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Diagnostic Delay in Pulmonary Thromboembolism with and without cancer

Abstract

Pulmonary thromboembolism (PTE) is a common and potentially perilous disease . The symptoms of this disease are variable and non-specific which makes the accurate diagnosis of the disease too difficult. Accordingly, this study aimed at investigating the diagnostic and therapeutic delay in PTE and its association with CTA findings in 100 patients admitted to Imam Reza Hospital, Tabriz University of Medical Sciences. The patients were evaluated retrospectively and the demographic information including age, gender, the season of symptoms onset, thromboembolism, and other risk factors (including previous thrombotic events, malignancy, thrombophilia, surgery with immobilization in the last eight weeks, pregnancy in the last six months, and post-thrombophlebitis syndrome), ultrasound and CTA results and the rate of patient delay and diagnostic delay were recorded. The age average of the patients was 18.44 to 69.64 years and 50% of them were male. Most patients (40%) had a risk factor and 32 of them had no risk factor. Most of the patients had involvement in one of the pulmonary vessels (47%). Most of the cases (60.8%) were unilateral and lobar involvement (75.9%). The right-sided involvement was associated with diagnostic delay and overall delay and the main artery involvement was associated with lower referral delay and overall delay. Reportedly, a record of malignancy, positive results in pulmonary CTA and legs ultrasound, more pulmonary risk factors, and pulmonary involvements on the right side are associated with shorter referral delay and the initiation of diagnostic procedures.

Keywords: *Diagnostic delay, Pulmonary thromboembolism, CT angiography, cancer*

1Mohammad Reza Ghaffary,
1Associate Professor of Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, Email: Mohammadrezaghaffary@gmail.com
zahra taghizadeh *,pediatrics department of pediatrics tabriz medical Tabriz:zahrataghizadeh1366@gmail.com ,0000-0002-4532-2260*
3Shamsi Ghaffari*
Associate Professor of Pediatric Cardiology, Medical Faculty, Tabriz University, Tabriz, Iran, Email: Shamsi.ghaffari@gmail.com

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Introduction

Pulmonary thromboembolism (PTE) is a common and potentially perilous disease that internists frequently encounter during their daily work. This disease might have different severity and consequences. The incidence of the disease increases with age (1.3 cases per 1000 individuals in the age range of 65 to 69 years and 3.1 cases per 1000 individuals in the age range of 85 to 89 years) (1,2) and the annual incidence of this disease is estimated at 0.7 cases per 1000 individuals (3). Also, the mortality rate during the first year after the diagnosis of the disease is reported to be 17%. This amount results in 60,000 deaths annually (4). Moreover, the mortality rate of symptomatic cases in the first hour of the disease onset is estimated to be up to 10% (5,6).

PTE patients usually experience symptoms after vascular obstruction (7). Unfortunately, the symptoms of this disease are variable and non-specific which makes accurate diagnosis of it very difficult. In addition, due to the non-specific nature of the disease, it is very common for patients to experience a referral and/or diagnostic delay. Reportedly, the average time of the incidence of symptoms without hospitalization is between 4 and 7 days (8 and 6).

Various studies have considered the association and effective role of the severity of the disease (the incidence of several symptoms, hypotension, and syncope) and various risk factors as the reasons for the incidence of such delays, i.e., the incidence of some symptoms such as syncope, dyspnea, or chest pain either alone and or in combination can increase the clinical suspicion of this disease (8, 6, 9, 10, and 11). Due to their low sensitivity and specificity, proper interpretation of these findings is very important. Selecting an appropriate diagnostic strategy is very important in reducing mortality and complications caused by this disease (12).

There are several methods such as simple chest X-ray, ventilation-perfusion scintigraphy, computed tomography scan (CT scan), and computed tomography angiography (CTA) to examine the suspected patients of PTE that are used by centers based on the available facilities. (13, 14). Previous studies have investigated the importance of diagnostic and therapeutic delay of the disease.

