Impact of Hormone Therapy Linked to Wells Prediction Score in the Diagnosis of Deep Vein Thrombosis in Women Submitted to Vascular Ultrasound

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Summary

Introduction: Deep venous thrombosis (DVT) presents high morbidity and mortality. The Wells score is designed to improve the pretest diagnosing capacity for DVT. The purpose of this study was to adjust the Wells score for Brazilian patients and include the variable hormone therapy (HT), comparing accuracy and power of reclassification of the new score with Wells' original score.

Methods: Cross-sectional observational study in which logistic regression was performed to include the variable hormone therapy (HT) to the Wells score, creating a new score (HT score), which has been calibrated and adjusted for the population studied. Data quality was evaluated by the Kappa statistics.

Results: We studied 461 patients aged 56.1 ± 20.8, of which 103 had sonographic diagnosis of DVT. The HT score included seven variables: patients who achieved a score of -4 to 0 are considered low risk; 1 to 3, moderate risk; and 4 to 11, high risk for DVT, with proper calibration (p = 0.59). The area under the ROC curve for the HT score was 0.92 (95% CI 0.90 – 0.95) and for the Wells score it was 0.87 (95% CI 0.84 – 0.91), showing a statistically significant difference (p < 0.05).

Conclusion: The inclusion of hormone therapy into a clinical prediction model showed higher accuracy compared to the model of Wells. (Arq Bras Cardiol: Imagem cardiovasc. 2015;28(4):208-215)

Keywords: Hormone Replacement Therapy; Contraceptive Agents; Risk Factors; Venous Thrombosis/mortality; Ultrasonography; Women.

Introduction

Deep vein thrombosis (DVT) is the third leading cause of vascular disease with high morbidity and mortality[1].In Brazil, the estimated incidence is 0.6 cases per 1,000 inhabitants per year, while the worldwide incidence in 2003 was 0.5 cases per 1,000 inhabitants in a year[2]. Analysis of outcomes in 51,233 patients hospitalized due to DVT found an incidence of 10.5% mortality within six months after the episode of DVT[3]. In another study evaluating 2,218 patients, 5.5% died within 30 days after they had DVT. DVT may result in complications such as post-thrombotic syndrome and pulmonary embolism (PE)[4]. Patients who received no treatment for proximal symptomatic DVT have about 50% chance of developing EP[5]. Post-thrombotic syndrome is the most frequent complication of DVT and occurs in about one third to one half of patients[6].

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The diagnosis of DVT can be a challenge, and in 50% of the cases, the initial clinical picture may not be typical. In order to improve pretest diagnosing capacity, Wells et al.[7] proposed a clinical prediction model for DVT (Wells score) containing risk factors, signs and symptoms of the disease. This score stratifies patients with suspected DVT at low, moderate or high pretest probability. Table 1 details the Wells score for DVT in symptomatic patients. Reproducibility and performance of the score were widely researched. The score was especially applied in the evaluation of DVT in outpatient care centers[8-10].

Hormone therapy (HT), which includes oral hormonal contraception and hormone replacement therapy (HRT), is a risk factor for DVT[11,12], and the users (exposed) have two to six times the risk of DVT compared to nonusers (unexposed)[7,12-14]. It is postulated that the effects of female sex hormones on the cardiovascular system are due to estrogen and progesterone receptors in the layers that make up the blood vessels[12].

Despite the association between HT and risk for DVT, the Wells score does not include this variable. The aim of this study was to adjust the Wells score for Brazilian patients and include the HT variable, comparing accuracy and power of reclassification of the new score with the original Wells score.

