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Anat Rabinovich
Ben Gurion University of the Negev

Chu-Shu Gu
McMaster University

Suresh Vedantham
Washington University School of Medicine in St. Louis

Clive Kearon
McMaster University

Samuel Z. Goldhaber
Brigham and Women's Hospital

See next page for additional authors

External validation of the SOX-PTS score (clinical prediction model for the post-thrombotic syndrome) in a prospective multicenter trial of patients with proximal deep vein thrombosis

Running head: External validation of the SOX-PTS score

Anat Rabinovich*, Chu-Shu Gu†, Suresh Vedantham‡, Clive Kearon§, Samuel Z. Goldhaber¶, Heather L.Gornik** and Susan R. Kahn†† for the ATTRACT Trial Investigators

*Thrombosis and Hemostasis unit, Hematology institute, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

† Department of Oncology, McMaster University, Hamilton, ON, Canada

‡ Mallinckrodt Institute of Radiology, Washington University in St. Louis, MO, USA

§ Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada

¶ Division of Cardiovascular Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA

**University Hospitals, Case Western Reserve University, Cleveland Ohio, USA

†† Jewish General Hospital, Lady Davis Institute, Center for Clinical Epidemiology, Montreal, QC, Canada

Corresponding author: Anat Rabinovich, MD, Hematology Department, Soroka University Medical Center, POB 151, Beer-Sheva Zip 84101, Israel. Phone: 972-8-6403325 Fax: 972-8-6400195 email: drrabino@bgu.ac.il

Abstract

Background

Using data from the SOX Trial, we recently developed a clinical prediction model for occurrence of the post-thrombotic syndrome (PTS) after proximal deep vein thrombosis (DVT), termed the SOX-PTS score. The score includes anatomical extent of DVT; body mass index; and baseline Villalta score.

Objective

To externally validate the SOX-PTS score.

Methods

Logistic regression analysis of data from the ATTRACT Trial which evaluated pharmacomechanical catheter directed thrombolysis in patients with proximal DVT. The primary outcome was the occurrence of PTS (defined as Villalta score ≥ 5) from 6 to 24 months after DVT. Secondary outcomes included moderate-severe PTS (Villalta scale ≥ 10) and severe PTS (Villalta scale ≥ 14). Predictive performance was assessed by discrimination and calibration. An updated score was evaluated in an exploratory analysis.

Results

691 ATTRACT patients were included, of whom 328 (47%) developed PTS. The c-statistic was 0.63; 95% confidence interval (CI) 0.59-0.67 for PTS. The model's performance appeared to be better for the outcomes moderate to severe PTS and severe PTS (c-statistic 0.67; 95% CI 0.62 to 0.72 for moderate-severe PTS and 0.70; 0.64 to 0.77 for severe PTS). An updated model with age as an additional variable performed similarly to the original model.

Conclusion

We externally validated the SOX-PTS score for estimating the risk of developing PTS, moderate to severe PTS, and severe PTS, in patients with proximal DVT. The score may be useful to predict PTS at the time of DVT diagnosis. Further external validation in different patient cohorts is required.

Keywords: Deep Vein Thrombosis, Postthrombotic Syndrome, Clinical Prediction Rule, Body Mass Index, Iliac Vein

Introduction

The post-thrombotic syndrome (PTS) is a chronic complication of deep vein thrombosis (DVT) that develops in up to 50% of patients despite optimal anticoagulation, usually becoming established in the first two years after DVT [1]. Manifestations range from mild leg pain and discomfort to chronic non-healing leg ulcers. In order to inform patients with DVT about their future outcome, improve their management, and optimally design studies of preventive and treatment strategies, better prognostication of the individual patient's risk of developing PTS is needed.

We recently developed the SOX-PTS score, a clinical prediction model for PTS that was derived in a prospective cohort of patients with proximal DVT (SOX Trial participants) [2]. The score identified 3 independent predictors, namely anatomical extent of DVT (1 point for iliac vein involvement); body mass index (BMI) (2 points for BMI $\geq$35 kg/m^2); and baseline Villalta score (1 point for $\geq$10; 2 points for $\geq$14), with a possible maximum score of 5, that were combined into a model that predicted the risk for PTS development. However, this score has not been externally validated in an independent sample. The aim of the current study was to apply the SOX-PTS score to patients whose data were not used in model development, quantify the model's predictive performance, and update the model if needed.

Methods

Validation cohort

The validation cohort consisted of participants in the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial, a multicenter randomized controlled trial of anticoagulation alone (control group) compared with anticoagulation plus pharmacomechanical catheter-directed thrombolysis (PCDT), for the

prevention of PTS. [3] Patients with symptomatic proximal DVT involving the femoral, common femoral or iliac vein (with or without other involved ipsilateral veins) were enrolled at 56 clinical centers in the United States (list of participating centers in Supporting Information). Patients were excluded if they were younger than 16 or older than 75 years of age, were pregnant, had symptoms for more than 14 days, were at high bleeding risk, had active cancer, had established PTS, or had ipsilateral DVT in the previous 2 years. All the patients provided written informed consent.

Patients in each treatment group received initial and long-term anticoagulant therapy, and were provided sized-to-fit, knee-high, elastic compression stockings (30 to 40 mm Hg of pressure) at the 10-day follow-up visit and every 6 months. [4] In the PCDT arm, recombinant tissue plasminogen activator (rt-PA) was delivered via one of three methods, as published previously. [3, 5]

Outcome

The primary outcome of the ATTRACT trial was the development of PTS according to the Villalta scale. The Villalta scale is a clinical measure for PTS that grades the severity of 5 patient-rated symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and 6 clinician-rated clinical signs (edema, redness, skin induration, hyperpigmentation, venous ectasia, and pain on calf compression) from 0 (absent) to 3 (severe). [6] A summative score of 5 or more or an ulcer in the leg with the index DVT indicates the presence of the PTS. In ATTRACT, these criteria had to be met at any time between the 6-month and the 24-month follow-up visits for patients to be classified as having PTS.

Statistical analysis

All available data in the database were used to maximize the power and generalizability of the results.

We assessed the predictive performance of the SOX-PTS score in the ATTRACT trial cohort by examining measures of discrimination and calibration. Discrimination is the ability of the risk score to differentiate between patients who do and do not experience an event during the study period. This measure is quantified by calculating the c-statistic, the equivalent of the receiver operating characteristic (ROC) based area under the curve, with a value of 0.5 representing chance and 1 representing perfect discrimination. Calibration refers to how closely the predicted 24-month PTS rates using the SOX-PTS score agreed with the observed 24-month PTS rates. This was assessed by plotting observed proportions versus predicted probabilities and by calculating the calibration slope. [7]

Because the PTS outcome in the derivation cohort was defined using Ginsberg PTS criteria [8], which are known to capture more severe PTS than Villalta PTS criteria [9], we planned a pre-specified secondary analysis that assessed model performance with moderate-severe PTS (Villalta score of 10-14) and severe PTS (Villalta score>14) as outcomes.

