes of venous thromboembolism.[31] It has been determined that this risk increases as BMI increases and even becomes more pronounced when combined with other risk factors.[31,32] Adipokines secreted from adipose tissue may affect platelet function and cause endothelial damage.[21] In this study, we found that increased BMI and immobilization were risk factors for PE in patients with DVT in univariate regression analysis.

Table 1. Comparison of baseline characteristics and variables of the study patients

	Pulmonary embolism			
Parameters	No (n=182)	Yes (n=54)	Total (n=236)	p values
Age (years)	63.7±9.6	62.5±10.8	63.4±9.9	0.455[a]
Gender, n (%) Male Female	 82 (45.1%) 100(54.9%)	 21(38.8%) 33(61.2%)	 103(43.6%) 133(56.4%)	0.422[c]
BMI (kg/m^2)	26.4±3.8	27.8±4.3	26.7±3.9	**0.024[a]**
Smoking, n (%) No Yes	 133 (73.1%) 49 (26.9%)	 35 (64.8%) 19 (35.2%)	 168 (71.1%) 68 (28.9%)	0.239[c]
HT, n (%) No Yes	 128 (70.3%) 54 (29.7%)	 34 (62.9%) 20 (37.1%)	 162 (68.6%) 74 (31.4%)	0.306[c]
DM, n (%) No Yes	 142 (78.1%) 40 (21.9%)	 29 (53.7%) 25 (46.3%)	 171 (72.5%) 65 (27.5%)	**<0.001[b]**
CAD No Yes	 135 (74.2%) 47 (25.8%)	 35 (64.8%) 19 (35.2%)	 170 (72.1%) 66 (27.9%)	0.178[c]
Dyslipidemia, n (%) No Yes	 126 (69.2%) 56 (31.8%)	 34 (62.9%) 20 (37.1%)	 160 (67.8%) 76 (32.2%)	0.387[c]
Immobility No Yes	 143 (78.5%) 39 (21.5%)	 35 (64.8%) 19 (35.2%)	 178 (75.5%) 58 (24.5%)	**0.039[c]**
Location of DVT Proximal Distal Mix	 44(24.2%) 83(45.7%) 55(30.1%)	 22(40.7%) 15(27.8%) 17(31.5%)	 66(27.9%) 98(41.5%) 72(30.6%)	**0.026[c]**
WBC (10^9/L)	8.6±2.9	9.7±2.3	8.8±2.8	0.014[d]
CRP (mg/dl)	2.4±1.8	2.3±1.1	2.3±1.7	0.590[d]
ESR (mm/h)	27.8±11.9	26.8±11.5	27.6±11.8	0.614[d]
Neutrophil (10^9/L)	4.7±1.6	5.1±1.7	4.8±1.6	0.124[d]
Lymphocyte (10^9/L)	2.1±0.9	2.1±1	2.1±0.9	0.410[d]
PLT (10^9/L)	287±52	294±54	289±53	0.390[d]
HDL (mg/dl)	38.4±10.4	35.6±9.3	37.8±10.2	0.079[d]
LDL (mg/dl)	118.2±19.8	124.2±21.1	119.3±20.2	0.058[d]
Total cholesterol (mg/dl)	191.7±29.7	200.4±30.7	194.4±30.5	0.063[d]
Triglyceride (mg/dl)	133.5±39.7	147.2±51.8	136.5±43.1	**0.037[d]**
Glucose (mg/dl)	96.9±14.4	101.8±22.9	98.1±16.8	0.06[d]
TyG index	8.58±0.29	8.85±0.38	8.64±0.32	**<0.001[d]**
D-dimer (ng/ml)	4645±3914	5444±4409	4828±4037	0.202[d]

Notes: [a]Student's t-test with mean±standard deviation (SD). [b]Fisher's Exact test with n (%). [c]Chi-Square with n (%). [d]Mann Whitney U-test with median±interquartile range (IQR). Statistically significant results (p<0.05).
Abbreviations: BMI: Body-mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, DVT: Deep vein thrombosis, HB: Hemoglobin, WBC: White blood cell count, CRP: C-reactive protein, ESR: Eritrocyte sedimentation rate, PLT: Platelets, TyG: Triglyceride-glucose index, HDL: High density lipoprotein; LDL: Low density lipoprotein