Table 1 - Wells Score for outpatient evaluation of deep vein thrombosis

Clinical characteristic	Score
Cancer in activity	+1
Paresis, paralysis, or cast immobilization of the lower limbs	+1
Immobilization (> 3 days) or major surgery (up to 4 weeks)	+1
Increased sensitivity along the deep venous system veins	+1
Edema around the member	+1
Calf edema (> 3 cm) in relation to the contralateral leg	+1
Greater depressible edema (pitting) in the affected leg (unilateral)	+1
Superficial collateral veins	+1
Differential diagnosis more probable than deep venous thrombosis	-2
Stratum of deep venous thrombosis risk	
High (three or higher score)	74.6%
Moderate (score between one and two)	16.6%
Low (zero or lower score)	3.0%

Source: Wells et al.[7]

Material and Methods

Study design

This is a cross-sectional observational study with analysis of secondary database (BD), built on information from patients evaluated in the vascular ultrasound service of Hospital Mater Dei (HMD), Belo Horizonte from January 2008 to December 2012.

Population

The study population consisted of female patients older than 18, in the outpatient care or hospitalized, symptomatic or asymptomatic, with suspicion for acute DVT undergoing vascular ultrasound. Patients under control of DVT, those with inconclusive test on ultrasound and those in which it was not possible to calculate the Wells score were excluded from the study.

Ethical aspects

The project was approved by the Research Ethics Committee (CEP) of Faculdade da Saúde e Ecologia Humana (FASEH). CAAE Number: 20641513.4.0000.5101.

Outcomes

The diagnosis of DVT was confirmed by vascular ultrasound of the affected leg. For the test, the patients were placed in the supine position with the symptomatic leg externally rotated and slightly bent at the knee. The venous segments were examined from the inguinal ligament level to the medial malleolus level. The common femoral vein, the femoral vein, the popliteal vein, the posterior tibial vein, the peroneal vein, the gastrocnemius plexus veins and the soleus veins were examined. The compressibility of these veins was evaluated at intervals of 1 to 2 cm in the transverse plane. The diagnosis of DVT was performed as previously described[12].

Exposure assessment

During the vascular ultrasound, the participants answered a semi-structured questionnaire containing the 1997 Wells model items for DVT prediction plus an additional item specific for HT. The HT item referred to the use or nonuse of hormone replacement therapy or combined hormonal contraception.

Statistical analysis

Analysis of data quality: To validate the BD, interobserver correlation analysis was performed by the kappa statistics (k) for the exposure variable (HT). In this evaluation, we compared the original BD records and those obtained in telephone interviews in an independent and random way with data masking.

The data were analyzed with descriptive statistical techniques. Factors associated with the response variable DVT (dichotomous) were identified by hypothesis tests considering a significance level of 5% ($\alpha = 0.05$). Univariate analysis applied Student's t test or equivalent nonparametric test (when necessary) to compare continuous variables, chi-square test and, when necessary, Fisher's exact test for categorical explanatory variables.

Logistic regression was used to include the variable HT in the clinical prediction model. We specifically used the adjusted odds ratio (OR) from the regression to calculate the effect of the Wells model variables in all models. For logistic regression, only variables with p-value smaller than or equal to 0.25 in the univariate analysis were selected[15]. For these variables, we calculated the coefficient β and OR. The calibration of the models was assessed with the Hosmer-Lemeshow test and

displayed on the calibration chart. To evaluate the power of discrimination, a ROC (receiver operating characteristic) curve of the models was built, then the Delong test was applied[16].

All analyzes were conducted in the free software R, version 3.1.0, using the PredictABEL, epicalc and pROC packages.

Description of the variables

The variables listed in Table 1 were extracted from the Wells score for DVT in symptomatic patients. These are dichotomous variables scored according to the presence or absence of DVT. They are: cancer in activity; paresis, paralysis, or cast immobilization of the lower limbs; immobilization (>3 days) or major surgery (up to 4 weeks); increased sensitivity along the deep venous system veins; superficial collateral veins; edema, which included three different types of edema described by Wells: edema around the limb; calf edema (>3 cm) in relation to the contralateral leg; and depressible edema (pitting) greater than in the affected leg (unilateral). Besides this, the variable *differential diagnosis more probable than deep venous thrombosis*.

Modeling

In the current study, we evaluated four models: the original score of Wells et al.[7] (Wells score), adjustment of the model with calibration of variables (Adjusted Wells Model) and in a third model we included the variable HT (hormone therapy) to the adjusted model (HT model). The last step was the determination of the score from the HT Model (HT Score). The flowchart in Figure 1 shows the evolution of modeling.

