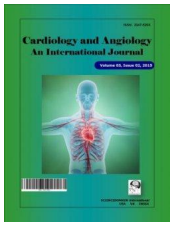

Cardiology and Angiology: An International Journal

7(1): 1-12, 2018; Article no.CA.38854
ISSN: 2347-520X, NLM ID: 101658392

Evaluation of Risk Factors Associated with Venous Thromboembolism in the Lebanese Population

Rizk Sara[1,2], Hammoud Nour[1,2], Zein Salam[1,2], Awada Sanaa[1,2], Rachidi Samar[1,2] and Al Hajje Amal[1,2*]

[1]Faculty of Pharmacy, Lebanese University, Beirut, Lebanon.
[2]Clinical and Epidemiological Research Laboratory, Faculty of Pharmacy, Lebanese University, Beirut, Lebanon.

Authors' contributions

This work was carried out in collaboration between all authors. Authors Rizk Sara and HN designed the study, performed the data collection and statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ZS, AS and Rachidi Samar wrote the protocol and performed manuscript preparation. Author Al Hajje Amal had the initial research concept, managed the literature searches and made the revision. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2018/38854
Editor(s):
(1) Jagadeesh Kalavakunta, Assistant Professor, Medicine, Cardiology Department, Michigan State University, Michigan and Homer Stryker M.D. School of Medicine, Western Michigan University, Michigan
Reviewers:
(1) Aşkın Ender Topal, Dicle University, Turkey.
(2) Antonione Santos Bezerra Pinto, Federal University of Ceará, Brazil.
(3) Masaki Hamamoto, JA Hiroshima General Hospital, Japan.
Complete Peer review History: http://www.sciencedomain.org/review-history/22767

Original Research Article

Received 16th October 2017
Accepted 13th January 2018
Published 18th January 2018

ABSTRACT

Background: Venous thromboembolism (VTE) is a multifactorial disease with a preventable characteristic. The knowledge of its predictive risk factors will help in preventing it. Therefore, the aim of this study is to assess the predictive risk factors of VTE in the Lebanese population so that effective recommendations can be drawn out.
Methodology: A retrospective case-control study was carried between the periods of March till June 2017 in two tertiary care hospitals in Beirut-Lebanon. Patients with a confirmed official diagnosis of VTE between the period going from 2008 till 2016 were taken as cases. Each case was randomly matched with 2 hospitalized controls. Questionnaires concerning VTE risk factors and symptoms were filled. Data were then entered into SPSS version 21 to explore the association between the risk factors and VTE. Bi-variate and multivariate logistic regression were done and a p-value less than *0.05* was considered.

**Corresponding author: E-mail: amalkeh@hotmail.com;*

Results: 430 patients were included in our study. Among these, 140 were cases of deep vein thrombosis and/or pulmonary embolism and 290 were matched controls. The results of the bi-variate analysis was significant for history of VTE, active cancer, general surgery, thrombophilia, immobility, active/recent pneumonia, trauma, and hormone replacement therapy/contraceptives use (p-value<0.001). It was also significant for history of coronary artery disease/myocardial infarction (p-value=0.018), neurological disease (p-value=0.001), stroke (p-value=0.033) liver diseases and varicose veins (p-value=0.045) and spinal cord injury (p-value=0.034). In multivariate analysis, the probability of VTE was significant for: VTE history (OR=32.8; p-value<0.001), thrombophilia (OR=25.4; p-value<0.001), major trauma (OR=11.5; p-value<0.001), general surgery (OR=10.2; p-value<0.001), immobility (OR=6.9; p-value=0.003), history of stroke (OR=6.8; p-value=0.001), serious liver disease (OR=6.5; p-value=0.016), cancer (OR=5; p-value<0.001), central venous catheter or pacemaker implantation (OR=4.4; p-value=0.025), active/recent pneumonia (OR=3.2; p-value=0.023), neurological disorders (OR=3; p-value =0.047), coronary artery disease/myocardial infarction (OR=2.3; p-value=0.017) and chronic lung diseases (OR= 2.2; p-value=0.033). There was a lack of testing for thrombophilia in the Lebanese hospitals.
Conclusion: The knowledge of these causative risk factors and their influence on VTE is crucial to initiate awareness in the population and strict prophylactic procedures for hospitalized patients. Furthermore, physicians must be more aware of the possible thrombophilic factors behind VTE cases by searching through thrombophilia testing. Larger studies must be done to investigate risk factors not detected in this study in order to further generalize the results.

Keywords: Venous thromboembolic diseases; deep vein thrombosis; pulmonary embolism; risk factors; clinical signs and symptoms.

1. INTRODUCTION

Venous thromboembolism (VTE) is a multifactorial disease with a preventable characteristic that often manifests clinically as deep vein thrombosis (DVT) or pulmonary embolism (PE) [1]. It is a recurrent disease, and 30% of previous cases can experience a recurrence within the next 10 years [2]. The pathophysiology and the risk factors behind this disease were described by Virchow by a triad of factors [3]. Hypercoagulable blood status is the first predisposing factor. It represents an abnormality in the level of blood constituents that belongs to thrombosis and which can be due to genetic or acquired risk factors such as deficiencies in Antithrombin, Protein C, Protein S, and factor V Leiden mutation [3,4] or acquired such as aging, obesity, cancer, and pregnancy [5]. Factor V Leiden mutation is a gain-of-function mutation [6] and found in 20% of patients with venous thrombosis [7]. In Lebanon, the prevalence in the general population reached 11.2% [8]. Cancer is also a major risk factor for VTE, by increasing the risk about 6-10 fold, caused by chemotherapy and immunosuppressive drugs and surgery [2,9]. Stasis in blood flow with the existence of other inflammatory disorders facilitates the activation of both intrinsic and extrinsic pathways [5]. Predisposing factors include: immobility, increased blood viscosity, obstruction and compression (tumors, pregnancy and obesity), heart failure (HF), previous VTE, antiphospholipid syndrome (aPL) and varicose veins [5,10]. Anti-phospholipid activates the coagulation factors and increases tissue factor (TF) [11]. The prevalence of aPL syndrome in patients with DVT reached 5% [12] and the risk for VTE in people with aPL increases 5 to 16 times [13]. Vessel wall injuries lead to platelet aggregation and activation of both intrinsic and extrinsic pathways [10]. This is mainly caused by major general surgeries, trauma, and central venous lines [4,10,14]. Major trauma associated DVT incidence reached 58% with PE occurring in 2% of these individuals [14].

