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A novel method for predicting the risk of thrombosis and thromboembolism

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Abstract **Introduction**: Thrombosis is a complex disease that is often silent and is characterized by thrombus formation within the blood vessel. It can lead to a venous obstruction in the body, severe sequelae and even death. Thrombus formation occurs when there is reduced blood flow and/or the release of procoagulant substances caused by external factors. In Brazil, the data on this pathology are still underestimated, and its incidence is approximately 0.8 cases/1000 inhabitants per year according to the literature. The aim of this study was to develop and validate a predictive method for the risk of thrombosis or thromboembolism according to various risk factors. **Methods:** This is an observational and retrospective study based on a convenience sample of records. It was approved by the Institutional Review Board (IRB) of the University Mogi das Cruzes and the Heart Hospital of the São Paulo. The sample was classified according to the risk, and the assessment of concordance was performed by determining the Kappa coefficient and accuracy. **Results:** Of the observed patients, 23 (46%) were women, and 86% were over 45 years old. The mean age of the patients was 60.8 years. Forty-eight percent of the patients underwent surgery for more than 30 minutes. In this study, the method categorized 29 (58%) patients as moderate risk, 10 as low risk and 11 as high risk. Two cases of thrombotic disease were sufficient for validation. **Conclusion:** The use of this software as a predictive method was feasible, providing fast filling, immediate scoring, flexibility and an upgrade over previous systems. The software will not substitute for diagnosis, which is a medical competence, but it may help as a warning of risk.

Keywords Predictive method, Risk factors, Thrombosis, Thromboembolism.

Introduction

Clot formation is the natural response of the body in response to injured tissue and provides a defense against bleeding, but there is a risk that clotting will occur irregularly in an inappropriate moment or site and will lead to thrombosis. Thrombosis is a complex disease that is characterized by a thrombus formation in a venous blood vessel that can lead to partial or total venous obstruction and subsequent thromboembolism. It is also characterized by the detachment and migration of the thrombus or clot in the blood system from one place in the body to another. The clot can migrate to vital regions of the body, leading to serious health consequences and preventing the recovery of the patient (Aventis… and Sociedade..., 2003; Hussein, 2002).

The formation of this type of clot is associated with the presence of Virchow's triad, venous stasis, endothelial injury and hypercoagulability (Bailly, 1950 apud Rezende, 2004), and it occurs when there is reduced blood flow to the body and/or a release of procoagulant substances caused by one or more external factors, such as long periods of rest, surgery, anesthetic action, use of venous catheters, trauma, long-term hospitalizations in bed or fixed paralysis and long trips.

Thromboses often do not show early signs that aid in its identification, leading to a delay in the diagnosis or a lack of diagnosis (Cassone et al., 2002). The thrombus in movement is called a 'plunger', and a thrombus that travels to the venous blood is called venous thromboembolism (VTE). If the thrombus reaches the pulmonary vessel, it is called a pulmonary embolism (PE), which can cause death (Barros-Sena and Genestra, 2008).

Another consequence of thrombosis is post-thrombotic syndrome (PTS), which is characterized by secondary varicose veins, edema, eczema, erysipelas, varicose ulcers, pain and inability to work (Gomes and Ramacciotti, 2002; Heit, 2006) or participate in socioeconomic activities (Aventis… and Sociedade..., 2003). PTS arises between 2 and 5 years after the disease due to the injury of the venous valves.

In the United States (U.S.), the annual incidence of deep vein thrombosis (DVT) is 0.7-1.1 cases per 100,000 inhabitants per year (White, 2003) in hospitalized patients. In Brazil, according to data from 2003, the incidence of DVT was estimated at 0.8 per 1,000 inhabitants, but experts believe that the rate is even higher because it is a disease in which many

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patients (between 50% to 80% of cases) do not have major symptoms (Aventis… and Sociedade..., 2003).

There are many risk factors that can lead to thrombosis and its consequences. Andrade et al. (2009) reported 23 risk factors for the developing of venous thromboembolism: surgery time exceeding half an hour, systemic blood pressure (SBP), major abdominal or pelvic surgery, immobilization in bed, limited ambulation, cancer, fracture of the lower limbs, varicose veins in the lower limbs, neurological disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), obesity, contraceptive use, atrial fibrillation, placement of orthopedic prosthesis, hormone replacement, nephrotic syndrome, use of a central venous catheter, peripheral venous thrombosis, thrombotic disease, inflammatory bowel diseases, postoperative intensive care unit (ICU) stay and congenital heart disease.

In addition to the factors cited by Andrade et al. (2009), the literature reports other risk factors, such as blood transfusion (Geerts et al., 1994), Chagas disease (Arteaga Fernández et al., 1989) and cigarette smoking (Hioki et al., 2001; Moreira et al., 2009; Pamplona et al., 1997).

It is known that a number of health risk factors can lead to thrombosis. Thus, there are several methods described in the literature to indicate thrombosis risk, but many of them are only oriented to detect thrombosis in specific cases. This is different from the objective of this study, which is to detect thrombosis in patients with coronary stent, venous leg ulcers, lupus erythematosus and cardiac valve replacement, among others. Furthermore, these models are for investigation purposes, and manual risk calculation shows only the risk and does not provide more information about the risk itself, such as the number and identity of the risk factors the patient has, or the most important factor of all factors identified, and they may be impractical and inflexible.