From the HT Model HT, a new adjusted score was created, in which the weight of each variable was taken from the β coefficient of the corresponding model. The score calibration was measured using the Hosmer-Lemeshow test and displayed on the calibration chart. To evaluate the power of discrimination of scores, a new ROC curve was built[17].

Results

Sample population

Among the 461 patients studied, the mean age was 56.1±20.8 years and the prevalence of DVT was 22%. Among the participating patients, 81 (17.6%) were in HT, and DVT was diagnosed in 33 of them (40.7%) and in 70 patients who were not using HT (21.5%) (OR of 3.05 with 95% CI [1.82 - 5.09]). Applying the Wells score, patients with low probability (LB) before the DVT test comprised 269 of 461 (58.4%), while 125 (27.1%) were classified as medium probability (MP) before the test and 67 (14.5%), high probability (HP) before the test. These data are shown in Table 2. Of patients with DVT, proximal involvement (iliac-femoral-popliteal) was found in 37.5% of patients, 1.7% of which with exclusive involvement of the iliac segment and distal DVT (infrapopliteal) in 62.5%, and 9.7% had thrombus located by duplex scan exclusively in the calf.

Interobserver agreement

The interobserver agreement analysis by the kappa coefficient (k) was 0.86 for the variable HT.

Modeling

In the model of Wells et al.[7], the β values of the variables predicting DVT have been rounded to 1 (according to the authors, aiming to simplify the model and not assign a unnecessary weight to the variables paresis, paralysis or cast

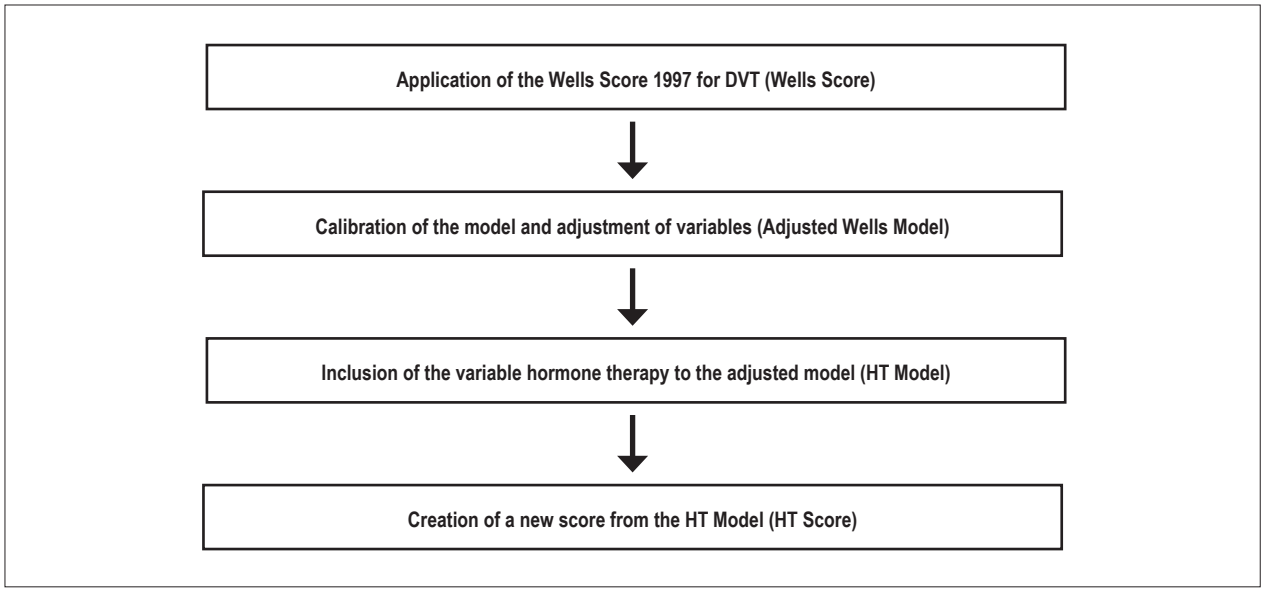


Figure 1 – *Flowchart of data modeling for DVT. Hospital Mater Dei, Belo Horizonte, 2008-2012 (n=461).*