The time of diagnosing the disease is very important in the incidence of therapeutic outcomes, recovery, complications, and mortality. Mortality caused by this disease in the first 7 days of the onset of the symptoms includes up to 25% of individuals which indicates the importance of timely diagnosis and avoiding diagnostic delay (15). Meanwhile, the accurate and timely diagnosis of the disease and its appropriate treatment can reduce the risk of disease recurrence and mortality.

Studies have found that the rapid treatment of patients leads to a decrease in in-hospital mortality (1.5%) compared to patients who were treated with a delay (more than 10 days from the onset of symptoms) (/5.23) (16) In addition, timely initiation of anticoagulant treatment reduces the mortality rate by decreasing the risk of post-thrombotic syndrome (17 and 18). According to a retrospective study in the United States, there is a diagnostic delay of DVT and PE in 20% of patients. This

delay was caused by patients' referral delay and the diagnostic and therapeutic delay (19).

Considering the limitations of previous studies and the lack of a similar study that investigated the association between the diagnostic and therapeutic delay of PTE with CTA findings and other parameters, we decided to investigate this issue in this study so that if there is a positive relationship between the findings of this study, we can use it for better control of the disease.

Materials and Methods

This was an applied and cross-sectional-analytical study in terms of objective and method, respectively. The study population included 100 PTE patients who had been admitted to Imam Reza Hospital of Tabriz from April 2011 to April 2012 and were evaluated retrospectively. A definitive diagnosis of the disease and defects in the patient's clinical records were the inclusion and exclusion criteria of the study, respectively.

This study consisted of reviewing files of 100 patients who had been admitted to Imam Reza Hospital with a diagnosis and PTE and were discharged from this hospital from April 2011 to April 2012. Accordingly, a patient was included in the study if the diagnosis of thrombosis and air in the lower limbs was confirmed by Doppler ultrasound, the pulmonary embolism was confirmed by CTA, and the above reports were available in the one's file. Demographic information including age, gender, the season of symptoms onset, thromboembolism, and other risk factors (including previous thrombotic events, malignancy, thrombophilia, surgery with immobilization in the last eight weeks, pregnancy in the last six months, and post-thrombophlebitis syndrome) was recorded. Also, the onset date of recent and related symptoms, the onset season of the date of the patient's visit by the medical staff due to the recent symptoms, and the date of definitive diagnostic tests including Doppler ultrasound and CTA were recorded. The findings of Doppler ultrasound were recorded as the location and the age of the clot, and the findings of CTA were recorded as unilateral or bilateral occlusion of the main or lobar arteries, the number of occluded arteries, and the age of the clot. The diagnostic delay has been expressed in days and no hours are used.

The method of data collection was through the review of patient's clinical records and the data collection tool was a questionnaire. Descriptive statistical methods (frequency, percentage, mean, and standard deviation) were used for statistical analysis. Chi-squared test (2) and the ANOVA statistical test were used respectively for comparing the qualitative and the quantitative findings between the groups. Data analysis was done by Spss16 software.

Findings

According to the results, 50 patients (50%) were male and 50 patients (50%) were female. The age average of the patients was 64.69 ± 18.44 years. The youngest and oldest patients were respectively 27 and 90 years old. The mean and median ages of the patients were 72 and 75 years, respectively (Figure 1).

Records of embolism in previous thrombosis, malignancy, surgery in the last 8 weeks, immobility in the last 8 weeks, and pregnancy in the previous 6 months were investigated in the study of risk factors.

As illustrated in Figure (2), most patients (40 patients, 40%) had a risk factor: Also, there were records of previous embolism and thrombosis in 13 patients (13%), malignancy in 13 patients (13%), surgery in the last 8 weeks in 39 patients (39%), immobility in the last 8 weeks in 34 patients (34%) and pregnancy in the last 6 months in 3% of the patients. Furthermore, 32 patients (32%) did not have any risk factors.

