Research article

Epidemiologic study of patients with thrombotic events referred to a tertiary hospital in Southern Iran

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ABSTRACT

Background and aim: Thromboembolic events mainly occur in older age is related with high morbidity and mortality, and considerable health-care costs particularly in developing countries. Both arterial and venous thromboembolism has known risk factors such as hyperlipidemia, obesity, diabetes, cancer, major surgery, central catheter. We aimed to evaluate the occurrence of thrombotic events and related risk factors in a group of Iranian patients.
Methods: In this cross-sectional study, all patients (n = 99) who were complicated by thrombotic events referred to the Hematology Research Center of Shiraz University of Medical Sciences were investigated from 2015 to 2017, in Shiraz, Southern Iran. Data were collected from their medical records by a designed data gathering form.
Results: The median age of the occurrence of thrombosis was 51 (IQR: 31) years. From all thrombotic events 52.5% occurred in females. Venous thrombosis was more prevalent than arterial (61.6% vs. 38.4%). Hypertension, diabetes mellitus and ischemic heart disease were the most associated disease with thrombosis. Most of the patients (79.8%) had no episodes of relapse and the occurrence of relapse had no significant relationship with thrombophilia and underlying disease. Acceptable response rate for warfarin therapy was achieved in 46.5% with 5 mg and 43.4% with 5–7.5 mg.
Conclusion: Knowing the frequency and risk factors for thrombotic events lead to timely diagnosis and management of thrombosis. Atrial fibrillation and valvular rheumatic heart disease are the most common risk factors of thrombosis in our study showing prophylaxis is necessary in high-risk patients.

1. Introduction

Acute arterial thrombosis is the main cause of myocardial infarction and the most common cause of death in the developed countries [1]. The usual site of arterial thrombosis is cardiac and cerebrovascular and thrombosis in these vital organs cause significant mortality and morbidity [2].Arterial thrombosis usually occur due to rupture of atherosclerotic plaque [3].

Venous Thromboembolism (VTE) is the 3rd main vascular disease [4]. This vascular disease is caused by clot formation in venous system. It has multifactorial pathogenesis and arises from some interactions between acquired or inherited susceptibilities to thrombosis and various risk factors. It is categorized to two major groups: Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) [5, 6].

Triad of VTE is venous stasis, endothelial damage and a hypercoagulable state [7]. VTE is usually a silent disorder and pulmonary embolism, which is fatal, is the first presentation in many patients [8]. So because of non-specific manifestations the clinical diagnosis is usually intensive and unreliable [9].

There are some known risk factors for VTE such as major surgery, multiple trauma, hip fracture, lower extremity paralysis, cardiac and respiratory failure, prolong immobility, central venous catheter specially in children, estrogens (oral contraceptive pills), obesity, smoking, some inherited and acquired hematologic disease and cancer [10, 11, 12]. The major risk factors for arterial thrombosis are hyperlipidemia, smoking, diabetes, hypertension and abdominal obesity [13].

Thromboembolic events are responsible for common disease with recurrence that has primary and secondary prophylaxis [14].

In this study we aim to evaluate the occurrence of arterial and venous thromboembolic events as well as the underlying and associated disorders in an Iranian population.

2. Materials and methods

In this retrospective study, all patients (n = 99) who were complicated by thrombotic events referred to the Hematology Research Center of Shiraz University of Medical Sciences were investigated from 2015 to 2017, in Shiraz, Southern Iran. Data were collected from their medical records by a designed data gathering form. Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences. (Grant number = 16764).

Acceptable INR range is considered 2-3 in most patients including artificial heart valve replacement and 2.5–3.5 in non-artificial heart valve replacement (pig/animal valve).

2.1. Statistical analysis

Data was analyzed by Statistical Package for Social science (SPSS) vs. 23 (SPSS Inc, Chicago, Illinois, USA). Descriptive data were presented as mean, standard deviation, frequency, and percentage. Comparison of quantitative data between two groups was done by Student t test for independent samples or Mann-Whitney U test, as appropriate. Qualitative data was compared by Chi-square test among different groups. P value less than 0.05 was considered statistically significant.

3. Results

During the study period, 99 patients with thrombotic events had been referred to our center. Fifty-two patients (52.5%) were female. The median age of the occurrence of thrombosis was 51 years (range: 4–89, IQR: 31 years). Heart, lower extremities, and brain were the most common places of thrombosis (37.9%, 25.3%, and 20.7% respectively). Atrial fibrillation and valvular rheumatic heart disease were present with the same frequency of 13.1% in the patients. Other risk factors of thrombosis were smoking, obesity, beta thalassemia intermedia, post operation, post-partum, pregnancy, oral contraceptive pill. (All women were on contraceptive LD pills), immobilization, thrombophilia, Cushing syndrome, coronary artery bypass graft and idiopathic. Among associated diseases, hypertension, dyslipidemia, diabetes mellitus and ischemic heart disease were the most prevalent ones (17.2%, 12.1%, 12.1% and 7.1%, respectively). Other associated disorders (51.5%) consisted of liver cirrhosis, nephritic syndrome, sickle thalassemia, severe anemia, hypothyroidism, vasculitis, systemic lupus erythematosus, congenital heart diseases; Alzheimer disease and gastrointestinal bleeding (Table 1).