Table 2 - Clinical characteristics of the participants evaluated in the cross-sectional design, Hospital Mater Dei, Belo Horizonte, 2008-2012 (n=461)

Clinical characteristic	Results
Age (mean/SD)	56.09 (20.8)
Low risk (≤ zero) N (%)	269 (58.4)
Moderate risk (1-2) N (%)	125 (27.1)
High risk (≥ 3) N (%)	67 (14.5)
DVT N (%)	103(22.3)
Pain in deep vein path N (%)	24 (5.2)
Unilateral edema N (%)	62 (13.3)
Pitting edema in the ankle N (%)	131 (28.1)
Edema of the entire limb N (%)	94 (20.2)
Neoplasia in activity or in palliative N (%)	31(6.7)
Patient in hospital bed or post-surgery N (%)	83 (17.8)
Paralysis or immobilization of the affected limb N (%)	69 (14.8)
Presence of collateral veins N (%)	3 (6)
Alternative diagnosis more probable than DVT N (%)	173 (37.1)
Use of hormone therapy N (%)	81 (17.4)

DVT: deep vein thrombosis.

immobilization of the lower limbs and superficial collateral veins that are more rarely found in patients) and rounded to -2, referring to the single variable with negative β[7]. All variables described by Wells et al. were analyzed by logistic regression to create a new adjusted model. The HT model had the following significant variables: cancer in activity; paresis, paralysis or cast immobilization of the lower limbs; immobilization or major surgery; calf edema in relation to the contralateral leg; increased sensitivity along the deep veins and differential diagnosis more probable than deep vein thrombosis and HT. To develop the score, we rounded the β coefficients for the first integer closer to its value. The weights ranged from - 4 (differential diagnosis more probable than deep venous thrombosis) to 4 (unilateral edema) (Table 3).

The Hosmer-Lemeshow test applied to the models presented a p value of 0.69 for the HT model and 0.59 for the HT score. These results indicate that the models are well calibrated (Figures 2 and 3, respectively).

The area under the ROC curve for the HT score was 0.92 (95% CI 0.90-0.95). For the original Wells score, the area under the curve was 0.87 (95% CI 0.84-0.91). The Delong test revealed statistically significant difference between these two scores ($p < 0.0001$). Figure 4 shows the comparison between the scores studied.

Figure 5 compares the DVT observed with those predicted by the HT score for each category of pretest probability.

Discussion

This study aimed to draw up a clinical prediction model for DVT including hormone therapy. We observed increased predictive power for DVT in female patients when we compared the HT score developed with the Wells model.