Handling of missing data

Multiple imputation was performed on patients in the ATTRACT cohort that had missing outcome data (Villalta scores) assuming they were missing at random. Patients who missed all four PTS assessments were included in the multiple imputation. In addition, missing PTS assessments in patients who were lost to follow up before completing all four PTS assessments were also imputed if all existing assessments had a Villalta score <5. Villalta scores were imputed using available Villalta scores in the first 6 months and baseline

covariates. We created 20 imputed datasets, with the missing values replaced by imputed values drawn from their predicted distribution by using the observed data. Fully conditional statement was chosen as the imputation method. In this method, the predictive mean matching method is used for all continuous variables and the logistic regression method is used for all classification variables. [10] No interaction terms were included in the imputation model. Performance of the SOX-PTS score in the imputed ATTRACT dataset was analyzed as a sensitivity analysis. The main analysis was performed on the non-imputed original dataset.

Exploratory analysis- model updating

In exploring model updating, we considered the following baseline covariates from the ATTRACT cohort: treatment arm, iliofemoral vs. femoral-popliteal DVT, sex, age, BMI, DVT symptom duration, previous ipsilateral DVT, contralateral DVT, and inpatient or outpatient status at the time of DVT diagnosis. Only statistically significant covariates ($P < 0.05$) in a multivariate logistic regression were used to construct a new risk score. The discrimination and calibration of the new risk score were examined using the ATTRACT data. A sensitivity analysis was conducted on the discrimination and calibration of the new risk score using the imputed ATTRACT dataset. The above analyses were repeated for two secondary outcomes: moderate to severe PTS, and severe PTS. Internal validation of the new score was performed within the ATTRACT database using the bootstrapping technique.

All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc).

Results

From December 2009 through December 2014, 692 patients underwent randomization to the

ATTRACT trial (337 to the PCDT group and 355 to the control group). One patient who was assigned to the PCDT group who was found not to have a DVT was excluded from all analyses. PTS developed over the 24-month period in 157 of 336 patients (47%) assigned to the PCDT group and in 171 of 355 patients (48%) assigned to the control group (risk ratio, 0.96; 95% confidence interval (CI) 0.82 -1.11). [3] As the intervention had no significant effect on the outcome, we addressed both arms of the study as one cohort.

Comparison of baseline characteristics of the SOX and ATTRACT cohorts

Compared to the SOX cohort, patients in the ATTRACT cohort were younger, had higher BMI, and a greater proportion had unprovoked DVT. None had cancer associated DVT (Table 1). Twenty five percent of patients in the ATTRACT cohort had previous DVT at baseline compared to none in the SOX cohort. Most patients in the SOX and ATTRACT trials were treated with low molecular weight heparin followed by a vitamin K antagonist. Patients in the ATTRACT cohort received a longer median duration of anticoagulation.

Another important difference between the two cohorts was how the anatomical extent of DVT was categorized. Both trials categorized patients according to the most proximal extent of DVT. However, in the ATTRACT trial, DVT was categorized as iliofemoral or femoral-popliteal, whereas in the SOX trial DVT was categorized as iliac, common femoral, femoral or popliteal. Unlike the SOX trial, the ATTRACT trial did not include patients with popliteal DVT (i.e., without more proximal involvement). We were not able to divide ATTRACT patients with iliofemoral DVT into those with only common femoral involvement and those with iliac involvement.

Validation of the SOX-PTS score

Table 2 shows results of the primary analysis, validation of the SOX-PTS score in the ATTRACT trial cohort. The odds ratio for PTS for patients with a SOX-PTS score of 1 (vs 0) in the ATTRACT cohort was 1.43 (95% CI 0.92 to 2.23), whereas in the SOX cohort it was 2.29 (1.27 to 4.11). The odds for PTS development increased to 4.52 (2.59 to 8.06) for patients in the ATTRACT cohort who had a SOX –PTS score of ≥4 (vs. 0) compared to 5.90 (2.09 to 16.62) in the SOX cohort. Within the ATTRACT cohort, 69% of patients who had a SOX-PTS score ≥4 developed PTS, vs. 42% of patients who had a score of 1 (Table 2). When applied to the ATTRACT population, the SOX-PTS score achieved good discrimination (c-statistic 0.63; 95% CI 0.59-0.67) and calibration (Figure 1).

Secondary analyses

Results of the secondary analysis using moderate-severe PTS (Villalta scale≥10) and severe PTS (Villalta scale>14) as the outcomes are shown in Table 3 and Figure 1. The model's performance (discrimination and calibration) improved for both secondary outcomes (c-statistic 0.67; 95% CI 0.62 to 0.72 for moderate-severe PTS and 0.70; 0.64 to 0.77 for severe PTS; Table 4).

Distributions of the SOX-PTS score in the SOX and ATTRACT cohorts for the primary and secondary outcomes are shown in Table 5. The ATTRACT cohort had more patients classified in the higher risk groups according to the SOX-PTS score (score 3 or higher). Interestingly, distribution of the scores in the validation cohort was closest to the distribution in the derivation cohort when considering moderate-severe PTS as the outcome, probably due to the above mentioned differences in definition of the PTS outcome in the two studies (i.e. Ginsberg criteria in SOX vs. Villalta criteria in ATTRACT).

Sensitivity analyses after multiple imputation to replace missing Villalta scores in the ATTRACT cohort

Results of the sensitivity analysis using multiple imputation for patients missing outcome data are shown in Table 1S Supporting information. Multiple imputation was performed on 170 patients, of whom 80 patients missed all four preplanned outcome assessments visits and 90 patients missed one to three outcome assessment visits. Imputation yielded 95 additional patients with PTS than the original dataset.

Distribution of the SOX-PTS score in the SOX trial cohort and imputed ATTRACT trial datasets is shown in Table 2S Supporting information. Similarly to results in the non-imputed dataset, distribution was closest to that of the derivation (SOX trial) cohort when considering moderate to severe PTS as the outcome. Application of the SOX-PTS score on the imputed ATTRACT dataset had little effect on the performance of the model (Table 3S of Supporting information).