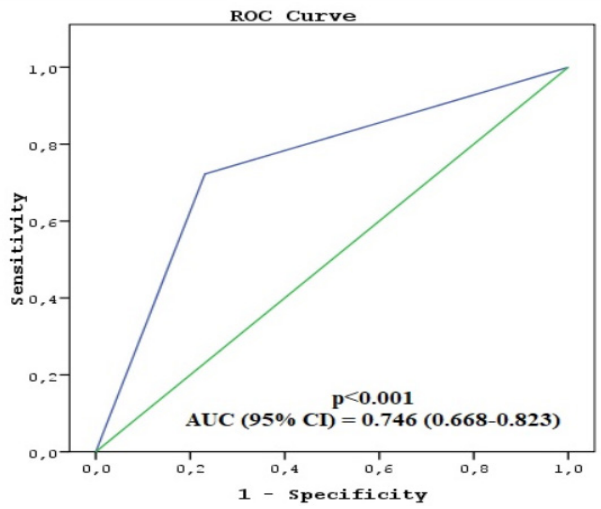

Figure 3. Receiver operating characteristic (ROC) curve and area under the ROC (AUC) of TyG index values in PE development

There are many studies reporting that diabetes is an independent risk factor for the development of PE.[33-37] Pathophysiologically, hyperglycemia-induced endothelial cytotoxicity and endothelial dysfunction, independent of insulin, induce a procoagulant and proinflammatory state, potentially leading to a prothrombotic environment in diabetic patients.[38,39] Chung et al.[33] found that diabetes increases the incidence of PE in a large nationwide study. This study findings revealed that diabetes was an independent risk factor for PE in multivariate logistic regression analysis, consistent with the literature.

It has been shown that the type of DVT that increases the risk of PE the most is the proximal type compared to other types.[32,40,41] Zhang et al.[1] reported that proximal-type DVT is an independent risk factor for PE. Konstantinides et al.[42] demonstrated that distal type DVT is stable and therefore less associated with PE. In this study, we found that the proximal

Table 2. Univariate and multivariate binary logistic regression analysis results to determine risk factors effective in pulmonary embolism

	Univariate		Multivariate	
	p values	OR (CI 95%)	p values	OR (CI 95%)
Obesity (BMI>30 kg/m²) Yes against no	0.037	1.96 (1.04-3.72)	ns	
DM Yes against no	<0.001	3.06 (1.61-5.8)	0.001	3.65 (1.68-7.92)
Immobility Yes against no	0.039	1.99 (1.02-3.85)	ns	
Location of DVT Proximal against distal and mix	0.013	0.45 (0.24-0.85)	ns	
TyG index ≥8.75 against <8.75	<0.001	8.66 (4.35-17.24)	0.005	11.2 (5-24.9)

Note: Statistically significant results (p<0.05).
Abbreviations: ns: Not significant, OR: Odds ratio, CI: Confidence interval, BMI: Body-mass index, DM: Diabetes mellitus, DVT: Deep vein thrombosis TyG: Triglyceride-glucose index

type was a risk factor for PE compared to other types in patients with DVT in univariate regression analysis.

Limitations

Our study had several important limitations. First, the retrospective nature of the study and its single-center nature prevented us from extrapolating our findings to the population. Secondly, due to the relatively small number of patients, future multicentre studies with a larger number of patients are needed to support our findings.

CONCLUSION

In conclusion, our findings suggest that diabetes, obesity, immobilisation, thrombus location and high TyG index are risk factors for PE in patients with lower extremity DVT, whereas diabetes and high TyG index are independent risk factors. This suggests that the incidence of PE in patients with DVT can be significantly reduced by controlling diabetes and associated factors contributing to high TyG index.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was obtained from the Siirt University Non-invasive Ethics Committee (Date: 05.07.2024, Decision No: 112266).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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