In this study, we propose a computerized predictive method to assist the professional in rapid risk prediction to compute and indicate the risks reported by the patient at each visit and to identify the most evident risk factor.

Among the methods in the literature chosen for comparison with the method in this study were the clinical methods by Wells et al. (1995) and the modified method of Wells et al. (1997) because these methods had the most appropriate methodology and an efficient categorization of patients. According to Kahn (1998), these methods were more effective than the method for the Protocol for the Prevention of Thrombosis from the Brazilian Society of Angiology and Vascular Surgery (BSAVS) cited by Maffei et al. (2005).

Furthermore, health professionals seek services to optimize their day-to-day work and, through technological advances, use computer methods in care planning and in monitoring the results of their actions in the short and long term. This monitoring represents an attempt to reduce expenses arising from the users themselves and throughout the health care system due to frequent readmissions, prolonged hospitalization and mortality.

Our objective in this study was to develop and validate a predictive risk method for thrombosis or thromboembolism based on the major risk factors.

Methods

Ethical aspects

The design of this study was submitted to the Institutional Review Board (IRB) of the Universidade de Mogi das Cruzes (UMC) and to the IRB of the Hospital do Coração because it was necessary to collect data from patient records.

Due to the nature of the study, the collection of consent forms was not required, that is, it was dispensed by two both Ethics Committees in Research. We collected retrospective data and several records of patients' records. For this way, it occured the not required, because some patients had died before of the collect of this study.

All data collected from the medical records had their sources properly preserved in secrecy to prevent any type of identification or exposure.

Sample selection

We collected a convenience sample of 50 records based on the resources available for the realization of the study. A total of 50 patients were initially defined. This total was to be increased if no cases were identified in any of the three proposed risk ratings. However, two cases of thrombosis were identified, and the initial sample was therefore maintained. Patient records for those admitted to the Hospital do Coração (HCor) in São Paulo from 2009 until 2012 were obtained by simple randomization to reduce the risk of selection bias. We suggest that, given the information on concordance presented in this study, future studies may perform sample size calculations to obtain more accurate estimates of the method's concordance; the sample size may be larger in a new study.

The patients who were included the study satisfied at least one of the criteria described below:

- Age over 45 years old;
- Surgery longer than 30 minutes;

- Abdominal or pelvic surgery or stent placement or previous neurosurgery (up to 6 months);
- Limited ambulation or immobilization in bed;
- Post-operative ICU stay;
- Chagas Disease;
- Major trauma (up to 6 months);
- Systolic hypertension (SAH);
- Atrial fibrillation (AF);
- Congestive heart failure (CHF);
- Acute coronary syndrome (ACS);
- Cerebrovascular accident (CVA);
- Cancer;
- Obesity;
- Pregnancy;
- Use of contraceptives;
- Hormone replacement;
- Previous thrombosis (up to 6 months);
- Disease thrombotic (clotting problems);
- Family history of thrombosis (relatives of the 1st degree);
- Use of central venous catheter;
- Prior blood transfusion;
- Prolonged travel;
- Chronic obstructive pulmonary disease (COPD);
- Nephrotic syndrome;
- Inflammatory bowel diseases;
- any blood group existing in the records patient's;
- High D-dimer;
- Hepatic impairment;
- Systemic lupus erythematosus;
- Alcohol consumption;
- Smoking.

Patient data were described as absolute frequencies and percentages in the case of categorical variables. Age was reported as the mean, standard deviation, minimum and maximum. To validate the risk classification algorithm used in the program, patients in the sample were classified according to the level of risk (low, medium or high). The agreement between the classifications obtained with the methods of Wells et al. (1995), the modified method of Wells et al. (1997) and the Brazilian Society of Angiology and Vascular Surgery (SBACV) protocol cited by Maffei et al. (2005) was evaluated using double entry tables and the concordance Kappa coefficient, in addition to the observed accuracy. The classification of concordance was made according to the suggestion by Altman (1991) and according to the Kappa value: < 0.20 (very low), 0.21-0.40 (low), 0.41-0.60 (moderate), 0.61-0.80 (good) and 0.81-1.00 (very good), as cited by Perroca and Gaidzinski (2003).

Parameters used for the construction and validation of the predictive method

- Identification of the risk factors for thrombosis in the literature;
- Estimate of the percentage of each risk factor described;
- Estimate of the percentage cutoff that determines the change in the risk score from low to moderate and from moderate to high;
- Estimation of the number of factors that determine the change in the risk score from low to moderate and from moderate to high;
- Selection of the categories of risk scores according to its use identified in literature, i.e., low risk, moderate and high, for the purposes of comparison between the two clinical models by Wells et al. (1995, 1997), the protocol for prophylaxis of deep venous thrombosis from the SBACV cited by Maffei et al. (2005) and the predictive method of this study.

Table 1 below shows each risk factor related to the thrombotic event probability used in the predictive method as well as the references from the literature used.