Venous thrombosis was more prevalent than arterial ones (61.6% versus 38.4%, respectively). Demographic and clinical characteristics of the patients with arterial and venous thrombosis were compared in Table 1.

All patients with venous thrombosis were on warfarin therapy and 40% of them have been on warfarin therapy for at least 2 years. Aspirin (80–100 mg, orally, once per day) was the most (74%) antiplatelet drug used in patients with arterial thrombosis. Thrombophilia tests including mutations of Factor V Leiden, Antithrombin III, methylenetetrahydrofolate reductase (MFTHFR), endothelial protein C receptor (EPCR), and Factor XIII deficiency, were present in 8 patients (8.1 %). Two of them have two, one has three and 5 patients have one thrombophilia risk factors.

The most common causes of hereditary thrombophilia were antithrombin III deficiency and mutation in MTHFR gene. Twenty patients (20.2%) had at least one episode of relapse and seventy-nine patients (79.8%) had no episode of relapse (15 patients (15.2%) experienced one episode and 5 patients (5.1%) experienced 2 or more episodes of thrombotic events). Demographic and clinical characteristics of the

patients with and without recurrence were compared and presented in Table 2. Median age of the patients had no significant difference between patients with and without relapse (45 (IQR: 26) vs. 55 (IQR: 31) years respectively, P = 0.10). Seventy five percent of the patients with relapse were females compared to 46.8% of patients without relapse (P = 0.03). The occurrence of relapse had no significant relationship with thrombophilia (P = 0.20). Moreover, the occurrence of relapse had no significant association with type of underlying or associated disease (P = 0.11, P = 0.13).

Acceptable response rate was achieved in 46.5% with 5 mg, 43.4% with 5–7.5 mg and 4% with more than 7.5 mg warfarin therapy.

4. Discussion

Our data suggest that common sites of thrombosis are lower extremities, heart, and brain. Deep vein thrombosis (DVT) is the most common type of thrombosis that affects 0.1% of persons per year. DVT is a potentially dangerous condition which is associated with morbidity and mortality. Therefore, prophylaxis and timely management of DVT are very crucial. Management of DVT can be mechanical or pharmacological by using anticoagulant therapy [15, 16]. Pulmonary embolism is the second most common type of VTE that is associated with high risk of mortality [17].

Our study populations are Caucasian ethnicity and the risk of recurrence thrombosis in Caucasians is lower than African Americans and Hispanics which is in accordance with our results showing 20% risk of relapse while 80 % of our patients had no episode of relapse [18].

Our study demonstrates a probable correlation of thromboembolic disease with atrial fibrillation and rheumatic heart disease. Enga KF and co-workers in a study investigated the relationship between atrial fibrillation and VTE and showed that risk of DVT and PE increase significantly during first 6 month of disease [19]. A population cohort

Table 1. Demographic and clinical characteristics of the patients with thrombotic events.

Clot type			
Parameters	Venous N = 61	Arterial N = 38	P value
Median Age (IQR), years	49 (28)	59 (36)	0.11
<30 N (%)	11 (19)	7 (18.9)	0.09
30-50 N (%)	21 (36.2)	6 (16.2)	
>50 N (%)	26 (44.8)	24 (64.9)	
Sex (female) N (%)	33 (54.1)	19 (50)	0.84
Relapse N (%)	14 (23)	6 (15.8)	0.45
Positive family history	14 (23)	11 (28.9)	0.63
Underlying disease N (%)			
Atrial fibrillation	7 (11.5)	6 (15.8)	0.66
Rheumatic heart disease (valvular)	7 (11.5)	6 (15.8)	
Others*	38 (62.3)	23 (60.5)	
Nothing	9 (14.8)	3 (7.9)	
Associated diseases N (%)			0.39
Hypertension	12 (19.7)	5 (13.2)	
Dyslipidemia	7 (11.5)	5 (13.2)	
Diabetes Mellitus	7 (11.5)	5 (13.2)	
Ischemic heart disease	2 (3.3)	5 (13.2)	
Others1**	33 (54.1)	18 (47.4)	

SD: standard deviation.

There are some missing data in some variables.

* Others: smoking, obesity, thalassemia intermedia, post operation and post-partum, pregnancy, oral contraceptive use, immobilization, thrombophilia, Cushing syndrome, coronary artery bypass graft and idiopathic.

** Others1: liver cirrhosis, nephritic syndrome, sickle thalassemia, severe anemia, hypothyroidism, vasculitis, systemic lupus erythematosus, congenital heart diseases, Alzheimer s disease, gastrointestinal bleeding.

Table 2. Comparison of demographic and clinical data between patients with and without recurrence.