Exploratory analysis- Model updating

We tried to improve the SOX-PTS model's performance by updating our model. Multivariable logistic analysis of the ATTRACT data (using the non-imputed original dataset) suggested that advancing age is a predictor of PTS (Table 4S Supporting information). Hence, we updated the model by adding age as an additional variable (Table 5S), categorized into three groups: <40, 40-64, ≥65 years. The updated model has possible scores from 1 to 7. Table 6S Supporting information shows the distribution of the updated SOX-PTS model in the ATTRACT Study cohort. We repeated secondary analyses with moderate-severe PTS and severe PTS as the outcomes (Table 5S). For both the primary analysis and the secondary analyses, performance of the updated model was very similar to

the original score (for the primary analysis, outcome PTS, c-statistic 0.65; 95% CI 0.61 to 0.69, for the secondary analyses, outcome moderate-severe PTS, 0.68; 0.63 to 0.72 and outcome severe PTS, 0.70; 0.64 to 0.76) (Table 7S). Calibration plots for the updated model are presented in Figure 1S supporting information. Internal validation by the bootstrapping technique for the updated model is shown in Table 8S Supporting information. Results show good agreement with the observed estimates. Sensitivity analysis after multiple imputation for patients with missing outcome data in the ATTRACT cohort was also performed for the updated model (Tables 9S-11S Supporting information). As in the original model, multiple imputation had little effect on the performance of the model.

Discussion

We externally validated the SOX-PTS score in an independent prospective cohort of patients with proximal DVT. The model's performance was good, despite differences in characteristics between the derivation and validation cohorts.

In terms of these differences, first, patients in the ATTRACT cohort might have had a higher baseline risk for PTS (25% of the cohort had recurrent DVT, more patients were in the higher BMI categories; both of these factors are known risk factors for PTS). [11, 12] Second, in the ATTRACT trial, DVT was categorized into iliofemoral vs femoral-popliteal, whereas in the SOX trial, most proximal extent of DVT was divided into four categories (iliac, common femoral, femoral and popliteal), hence we were able to pick out iliac DVT, which proved to be an important predictor of PTS. [2] Unfortunately, we did not have information on the proportions of patients with iliac DVT in the ATTRACT cohort. Nevertheless, we chose not to remove this predictor from the score, as we believe that other groups will try to validate the SOX-PTS score in other populations (that hopefully will have information on the four

categories of extent of DVT, like the SOX cohort did). If we removed this predictor, the opportunity to look at the performance of what is considered to be an important predictor of PTS, in other populations, would have been lost. Third, outcome definition was also different between the two cohorts: in the derivation cohort (SOX cohort), Ginsberg's criteria were used to define PTS, whereas in the validation cohort (ATTRACT cohort), the Villalta scale was used. Ginsberg-defined PTS captures more severe PTS than Villalta-defined PTS. [9] To overcome this issue, we preplanned a secondary analysis looking at moderate-severe and severe PTS according to the Villalta scale as the outcomes in the ATTRACT cohort. Indeed, the model's performance was better when these secondary outcomes were considered.

One additional difference between the derivation and validation cohorts should be considered. The experimental interventions that the study participants in the two cohorts received were different (active elastic compression stockings in the SOX trial and PCDT in the ATTRACT trial) and might have modified the likelihood of developing PTS. However, during ATTRACT trial follow up, there was no significant between-group difference in the percentage of patients who developed PTS (47% in the PCDT group and 48% in the control group; risk ratio, 0.96; 95% CI, 0.82 to 1.11). Therefore, we analyzed both arms of the study as one combined cohort. We also accounted for this fact by including assigned treatment arm as a parameter in the multivariable analysis, and it did not influence the final model.

To the best of our knowledge, only two other prediction models for PTS have been published. [13, 14] The model by Amin and colleagues is [13] a two-step model consisting of a first model to be applied at baseline to predict the probability of developing PTS at 6 months, and a second model to be applied at 6 months to predict the probability of PTS at 24 months for those patients who had not developed PTS by 6 months. Predictor variables in the first step

were: age>56, BMI>30, male sex, varicose veins, history of venous thrombosis, smoking status, provoked DVT and iliofemoral DVT. Predictor variables in the second step were the same as in the first step with the addition of residual vein obstruction. The model by Méan and colleagues [14] includes age > 75years, prior varicose vein surgery, multi-level thrombosis, concomitant use of antiplatelet/ non-steroidal anti-inflammatory drugs, and number of leg symptoms and signs. We could not validate these two prediction models in the ATTRACT cohort because of lack of data on some predictor variables (smoking status, varicose veins and residual obstruction for the prediction model by Amin et al [13], and prior varicose vein surgery for the prediction model by Méan et al [14]). However, the three models are in agreement regarding some of the predictor variables (e.g., age, iliofemoral involvement in DVT, severe symptoms and signs at DVT diagnosis). A comparative validation study evaluating the performance of different PTS prediction models on the same data set would generate additional important information.

The present study has potential limitations. In addition to differences between the two cohorts as elaborated above, this validation cohort (like the derivation cohort) is based on data from a randomized trial and not a prospective cohort study designed specifically for this purpose. However, we controlled for this by including the treatment arm as a parameter in the multivariable analysis, and it did not influence the final model. Also, as most patients in the SOX and ATTRACT trials were treated with low molecular heparin followed by warfarin, the validity of this model in patients treated with the newer direct oral anticoagulants should be addressed.

In conclusion, we externally validated the SOX-PTS score for estimating the risk of developing PTS, moderate to severe PTS, and severe PTS, in patients with proximal DVT.

All items in the model are readily available at the time of DVT diagnosis and thus the score may be useful to estimate the risk of developing PTS at the time of DVT diagnosis. Further external validation in different patient cohorts is required.