The probability of thrombus formation or thrombotic event was estimated from the average of the percentages of thrombosis observed in the studies of the authors listed in Table 1 for each risk factor studied. Therefore, a cutoff of 25% was estimated from the average of the percentage of thrombus formation or thrombotic event listed in Table 1, which was 21.72%. The 25% cutoff showed the best concordance with pre-established methods, mainly for the SBACV as cited by Maffei et al. (2005). From this, we created the functional diagram shown in Figure 1. A cutoff calculated using the mean of each factor was found as the best for this specific study because the literature is poor in explaining the best cutoff for this type of proposed study. We suggest that this point be adjusted, if necessary, in a new study with a larger sample of patients, and prospectively if possible. Then, a new study with a larger sample will ensure the best calculation for the cutoff. The number of risk factors was divided into 3 groups based on the data collection and patient responses; the patients were divided into 3 groups, after the data were adjusted, and we then obtained the cutoffs: up to 5, 5-10 and greater than 10. We chose 3 groups for consistency with the classical methods of comparison; if we had used 2 or more than 3 groups, it would not have been possible to compare

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Table 1. Risk factors and percentages estimated for thrombus formation or thrombotic event.

Risk factors selected	Percentage of thrombus formation or thrombotic event used in the predictive method	References
Age > 45	Exponential growth by Anderson Jr et al. (1991)	Anderson Jr et al. (1991) - (1% per year after 45 years). Anderson Jr and Spencer (2003) - increased risk beginning at age 40. Oger (2000) and Rosendaal (1997) - (1% per year after 45 years). Lee et al. (2011) - exponential growth. Orra (2002) - points increase with increase in the age range. Oger (2000) - increasing of incidence of thromboembolism in both genders with increased age.
Surgery > 30 minutes	27.5%	Gualandro et al. (2011) - II Guideline - general surgery, 15 to 40%. Nicolaides et al. (2002) - frequency of 25% in general surgery. Nicolaides (1975) apud Piccinato (2008) - 26 to 65%, thoracic surgery.
Abdominal or pelvic surgery; major surgery	40.0%	Mayo et al. (1971) - prostatectomy 30%. Nicolaides et al. (1972) - 24% to 47.6% thrombosis in prostatectomy. Maffei (1995) and Kahn (1998) - incidence of 25 to 30% in abdominal surgery. Nicolaides et al. (2002) - frequency of 51%, hip surgery. Gualandro et al. (2011) - II Guideline - general surgery, 15 to 40%. Nicolaides (1975) apud Piccinato (2008) - 10% to 42% in abdominal surgery, 23% in hysterectomy, 24% to 47% in prostatectomy and 41% to 75% in hip surgery. Nicolaides et al. (2002) - frequency of 32% in prostatectomy.
Neurosurgery	27.5%	Gualandro et al. (2011) - II Guideline – neurosurgery, 15 to 40%. Nicolaides et al. (2002) - frequency of 22% in neurosurgery and 35% in spinal surgery.
Immobilization in bed or postoperative ICU stay (over 3 days)	41.4%	Gualandro et al. (2011) - II Guideline - hospitalized in ICU, 10-80%. Maffei (1995) and Kahn (1998) - incidence of 15 to 80%. Nacif et al. (2009) - 27% - 30% thromboembolism.
Limited ambulation	10.0%	Gualandro et al. (2011) - II Guideline - hospitalized in ICU, 10-80%.
Chagas disease	73.0%	Arteaga Fernández et al. (1989).
Placement of orthopedic prosthesis	60.0%	Cohen et al. (1973) - thrombosis in 57% of the sample. Hull and Raskob (1986) - hip and knee, 30 to 50%. Geerts et al. (1994) - 69%. Hjelmstedt and Bergvall (1968) apud Rosendaal (2005) - 50 to 60%. Maffei (1995) and Kahn (1998) - incidence of 51% for hip prosthesis and 71% for knee prosthesis. Gualandro et al. (2011) - II Guideline - knee and hip arthroplasty, 40-60%.
Trauma (brain injury, spinal, femoral, pelvic, tibial and hip)	55.0%	Nordström et al. (1992) - men, 29%; women, 46%. Cohen et al. (1973) - 57%. Hull and Raskob (1986) - hip and knee sites, 30 to 50%. Geerts et al. (1994) - face, chest, or abdomen, 50%; head, 54%; spinal, 62%; pelvis, 61%; femur, 80%. Myllynen et al. (1985) - 64%. Hjelmstedt and Bergvall (1968) apud Rosendaal (2005) - 50 to 60%. Gualandro et al. (2011) - II Guideline - arthroplasty or fracture surgery for the knee or hip, 40-60%; major trauma, 40 to 80%. Maffei (1995) and Kahn (1998) - incidence 50 to 69%. Nicolaides et al. (2002) - frequency of 45% in hip fracture and 50% in trauma.
SAH	19.7%	Redón et al. (2007) - 19.7% risk of stroke (thrombosis or thromboembolism to the brain).
Atrial fibrillation (submitted to cardioversion without prior anticoagulation)	4.0%	Sociedade Brasileira de Cardiologia (2003) - Atrial fibrillation – 1 to 7%

Table 1. Continued...