	Recurrence		
Parameters	Yes N = 20	No N = 79	P value
Median Age (IQR), years	45 (26)	55 (31)	0.10
<30 N (%)	5 (25)	13 (17.3)	0.44
30-50 N (%)	7 (35)	20 (26.7)	
>50 N (%)	8 (40)	42 (56)	
Sex (female) N (%)	15 (75)	37 (46.8)	0.03
Thrombophilia N (%)	3 (15)	5 (6.3)	0.20
Underlying disease N (%)			
Atrial fibrillation	0 (0)	13 (16.5)	0.11
Rheumatic heart disease	5 (25)	8 (10.1)	
Others*	13 (65)	48 (60.8)	
Nothing	2 (10)	10 (12.7)	
Associated diseases N (%)			0.13
Hypertension	5 (25)	12 (15.2)	
Dyslipidemia	0 (00)	12 (15.2)	
Diabetes Mellitus	4 (20)	8 (10.1)	
Ischemic heart disease	0 (0)	7 (8.9)	
**Others1	11 (55)	40 (50.6)	

There are some missing data in some variables.

* Others: smoking, obesity, thalassemia intermedia, post operation and post-partum, pregnancy, oral contraceptive use, immobilization, thrombophilia, Cushing syndrome, coronary artery bypass graft and idiopathic.

** Others1: liver cirrhosis, nephritic syndrome, sickle thalassemia, severe anemia, hypothyroidism, vasculitis, systemic lupus erythematosus, congenital heart diseases, Alzheimer s disease, gastrointestinal bleeding.

based study also confirms that incidence of DVT and PE is significantly higher in patients with AF in comparison to control group [20]. Thromboembolism occurs frequently in patients with rheumatic heart disease [21].

In our results thrombotic events occurred 52.5 in females and 47.5% in males. This result is comparable with some published data that show no significant difference for the occurrence of VTE among men and women. However, there association between oral contraceptive consumption and post-menopausal hormone replacement therapy that can cause a higher frequency of thrombotic events in women in some situations [22].

The most prevalent associated disease in our study was hypertension, dyslipidemia, diabetes mellitus and ischemic heart disease.

In our study the prevalence of venous thrombosis was more than arterial thrombosis. Also, both arterial and venous thrombosis was more prevalent after age of 50; however, it was not statistically significant. Fritz R Rosendaal in his study demonstrate that the prevalence of arterial and venous thrombosis is age dependent and VTE is the most common type of thromboembolism up to age 40 but after that myocardial infarction and arterial embolism are at the top [23]. In fact, aging is a major risk factor for thrombosis and the incidence of venous thrombosis increases with age and it is very rare in young people as we observed in our study [16, 24, 25].

In this study most of patients had no experience of relapse. The process of relapse was more in females. The occurrence of relapse had no association with thrombophilia or type of underlying or associated disease. In contrast to our result, a study on 2554 patients with 1st episode of thromboembolism and their follow up showed that relapse occurs more in male [26]. The lower risk of relapse in female can contribute to higher prevalence of deep vein thrombosis in female which has low risk for relapse but risk of relapse is more in proximal deep vein thrombosis and pulmonary embolism [27]. In a prospective study to estimate incidence and risk factors for recurrence of VTE data analysis showed that proximal DVT, short course of anticoagulant medications, history of

thromboembolic events and cancer are major risk factors for relapse but patients with postoperative DVT had low rate of recurrence [28]. Thrombophilia is a challenging risk that in some studies similar to our study is independent risk factor for recurrence [29] but some studies showed a relationship between thrombophilia and recurrence of VTE [30, 31]. However, the importance of thrombophilia in adults is less than pediatric group and most of our study population was adults showing just 8% of thrombosis were related to hereditary thrombophilia.

Warfarin is drug of choice for VTE. Acceptable response rate of treatment with warfarin was achieved with 5–7.5 mg in our study. According to underlying cause of thrombotic events and achieving to target INR, we consider acceptable response rate. Guidelines recommend starting warfarin with 5 or 10 mg for most patients and keep INR 2–3 [32]. There is also evidence that long term use of low intensity warfarin with target INR of 1.5–2 significantly decreased risk of recurrent VTE [33].

One quarter of our patients had positive family history. Bezemer ID and co-workers conclude that family history is an important risk factor for patients with first episode of VTE [34]. On the other hand, there is evidence that demonstrate that family history is not strong risk factor [35].

It is reasonable to recognize high risk patients for recurrence of VTE and by available prophylaxis reduce the complications and health-care cost.

Our study was limited due to the retrospective design of the study, small number of patients, lack of the control group, and not available data in some cases.

5. Conclusion

Given the frequency and risk factors for thrombotic events in our study, timely diagnosis and management of thrombosis are vital to decrease morbidity and mortality rate. Atrial fibrillation and rheumatic heart disease are the most common causes of thrombosis in our study although other acquired and hereditary risk factors are also contributed in VTE that underscore prophylaxis and timely management are necessary in high-risk patients.

Declarations

Author contribution statement

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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