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Table 1: Baseline Characteristics of the SOX trial and ATTRACT trial participants

Characteristics	SOX n = 762	ATTRACT n = 691	p-value
Sex - female: *n (%)*	305 (40)	265 (38)	0.51
Age Category (years): *n (%)*			< 0.001
< 40	129 (17)	152 (22)	
40-64	423 (56)	418 (60)	
≥ 65	210 (28)	121 (18)	
Ethnicity: *n (%)*			< 0.001
Caucasian	688 (90)	542 (78)	
Other	74 (10)	149 (22)	
Iliac DVT - yes: *n (%)*	90 (12)	NA	NA
Common femoral vein or Iliac vein DVT - yes: *n (%)*	NA	391 (57)	NA
Baseline Villalta Score category			0.002
0-4 (none)	164 (22)	126 (18)	
5-9 (mild)	298 (39)	239 (35)	
10-14 (moderate)	216 (28)	192 (18)	
>14 (severe)	84 (11)	132 (19)	
Unknown	0	2 (<1)	
DVT Type: *n (%)*			< 0.001
Cancer associated	79 (10)	0	
Secondary Risk Factors	206 (27)	101 (15)	
Unprovoked	477 (63)	590 (85)	
Side of DVT: *n (%)*			0.018
Left	422 (55)	425 (62)	
Right	340 (45)	266 (38)	
Previous DVT or PE: *n (%)*	0	170 (25)	< 0.001
BMI category (kg/m^2): *n (%)*			< 0.001
< 25	193 (25)	115 (17)	
25-34	457 (60)	388 (57)	
≥ 35	112 (15)	184 (27)	
Unknown	0	4 (1)	
Duration of anticoagulation (days): *median (Q1, Q3)*	185 (111-233)	223 (186, 372)	< 0.001*

PTS; post thrombotic syndrome, DVT; deep vein thrombosis, BMI; body mass index

* Non-parametric Wilcoxon rank sum test

Table 2: Performance of SOX-PTS score in SOX Trial (derivation set) and ATTRACT Trial (validation set) data

Variable	SOX Study (N = 762)		ATTRACT Study (N = 691)	
	Events/n (%)	**OR** (95% CI)	**Events/n (%)**	**OR** (95% CI)
More extensive (vs less extensive) DVT*, 1 point		1.96 (1.08 to 3.57)		1.14 (0.83 to 1.55)
BMI ≥ 35 (vs < 35), 2 points		2.17 (1.27 to 3.72)		1.94 (1.37 to 2.78)
Baseline Villalta score category[#] (vs None to Mild)				
Severe, 2 points		2.64 (1.41 to 4.96)	86/132 (65)	2.60 (1.71 to 4.00)
Moderate, 1 point		2.00 (1.21 to 3.29)	98/192 (51)	1.49 (1.04 to 2.14)
None to Mild		n/a	144/367 (39)	n/a
SOX-PTS Score (vs 0)				
≥ 4	6/21 (29)	5.90 (2.09 to 16.62)	61/88 (69)	4.52 (2.59 to 8.06)
3	14/56 (25)	4.91 (2.35 to 10.27)	74/120 (62)	3.22 (1.96 to 5.34)
2	20/122 (16)	2.89 (1.53 to 5.47)	61/136 (45)	1.63 (1.01 to 2.63)
1	27/201 (13)	2.29 (1.27 to 4.11)	82/197 (42)	1.43 (0.92 to 2.23)
0	23/362 (6)	n/a	50/150 (33)	n/a

PTS; post thrombotic syndrome, DVT; deep vein thrombosis, BMI; body mass index OR; odds ratio.

*Iliac vs non iliac vein involvement in the SOX trial; Common femoral and/or iliac vein vs femoral-popliteal vein involvement in the ATTRACT trial

[#]Villalta score categories: None, score of 0-4; Mild, 5-9; Moderate, 10-14; Severe, >14

Table 3: Secondary analyses: Performance of SOX-PTS score using moderate-severe PTS and severe PTS as the outcomes

Category	ATTRACT Moderate to Severe PTS	ATTRACT Severe PTS
	OR for PTS (95% CI)	**OR for PTS** (95% CI)
More extensive (vs. less extensive) DVT*	1.25 (0.84 to 1.87)	1.31 (0.76 to 2.26)
BMI ≥ 35 (vs < 35)	1.61 (1.07 to 2.41)	2.03 (1.20 to 3.43)
Baseline Villalta score category[#] (vs None to Mild)		
Severe	4.19 (2.61 to 6.77)	4.59 (2.48 to 8.51)
Moderate	2.16 (1.36 to 3.42)	1.70 (0.88 to 3.30)
SOX-PTS Score (vs 0)		
≥ 4	6.72 (4.42 to 13.86)	12.17 (4.03 to 36.71)
3	4.33 (2.26 to 8.74)	6.87 (2.27 to 20.79)
2	2.30 (1.16 to 4.72)	3.53 (1.11 to 11.23)
1	1.81 (0.94 to 3.65)	2.58 (0.82 to 8.08)

PTS; post thrombotic syndrome, DVT; deep vein thrombosis, BMI; body mass index OR; odds ratio

*Iliac vs non iliac vein involvement in the SOX trial; Common femoral and/or iliac vein vs femoral-popliteal vein involvement in the ATTRACT trial

[#]Villalta score categories: None, score of 0-4; Mild, 5-9; Moderate, 10-14; Severe, >14

Table 4: Model Fit Statistics and Association of Predicted Probability and Observed Response for the primary outcome and secondary outcomes

Model Fit Statistics	PTS		Moderate- Severe PTS		Severe PTS	
	based on baseline variables	based on SOX-PTS score	based on baseline variables	based on SOX-PTS score	based on baseline variables	based on SOX-PTS score
% Concordant*	58.0	53.1	63.6	57.3	67.3	61.4
% Discordant	30.0	26.7	26.6	23.8	23.9	20.6
% Tied	12.0	20.2	9.8	18.9	8.8	18.0
Somers' D	0.28	0.27	0.37	0.34	0.43	0.41
Gamma	0.32	0.33	0.41	0.41	0.48	0.50
Tau-a	0.14	0.13	0.12	0.11	0.08	0.07
c-statistic (95%CI)	0.64 (0.60 to 0.68)	0.63 (0.59 to 0.67)	0.69 (0.64 to 0.73)	0.67 (0.62 to 0.72)	0.72 (0.65 to 0.78)	0.70 (0.64 to 0.77)

*To evaluate concordance, all possible pairs of patients (i.e. one patient has a PTS event and the other has no PTS event) are assessed. For a pair of patients, the actual outcome (i.e. PTS) and the predicted probability of outcome from the logistic model can have 3 types of results:

1) Concordant: in the pair, the patient with higher predicted probability had PTS event
2) Discordant: in the pair, the patient with lower predicted probability had PTS event
3) Both patients in the pair have the same predicted probability (Tie condition)

Table 5: Distribution of the SOX-PTS Score in the SOX and ATTRACT Studies

SOX-PTS Score	SOX (N = 762)	ATTRACT (N = 691)		
	PTS* N (%)	PTS# N (%)	Moderate-Severe PTS# N (%)	Severe PTS# N (%)
0	23/362 (6)	50/150 (33)	14/150 (9)	4/150 (3)
1	27/201 (13)	82/197 (42)	31/197 (16)	13/197 (7)
2	20/122 (16)	61/136 (45)	26/136 (19)	12/136 (9)
3	14/56 (25)	74/120 (62)	37/120 (31)	19/120 (16)
4	6/20 (30)	38/54 (70)	22/54 (41)	14/54 (26)
5	0/1	23/34 (68)	14/34 (41)	8/34 (24)