Risk factors selected	Percentage of thrombus formation or thrombotic event used in the predictive method	References
CHF	15.0%	Bocchi et al. (2005) - I Guideline CHF, 10 to 20%.
Cerebrovascular accident (CVA)	50.0%	Gualandro et al. (2011) - II Guideline CVA, 20-50%. Nicolaides et al. (2002) - frequency of 56% in stroke. Zétola et al. (2001) - thrombosis in 48%. McCarthy et al. (1977) - rates 28% to 75%.
Cancer	33.0%	Van Rooden et al. (2003) - more than 28.6%. Nordström et al. (1994) - 20 to 44%. Cohen et al. (2006) - 34.4%. Otten et al. (2004) - 7.3 to 15%. Sallah et al. (2002) - 7.8%. Agnelli et al. (2006) - incidence of 2.8% and 46.3% for death due to VTE.
Obesity (surgery for obesity)	2.4%	Eriksson et al. (1997) - incidence of thromboembolism, 2.4%. Barnes (1977) - 1.8% VTE. Bajardi et al. (1993) - 1.6% DVT and 3.2% EP. Shepherd et al. (2003) - 0.4% PE.
Pregnancy	0.6%	Kalil et al. (2008) - incidence of 0.17%. Parente et al. (2012) - 0.29% to 1%. Aurousseau et al. (1995) - 1% in vitro fertilization. Avila et al. (2003) - 1.9% thromboembolism.
Use of contraception	0.5%	Lidegaard et al. (2009) - 0.06 to 0.13% depending on the type of contraceptive. Vessey et al. (1989) - 0.96% risk in users of oral contraceptives.
Hormone replacement	42.9%	Barros et al. (2011) - thrombosis event in 42.9% of hormone therapy users.
Varicose veins of the lower limbs (varices)	0.3%	Critchley et al. (1997) - 0.5% thrombosis.
Thrombotic disease (clotting problems)	25.0%	Kluijtmans et al. (1998) - hyperhomocysteinemia, 16%. Den Heijer et al. (2005) - 27% of patients with elevated homocysteine and 20% of patients with the 677TT genotype. Poort et al. (1996) - 6.3% of patients with elevated prothrombin and 18% of patients with the 20210A allele and thrombosis in the family. Rosendaal et al. (1995) - resistance in the activation of protein C in 18% of patients with thrombosis versus 2.9% in patients without thrombosis. De Groot et al. (2005) - lupus anticoagulant in 3.1% of patients with thrombosis compared with 0.9% in individuals without thrombosis, antibody anti-b2GPI 7.5% in thrombosis group versus 3.4% in controls. Vaarala et al. (1986); Canoso and de Oliveira (1986) - of patients with antiphospholipid antibody (anticardiolipin and lupus anticoagulant), 30% develop thrombosis. Hamerschlak and Rosenfeld (1996) - 20% related to changes in general factors such as protein C, S, antithrombin III. Ford et al. (1994) - 20.5% high antiphospholipid (68% association with thrombosis). Duque and Mello (2003) - mean prevalence of the following factors: association of genetic abnormalities, 30% - 60%; resistance to activated C protein (Leiden), 20% - 50%; fibrinolytic abnormalities, 10% - 15%; genetic mutation of G20210A prothrombin, 5% - 15%; antithrombin deficiency III, 4% - 10%; C protein deficiency, 3% - 6%; S protein deficiency, 5% - 15%. Sode et al. (2013) - Factor V Leiden, 10%.
Previous thrombosis	25.0%	White (2003) - recurrence rate of 7.7% at 6 months and 14% in patients with cancer. Prandoni et al. (1996) - 8.6% within 6 months and 30.3% within 8 years. Hansson et al. (2000) - 7.0% within 1 year and 22.0% within 5 years. Heit et al. (2000) - recurrence incidence of 10.1% within 6 months, 12.9% within 1 year and 30.4% within 10 years.

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Table 1. Continued...

Risk factors selected	Percentage of thrombus formation or thrombotic event used in the predictive method	References
Family history of thrombosis (1st degree relative)	5.3%	Couturaud et al. (2009) - incidence of 4.9% to 7.9%;5.3% for family history of VTE.
Use of central venous catheter (CVC)	22.4%	Marie et al. (1998) - 22.4% by catheter. Jesus and Secoli (2007) - incidence of 4 to 38% of thrombosis. Galloway and Bodenham (2004) - 21% to 60%, depending on the location of the catheter tip.
Transfusion prior	4.7%	Godoy (1997) - 7% anticardiolipin present in the donor with 4.76% directly associated with thrombosis. Geerts et al. (1994) - thrombosis in 66% of transfused patients.
COPD	9.0%	Dutt and Udwadia (2011) - 9% had thrombosis.
Nephrotic syndrome	0.8%	Resh et al. (2011) - 0.81% thrombosis without statin use and 0.31% with statin use.
Inflammatory bowel diseases (operated)	2.5%	Merrill and Millham (2012) - 2.5% rate of thrombosis occurrence.
Edema (pitting)	28.4%	De Souza (2001) - increase in volume of the lower limbs in 70.8% of patients with thrombosis and 37.9% of patients without thrombosis; increased circumference of the leg in 70.8% of patients with thrombosis and 27.6% of patients without thrombosis; edema found in 90.8% of patients with thrombosis and 79.3% of cases without thrombosis.
Edema in leg and calf	28.4%	De Souza (2001) - increase in volume of the lower limbs in 70.8% of patients with thrombosis and 37.9% of patients without thrombosis; increased circumference of the leg in 70.8% of patients with thrombosis and 27.6% of patients without thrombosis; edema found in 90.8% of patients with thrombosis and 79.3% of patients without thrombosis.
Dilated superficial veins (not varicose)	17.2%	De Souza (2001) - 58.5% in patients with thrombosis and 17.2% in patients without thrombosis. Stein et al. (1993): "the signs of DVT" are featured in 11% of cases
Localized tenderness along the course of the deep venous system	20.0%	De Souza (2001) - reports pain in 64.6% of cases of thrombosis and 41.4% of exams with normal results for thrombosis. Stein et al. (1993) - leg pain is found 30% of patients with thrombosis; "Signs of Homans" are found in 4%, and signs of DVT are found in 11%.
Erythema	15.0%	Wells et al. (1995) - erythema entered as 'minor point' for thrombosis prediction in predictive method; the percentage of studied patients with erythema is not mentioned. Vine et al. (1981) - 26% frequency of erythema found in cases of thrombosis, with 44% of these true positives. Stein et al. (1993) - signs of DVT are found in 11%.
Alcohol consumption	10.0%	Moreira et al. (2009) - presence of alcohol use in 8.5% of thrombosis patients. The use of alcohol was associated with thrombosis, increasing the chances of developing thrombosis by 5-fold overall and 12.5-fold when the data were adjusted. On the other hand, there are studies that speak of the protective effect of alcohol. This is therefore controversial. Pamplona et al. (1997) - case of a thrombus in a smoker with alcohol abuse; reports prevalence of acute myocardial infarction (AMI) as 1-12%.
Cigarette smoking	15.0%	Moreira et al. (2009) - presence of smoking in 20.1% of patients with thrombosis. Hioki et al. (2001) - current use of cigarette products or nicotine induces a prothrombotic state, i.e., platelet activation. Pamplona et al. (1997) - case of a thrombus in a smoker with alcohol abuse; report prevalence of AMI as 1-12%.
Prolonged travel	7.0%	Schwarz et al. (2003) - 2.8%. Scurr et al. (2001) - 10% developed thrombosis. Geerts et al. (2008) - the rate of thrombosis development in trips longer than 4 hours ranges from 1.1% to 3.9%. Gavish and Brenner (2011) - 3% to 12% in cases of prolonged travel.