Usually, the clinical signs and symptoms of DVT and PE are variable and dependent upon the degree of blockage and inflammation in the vessel wall. However, in some other cases, it may be clinically silent [15]. DVT can extend to the pulmonary circulation producing PE symptoms [16,17]. Diagnostic evaluations that are used to confirm the diagnosis of DVT include D-dimer assay, venous duplex ultrasound (VDU), impedance plethysmography, Magnetic Resonancy Imaging (MRI), and/or contrast venography [15].

The morbidity and mortality rates are high with VTE and therefore knowing its risk factors is necessary in order to maximize the prevention of

this disease in high-risk patients. These risk factors differ between populations since they depend on the genetic background. Since the evaluation of all these predisposing factors for VTE is not done in the Lebanese population yet, so the aim of this study is to assess the predictive risk factors of VTE in the Lebanese population so that effective recommendations can be drawn out.

2. METHODOLOGY

This is a retrospective observational case-control study. It was conducted using the inpatient records at two tertiary care Hospitals in Beirut-Lebanon from March 2017 till July 2017. All cases of VTE were collected in the period going from April 2008 till April 2016. Cases were included if they were aged 18 years and above and have a confirmed official diagnosis of DVT and/or PE [15]. Patients with no official confirmation of VTE were excluded from the study. Controls were those hospitalized patients in the internal medicine ward of the hospitals, aged 18 years and above, who were diagnosed with any condition other than VTE disease and selected by simple random sampling at the same study period. For every included case in the study up to two controls were recruited.

Data collection was done by two clinical pharmacy students (Master 2 research in clinical pharmacy and pharmaco-epidemiology) under the supervision of a senior clinical pharmacist (PhD) using computerized data records regarding the patients. A questionnaire including 5 parts was filled.

- The first part included the socio-demographic characteristics of the patients.
- The second part included some data regarding weight, height, smoking status of the patients, VTE diagnosis, diagnostic methods and medications history.
- The third part included the symptoms of DVT and PE including: edema, calf pain on dorsiflexion of the foot (Homan's sign), fragility or tenderness, warmth or erythema of the skin over the area of the thrombus, indurated cordlike tender subcutaneous venous segment, discolorations at the lower limbs, abrupt onset of pleuritic chest pain, shortness of breath, hypoxia, seizures, syncope, abdominal pain, fever, wheezing, hemoptysis, flank pain, delirium, tachycardia and tachypnea.
- The fourth part included the risk factors for VTE consisting of: obesity, diabetes (fasting plasma glucose ≥126 mg/dl [18]), hypertension (HTA) (systolic blood pressure ≥140/90 [19]), dyslipidemia (low density lipoprotein ≥130 mg/dL or Total cholesterol ≥200 mg/dL [20]), history of VTE, history of central venous catheter (CVC) or transvenous pacemaker placement, varicose veins, history of coronary artery disease/myocardial infarction (CAD/MI), history of cardiac arrhythmia, peripheral artery disease (PAD), history of HF, chronic lung diseases (asthma or chronic obstructive pulmonary disease COPD), liver diseases (cirrhosis or hepatitis), inflammatory bowel disease, chronic renal disease (glomerular filtration rate ≤90 mL per minute per 1.73m^2 for more than 3 months [21]), mixed connective tissue disease (features of systemic lupus erythematosus, systemic sclerosis, and polymyositis [22]), spinal cord injury, neurological diseases (schizophrenia and alzheimer), ischemic stroke, active/recent pneumonia, active cancer with or without chemotherapy (all cancer types), infectious diseases or sepsis, major general surgeries within the past 12 months (orthopedic surgeries, major vascular surgery, neurosurgery, abdominal or thoracic), major trauma within the past 12 months (pelvic fractures and femoral or hip fractures), thrombophilia (Antithrombin deficiency, protein C and S deficiency, factor V leiden mutation, aPL syndrome, prothrombin G20210A mutation), history of sleep apnea, recent burns, thyroid dysfunction (hypo or hyperthyroidism), history of inflammatory and hemostatic markers, immobility (limited or absolute lack of movement by the patient), cigarette smoking, alcohol consumption and family history of VTE (affected parents and/or siblings). For females pregnancy/post-partum and hormone replacement therapy (HRT) or contraceptives (generation type specification) are two identified risk factors.

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 21.

Epi-info was used to calculate the required sample size and 137 cases with 274 controls were needed. Descriptive analysis was done

first, followed by bi-variate analysis for qualitative and quantitative variables using chi-square, fisher exact and student-T test respectively. Differences with a two-tailed *p-value*<0.05 were considered as statistically significant. Adjusted odds ratio (OR) and 95% confidence intervals generated by the multiple logistic regression models were used to describe the relationship of the risk factors of VTE. Dependent variable is the occurrence of VTE or not (VTE / no VTE), and all other mentioned variables are the independent variables. Only variables with *p-value*<0.2 were used in multiple logistic regression.