PTS; post thrombotic syndrome

* PTS was defined according to the Ginsberg criteria

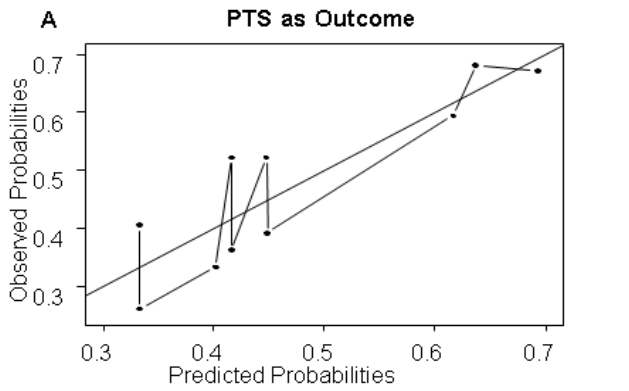
PTS was defined according to Villalta score categories: None, score of 0-4; Mild, 5-9; Moderate, 10-14; Severe, >14

Figure 1. Calibration plots for the SOX-PTS score applied to the ATTRACT cohort

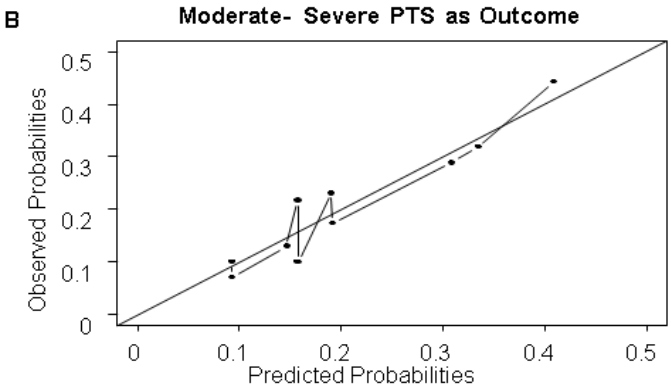
A. PTS as outcome

B. Moderate-severe PTS as outcome

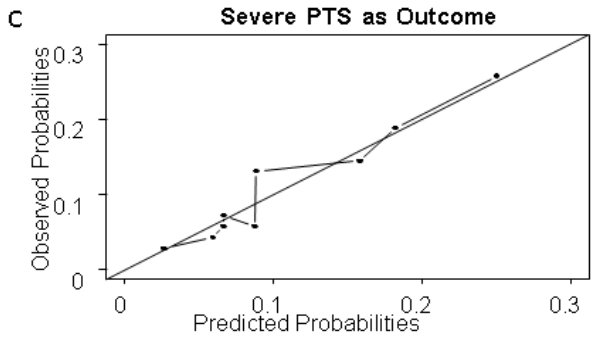
C. Severe PTS as outcome



Parameter Estimates for Linear Regression					
Variable	DF	Parameter Estimate	Standard Error	t-Value	Pr > |t|
Intercept	1	-0.002	0.091	-0.026	0.98
B	1	1.005	0.186	5.397	0.00065



Parameter Estimates for Linear Regression					
Variable	DF	Parameter Estimate	Standard Error	t-Value	Pr > |t|
Intercept	1	-0.01	0.03	-0.36	0.73
B	1	1.05	0.12	9.01	<0.0001



Parameter Estimates for Linear Regression					
Variable	DF	Parameter Estimate	Standard Error	t-Value	Pr > |t|
Intercept	1	-0.002	0.011	-0.19	0.85
B	1	1.02	0.093	11.03	<0.0001

Supporting materials for "External validation of the SOX-PTS score (clinical prediction model for the post-thrombotic syndrome) in a prospective multicenter trial of patients with proximal deep vein thrombosis"

ATTRACT Clinical Centers

Adventist Midwest Health
Albert Einstein Medical Center
Allegheny General Hospital
Ann Arbor VA Health Center
Baptist Cardiac and Vascular Institute
Central DuPage Hospital
Christiana Care Hospital
Cleveland Clinic Foundation
Danbury Hospital
Eastern Connecticut Hematology & Oncology Associates
Florida Hospital
Forsyth Medical Center
Gundersen Clinic, Ltd
Georgetown University
Henry Ford Health System
Holy Name Medical Center
Jobst Vascular Center
Maine Medical Center
Massachusetts General Hospital
Mayo Clinic
Mease Countyside Hospital
Medical College of Wisconsin/Froedtert Hospital & Clinics
Medical University of South Carolina
Oregon Health & Science University
Pepin Heart Hospital and Dr. Kiran C. Patel Research Institute
Phoenix Heart & Cardiovascular
Riverside Methodist Hospital
Rhode Island Hospital
Providence Sacred Heart Medical Center & Children's Hospital
Southern Illinois University
St. Elizabeth Regional Medical Center (NE)
St. Joseph Hospital
St. Luke's Hospital and Health Network
St. Luke's Hospital: Brandt Wible
St. Vincent Medical Group

Stanford University Medical Center
Staten Island University Hospital
Temple University Hospital
The Reading Hospital
TriHealth/Good Samaritan Hospital
University of Iowa
University of Illinois- Chicago
University of Maryland
University of Michigan Hospitals and Health Centers
University of Minnesota
University of New Mexico
University of North Carolina
University of Pittsburgh
University of Utah Medical Center
University of Virginia Health System
Utah Valley Reginal Medical Center
Weill Cornell Medical College
Western Penn Allegheny Health System
Washington University in St. Louis

Table 1S: Performance of SOX-PTS score using the ATTRACT Data after Multiple Imputation