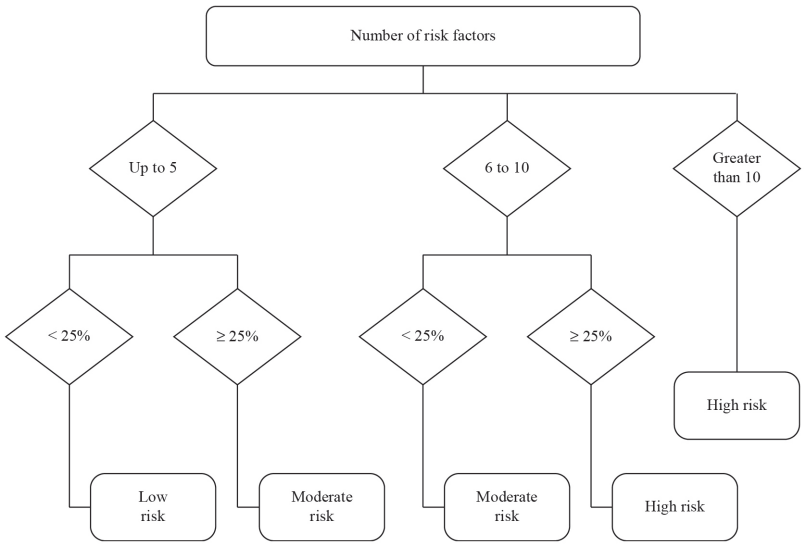

Figure 1. Functional diagram for defining the risk score based on the number of risk factors and the percentage cutoff.

them with the methods chosen for this study, each of which had 3 categories of response.

For each of the risk factors indicated, the patient received one point for each presented factor and zero points for each factor that was not presented. Thus, we calculated the number of risk factors that each patient had, and this value was used to classify the risk and identify the greatest risk factor. The assignment of one point for each factor was linked to the weighted numerical value (Table 1) after a review of the literature along with an indicator of the most relevant or most obvious influencing factor in the thrombosis among all the factors pertaining to the patient because not all risk factors for thrombosis are equal. Setting the appropriate weight for each factor will require an epidemiological study, perhaps with a sample size greater than 1,000 patients.

The program was developed using the Visual Basic object-oriented language, which had a visual interface that is easy for the user to interpret, and it was configured with restrictions and types of distinct changes and features requested upon consultation, creating dynamism for the tool and secure data entry. This program also offered access by login/password, a simple dropdown menu and easy access to the following functions: main menu, settings, patient search button (by record, by 'Natural Persons Register' (NPR), or by 'National Identification Number' (NIN)), print history and information about the program.

The user can change the information associated with the patient, except for the NPR or the NIN, because the NPR or NIN is a priority key in the system (the system will search the database for existing patients using the NPR or the NIN). The other attributes of the patient may be changed. For existing patients, the user will see the patient information in the 'HISTORY' tab and can use this information to create a new 'risk analysis'.

On the tab "CREATE NEW RISK ANALYSIS", several *checkboxes* are shown. After selecting the relevant patient attributes, the user must click CALCULATE RISK and then SAVE for the system to calculate and save the information in the database.

The flowchart in Figure 2 below is a visual representation of how the system works. Each box shown in the flowchart indicates 1, 2 and N included functions.

Results

We observed 50 patients, 23 (46%) of whom were women. The mean age of the patients was 60.8 ± 14.3 years, 86% of the patients were older than 45, and 48% of the patients underwent a surgery that lasted longer than 30 minutes. A description of all the risk factors observed is presented in Table 2.

Table 3 follows the risk ratings according to the different methods. Each patient was rated 4 times, once for each method.