3. RESULTS

This population consists of 140 cases of VTE and 290 controls for a total of 430 patients. The 140 cases were divided as follows: 78 with DVT, 38 with PE and 24 with both conditions DVT and PE. No significant differences were found between cases and controls for any of the socio-demographic variables. Age and gender didn't affect the occurrence of VTE. Only weight had significant effects on increasing VTE risk (p-value=0.031). The former was higher in VTE patients (Table 1).

Most of the patients with VTE were diagnosed using only Venous Duplex Ultrasound (VDU). The rest of the diagnostic procedures are shown in Table 2.

Out of the 140 patients diagnosed by VTE, the D-dimer test was done only for 25.7% of the patients and all patients except one had an abnormal elevated D-dimer result. History of thrombophilia was presented in 15.7% of the patients, and the majority had aPL syndrome (31%). One hundred eighteen patients with VTE were not tested for thrombophilia. Most of the patients had normal platelet count. Values are listed in Table 3.

Table 1. Population sociodemographic and behavioral characteristics (N= 430)

Characteristic		Cases (%)	Controls (%)	*p*-value
Total		**140**	**290**	
Gender	Male	68 (30.9%)	152 (69.1%)	0.455*
	Female	72 (34.3%)	138 (65.7%)	
Age groups (years)	<30	10 (35.7%)	18 (64.3%)	0.738*
	31-45	28 (35.4%)	51 (64.6%)	
	46-60	46 (31.1%)	102 (68.9%)	
	61-75	33 (28.9%)	81 (71.1%)	
	>76	23(37.7%)	38 (62.3%)	
Marital status	Single	26 (40%)	39 (60%)	0.087*
	Married	94 (29.3%)	227 (70.7)	
	Widowed	14 (48.3%)	15 (51.7%)	
	Divorced	6 (40%)	9 (60%)	
Weight average		77.57 ± 19.36	73.47 ± 17.78	0.031**
Active smoker	Yes	67 (31.5%)	146 (68.5%)	0.629*
	No	73 (33.6%)	144 (66.4%)	
Alcohol consumption	Never	133 (33.1%)	269 (66.9%)	0.62*
	Currently alcoholic	4 (22.2%)	14 (77.8%)	
	Ex-alcoholic	3 (30%)	7 (70%)	

**: Bi-variate chi-square and fisher exact test; **: Bi-variate student T-test, p-value< 0.05 is considered significant*

Table 2. Diagnostic procedures for cases (N=140)

Diagnostic procedures	Number	Percentage (%)
CUS with Doppler imaging only (VDU)	77	55%
CT Pulmonary angiography only	34	24.3%
Pulmonary angiography + Doppler	15	10.7%
CT angiography or MRI	8	5.7%
CT chest + Doppler	4	2.9%
Chest radiography only	2	1.4%
Total	140	100%

CUS: Compression UltraSonography; VDU: Venous Duplex Ultrasound; CT: Computed Tomography

Table 3. Laboratory tests for cases (N=140)

Laboratory test			Number	Percentage (%)
D-dimer	Tested (n=36)	Normal	1	2.8%
		Abnormal	35	97.2%
	Not tested		104	74.3%
Thrombophilia History	Tested (n=22)	Antithrombin deficiency	2	9.1%
		Protein C and S deficiency	3	13.6%
		Factor V leiden mutation	1	4.5%
		aPL syndrome	9	41%
		Others (Methylenetetrahydrofolate reductase C and A, prothrombin G20210A mutations)	7	31.8%
	Not tested		118	84.3%
Platelets	Tested (n=117)	Normal	86	73.5%
		Low	17	14.5%
		High	14	12%
	Not tested		23	16.4%

Diagnostic procedures confirmed the occurrence of 102 case of DVT and 62 cases of PE. The most prevalent symptoms for DVT were edema and leg pain, while the most prominent symptoms expressed in PE patients were shortness of breath, tachycardia and tachypnea, and pleuritic chest pain. Hemoptysis and hypoxia were as well presented in Tables 4 and 5.

Table 4. DVT symptoms (N=102)

Symptoms	Cases (%) 102
Edema	92 (90.2%)
Leg pain	76 (74.5%)
Warmth and erythema	36 (35.3%)
Homan's sign	33 (32.4%)
Leg discoloration	33 (32.4%)
Tenderness	25 (24.5%)
Abdominal pain	12 (11.8%)
Flank pain	6 (5.9%)

Table 5. PE symptoms (N=62)

Symptoms	Cases (%) 62
Shortness of breath	53 (85.5%)
Tachycardia	23 (37.1%)
Tachypnea	23 (37.1%)
Pleuritic chest pain	15 (24.2%)
Hypoxia	14 (22.6%)
Hemoptysis	8 (12.9%)
Fever	9 (14.5%)
Delirium	6 (9.7%)
Syncope	2 (3.2%)
Wheezing	1 (1.6%)

Concerning risk factors, the number of cases with a history of VTE was 39 (27.9%) compared to 5 patients (1.7%) in the control group (*p-value*<0.001).

Twenty seven patients (19.2%) in the cases group performed a recent general surgery (≤12 months) compared to 5 out of 290 patients in the control group (1.7%) (p-value<0.001). It was observed that a significantly high percentage of the patients in the cases group had a recent major trauma (*p-value*<0.001). A total of 22 patients (15.6%) in the cases group were presented with a history of thrombophilia compared to only 2 controls (*p-value*<0.001). The rest of the results are shown in Table 6.