Category	PTS	Moderate to Severe PTS	Severe PTS
	OR for PTS (95% CI)	**OR for PTS (95% CI)**	**OR for PTS (95% CI)**
More extensive DVT*(vs less extensive)	1.15 (0.80 to 1.66)	1.19 (0.81 to 1.73)	1.30 (0.77 to 2.21)
BMI ≥ 35 (vs < 35)	1.77 (1.13 to 2.77)	1.35 (0.89 to 2.05)	1.65 (1.00 to 2.74)
Baseline Villalta score category# (vs None to Mild)			
Severe	1.78 (1.17 to 2.71)	5.06 (2.93 to 8.73)	5.72 (2.96 to 11.05)
Moderate	3.78 (2.17 to 6.59)	2.22 (1.41 to 3.52)	2.00 (1.02 to 3.91)
SOX-PTS Score (vs 0)			
≥ 4	5.54 (2.74 to 11.18)	6.01 (2.85 to 12.65)	10.38 (3.29 to 32.76)
3	3.33 (1.86 to 5.96)	4.15 (2.11 to 8.18)	6.09 (1.97 to 18.79)
2	1.74 (1.04 to 2.91)	2.38 (1.18 to 4.78)	3.30 (1.03 to 10.56)
1	1.48 (0.92 to 2.36)	1.92 (1.01 to 3.63)	2.42 (0.79 to 7.43)

Note: ATTRACT results are based on 20 multiple imputation datasets
PTS; post thrombotic syndrome, DVT; deep vein thrombosis, BMI; body mass index OR; odds ratio.
* Iliac vs non iliac vein involvement in the SOX trial; Common femoral and/or iliac vein vs femoral-popliteal vein involvement in the ATTRACT trial
#Villalta score categories: None, score of 0-4; Mild, 5-9; Moderate, 10-14; Severe, >14

Table 2S: Distribution of the SOX-PTS Score in the SOX trial cohort and imputed ATTRACT trial Datasets

SOX-PTS Score	SOX* (N = 762)	ATTRACT, multiple imputation (N = 691)		
	PTS N (%)	PTS# N (%)	Moderate-Severe# PTS N (%)	Severe PTS# N (%)
0	23/362 (6)	69.4/150 (45)	22.5/150 (15)	7.9/150 (5)
1	27/201 (13)	110.3/197 (56)	49.5/197 (25)	22.4/197 (11)
2	20/122 (16)	81.5 /136 (60)	40.0/136 (29)	20.3/136 (15)
3	14/56 (25)	89/120 (74)	50.5/120 (42)	29.2/120 (24)
4	6/20 (30)	41.6/54 (77)	24.1/54 (45)	17.3/54 (32)
5	0/1	31.2/34 (92)	21.0/34 (62)	13.8/34 (41)

PTS; post thrombotic syndrome

* PTS was defined according to the Ginsberg criteria

PTS was defined according to Villalta score categories: None, score of 0-4; Mild, 5-9; Moderate, 10-14; Severe, >14

Table 3S: Model fit statistics of the SOX-PTS Score in the imputed ATTRACT trial cohort

Model Fit Statistics	PTS as Outcome	Moderate-Severe PTS as Outcome	Severe PTS as Outcome
% Concordant	53.5 (50.9 to 55.5)	55.8 (52.8 to 59.8)	60.0 (55.7 to 64.2)
% Discordant	25.8 (24.1 to 28.1)	24.9 (21.6 to 27.4)	21.7 (18.3 to 25.3)
% Tied	20.7 (20.4 to 21.0)	19.4 (18.6 to 19.9)	18.3 (17.5 to 19.0)
Somers' D	0.28 (0.23 to 0.31)	0.31 (0.25 to 0.38)	0.38 (0.30 to 0.46)
Gamma	0.35 (0.29 to 0.39)	0.38 (0.32 to 0.47)	0.47 (0.37 to 0.56)
Tau-a	0.13 (0.11 to 0.15)	0.13 (0.11 to 0.16)	0.10 (0.09 to 0.13)
C statistic (95% CI)	0.64 (0.61 to 0.66)	0.65 (0.63 to 0.69)	0.69 (0.65 to 0.73)

Table 4S: Multivariable logistic regression model of the association between ATTRACT population baseline characteristics and PTS development

Baseline Variables	OR (95% CI)	P-value
Treatment arm (PCDT vs. No PCDT)	0.91 (0.65, 1.27)	0.57
Iliofemoral vs. Popliteal DVT	1.17 (0.82, 1.68)	0.39
Clinical Centre		0.0008
Age (per year)	1.03 (1.01, 1.04)	<0.0001
Sex (Female vs. Male)	0.70 (0.49, 1.01)	0.060
BMI, kg/m^2 (per unit increase)	1.05 (1.02, 1.07)	0.0003
DVT Symptom Duration (per day)	1.04 (1.00, 1.09)	0.064
Ipsilateral DVT (No vs. Yes)	1.02 (0.19, 5.51)	0.77
Contralateral DVT (No vs. Yes)	1.06 (0.49, 2.31)	0.17
Inpatient (No vs. Yes)	1.06 (0.65, 1.75)	0.81
Baseline Villalta Score (per point increase)	1.13 (1.09, 1.17)	<0.0001

PTS; post thrombotic syndrome, DVT; deep vein thrombosis, BMI; body mass index

Table 5S: Updated SOX-PTS score including age as an additional variable applied to the ATTRACT cohort

Parameter	PTS	Moderate-Severe PTS	Severe PTS	Points
	OR (95%CI)	OR (95%CI)	OR (95%CI)	
More extensive (vs less extensive) DVT*	1.17 (0.85 to 1.61)	1.30 (0.87 to 1.95)	1.36 (0.78 to 2.36)	1
BMI ≥ 35 (vs < 35)	2.03 (1.42 to 2.91)	1.67 (1.10 to 2.53)	2.04 (1.20 to 3.47)	2
Baseline Villalta score category# (vs None to Mild)				
Severe	2.66 (1.73 to 4.11)	4.11 (2.52 to 6.71)	4.34 (2.32 to 8.13)	2
Moderate	1.59 (1.10 to 2.30)	2.26 (1.42 to 3.59)	1.71 (0.88 to3.32)	1
Age Category (vs < 40)				
≥ 65	2.37 (1.42 to 3.95)	2.20 (1.11 to 4.37)	1.28 (0.48 to 3.40)	2
40-64	1.90 (1.27 to 2.83)	2.23 (1.30 to 3.83)	1.83 (0.91 to 3.69)	1
Intercept	-0.73 (-1.02 to- 0.43)	-2.90 (-3.53 to -2.27)	-3.63 (-4.48 to -2.78)	
Updated SOX-PTS score (vs 0)				
≥ 6	13.22 (3.76 to 46.53)	6.86 (1.71 to 27.58)	10.02 (3.01 to 33.29)	
5	9.93 (3.27 to 30.11)	5.56 (1.51 to 20.47)	6.47 (2.14 to 19.53)	
4	7.47 (2.63 to 21.24)	3.99 (1.13 to 14.14)	7.20 (2.62 to 19.80)	
3	4.66 (1.69 to12.88)	2.00 (0.57 to 7.07)	2.86 (1.00 to 8.15)	
2	2.78 (1.01 to 7.64)	1.43 (0.41 to 5.06)	1.76 (0.60 to5.18)	
1	2.63 (0.93 to7.40)	0.83 (0.22 to 3.21)	NA§	