The patients evaluated had 1-15 risk factors, and many patients had 2 (12%), 3 (22%), 4 (20%) or 5 (20%) risk factors for thrombosis.

Of the factors associated with the highest risks, 80% of the patients had at least one risk factor equal to or greater than the cutoff of 25%, and 20% of the patients had a 'higher risk percentage' below this cutoff.

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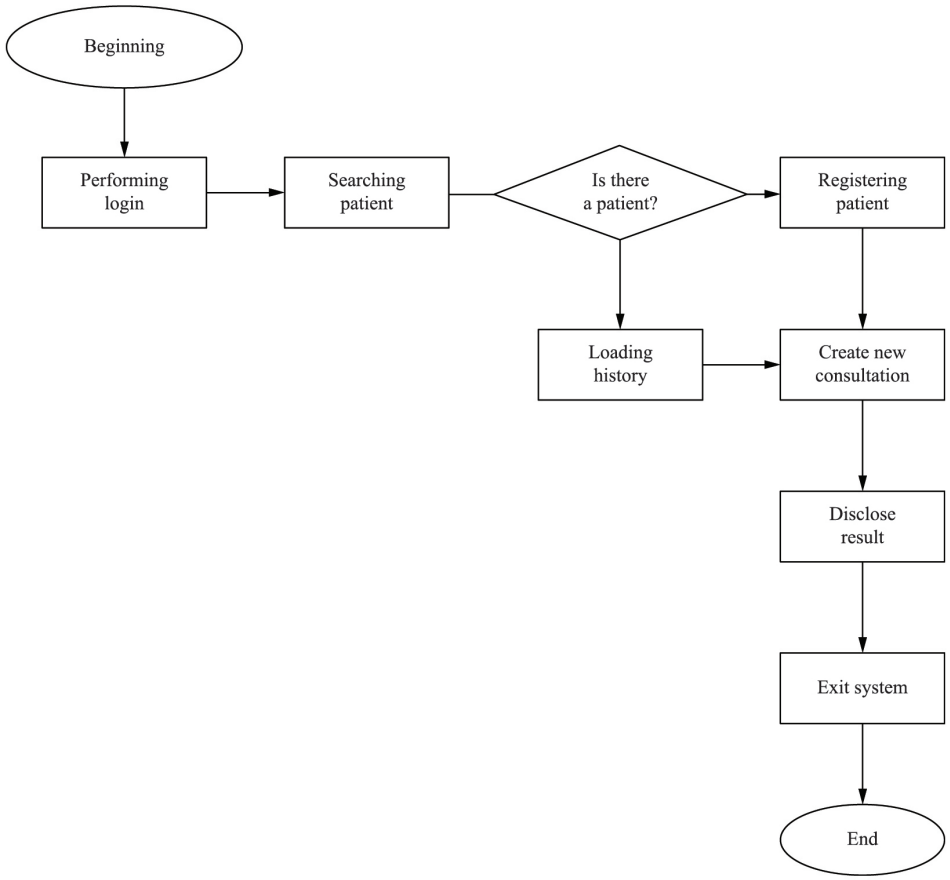

Figure 2. Flowchart representing a macro view of the system's functionality.

Table 4 below shows the evaluation of the concordance between the risk classification proposed in this paper and the classification proposed by Wells et al. (1995).

Of the 50 subjects evaluated, 12 were classified in the same way by the two methods (accuracy = 24%). The Kappa coefficient of concordance calculated for these two methods was 0.02 (confidence interval of 95%: –0.11 to 0.16). Therefore, the concordance was considered low.

Table 5 below shows the evaluation of the concordance between the risk classification proposed in this study and the classification proposed by the modified method of Wells et al. (1997).

Of the 50 subjects studied, 10 were classified in the same way by the two methods (accuracy = 20%) and were given a low risk rating by both methods. The Kappa coefficient of concordance calculated for these two methods was –0.04 (confidence interval of 95%: –0.17 to 0.09) and was considered low.

Table 6 below reports the evaluation of the concordance between the risk classification proposed in this study and the classification proposed by the protocol SBACV by Maffei et al. (2005).

Of the 50 subjects evaluated, 42 were classified in the same way by the two methods (accuracy = 84%). The Kappa coefficient of concordance calculated for these two methods was 0.73 (confidence interval of 95%: 0.60 to 0.86) and was considered good. Thus, the algorithm proposed in this study is considered valid for the classification of risk of thrombosis according to the SBACV protocol cited by Maffei et al. (2005).

Table 7 shows the risk classification according to predictive method in this study and the actual thrombosis occurrence in 2 patients.

The two cases of thrombosis were both classified as a high risk by the SBACV protocol and as moderate risk according to the modified method of Wells et al. (1997). When the method of Wells et al. (1995), one case was classified as high and the other as moderate. The two patients with thrombosis were female and were 65 and 87 years old.

Discussion

Regarding the risk factors observed, 86% of the patients were over 45 years old, and the majority of the patients were judged to be at moderate risk or high risk of thrombosis based on the method of this study and the SBACV protocol cited by Maffei et al. (2005). The results agree with the literature, which reports the increased risk of thrombosis and/or thrombus formation with age, e.g., Anderson Jr et al. (1991), Oger (2000), Rosendaal (1997), Lee et al. (2011) and Orra (2002). When using the method of Wells et al. (1995, 1997), the two patients with thrombosis were rated at least moderate, which was consistent with the occurrence of thrombosis. For the purpose of this study, it was not possible to use a very specific sample, for instance, only patients who developed thrombosis or 50% of the patients who developed thrombosis at this moment; rather, we used a pragmatic sample so that the method would approximate the routine of attending to local medical and surgical patients so that the method helps to detect and provide an alert to possible candidates for thrombosis. Therefore, a new study using this method prospectively, that is, applying this method to a larger sample and prospectively monitoring who develops thrombosis and who does not, in each of the three categories of the method, is necessary.