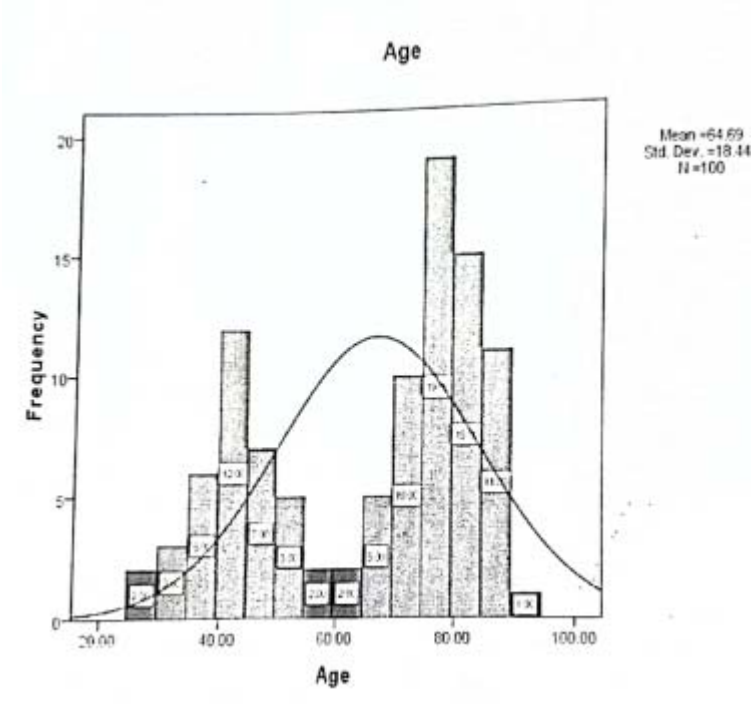

Figure 1: Age distribution of examined patients

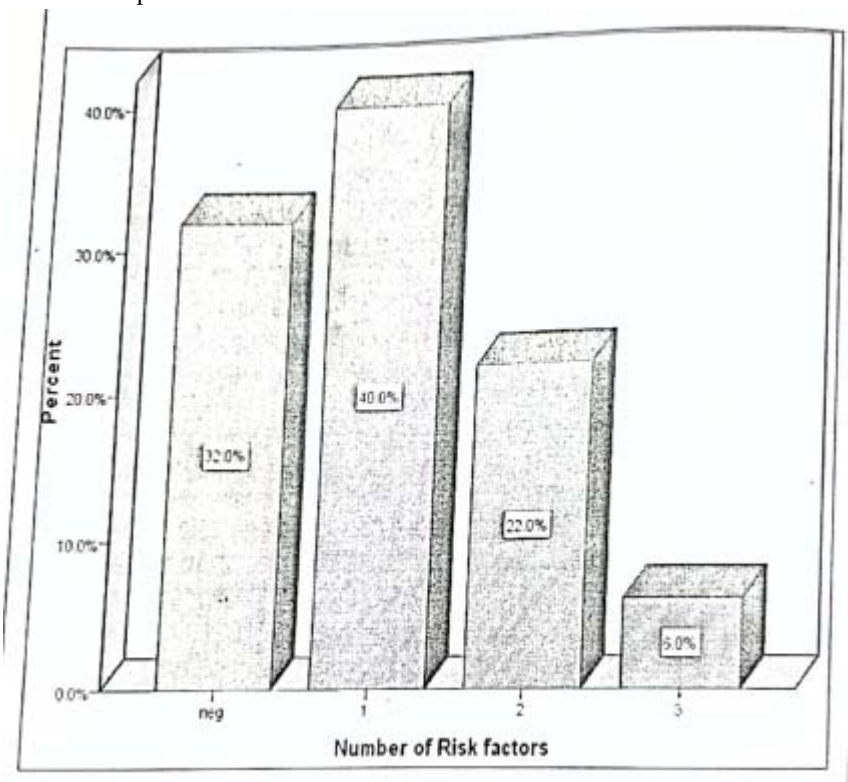

Figure 2: The number of risk factors for the incidence of thromboembolic events in the examined patients