For the multivariate logistic regression analysis, the highest risk was observed for the patients having a previous history of VTE as it increases the risk of recurrence by 33 times (ORa=32.8; p-value<0.001). Being diagnosed with thrombophilia will as well increase the risk by 25 times compared to those who don't have these genetic disorders (ORa= 25.4; p-value<0.001). Trauma and surgery can increase the risk by 11 and 10 times respectively. Analysis also shows that having an active cancer or placement of a CVC or pacemaker can also increase significantly the risk by about 5 times, active/recent pneumonia, neurological diseases, chronic lung diseases, and CAD/MI can significantly increase VTE risk (Table 7).

4. DISCUSSION

Each person at risk of VTE should be identified for their independent risk factors in order to

Table 6. Risk factors for VTE in cases and control groups (N= 430)

Risk factor	Cases (%)	Controls (%)	*p*-value
Total	**140**	**290**	
VTE history	39 (27.9%)	5 (1.7%)	<0.001*
History of CAD/MI	35 (25%)	45 (15.5%)	0.018*
Active cancer	28 (20%)	18 (6.2)	<0.001*
History of general surgery	27 (19.3%)	5 (1.7%)	<0.001*
History of thrombophilia	22 (15.7%)	2 (0.7%)	<0.001*
Immobility	21 (15%)	6 (2.1%)	<0.001*
Active/ recent pneumonia	21 (15%)	12 (4.1%)	<0.001*
History of neurological diseases	20 (14.3%)	14 (4.8%)	0.001*
History of major trauma	17 (12.2%)	8 (2.7%)	<0.001*
History of stroke	10 (7.1%)	8 (2.8%)	0.033*
History of CVC/pacemaker placement	10 (7.1%)	6 (2.1%)	0.009*
History of varicose veins	7 (5%)	4 (1.4%)	0.045*
History of liver disease	7 (5%)	4 (1.4%)	0.045*
History of use of HRT/oral contraceptives	7 (5%)	0 (0%)	<0.001*
History of connective tissue disease	5 (3.6%)	1 (0.3%)	0.015*
History of spinal cord injury	3 (2.1%)	0 (0%)	0.034*
Family VTE history	3 (2.1%)	0 (0%)	0.034*

**: Bi-variate chi-square; p-value< 0.05 is considered significant*
VTE: Venous thromboembolism; CVC: Central venous catheter; CAD: Coronary artery disease; MI: Myocardial infarction; HRT: hormone replacement therapy,
Non-significant variables (p-value >0.05): History of HTN (p-value=0.945) diabetes mellitus (p-value=0.121), chronic lung diseases (p-value=0.059), dyslipidemia (p-value=0.267), HF (p-value=0.061), Inflammatory markers (p-value=0.073), chronic renal disease (p-value=0.608), peripheral artery disease (p-value=0.439), cardiac arrhythmia (p-value=0.746), sleep apnea (p-value=0.091), inflammatory bowel disease (p-value=1); Active infectious disease/sepsis (p-value=0.137), pregnancy/postpartum (p-value=0.105)

reduce the risk of VTE. It is a multifactorial disease with both inherited and acquired characteristics. Major predisposing factors include trauma and surgery, active cancer, acute illness, neurological diseases, pregnancy and puerperium, oral contraception, and hormone therapy [23].

Age was not directly correlated with the development of VTE. A previous work on the evaluation of venous thrombosis in medical inpatients found that the association of VTE with age is non-significant [24].

Varicose veins is known as a predictive risk factor causing venous dilatation and stasis [10], but it was not found to be associated with VTE. This is similar to another Lebanese based study that found no significant correlation as well [8].

In multivariate analysis, weight was not associated with VTE events. Patients with increased weight will have an increased level of procoagulant factors as well as fibrinogen with decreased fibrinolysis being reflected by increased level of plasminogen activator inhibitor. This may reflect the increase of the risk of VTE by 2-3 times [5]. The increase of the weight gained imposes a higher VTE risk, where a linear relationship between obesity and VTE risk is found [25]. VTE risk can be potentially modified by nutritional counseling, exercise, medication and bariatric surgery [26].

Table 7. Multivariable logistic regression analysis for VTE risk factors

Risk factor	Exp (B) or ORa	*p*-value
VTE previous history	32.8	<0.001
History of thrombophilia	25.4	<0.001
Acute/ recent major trauma	11.5	<0.001
History of general surgery	10.2	<0.001
Immobility	6.9	0.003
History of stroke	6.8	0.001
Serious liver diseases	6.6	0.016
Active cancer	5	<0.001
Central venous catheter or pacemaker placement	4.4	0.025
Active/recent pneumonia	3.2	0.023
History of neurological diseases	3	0.047
History of CAD/MI	2.3	0.017
History of chronic lung diseases	2.2	0.033

HRT and pregnancy/postpartum can increase VTE risk [27]. The overall incidence of pregnancy-associated VTE is about 200 per 100,000 woman-years [2] Women who are on HRT have a 2 to 4 fold increased risk [27], while the incidence of DVT in post-partum period was 20 times higher compared to an age-matched cohort of non-pregnant women [4]. In this study both were not seen to be associated with VTE. The cause can be linked to the missing data in patient files and to the fact that this sample size was small to detect pregnancy associated VTE.

Having a family history didn't influence VTE risk which contradicts with a study done with an ORa= 2.7 [28]. Such information is not well recognized as a key factor and thus collected data were missing some information regarding the family history.