Most of the sampled patients were over 45 years old, possibly because the sample was taken from the general hospital population and from the specialties of cardiology, orthopedics, oncology, neurology, and renal pathologies, among others, and these hospital populations follow the general trend of population aging.

Some risk factors were very common in the sample, including SAH (68%), limited ambulation (50%) and surgery lasting longer than 30 minutes (48%), and which were frequently present in patients who developed thrombosis. Approximately one-third of those with SAH may develop thrombus, according to Redón et al. (2007). Limited ambulation as well as immobilization and/or post-operative time in bed (18% of sample), may favor Virchow's triad: venous stasis, endothelial injury and hypercoagulability that can lead to thrombus formation (Bailly, 1950 apud Rezende, 2004). Surgeries lasting longer than 30 minutes can occur in 10% to 75% of cases, depending on the surgery (Gualandro et al., 2011; Maffei, 1995; Kahn, 1998; Mayo et al., 1971; Nicolaides et al., 1972; Nicolaides et al., 2002; Nicolaides, 1975 apud Piccinato, 2008).

Table 2. Risk factors observed, with the number and percentage of patients.

Factor	n	%
Age > 45	43	86%
SAH	34	68%
Limited ambulation	27	54%
Surgery> 30 minutes	24	48%
Prolonged travel	15	30%
Alcohol consumption	13	26%
Immobilization in bed and or postoperative in ICU for more than 3 days	9	18%
Cancer	9	18%
Smoking	8	16%
Thrombotic disease (clotting problems)	7	14%
Edema (pitting)	7	14%
CHF	7	14%
Transfusion prior	7	14%
Use of central venous catheter	7	14%
COPD	5	10%
Varicose veins in the lower limbs	5	10%
Nephrotic syndrome	4	8%
Previous thrombosis	4	8%
Edema in leg and calf	3	6%
Erythema	2	4%
CVA	1	2%
Obesity (surgery for obesity)	1	2%
Trauma (brain, spinal, femoral, pelvic, tibial and hip injury)	1	2%
Dilated superficial veins (not varicose)	1	2%

Table 3. Classification of risk according to the different methods.

Risk Classification	Methods							
	Method of this study		Wells et al. (1995)		Modified by Wells et al. (1997)		Protocol SBACV	
	n	%	n	%	n	%	N	%
Low	10	20%	45	90%	46	92%	8	16%
Moderate	29	58%	3	6%	4	8%	27	54%
High	11	22%	2	4%	0	0%	15	30%
Total	50	100%	50	100%	50	100%	50	100%

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Table 4. Evaluation of the concordance between the risk classification proposed in this paper and the classification proposed by Wells et al. (1995).

Method of this study	Risk by Wells et al. (1995)			Total
	Low	Moderate	High	
Low	10 (20%)	0 (0%)	0 (0%)	10
Moderate	29 (58%)	0 (0%)	0 (0%)	29
High	6 (12%)	3 (6%)	2 (4%)	11
Total	45	3	2	50 (100%)

Table 5. Evaluation of the concordance between the risk classification proposed in this study and the classification proposed by the modified method of Wells et al. (1997).

Method of this study	Risk by modified method of Wells et al. (1997)			Total
	Low	Moderate	High	
Low	10 (20%)	0 (0%)	0 (0%)	10
Moderate	29 (58%)	0 (0%)	0 (0%)	29
High	7 (14%)	4 (8%)	0 (0%)	11
Total	46	4	0	50 (100%)

Table 6. Evaluation of the concordance between the risk classification proposed in this study and the classification proposed by the SBACV protocol cited by Maffei et al. (2005).

Method of this study	Risk by Protocol SBACV cited by Maffei et al. (2005)			Total
	Low	Moderate	High	
Low	7 (14%)	3 (6%)	0 (0%)	10
Moderate	1 (2%)	24 (48%)	4 (8%)	29
High	0 (0%)	0 (0%)	11 (22%)	11
Total	8	27	15	50 (100%)

Table 7. Evaluation of the risk classification and thrombosis occurrence.

Method of this study	Thrombosis occurrence or thrombotic event		Total
	No	Yes	
Low	10	0	10
Moderate	29	0	29
High	9	2	11
Total	48	2	50

Other factors appeared in approximately one-third of the sample: prolonged travel (30%), which was present in both patients with thrombosis in this study, and alcohol consumption (26%), a factor that is still controversial but not negligible; there are authors who argue that it may be associated with the occurrence of thrombus (Moreira et al., 2009) and thrombus related to acute myocardial infarction (Pamplona et al., 1997).

Cancer, which was present in 18% of patients, may also be associated with thrombotic events. Malignant cells alter the chain of coagulation factors and activate coagulation through the release of procoagulant molecules, leading to hypercoagulability in 50% to 70% of patients and to an increased incidence of thrombosis (Tabak et al., 2011). The next most common risk factor was cigarette smoking (16%). Cigarette products induce a prothrombotic state. Nicotine, for example, increases the likelihood of platelet aggregation and thrombus formation (Hioki et al., 2001; Hung et al., 1995). The blood viscosity increases, which induces the production of red blood cells (Murray et al., 1993).