Diagnostic methods

1. Ultrasound findings

The performed ultrasound on 69 patients was negative. Reportedly, among the patients with a positive ultrasound result, thrombosis has occurred in the left common femoral vein of 16 patients (16%), the right common femoral vein of 9 patients (9%), the left pinball vein of 3 patients (3%), and left external iliac vein of 3 patients (3%).

2. CTA findings

CTA reported pathological findings in 79 patients (79%). In other cases, CTA was not performed due to positive ultrasound. The number of involved pulmonary vessels was one vessel in 47 patients (247), two vessels in 29 patients (/29),

three vessels in 1 patient (1%), four vessels in one patient (1%), and five vessels in one patient (1%).

Among the 79 pathological cases, involvement was unilateral in 48 patients (60.8%) and bilateral in 31 patients (39.2%). Also, among 48 patients with unilateral involvement, 27 cases (56.3%) were on the right side and 21 cases (43.8%) were on the left side.

Pulmonary vascular involvement was experienced by 19 patients (24.1%) in the form of main vascular involvement and 60 patients (75.9%) in the form of lobar vascular involvement.

In terms of the incidence of the disease in different seasons of the year, 40 cases (40%) were in the fall, 33 (33%) in the spring, 14 (14%) in winter, and 13 (13 %) in summer.

3. Rate of referral and diagnostic delays

The average delay of the patients from the time of symptoms to the referral to the Imam Reza Medical Education Center was 4 ± 2.86 days. The minimum and maximum delay were 10 days (Figure 3). The average delay from the time of referral to performing diagnostic measures was 1.47 ± 1.36 days. The minimum and maximum delay were 0 to 4 days (Figure 4).

The average delay from the onset of symptoms to the completion of diagnostic procedures was 5.47 ± 3.27 days. The minimum and maximum delays were 1 and 14 days (Figure 5).

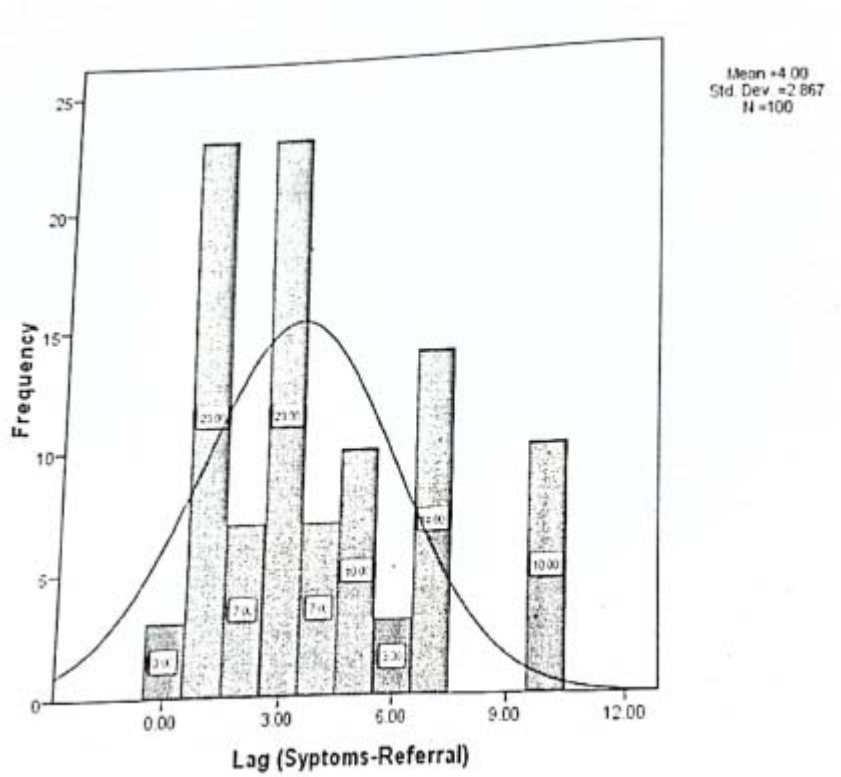

Figure 3: Distribution of patients' delay from the time of symptoms to the referral to Imam Reza Center