Patients having a history of VTE are at 33 times increased risk of recurrence. A previous VTE is the main risk factor for a second one [29]. The risk of recurrence of DVT or PE is equal to 15.5 and the risk is higher for individuals with previous idiopathic VTE than for those with secondary VTE [30]. Because of this high possibility, continued anticoagulation after the initial VTE will reduce the risk of recurrence, but must carefully weigh the bleeding risk of treatment [31].

Thrombophilia was the second most implicating risk factor that increased the occurrence of VTE diseases in Lebanese patients (ORa=25.4, p-value<0.001) with a prevalence of 15.7% of the cases. Another Lebanese study found that the relative risk for VTE increases 2 to 3 folds for prothrombin G20210A mutation alone and 20 folds for a combination of prothrombin mutation and factor V Leiden mutation [6]. The prevalence of factor V mutation in Lebanon reached 17.4% and 1.2% for protein C and S deficiency [32] compared to 4.5% for factor V mutation and 13.6% for protein C and S deficiency in this study. On the other hand, the prevalence of aPL syndrome was 41%. This discrepancy may be due to differences in the study design and to the fact that patient files were missing some data including thrombophilia tests which are not routinely done in Lebanese hospitals. One hundred and eighteen cases of VTE were not investigated for thrombophilic disorders. Anti-phospholipid antibodies such as the lupus anti-coagulant and anti-cardiolopin anti-bodies target the phospholipid binding plasma proteins and cardiolipin (anionic phospholipid) respectively, leading to the activation of coagulation factors, cellular apoptosis and increased TF [11]. Testing for thrombophilia helps in secondary prevention, determines the duration of anti-thrombotic medications post thrombosis and aids in primary prevention for the patient's relatives. Patients with unprovoked thrombophilia and unidentified thrombophilic disorders in which anti-coagulant medications has been stopped could be placed at a high risk of recurrence [33]. Because of this high risk, it is recommended that anticoagulation should be given for 3 months for patients with a first unprovoked VTE and a high risk of bleeding and continued without a scheduled stop date except for patients with a high risk of bleeding [34].

Temporal conditions such as trauma and surgeries are associated with increased blood coagulability due to tissue thromboplastin release, a stasis of blood due to immobility and with the reduced fibrinolytic activity especially after surgeries [10]. Risk is highest with major traumas involving surgeries such as pelvic fractures (61%), or leg fractures (femoral or hip) (80%) and it is low (19%) people without surgery with lower limb plaster casts [12]. The first controlled trial of anticoagulant prophylaxis after hip fracture showed a reduction from 10% to 0% of death from PE [4]. In a large population based retrospective case-control study, trauma was seen to increase the risk of VTE occurrence by 12 times (ORa=12.69, p-value<0.001) [35]. Results in this study are similar (ORa=11.5, p-value<0.001). The probability for VTE after general surgeries is augmented 10 times (ORa= 10, p-value<0.001). These patients are at a high risk for VTE as it is seen that half of the patients undergoing such surgeries will develop VTE with 10 times increased risk [4]. Antithrombotic prophylaxis is recommended for patients undergoing total hip or knee arthroplasty and hip fracture surgery for a minimum of 10 to 14 days. An extending thromboprophylaxis, VDU before discharge and the use of a compression device is recommended as needed [36]. Thus, strict adherence to anti-coagulant medications and reconsiderations about surgical decisions when elective and heading towards the use of laparoscopic techniques can decrease the risk of VTE.

Immobility increased the risk of VTE occurrence by 7 times (ORa=6.9; p-value=0.003). It predisposes to VTE through blood stasis especially in the venous valves pockets, leading to inflammation and hypercoagulability [37] and will ultimately increase the level of pro-coagulant

factors, decrease their elimination and increase oxygen tension. This will facilitate the activation of the intrinsic and extrinsic pathways [5]. The occurrence of VTE after bed resting for less than 1 week reached 15% of patients and this incidence even increased to 80% after being immobile for a longer period [4]. The relative risk estimates ranges from 3 to 11% [38]. Limited evidence based from studies on immobile patients secondary to spinal cord injury, recommend 4 to 6 months of initial anticoagulation for permanently disabled patients with lifelong prophylaxis provided only to those who have recurrent or a strong genetic susceptibly for thrombosis [39].

The effect of liver diseases is still not very well established. The risk for VTE was increased by approximately 7 times (ORa=6.6, p-value=0.016). Some studies found a 90% reduction of risk of VTE, while some observed VTE in 6.3% of hospitalized patients with liver diseases [40]. A nationwide Danish case-control study found that the relative risk of VTE was significantly higher in patients with liver disease, ranging from 2.06 for liver cirrhosis to 2.10 for non-cirrhotic liver disease [41]. Although patients with liver diseases may have a declined count in the coagulation factors, they may also have a decreased production of protein C and S, thrombomodulin and tissue plasminogen activator [42]. This indicated that there is still a need to prove the association between VTE and liver diseases and therefore the use of VTE prophylaxis should be individualized [42]. The safety of VTE prophylaxis or treatment in cirrhosis is unclear [41].

The risk of VTE in patients having a history of stroke was increased by 7 times (ORa=6.8; p-value=0.001). Incidence of DVT after stroke reached 50% within 2 weeks without and 2 to 22% with heparin prophylaxis [43]. Patients with ischemic stroke had an overall of 3 times higher risk of VTE [44]. The risk is increased in individuals with limb paralysis or weakness, physical immobility, previous VTE, dehydration, or comorbidities such as malignant diseases or blood hypercoagulability [45]. Patients with such increased risk should receive prophylactic treatment, keep well hydrated and be mobilized as soon as possible [45].