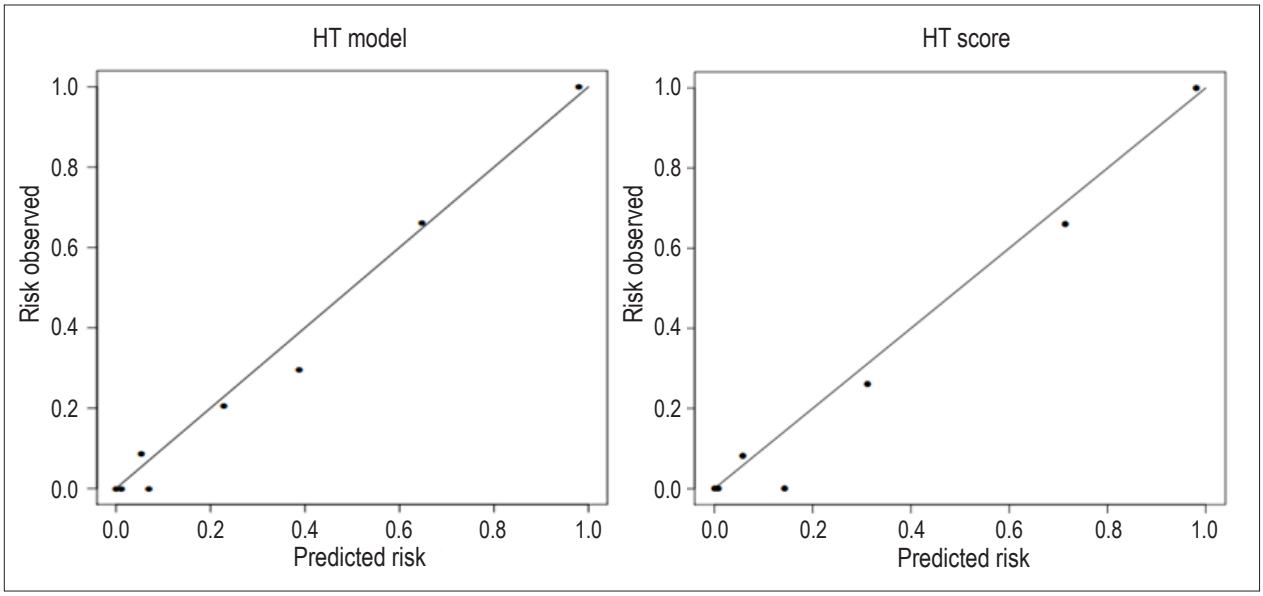
Clinical studies conducted in recent decades have demonstrated an association between thromboembolism and HT. The clinical study Heart and Estrogen/Progestin Replacement Study (HERS) demonstrated that HRT increased relative risk of thromboembolism by two to three times[17]. The study Estrogen in Venous Thromboembolism Trial conducted in women with a history of deep venous thrombosis showed that there was a higher risk of recurrence of this event in patients who received HRT compared to the group of those who did not (8.5% per year, in the treatment group, compared to 1.1% in the placebo group). The study was discontinued prematurely[18]. The Women's Health Initiative Hormone Program (2002), which followed 16,608 postmenopausal women for about five years randomized patients in a treatment group with estrogen and progestin and, in another placebo group, it also confirmed the increased incidence of PTE, with relative risk of 2.13 (95% CI: 1.39 to 3.25)[19]. Canonico et al.[20] performed a systematic review and meta-analysis that analyzed nine randomized controlled trials and all of these confirmed increased risk of DVT in about two to three times in women receiving HRT[20].

The MEGA study (2009) included 1,524 patients and 1,760 controls and the use of hormone therapy was associated with a five times higher risk of thromboembolic events (OR 5.0, 95% CI 4.2 to 5.8)[21]. In a systematic review and meta-analysis, Stegeman et al.[22] examined the relationship of different types of combined oral contraceptives with DVT in healthy women. They found an increased risk of DVT with the use of combined oral contraceptives (relative risk 3.5, CI 2.9 to 4.3), which was observed for all the different types studied[22]. These

Table 3 – Logistic regression of predictors for deep vein thrombosis (n = 461)

Model adjusted with HT (HT Model) and HT score coefficients	Weight*	β	Standard Error	P value	OR [CI 95%]
Cancer in activity	1	1.2	0.7	0.07	3.18 [0.89-11.33]
Paresis, paralysis, or cast immobilization of the lower limbs	2	1.6	0.4	< 0.01	4.30 [2.29-10.60]
Immobilization (>3 days) or major surgery (up to 4 weeks)	2	1.8	0.4	< 0.01	6.13 [2.74-13.69]
Increased sensitivity along the deep venous system veins	3	2.8	0.7	< 0.01	15.85 [3.87-64.90]
Unilateral edema	4	4.0	0.6	< 0.01	53.18 [15.43-183.26]
Differential diagnosis more probable than deep venous thrombosis	-4	-3.9	0.8	< 0.01	0.02 [0.00-0.09]
Use of hormone therapy	2	2.4	0.5	< 0.01	11.112 [4.60-26.86]

HT: hormone therapy; CI: confidence interval; DVT: deep vein thrombosis.