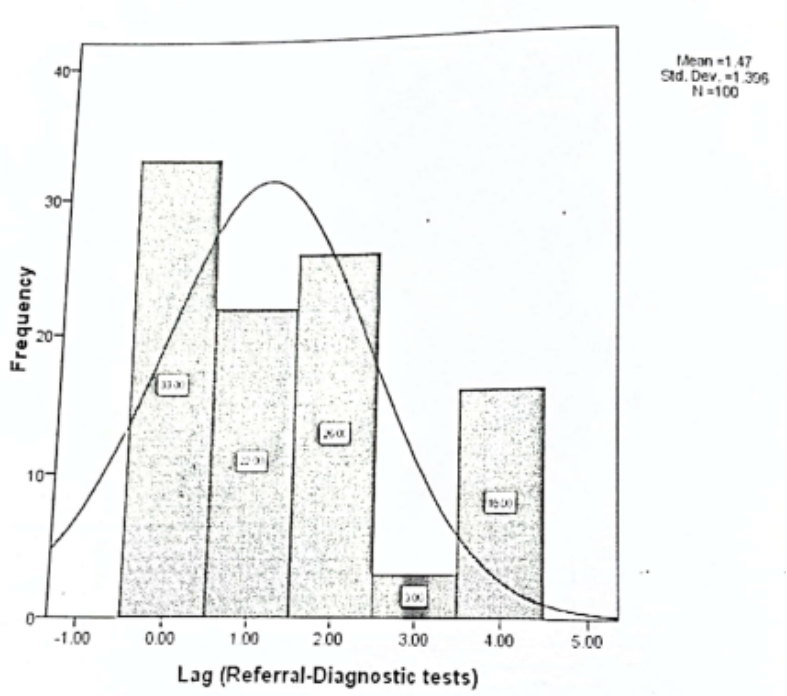

Figure 4: Distribution of patients' delay from the time of referral to performing diagnostic procedures

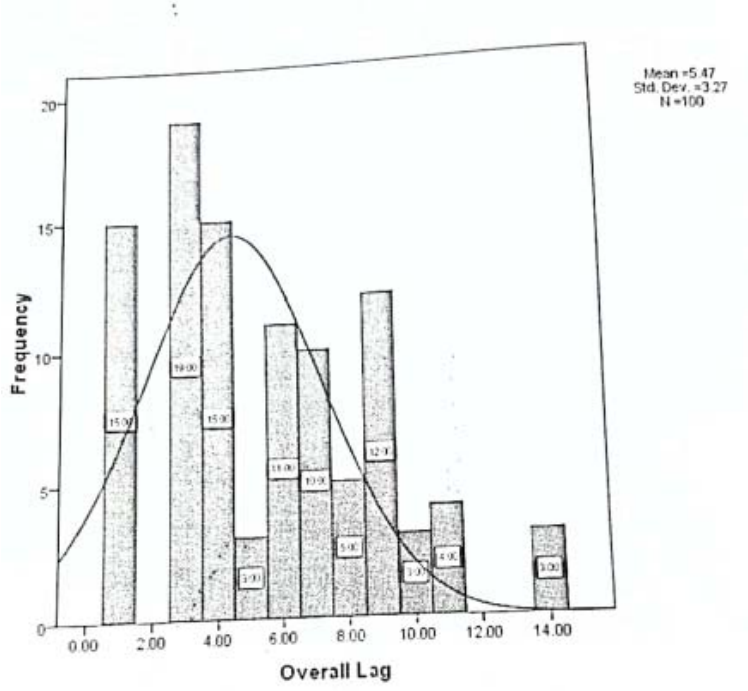

Figure 5: Distribution of patients' delay from the time of symptoms to diagnostic procedures

3. Examining the correlation of various findings of patients

Table (1) shows the rate of referral delay, diagnostic measures, and overall delay compared to different parameters.

