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ORIGINAL PAPER

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Venous Thromboembolism During Ten-year Follow up on Clinical Center University of Sarajevo

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ABSTRACT

Introduction: Venous thromboembolism (VTE) consists of two entities, deep venous thrombosis (DVT), and its complication, pulmonary embolism (PE). The main therapeutic goal is the prevention of this complication. **Aim:** The aim of the study was to present epidemiological data of patients with the diagnosis of deep venous thrombosis, with regard to the location of thrombosis, the value of fibrinogen and D-dimer in relation to the sex of the patients, the presentation of therapeutic modality, with the presentation of PE and treatment outcomes. **Methods:** The study has a retrospective and observational feature, covering the period from 2008 to 2017, and included 1154 patients with the diagnosis of deep venous thrombosis as a basic criterion for inclusion. Data on sex, age, diagnosis with thrombosis localization, hospitalization duration, administered therapy, D-dimer and fibrinogen values, pulmonary thromboembolism and mortality were collected. **Results:** The deep venous thrombosis was mostly located at the lower limbs - in 1079 respondents (93.5%), then at the upper limbs in 65 (5.63%) cases. The left side is more represented (58.9%) than the right (40.3%), which is statistically significant ($\chi^2=40.03$, $p<0.005$), while 0.9% of patients had DVT bilaterally. At the lower limbs is the most common iliac thrombosis, represented in 47% of thrombosis cases at the lower limbs. Subclavian axillary thrombosis has been reported in 3/4 cases at the upper limbs. The mean fibrinogen concentration in all respondents is 5.2 mg/L, for men 5.0 mg/L and for women 5.3 mg/L, above the reference values (1.8-3.8 g/L). The mean value of D-dimer was 7.33 mg/L for all respondents, 8.46 mg/L for women and 6.5 mg/L for men, which was high above the reference limit (0.55 mg/L). From baseline, 88 (7.6%) of respondents had proven/

high-grade pulmonary thromboembolism as a DVT complication in the observed period. Pearson correlation established a positive correlation between lethal outcome and patient age, $r=0.13$, $p<0.005$, followed by a higher incidence of lethal outcome after DVT in older patients. **Conclusion:** The incidence of venous thromboembolism is approximately equal among the genders, and increases with the age of the patients, especially in men. Fibrinogen and D-dimer values in hospitalized patients are higher than the reference, in both cases more among women. Multidisciplinary approach to patients, in cooperation with angiologists, pulmonologists, cardiologists and nuclear medicine specialists is an imperative. The development of a state-level registry that would follow the incidence of deep venous thrombosis, with reference to risk factors, is imperative and necessary in planning of community health system.

Keywords: deep venous thrombosis, treatment, D-dimer, pulmonary embolism, mortality.

1. INTRODUCTION

Venous Thromboembolism (VTE) consists of two entities, deep venous thrombosis (DVT), and its complication in form of pulmonary embolism (PE) (1). The incidence is about 1 in 1000 in the adult population (1), with an occurrence before age of 40 years (1 in 10,000), or a higher rate of occurrence later in life (5-6 in 1000 in patients after age of 80) (2, 3). Timely diagnosis of DVT is immensely important for preventing possibly fatal complications, pulmonary embolism, and later complications in the form of postflebotomy syndrome and pulmonary hypertension, or right heart strain (4). In the pulmonary embolism, a complete or partial obstruction of the lung ar-

tery circulation of the distal part of the lungs occurs, and in the event of an untimely (if possible) therapeutic action, a right heart failure (4) occurs. Prevention of venous thromboembolism emerges as an imperative, as well as the knowledge of risk factors that can lead to it. The development of venous thromboembolic registry in Bosnia and Herzegovina would provide us a much clearer insight into the direction in which preventive action should be taken. The therapeutic modality of acute conditions is based on therapy with heparin preparations and long-term therapy on derivatives of warfarin (with mandatory titration of therapy in relation to the values of prothrombin time and value of INR) or new oral anticoagulants (dabigatran, apixaban, rivaroxaban and edoxaban, while betrixaban has an indication for use in patients with acute, hospitalized patients and is not approved for use in the European Union) (5).

2. AIM

The aim of the study was to present the epidemiological data of patients with deep venous thrombosis diagnosis with reference to the location of thrombosis, the fibrinogen and D-dimer values in relation to the sex of the patients, the presentation of therapeutic modalities, and the description of the appearance of pulmonary embolism, with reference to the occurrence of mortality.

3. METHODS

The study has a retrospective and observational feature, covering the period from 2008 to 2017, and involved 1154 patients with the diagnosis of deep venous thrombosis as a basic criterion for inclusion. Data on sex, age, diagnosis with thrombosis localization, hospitalization duration, administered therapy, D-dimer and fibrinogen values, pulmonary thromboembolism and mortality were collected. The results of all of these analyzes were considered statistically significant at $p < 0.05$ or 95% confidence level. SPSS for iOS (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis of the data obtained. The following statistical techniques were used: chi-square test for the matching quality, chi-square independent test, Mann-Whitney U test, as well as Person's and Spearman correlation factor.