PTS; post thrombotic syndrome, DVT; deep vein thrombosis, BMI; body mass index OR; odds ratio
*Iliac vs non iliac vein involvement in the SOX trial; Common femoral and/or iliac vein vs femoral-popliteal vein involvement in the ATTRACT trial
#Villalta score categories: None, score of 0-4; Mild, 5-9; Moderate, 10-14; Severe, >14
§ Quasi-complete separation data, score categories 0 and 1 are combined as reference level

Table 6S: Distribution of the updated* SOX-PTS score in the ATTRACT Study cohort

Updated SOX-PTS score	ATTRACT cohort (N = 691)		
	PTS N (%)	Moderate-Severe PTS N (%)	Severe PTS N (%)
0	5/28 (18)	3/28 (11)	0/28 (0)
1	44/121 (36)	11/121 (9)	5/121 (4)
2	72/191 (38)	28/191 (15)	11/191 (6)
3	78/155 (50)	30/155 (19)	14/155 (9)
4	65/105 (62)	34/105 (32)	21/105 (20)
5	41/60 (68)	24/60 (40)	11/60 (18)
6	21/29 (72)	12/29 (41)	7/29 (24)
7	2/2 (100)	2/2 (100)	1/2 (50)

*Updated model includes age as an additional variable

Table 7S: Model Fit Statistics and Association of Predicted Probability and Observed Response, updated* SOX-PTS Score

Model Fit Statistics	PTS as outcome		Moderate- severe PTS as outcome		Severe PTS as outcome	
	based on baseline variables	based on SOX-PTS score	based on baseline variables	based on SOX-PTS score	based on baseline variables	based on SOX-PTS score*
%Concordant	63.3	55.8	66.3	59.3	70.2	61.7
%Discordant	31.5	26.0	27.7	24.1	25.6	21.8
% Tied	5.2	18.2	6.0	16.7	4.2	16.5
Somers' D	0.32	0.30	0.39	0.35	0.45	0.40
Gamma	0.34	0.37	0.41	0.42	0.47	0.48
Tau-a	0.16	0.15	0.13	0.12	0.08	0.07
C statistic (95% CI)	0.66 (0.62 to 0.70)	0.65 (0.61 to 0.69)	0.70 (0.65 to 0.75)	0.68 (0.63 to 0.72)	0.73 (0.66 to 0.79)	0.70 (0.64 to 0.76)

*Updated model includes age as an additional variable

Table 8S: Internal Validation with Bootstrapping Technique of updated* SOX-PTS score- Odds Ratio estimates (95% CL)

Updated SOX-PTS Score (vs 0)	ATTRACT					
	PTS		Moderate-Severe PTS		Severe PTS§	
	Raw	Boot#	Raw	Boot#	Raw	Boot#
≥6	13.22 (3.76 to 6.53)	14.62 (4.68 to 65.00)	6.86 (1.71 to 27.58)	7.07 (1.91 to 30.00)	10.02 (3.01 to 33.29)	9.95 (3.01 to 54.50)
5	9.93 (3.27 to 30.11)	10.40 (3.90 to 42.40)	5.56 (1.51 to 20.47)	5.82 (1.84 to 23.76)	6.47 (2.14 to 19.53)	6.55 (2.11 to 32.68)
4	7.47 (2.63 to 21.24)	7.50 (3.13 to 28.36)	3.99 (1.13 to 14.14)	4.07 (1.34 to 15.87)	7.20 (2.62 to 19.80)	7.11 (2.96 to 37.73)
3	4.66 (1.69 to 12.88)	4.74 (1.95 to 18.68)	2.00 (0.57 to 7.07)	2.06 (0.69 to 7.63)	2.86 (1.00 to 8.15)	2.89 (1.01 to 14.79)
2	2.78 (1.01 to 7.64)	2.87 (1.18 to 11.14)	1.43 (0.41 to 5.06)	1.46 (0.48 to 5.32)	1.76 (0.60 to 5.18)	1.75 (0.60 to 9.87)
1	2.63 (0.93 to 7.40)	2.67 (1.05 to 10.26)	0.83 (0.22 to 3.21)	0.85 (0.23 to 3.38)		

C Statistics for Bootstrap Samples, Updated SOX-PTS Score	
Data	**C-Statistics (95% CI)**
ATTRACT – PTS (Continuous)	0.65 (0.61 to 0.69)
ATTRACT – Moderate-Severe PTS (Continuous)	0.68 (0.63 to 0.73)
ATTRACT – Severe PTS (Continuous)	0.70 (0.64 to 0.76)
ATTRACT – PTS (Categorical)	0.64 (0.60 to 0.68)
ATTRACT – Moderate-Severe PTS (Categorical)	0.66 (0.62 to 0.71)
ATTRACT – Severe PTS (Categorical)	0.68 (0.62 to 0.74)

*Updated model includes age as an additional variable

#Boot = bootstrap estimate;

§ Reference level is score 0 and 1

Table 9S: Final Models for the Updated* SOX-PTS Score using ATTRACT Data, after Multiple Imputation

Category	PTS	Moderate to Severe PTS	Severe PTS
	OR for PTS (95% CI)	**OR for PTS** (95% CI)	**OR for PTS (95% CI)**
More extensive (vs less extensive) DVT*	1.19 (0.82 to 1.72)	1.23 (0.84 to 1.79)	1.34 (0.78 to 2.29)
BMI ≥ 35 (vs < 35)	1.82 (1.15 to 2.86)	1.36 (0.89 to 2.08)	1.67 (1.00 to 2.79)
Age (vs. < 40)			
≥ 65	3.82 (2.17 to 6.71)	4.88 (2.81 to 8.50)	5.41 (2.80 to 10.45)
40-64	1.85 (1.21 to 2.83)	2.25 (1.41 to 3.59)	1.99 (1.01 to 3.93)
Baseline Villalta score category# (vs None to Mild)			
Severe	1.67 (0.94 to 2.96)	1.24 (0.63 to 2.45)	0.91 (0.35 to 2.33)
Moderate	1.54 (0.98 to 2.40)	1.52 (0.90 to 2.58)	1.31 (0.62 to 2.75)
SOX-PTS Score (vs 0)			Quasi-complete Data#
≥ 6	12.74 (2.42 to 67.00)	6.44 (1.40 to 29.73)	7.71 (2.21 to 26.90)
5	5.56 (1.71 to 18.05)	4.52 (1.07 to 19.00)	5.35 (1.87 to 15.32)
4	4.22 (1.35 to 13.13)	3.55 (0.91 to 13.81)	5.62 (2.04 to 15.52)
3	2.43 (0.84 to 7.02)	1.91 (0.47 to 7.78)	2.47 (0.89 to 6.87)
2	1.53 (0.55 to 4.24)	1.51 (0.40 to 5.68)	1.55 (0.59 to 4.04)
1	1.37 (0.47 to 4.01)	0.94 (0.24 to 3.64)	