Table 1: Examining the rate of delay according to other findings of the study

Variable		Referral Symptoms	P-value	Diagnostic Referral	P-value	Overall Delay	P-value
Gender	Male	4.2±3.04	0.44	1.18±0.19	0.03	5.4±3.3	0.83
	Female	3.7±2.69		1.76±1.33		5.5±3.2	
	Positive	3.76±2.7	0.75	1.3±0.63	0.65	5.07±2.49	0.64

Record of the previous thrombosis	Negative	4.03±2.89		1.49±1.47		5.52±3.37	
Malignancy	Positive	2.46±1.45	0.03	0.76±0.28	0.04	3.23±1.92	0.007
	Negative	4.22±2.95		1.57±1.41		5.8±3.3	
Surgery	Positive	4.07±2.95	0.83	1.35±0.23	0.52	5.43±3.66	0.93
	Negative	3.95±2.83		1.54±0.17		5.49±3.02	
Immobility	Positive	4.47±2.89	0.34	1.38±1.61	0.65	5.85±3.42	0.4
	Negative	3.75±2.84		1.51±1.27		5.27±3.19	
Pregnancy	Positive	2	0.22	2	0.5	4	0.43
	Negative	4.06±288		1.45±1.41		5.51±3.31	
CTA finding	Positive	3.92±2.69	0.6	1.81±1.31	P=0.000	5.73±3.05	0.11
	Negative	4.28±3.49		0.19±0.18		4.47±3.9	
Side of involvement	Right	3.37±1.9	0.17	1.22±1.01	P=0.000	4.59±2.45	0.002
	Left	4.52±3.77		2.85±1.38		7.38±3.55	
Being unilateral or bilateral	Unilateral	3.87±2.92	0.84	1.93±1.43	0.28	5.81±3.26	0.77
	bilateral	4.4±0.33		1.61±1.08		5.61±2.74	
Main or lobar artery	Main	5.1±2.57	0.02	1.89±0.87	0.74	5.33±3.13	0.03
	Lobar	3.55±2.64		1.78±1.42		5.33±3.13	

ANOVA test was used to evaluate the difference in the calculated delay values based on other findings, which were used for the season (P=0.26, P=0.53, P=13) and the number of involved pulmonary vessels (P=0.79, P = 0.84, and P = 0.95). The difference was not significant in any of the three referral delays, diagnostic and overall delays. Considering the ultrasound findings, diagnostic and overall delays between patients with different ultrasound results were significant ($p < 0.001$ for the diagnostic delay and $p = 0.002$ for the overall delay). Also, a statistically significant difference was observed between different groups with different risk factors concerning the overall delay (P=0.03).

Discussion

This study included the evaluation of 100 PTE patients who had been admitted to and treated in Imam Reza Hospital of Tabriz from April 2011 to April 2012. In this study, 50 patients (50%) were male and 50 patients (50%) were female, and the age average of the patients was 64.69 ± 18.44 years. The youngest and oldest patients were respectively 27 and 90 years old. Although there were nuance differences (22), the gender composition of this study was similar to most of the conducted studies such as Kaylain et al. (20), Alonso-Martinez et al. (21), and Castro et al. (8). Regarding the age average of the patients, there were similarities (8, 9) and differences (21, 22, 20), which might be considered as a result of the epidemiology of the disease, as well as differences in the underlying factors of PTE incidence in different regions.