Figures 2 and 3 – *DVT calibration charts observed versus DVT predicted by the HT model and HT score (n=461).*

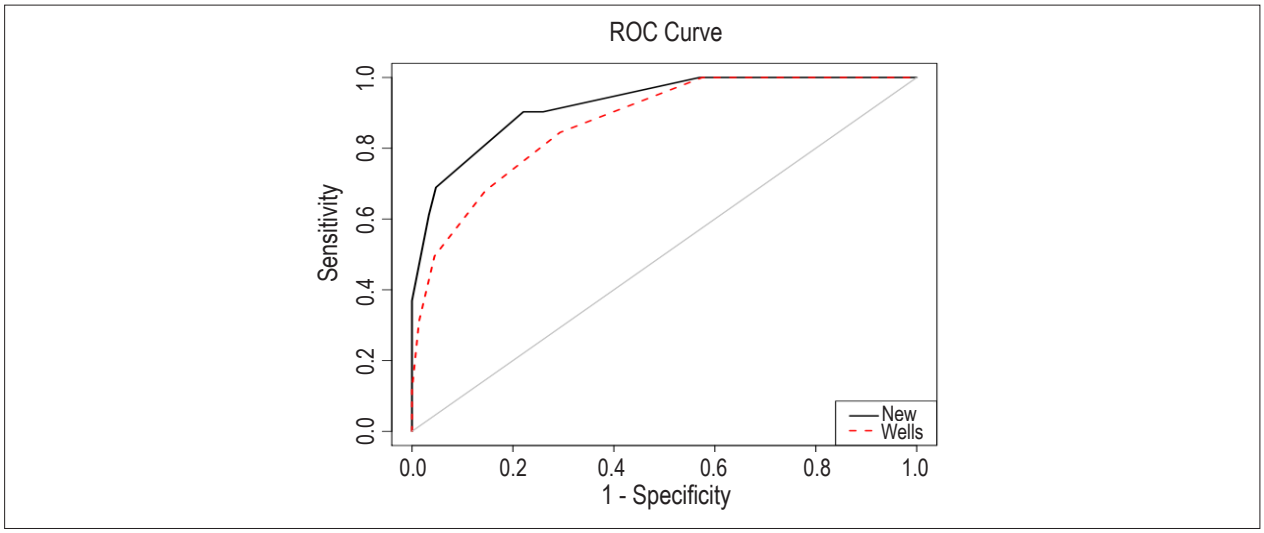


Figure 4 – *HT score ROC curve comparing with the Wells score.*

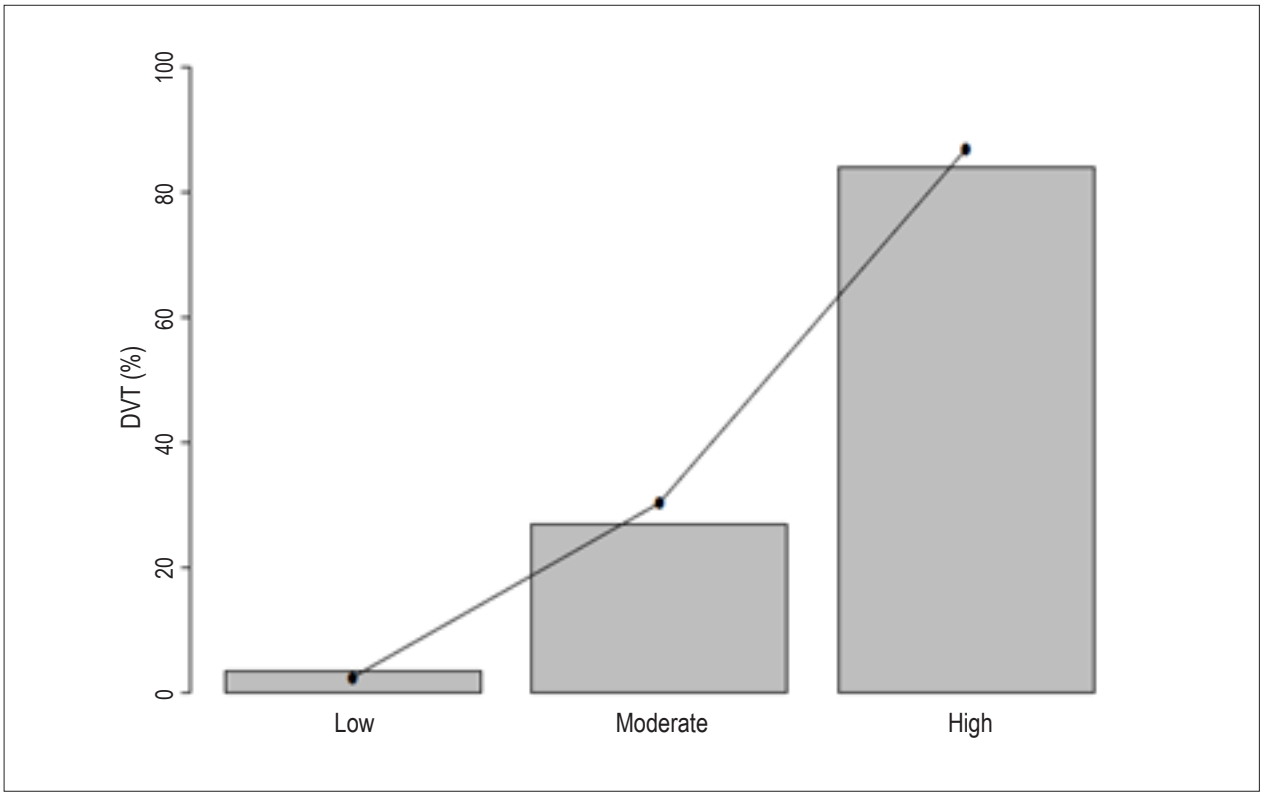


Figure 5 – *DVT observed (bar) versus DVT predicted by the HT score (black dot).*

studies demonstrate the importance of hormone therapy in managing patients with suspected DVT.

Constans et al.[23] compared three existing scores, including Wells, with a new score. The best performance score by the ROC curve was the Wells score, which had a statistically similar result to the new score that they developed ($p = 0.92$)[23]. A meta-analysis published in 2005 compared studies that analyzed isolated clinical findings, risk scores (including the Wells score) and empirical judgments of doctors in the ability to detect DVT and how they affect the Likelihood Ratio (LR). The Wells clinical score was proven to be more valuable through the LR than isolated clinical findings and than empirical judgment[24]. The new proposed model — HT score — showed a better performance compared to the Wells score, although both had presented excellent discriminatory power assessed by the high value of the area under the ROC curve of the proposed models.