Note: ATTRACT results are based on 20 multiple imputation datasets
*Updated model includes age as an additional variable
Quasi-complete separation data, score 0 and 1 are combined as reference level

Table 10S: Distribution of the updated* SOX-PTS Score in the imputed ATTRACT Datasets

New Score	ATTRACT cohort (N = 691)		
	PTS / N (%)	Moderate-Severe PTS / N (%)	Severe PTS / N (%)
0	11.7/28 (42)	5.1/28 (18)	0.9/28 (3)
1	59.5/121 (49)	20.1/121 (17)	9.4/121 (8)
2	99.3/191 (52)	46/191 (24)	19.3/191 (10)
3	98.1/155 (63)	44.4/155 (29)	23.4/155 (15)
4	78.6/105 (75)	44.9/105 (43)	30.2/105 (29)
5	47.8/60 (80)	29.2/60 (49)	16.7/60 (28)
6	25.9/29 (89)	15.8/29 (54)	10.1/29 (35)
7	2/2 (100)	2/2 (100)	1/2 (50)

Note: ATTRACT results are based on 20 multiple imputation datasets

*Updated model includes age as an additional variable

Table 11S: Model Fit Statistics for updated* SOX-PTS Score, after multiple imputation

Model Fit Statistics	PTS		Moderate-Severe PTS		Severe PTS	
	Mean	**Min, Max**	**Mean**	**Min, Max**	**Mean**	**Min, Max**
%Concordant	55.1	50.8, 57.8	56.2	53.2, 59.9	59.5	55.5, 65.0
%Discordant	25.7	20.6, 28.5	26.0	23.1, 28.5	23.3	19.0, 26.7
% Tied	19.2	18.4, 28.6	17.8	16.9, 19.7	17.2	16.0, 19.3
Somers' D	0.29	0.24, 0.34	0.30	0.25, 0.37	0.36	0.29, 0.46
Gamma	0.36	0.30, 0.42	0.37	0.30, 0.44	0.44	0.35, 0.55
Tau-a	0.14	0.11, 0.16	0.13	0.11, 0.15	0.10	0.08, 0.12
c-statistic (95%CI) continuous	0.65 (0.60 to 0.69)		0.65 (0.59 to 0.70)		0.68 (0.61 to 0.74)	
c-statistic (95%CI) categorical	0.65 (0.60 to 0.69)		0.65 (0.60 to 0.70)		0.68 (0.61 to 0.75)	

*Updated model includes age as an additional variable

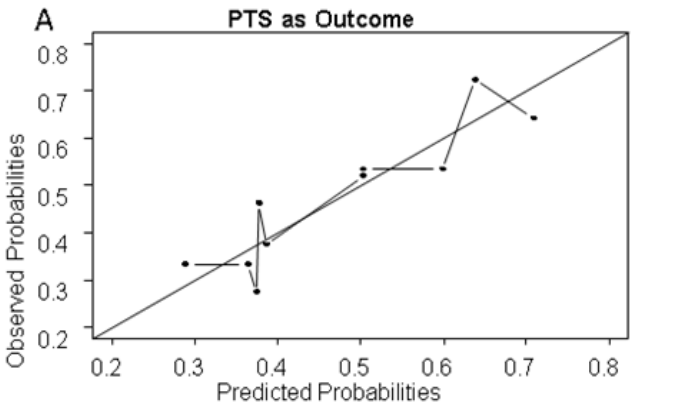
Figure 1S. Calibration plots for updated* SOX-PTS score applied to the ATTRACT cohort

A. PTS as outcome

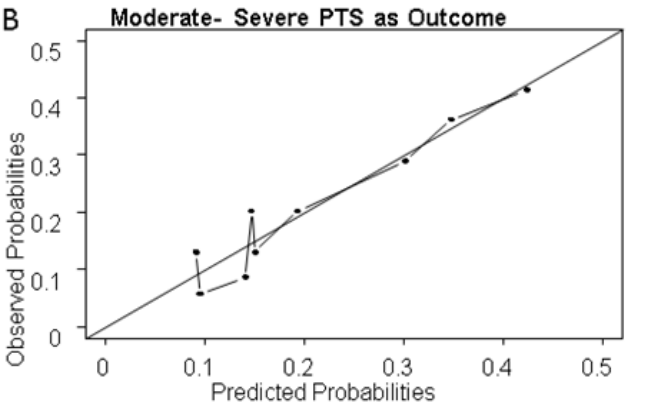
B. Moderate- severe PTS as outcome

C. Severe PTS as outcome

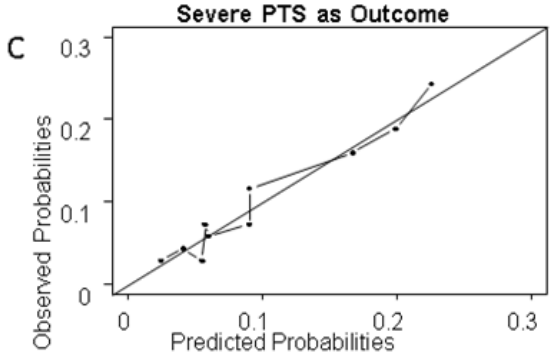
***Updated model includes age as an additional variable**



Parameter Estimates for Linear Regression					
Variable	DF	Parameter Estimate	Standard Error	t-Value	Pr > |t|
Intercept	1	0.029	0.080	0.359	0.73
B	1	0.939	0.163	5.752	0.00043



Parameter Estimates for Linear Regression					
Variable	DF	Parameter Estimate	Standard Error	t-Value	Pr > |t|
Intercept	1	0.000	0.025	0.015	0.99
B	1	0.998	0.105	9.513	0.00001



Parameter Estimates for Linear Regression					
Variable	DF	Parameter Estimate	Standard Error	t-Value	Pr > |t|
Intercept	1	-0.001	0.010	-0.15	0.89
B	1	1.014	0.081	12.50	< 0.0001