Active cancer increased the risk of VTE by 5 folds (ORa=5; p-value<0.001). Active cancer accounts for about 20% of all incident VTEs especially after chemotherapy [46]. Cancer alone was associated with a 4.1-fold risk of thrombosis [46]. The cause of this association results from stasis of blood due to tumor compression, vascular injury caused by extravasation of tumor cells or the therapeutic process, and hypercoagulability caused by released pro-coagulant factors from cancerous cells [47]. Despite the risk, there is still a need for randomized controlled trials to determine the benefits of long term anti-coagulant therapy [37]. The American Society of Clinical Oncology recommends the use of a validated scoring system to identify patients with a high risk of VTE and so requiring thromboprophylaxis [48].

A CVC or transvenous pacemaker associated VTE incidence reached 9% [23], while others found a range between 0 and 28% [49]. A previous population based case control study found that the imposed risk reached an ORa of 5.6 [35]. The obtained results correspond to those of previous studies (ORa=4.4, p-value=0.025). The cause behind this is related to the interaction between the risk factors with CVC and pacemaker and to the CVC itself, such as its material polyvinyl chloride, tip location, vascular trauma (inflammation, stasis, hypercoagulability) or even the entry site [49].

Pneumonia and chronic lung diseases such as asthma and COPD are well known risk factors [26]. Patients with chronic lung diseases had a 2 times increased risk of VTE (ORa=2.2, p-value=0.033). It is found that the hazard ratio of COPD associated VTE is found to be 2.05 [50]. Active/recent pneumonia increased the risk by 3 times (ORa=3.2; p-value=0.023). In a nationwide study, patients with pneumonia had the risks of developing DVT and PE by 1.78 and 1.97-fold respectively. The incidence was the highest in the first 4 weeks following an acute infection [51]. This is caused by persistent systemic inflammation and fibrin deposition, endothelial dysfunction and vessel wall damage [51]. Pneumonia should be considered as a risk factor for VTE even after the recovery of the patient [51]. Vaccination against pneumonia especially in elderly can prevent its occurrence.

Neurological diseases are associated with 3 times increased risk (ORa=3; p-value=0.047). This is linked to the lack of mobility and hypercoagulable state. The incidence of VTE in hospitalized psychiatric patients with dementia who are older than 75 years reached 8.2% and further increased with increased hospitalization period [52].

The association was significant with a 2 times increase in the risk (ORa=2.3, p-value=0.017). Patients with a previous MI had 51% higher risk of VTE (OR=1.51) compared to those without [53]. Both hospitalization and the temporary inflammatory or procoagulant conditions are behind this relation [54]. Studies are still paradoxical without drawing a conclusion about the relationship between VTE and arterial thrombosis [54].

Other disorders such as HTA, diabetes mellitus and dyslipidemia were not associated with VTE. A meta-analysis found no association between HTA and VTE (*p-value*=0.11) [55]. HTA may be associated with inflammation and vascular wall damage, but the relation is still to be investigated [55]. For diabetes mellitus, the results obtained in this study were consistent with other studies concluding an absence of correlation between diabetes and VTE and that in many of them it was confounded with surgery, illnesses, or residency [56]. For dyslipidemia, the Copenhagen study found no association between dyslipidemia and VTE [57].

HF and VTE were not associated although VTE is more likely to occur for patients with HF in which the risk is significantly increased from 1 to 3 times (ORa ranging from 1.74 to 2.93) [58]. The majority of VTE events in congestive HF are clinically silent [58] making it more undetectable as the screening for asymptomatic patients in Lebanese hospitals is not done. The incidence of VTE in hospitalized HF patients is probably low. It is low to the extent that the European Society of Cardiology doesn't warrant thromboprophylaxis for these patients [59].

Diagnostic evaluations that are utilized to confirm the diagnosis of DVT include: D-dimer assay, VDU, impedance plethysmography, MRI, and/or contrast venography [15]. D-dimer test measures the degradation product of cross-linked fibrin. This technique has low specificity and thus additional tests such as ultrasonography must be done when it is positive [18,60]. The first step in making the diagnosis of DVT is to establish the probability that a DVT is present using the Well's score and D-dimer level [60]. When the Well's score result is >2 then the condition is likely, but if the result is <2 then patients are unlikely to have a DVT. D-dimer evaluation should be done when well's score is <2 to further exclude the VTE. However, VDU should be done for all patients with a Wells' score of 2 or more, or for patients with a result <2 but have an elevated D-dimer level. Diagnosis of PE can be done through pretest probability testing similar to that of DVT and followed by: conventional pulmonary angiography, CT angiography and ventilation-perfusion (V/Q) scanning [60]. From a total of 140 VTE cases, the D-dimer test was only done for 36 patients. Screening for thrombophilia was not performed in Lebanese hospitals. Only 22 patients with VTE came with a history of thrombosis compared to 118 patients with VTE and without investigation.

5. STRENGTH POINTS

Only two well trained investigators filled the questionnaires. This decreased investigator bias. Cases were well selected and identified in the hospitals by choosing patients with proved occurrence of VTE through diagnostic imaging techniques. Therefore they were well separated from the controls avoiding thus misclassification bias. Controls were selected by simple random sampling from lists of hospitalized patients preventing the selection bias as well. Multi-variable logistic regression analysis was done to eliminate the confounding bias. This study has a good external validity as the results obtained are well conformed to the literature from an epidemiological and biological point of view.