The number of underlying factors was evaluated in this study. Most of the patients (40 patients, 40%) had at least one risk factor and 32 patients (32%) did not have any risk factors. Also, there were records of previous embolism and thrombosis in 13 patients (13%), malignancy in 13 patients (13%), surgery in the last 8 weeks in 39 patients (39%), immobility in the last 8 weeks in 34 patients (34%) and pregnancy in the last 6 months in 3% of the patients.

The number of risk factors has not been mentioned in previous studies. Only in Ageno et al. (23), 68.5% of patients had at least one risk factor for PE, which is remarkably similar to our results. In this study, 17% of patients had malignancy and 13.8% of them had a previous record of PE and DVT, which is similar to the results of this study. This similarity in the incidence of malignancy is also observed in Berghaus et al. (25) (16.5%). Bulbul et al. (26) reported that 69.4% of patients had at least one risk factor for the incidence of PTE. According to the results of this study, 30.6% of patients had a recent record of surgery with trauma. Kayhan et al. (20) introduced immobility of patients as one of the most common types of risk factors that had been observed in 0.36 patients. Contrary to this study, 5.8% of patients in Kayhan et al. (20) had malignancies. The results of Castro et al. (24) were different. Overall, the prevalence of risk factors seems to have many similarities in different studies.

It is noteworthy that CTA findings and their association with diagnostic delay were not mentioned in any study. In this study, most of the patients had involvement in one of the pulmonary vessels (47%). Most of the cases (60.8%) were unilateral and in the form of lobar involvement (75.9%). Furthermore, among 48 patients with unilateral involvement, 27 cases (56.3%) were on the right side and 21 cases (43.8%) were on the left side. The right-sided involvement was

associated with diagnostic and overall delay, and the main artery involvement was associated with lower referral and overall delay.

The average delay of patients from the time of symptoms to referral, the average delay from the time of referral to performing diagnostic procedures, and the average delay from the time of symptoms to performing diagnostic procedures were respectively 4±2.86, 1.47±1.36, and 5.47±3.27. The minimum and maximum delays were respectively 1 and 14 days. Unlike this study, in Kayhan et al. (20), the average referral and diagnostic delay of patients were respectively 7.9±15.2 and 0.5 ± 3.9. In Rahimizad et al. (22), the average incidence of symptoms until the first visit and the average time of incidence of symptoms until the definitive diagnosis of the patients was 4.19 ± 5.87 and 6.29 ± 7.28 days, respectively.

Various factors such as the cultural and educational status of the society and the access level of patients to different health services are effective in referring to medical centers. Hence, the diagnostic delay of patients since the onset of symptoms, regardless of the differences in the referral delay of patients, is very similar and it is between 5 and 7 days.

It was also observed that the malignancy test, positive results of CTA and ultrasound, and more risk factors and involvement to the right side are associated with shorter referral delay time in referring and diagnostic procedures, and the difference between the groups is significant in these cases. In the study of Ageno et al. (23), there was a significant relationship between the number of clinical findings and earlier diagnosis of the disease. In Kaylan et al. (20), non-specific findings in CTA were associated with diagnostic delay. Contrary to our study, Alonso-Martinez et al. (22) showed that patients with a previous record of VTE refer to the hospital earlier than other patients. In Castro et al.' (24), previous surgical history is associated with less diagnostic delay. In this study and other similar studies, risk factors have been associated with a shorter referral and diagnostic delay. Also, CTA findings can reduce the diagnostic delay if they are specific.

Conclusion

In this study, the rate of referral and diagnostic delay of patients was not higher than in similar foreign and domestic studies which are considered a positive factor. A record of malignancy, positive results in pulmonary CTA and ultrasound, more risk factors, and pulmonary involvements on the right side is associated with shorter referral delay and the initiation of diagnostic procedures. This shows the importance of paying attention to the history of patients and making the right decision to perform diagnostic procedures.

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