4. RESULTS

Out of the total number, 51.99% of patients were women. The chi-square matching test shows that the sex distribution in the sample is statistically not significantly different from the equal proportionality of the categories, χ^2 (1, $n=1154$) = 1.997, $p=0.15$. Analyzing the representation of males and females in the period from 2008 to 2017, on average, due to DVT is hospitalized annually about 60 ± 9.7 women and about 55 ± 7.2 men. The youngest respondent was 16 years old and the oldest 92 years with an average age of 58.67 ± 17 years. Most respondents were at age 35-64 years, or 543 (47.1%). In the 65+ group there were 474 (41.1%) of the respondents. A smaller percentage of respondents is at the age 18-34 years-134 (11.6%). Three respondents (0.3%) were the minors (<18 years). The deep vein thrombosis was

DVT location	Right		Left		Bilateral		Total	
	N	%	N	%	N	%	N	%
Iliac	178	15.4	324	28.1	6	0.5	508	44.0
Femoral	156	13.5	209	18.1	0	0	365	31.6
Popliteal	68	5.9	77	6.7	1	0.1	146	12.7
Crural	21	1.8	38	3.3	1	0.1	60	5.2
Jugular vein	5	0.4	3	0.3	1	0.1	9	0.8
Subclavian-axillary	28	2.5	21	1.8	0	0	49	4.3
Brachial vein	6	0.5	6	0.5	0	0	12	1.0
Forearm veins	3	0.3	1	0.1	0	0	4	0.4
Portal vein							1	0.1
Total	465	40.3	679	58.9	9	0.8	1154	100

Table 1. Location of deep venous thrombosis in the sample

Medications at discharge or lethal outcome	N	%
OAK (Acenocoumarol, Warfarin)	677	53.47
DOAK (Rivaroxaban, Apixaban, Dabigatran)	203	17.59
LMWH (Enoxaparin Na, Reviparin Na, Fondaparinux)	224	19.41
UF heparin	4	0.35
Other drugs (Acetylsalicylic acid, clopidogrel, dipyridamol)	6	0.52
Lethal outcome	40	3.47
Total	1154	100.00

Table 2. Pharmacological modalities

mostly located at the lower limbs—in 1079 respondents (93.5%), then at the upper limbs in 65 (5.63%) cases. Other reported cases were 9 (0.8%) of patients with DVT in the jugular vein area and 1 (0.1%) patients with thrombosis in portal vein. The left side is more represented (58.9%) than the right (40.3%), which is statistically significant ($\chi^2=40.03$, $p<0.005$), while 0.9% of patients had DVT bilaterally. The left side is more represented (60%) also observed for DVT in patients the lower limbs ($\chi^2=47.26$, $p<0.005$), while for upper limbs prevail the right hand 56.9%, though for the upper limbs this difference is not statistically significant ($\chi^2=1.24$, $p=0.26$).

At the lower limbs, the most common was iliac thrombosis, representing the 47% of thrombosis at the lower limbs. Subclavian axillary thrombosis has been reported in $\frac{3}{4}$ cases at the upper limbs (Table 1).

The mean fibrinogen concentration in all respondents is 5.2 mg/L, for men 5.0 mg/L and for women 5.3 mg/L, which is above the reference values (1.8-3.8 g/L). The mean value of D-dimer was 7.33 mg/L for all respondents, 8.46 mg/L for women and 6.5 mg/L for men, which was high above the reference limit (0.55 mg/L). The therapy that was most frequently prescribed at discharge was old oral anticoagulants (acenocoumarol and warfarin). Since September 2013, we have started to use direct oral anticoagulants in venous thromboembolism therapy, we usually prescribed rivaroxaban (at 17.33% of patients), and 19.15% of patients were released on enoxaparin sodium, while a small percentage of hospitalized patients were discharged/transferred to other clinics on unfractionated heparin, for example, at a

unit of intensive internist care in case of massive PTE, and a small percentage (0.5%) of hospitalized were discharged on antiaggregates (Table 2).

From baseline, 88 (7.6%) patients had proven/high-grade pulmonary thromboembolism as a DVT complication in the observed period. Pearson correlation was used to investigate the relationship between PTE and patient age and weak negative correlation was found, $r=-0.028$, $p=0.338$, which indicates a reduction in PTE frequency as a DVT complication in older patients. Among PTE patients, 51.1% were women and the remaining 48.9% were men. Chi-square independent test showed that this difference in PTE frequency among sexes is not significant, $\chi^2(1, n=1154)=0.003$, $p=0.955$, $\phi=0.005$. In 40 (3.47%) patients, lethal outcome was observed. There is a higher percentage of deceased women (65% women, 35% male), but the statistical significance is not confirmed by a matching chi-square test ($\chi^2=2.29$, $p=0.13$, $\phi=-0.49$).