Among the limitations of the study we can mention that data analysis was based on a secondary database. To guarantee data quality, we conducted a Kappa test with good agreement between the data in relation to hormone therapy. Another limitation of the study refers to internal validity: it was not possible to apply the adjusted model in a second sample of patients. We do not apply the model in different populations to check the generability of the adjusted model. Another limitation is the lack of discrimination between the type and the dosage of hormone therapy used.

Conclusion

The inclusion of hormone therapy to a clinical prediction model showed higher accuracy compared to the Wells model. The new model may prove useful in the risk stratification for DVT in women once it is validated in different populations.

Authors' contributions

Research creation and design: Barros MVL, Arancibia AEL, Costa AP, Bueno FB, Martins MAC, Magalhães MC, Bastos M; Data acquisition: Barros MVL, Arancibia AEL, Costa AP, Bueno FB, Martins MAC, Magalhães MC, Bastos M; Data analysis and interpretation: Barros MVL, Bastos M, Silva JLP; Statistical analysis: Barros MVL, Silva JLP; Funding: Barros MVL, Bueno FB, Martins MAC; Manuscript drafting: Barros MVL, Arancibia AEL, Costa AP, Magalhães MC, Bastos M; Critical revision of the manuscript as for important intellectual content: Barros MVL, Bastos M, Silva JLP.

Potential Conflicts of Interest

There are no relevant potential conflicts of interest.

Sources of Funding

This study had no external funding sources.

Academic Association

This study is not associated with any graduate program.

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