6. LIMITATIONS

The retrospective nature of this study created some limitations as some data and laboratory tests were missing. Furthermore, such type of studies doesn't allow us to investigate some important risk factors such as the effect of traveling, stress and food regimen. Controls are taken from hospitals, where patients are usually poly-pathological and thus may underestimate or overestimate certain risk factors. The results obtained are restricted for hospitalized patients, thus, they may not be extrapolated to the general population.

7. CONCLUSION

Having a thrombophilic disorder was the second most implicating factor for VTE. Despite, these results showed a remarkable lack of research for thrombophilia in the Lebanese hospitals. Physicians must recognize the importance of such risk in the Lebanese population. Rigorous testing for genetic abnormalities in young patients especially those with a family history of VTE is recommended. It is also shown that the evaluation of D-dimer level was highly missing.

Such laboratory test can conclude the absence of VTE by its high sensitivity. This procedure is effective and decreases the cost burden on the patients. The risk factors, which were proved to highly increase the risk of VTE, are preventable ones including previous VTE, immobility, traumas, surgeries, and cancer. The importance of patient education regarding the risk factors and symptoms of VTE can play an important role in the prevention and thus reducing its prevalence in the Lebanese society.

Further studies incorporating a larger sample size and covering a wider number of Lebanese hospitals will help to further generalize the results and effectively identify other risk factors that this study was not powered enough to recognize.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zhu T, Martinez I, Emmerich J. Venous thromboembolism risk factors for recurrence. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;29:298–310.
2. Heit J, Spencer F, White R. The epidemiology of venous thromboembolism. Journal of Thrombosis and Thrombolysis. 2016;41:3–14.
3. Makin A, Silverman SH, Lip GYH. Peripheral vascular disease and Virchow's triad for thrombogenesis. Q J Med: An International Journal of Medicine. 2002;95: 199–210.
4. Anderson F, Spencer F. Risk factors for venous thromboembolism. Circulation. 2003;107:9-16.
5. Reitsma PH, Versteeq HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012; 32:563–568.
6. Khan S, Dickerman J. Hereditary thrombophilia. Thrombosis Journal. 2006;4(15):1–17.
7. Rosendaal F, Reitsma P. Genetics of venous thrombosis. Journal of Thrombosis and Haemostasis. 2009;7:301–304.
8. Zaatari GS, Otrock ZK, Sabbagh AS, Mahfouz RA. Prevalence of factor V R2 (H1299R) polymorphism in the Lebanese population. Pathology. 2006;38(5):442–444.
9. Esmon C. Basic mechanisms and pathogenesis of venous thrombosis. Blood Reviews. 2009;23(5):225–229.
10. Hirsh J, Hull R, Raskob G. Epidemiology and pathogenesis of venous thrombosis. Journal of the American College of Cardiology. 1986;8(6):104–113.
11. Farmer-Boatwright MK, Roubey RA. Venous thrombosis in the antiphospholipid syndrome. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;29(3):321–325.
12. Kyrle P, Eichinger S. Deep vein thrombosis. The Lancet. 2005;365(9465): 1163–74. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;29:321–325.
13. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factorsfor thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: A systematicreview of the literature. Blood. 2003;101(5):1827–1832.
14. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Journal of Blood Transfusion. 2011;9(2):120–138.
15. Skinner N, Moran P. Deep Vein Thrombosis - DVT, Case Management Adherence Guidelines. 2008;1. Available:https://www.scribd.com/document/71686752/DVT
16. Tapson VF. Advances in the diagnosis and treatment of acute pulmonary embolism. F1000 Medicine Reports. 2012;4(9):1–11.
17. Miniati M, Cenci C, Monti S, Poli D. Clinical presentation of acute pulmonary embolism: Survey of 800 cases. PLOS ONE. 2012; 7(2):1–7.
18. Herman W, Kalyani R, Cherrington A, Coustan D, Boer I, Dudle R, et al. Standards of medical care in diabetes – 2017. American Diabetes Association. 2017;40:1-142.
19. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults (JNC 8). JAMA. 2014;311(5):507-520.