Pearson correlation determined a positive correlation between lethal outcome and patient age, $r=0.13$, $p<0.005$, which mean higher incidence of lethal outcome after DVT in elderly patients. Spearman correlation indicated that a greater incidence of lethal outcome was present in patients with a provoked DVT, $r=0.128$, $p<0.000$; and in patients with pulmonary thromboembolism, $r=0.16$, $p<0.005$.

5. DISCUSSION

Most of the previous studies indicate that the DVT incidence is approximately equal among the genders, which corresponds to our results (6). The incidence of DVT increases with age, and the disease is rare before early adolescence; only 0.3% of patients in our study were in the group of minors. These results are consistent with previous reports. The study of incidence of deep venous thrombosis and pulmonary embolism in the observed 25-year period, states that in patients under 55 years of age, the incidence of venous thromboembolism is higher in women, which may be related to factors such as pregnancy, postpartum status, oral contraceptives, and in men, there is a notice of clear increase in incidence with age (7). However, the highest number of respondents in our study is in the 35-64 age group and there is an even higher incidence of DVT in men in this age group compared to women, and in the 65+ group there is a slightly higher number of women, corresponding to the data which are cited in the 2017 report that has compiled data from major epidemiological studies over the last 25 years, primarily on DVT at the lower limbs (8).

Our study has revealed that DVT is statistically significantly more present on the left side, which supports the above-mentioned report. This report also states that ilio-femoral DVT is 2 to 3 times more frequent than the crural DVT, while in our results in 4/5 cases of DVT at the lower limbs affected the iliac, the femoral vein or both. A Belgian study involving 1338 patients with DVT at the lower limbs found a similar distribution of thrombosis site as reported in our results (9).

The DVT is much rarer on the upper limbs, although its incidence increased from the 70s of the last century due to the use of transvaginal pacemakers and central venous catheters (10). Previous studies indicate that DVT occurs at

the upper limbs in 1 to 4% of all cases of DVT and in 18% of patients hospitalized with DVT (11). Since our respondents were hospitalized patients and that in 5.6% of DVT cases were at the upper limbs, this percentage was considerably lower than that reported in the literature. Usually DVT in upper limbs affect more than one vein, most commonly the vein of the subclavian and axillar vein. Deep distal veins (e.g. brachial, ulnar and radial) are affected in about 14% of cases; in our study the percentage is somewhat higher—24.6%. A real accurate estimate of the incidence and DVT prevalence of the upper limbs is difficult to make because the studies use different diagnostic means. Contrasting venography more often identifies this location of DVT in relation to ultrasonography or impedance plethysmography (12).

Pulmonary embolism diagnosis is a huge challenge, as classical symptoms are in many cases not present. In anamnesis, the most common symptom is dyspnea, while syncope indicates a massive, life-threatening pulmonary embolism. In essence, the clinician should have a look at highly predisposing factors—hip or leg fractures (surgery), spinal cord injuries, predisposing factors—arthroscopic knee surgery, central venous catheter, chemotherapy, chronic cardiac or respiratory cardiomyopathy, hormonal therapy, malignancy, oral contraceptive therapy, paralytic CVI, pregnancy, and thrombophilia (3). Minor factors include lying in bed for longer than 3 days, longer sitting (flight by plane or driving), age, laparoscopic surgery, obesity, varicose veins. Detection of thromboembolic disease remains an open field, where many innovations are possible, and corrections of the aforementioned findings. The results of the presented study are good grounds for further research, which would include a much larger sample.

Thromboembolic disease in the contemporary world, with an increasing incidence, represents a health problem, in which through counseling within the entire health care system, along with numerous preventive measures, could lead to much less incidence of recurrence, to a much better quality of life of the patient, with quality and timely diagnostic tests, and most importantly, to reduce the mortality of patients (14-16). In general, 3.5% of patients hospitalized with DVT in our study had a lethal outcome, which is a higher percentage compared to a large US study with mortality of 0.6% to 1.3% (13). In this study, it was confirmed that the incidence of mortality of all causes of DVT patients increases with age, indicating that the lethal outcome is probably due to PE in patients without comorbidity.

6. CONCLUSION

The incidence of venous thromboembolism is approximately the same among sexes, and increases with the age of the patients, especially among men. Deep venous thrombosis in 4/5 cases affect iliac or femoral vein, or both, and is more common on the left side. Fibrinogen and D-dimer values in hospitalized patients are higher than the reference, in both cases more among women. Multidisciplinary approach to patients, in cooperation with angiologists, pulmonologists, cardiologists and nuclear medicine specialists is imperative. The development of a state-level registry that would follow the incidence of deep venous thrombosis, with

reference to risk factors, is imperative and necessary to plan for the development of a community health system.

- **Author's contribution:** A.M., N.M. D.B. and M.S. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. A.M. and M.S. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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