Other factors were less frequent (14% each), including thrombotic disease (clotting problems), edema (pitting), CHF, transfusion and prior use of CVC. However, De Souza (2001), Duque and Mello (2003), Ford et al. (1994) and Galloway and Bodenham (2004) report that these factors may be present together with thrombosis in over 50% of patients who experience them.

Of the 35 factors reported in Table 2, 24 of them were present in the sample collected. Therefore, all 35 studied factors were entered into the predictive method of this study for greater coverage and validation. This

does not prevent the inclusion of others risk factors in the future for the purpose of updating and improving of the method.

Regarding the risk ratings produced by the 4 predictive methods, the method in this study showed low similarity in terms of risk factors, accuracy and concordance of the Kappa coefficient with the methods of Wells et al. (1995, 1997) but greater similarity to the SBACV protocol cited by Maffei et al. (2005), suggesting a broad relationship of the risk factors. In this case, a good concordance is a strong indication that the method meets the proposed purpose. For this first phase of validation of the method, we obtained validation of the method's function. In this case, the same dataset of 50 patients was rated by each of the four methods, that is, the method of this study, the method of Wells et al. (1995, 1997) and the SBACV cited by Maffei et al. (2005). Thus, the next phase should be further validation in a new study, such as cross-validation with another group of patients.

The most prevalent risk factor identified in this study (above the cutoff of 25%) was present in 40 (80%) patients, where the average major risk factor was present in 33.5% of patients; the median was 33%, the mode was 27.5% (12 patients) and 33% (8 patients).

The results of this study were used exclusively for the objective of the development and validation of the predictive method. For other purposes, a deeper study should be conducted. Thus, it is suggested that this predictive method should be tested and used prospectively in other populations, "beyond the assessment of its clinical applicability" or the role of the method in predicting the benefit of certain approaches as to test the method in care protocols (Dangas et al., 2012).

The predictive method elaborated here cannot be used to perform a diagnosis, which is made exclusively by a professional expert, and adds to the existing set of complementary exams (Anand et al., 1998). The use of "[…] clinical prediction methods and imaging may help in the diagnostic process and may be more cost effective, thus emphasizing the importance of clinical judgment in the management of these patients […]", according to Rollo et al. (2005, p. 87).

In the future, the predictive method and the application (software) presented in this study may be used through the internet and will thus be available to the large population of health professionals. Therefore, it is expected that this will lead to greater and more careful attention to this pathology by professionals and a reduction of thrombotic cases in outpatient units and hospitals. Pereira et al. (2008) showed that only 38.46% of the physicians surveyed knew the incidence of DVT.

Limitations of the study

This study had several limitations that can be best addressed in further studies:

- multifactorial action of the risk factors and preventive factors associated with confounding factors present in patients;
- the limited extent of the literature, i.e., the absence of a wide range of studies, systematic reviews or meta-analyses on the correlation of risk factors with the development of thrombosis and its consequences; most studies were small and isolated;
- the limited quality of articles in the literature, many of which do not even mention the percentage of patients who could be affected by thrombosis and its consequences due to a particular risk factor, limiting itself to reporting that the factor had 'much' or 'little' influence on thrombosis;
- the disease incidence in the population is <1/1000 inhabitants, and in 50% to 80% of cases, patients do not have major symptoms, which hinders the ability to reach conclusions on the influence and frequency of the event (Aventis… and Sociedade..., 2003);
- limitation of the study itself due to the use of retrospective data collection, which depends on the quality of the data from the medical records. Partial notes and cases without records were found;
- due to the limitations of this study, the five risk factors listed as follows should be studied more deeply and analyzed for their inclusion or non-inclusion in the predictive method of this study in a future study: blood group, D-dimer, obesity, liver failure and acute coronary syndrome;
- due to the rarity of research on the impact of the preventive factors in reducing the risk of thrombosis, these factors could not be included in the predictive method of this study. Such factors may include early ambulation, elevation of the lower limbs, active and passive exercises, use of compression stockings, intermittent pneumatic compression (IPC); standard low-dose, low molecular weight heparin (LMWH); vena cava filtration, normal body mass index (BMI); nutrition with fruits and vegetables; daily hydration, control of blood pressure (BP); restriction of sugar and fats, regular physical exercise; abstinence from alcohol and

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abstinence from smoking or quitting smoking (more than 6 months).

The predictive method of this study for thrombosis and thromboembolism was successful, despite the difficulties and limitations described above, and we produced a software application that reached the proposed objective. However, it is suggested that this method may be validated in a new prospective study with a larger patient sample. It was observed that the software application is usable, is easy to access and handle, may be filled out rapidly, produces an immediate response with the number of risk factors and the major estimated percentage of the risks and the presentation of the score, has a database that may be widely used, may generate a report upon request, has flexibility, allows the system administrator or authorized person to perform updates when necessary, has low risk and has reasonable cost.

In the future, improving the predictive method that addresses the preventive factors of thrombosis may further assist in drawing attention to this problem; the predictive methods that currently exist only punctuate the risk factors and do not include scores for preventative factors that could theoretically reduce the impact of the risk factors.

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