20. Lloyd-Jones D, Morris P, Ballantyne C, Birtcher K, Daly Jr. D, DePalma S, et al. 2016 ACC expert consensus decision pathway on the role of Non-Statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. American College of Cardiology. 2016;68(1):92-125.
21. Razmaria A. Chronic kidney disease. JAMA. 2016;315(20):2248. Available:https://jamanetwork.com/journals/jama/fullarticle/2524193
22. Greidinger EL. Mixed Connective Tissue Disease (MCTD); 2016. Available:https://rarediseases.org/rare-diseases/mixed-connective-tissue-disease-mctd/
23. Heit JA. Epidemiology of venous thromboembolism. Nature Reviews Cardiology. 2015;12(8):464–474.
24. Zakai N, Wright J, cushman M. Risk factors for venous thrombosis in medical inpatients: Validation of a thrombosis risk score. Journal of Thrombosis and Haemostasis. 2002;2(12):2156– 2161.
25. Horvei L, Braekkan S, Hansen JB. Weight change and risk of venous thromboembolism: The Tromso study. PLos One. 2016;11(12):1-13.
26. Goldhaber S. Risk factors for venous thromboembolism. American College of Cardiology. 2010;56(1):1–7.
27. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism: A five-year national case-control study. Contraception. 2002; 65:187–196.
28. Noboa S, Le Gal G, Lacut K, Mercier B, Leroyer C, Nowak E, et al. Family history as a risk factor for venous thromboembolism. Thrombosis Research. 2008;122(5):6244–629.
29. Galioto N, Danley D, Van Maanen R. Recurrent venous thromboembolism. American Family Physician. 2011;83(3): 293 –300.
30. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: The Sirius study. Archives of Internal Medicine 2000; 160(22):3415–3420.
31. Fahmi J, Husmann M, Gretener S, Keo H. Assessing the risk of recurrent venous thromboembolism – a practical approach. Vascular Health and Risk Management. 2015;11:451–459.
32. Kreidy R, Waked M, Stephan E, Irani J, Chemali R, Jureidini I, et al. Acquired and genetic risk factors for deep vein thrombosis of the lower extremities among Lebanese patients. J Med Liban. 2012; 60(1):24–29.
33. Stevens S, Woller S, Bauer K, Kasthuri R, Cushman M, Streiff M, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. Journal of Thrombosis and Thrombolysis. 2016;41: 154-164.
34. Kearon C, Akl E, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease. American College of Chest Physicians. 2016;149(12):315-352.
35. Heit J, Silverstein M, Mohr D, Petterson T, O'fallon M, Melton J. Risk factors for deep vein thrombosis and pulmonary embolism. Archives of Internal Medicine. 2000;160(6): 809–815.
36. Falck-yetter Y, Francis C, Johanson N, Curley C, Dahl O, Schulman S, et al. Prevention of VTE in orthopedic surgery patients. American College of Chest Physicians. 2012;141(2):278-325.
37. Cushman M. Epidemiology and Risk factors for venous thrombosis. Seminars in Hematology. 2007;44(2):62–69.
38. Engbers J, Blom W, Cushman M, Rosendaal R, van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. Journal of Thrombosis and Haemostasis. 2014;12(3):290–296.
39. Khan M, Sipra Q, Asawaeer M, Riaz I. The role of thromboprophylaxis in patients with permanent immobility. The American Journal of Medicine. 2015;128(3):7-8.
40. Saleh T, Matta F, Alali F, Stain P. Venous thromboembolism with chronic liver disease. The American Journal of Medicine. 2011;124(1):64–68.
41. Buresi M, Hull R, Coffin C. Venous thromboembolism in cirrhosis: A review of the literature. Canadian Journal of Gastroenterology. 2012;26(12):905–908.
42. Pinkus KJ, Tata AL, Watson K. Risk of venous thromboembolism in patients with chronic liver disease and the utility of venous thromboembolism prophylaxis. Annals of Pharmacotherapy. 2012;46(6): 873–878.
43. Kelly J, Rudd A, Lewis R, Hunt B. Venous thrombosis after acute stroke. Stroke. 2001;32:262–267.

44. Rinde LB, smabrekke B, Mathiesan EB, Lochen ML, Njolstad I, Hald EM, et al. Ischemic stroke and risk of venous thromboembolism in the general population: The Tromso study. American Heart Association. 2016;5(11):1–8.
45. Kappelle L. Preventing deep vein thrombosis after stroke: Strategies and recommendations. Current Treatment Options in Neurology. 2011;13(6):629–635.
46. Lee AY, Levine MN. Venous thromboembolism and cancer: Risks and outcomes. Circulation. 2003;107:17–21.
47. Khalil J, Bensaid B, Elkacemi H, Afif M, Bensaid Y, Kebdani T, et al. Venous thromboembolism in cancer patients: An underestimated major health problem. World Journal of Surgical Oncology. 2015; 13:1-17.
48. Khorana A, Carrier M, Garcia D, Lee A. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. 2016; 41:81-91.
49. Rooden C, Tesselaar E, Osanto S, Rosendaal F Huisman M. Deep vein thrombosis associated with central venous catheters - a review. Journal of Thrombosis and Haemostasis. 2005;3: 2409–2419.
50. Borvik T, Braekkan S, Enga K, Schirmer H, Brodin E, Melbye H, et al. COPD and risk of venous thromboembolism and mortality in a general population. European Respiratory Journal. 2016;47:473–481.
51. Chen YG, Lin TY, Huang WY, Lin CL, Dai MS, Kao CH. Association between pneumococcal pneumonia and venous thromboembolism in hospitalized patients: A nationwide population-based study. Asian Pacific Society of Respirology. 2015;20(5):799–804.
52. Delluc A, Montavon S, Canceil O, Carpentier M, Nowak E, Mercier B. Incidence of venous thromboembolism in psychiatric units. Thrombosis Research. 2012;130(6):283-288.
53. Rinde LB, Lind C, Smabrekke B, Njolstad I, Mathiesen EB, Wilsgaard T, et al. Impact of incident myocardial infarction on the risk of venous thromboembolism: The Tromso study. Journal of Thrombosis and Haemostasis. 2016;14(6):1183–1191.
54. Barsoum M, Cohoon K, Roger V, Mehta R, Hodge D, Bailey K, et al. Are myocardial infarction and venous thromboembolism associated? Population-based case-control and cohort studies. Thrombosis Research. 2014; 134(4):593–598.
55. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: A meta-analysis. Circulation. 2008;117(1): 93–102.
56. Wattanakit K, Lutsey PL, Bell J, Gornik H, Cushman M, Heckbert SR, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. Thrombosis and Haemostasis. 2012;108(3): 508–515.
57. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: Results from the Copenhagen city heart study. Circulation. 2010;121(17):1896-903.
58. Dean SM, Abraham W. Venous thromboembolic disease in congestive heart failure. Congestive Heart Failure. 2010;16(4):164–169.
59. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: A subgroup analysis of the MEDENOX study. Blood Coagulation and Fibrinolysis. 2003; 14(4):341-346.
60. Wilbur J, Shian B. Diagnosis of deep venous thrombosis and pulmonary embolism. American Academy of Family Physicians. 2012;86(10):913–919.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/22767