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A Risk Score for Iliofemoral DVT Patients

Soroosh Shekarchian, MD, PhD candidate, Pascale Notten, MD, PhD, Mohammad Esmail Barbati, MD, Crystal Razavi, Msc, Jorinde Van Laanen, MD, Fred Nieman, PhD, Mahmood K. Razavi, MD, PhD, Wim Moosdorff, Msc, Barend Mees, MD, PhD, Houman Jalaie, MD

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1 A Risk Score for Iliofemoral DVT Patients

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3 Soroosh Shekarchian, MD, PhD candidate^{1,*}, Pascale Notten, MD, PhD^{1,*}, Mohammad Esmaeil

4 Barbati, MD², Crystal Razavi, Msc³, Jorinde Van Laanen, MD¹, Fred Nieman, PhD¹, Mahmood

5 K Razavi MD, PhD⁴, Wim Moosdorff Msc⁵, Barend Mees, MD, PhD¹, Houman Jalaie, MD^{1,2,#}

6 ¹ Department of Vascular Surgery, Maastricht University Medical Centre, Maastricht, the

7 Netherlands.

8 ² European Vascular Center Aachen-Maastricht, University Hospital RWTH Aachen, Aachen,

9 Germany.

10 ³ Alfred E. Mann Institute for Biomedical Engineering, University of Southern California,

11 Orange, CA, United States.

12 ⁴ St. Joseph's Hospital, Orange, CA, United States.

13 ⁵ STAR-Medical Diagnostic Center, Primary Care Medicine, Rotterdam, the Netherlands.

14 * Equally contributed

15 # Corresponding author and post-publication corresponding author:

16 Dr. Houman Jalaie, E-Mail: houman.jalaie@mumc.nl

17 Maastricht University Medical Centre, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht

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20 **ARTICLE HIGHLIGHTS**

21 **Type of Research:** Single-center retrospective cohort study

22 **Key Findings:** A multivariate model [sensitivity 77% and specificity 82%, area under the curve
23 (AUC)=0.90, 0.86-0.93)] based on D-dimer, Wells score, age, and anticoagulation use is able to

1 distinguish iliofemoral deep venous thrombosis (IFDVT) patients from all patients suspected of
2 deep venous thrombosis (DVT).

3 **Take Home Message:** The proposed model in patients with suspected DVT, allows refined risk
4 stratification for IFDVT that could be used in aiding decisions regarding urgency of imaging
5 referral to confirm or exclude IFDVT.

6 **Table of Contents Summary**

7 In a single-center retrospective cohort study, we developed a model (sensitivity 77% and
8 specificity 82%) based on D-dimer, Wells score, age, and anticoagulation use which is able to
9 distinguish iliofemoral DVT patients from all patients suspected of DVT. The model could be
10 used for referral prioritizing to prompt imaging.

11

12 Abstract

13 **Objectives**

14 Deep vein thrombosis (DVT) is a common condition with a high risk of post-thrombotic
15 morbidity, especially in patients with a proximal thrombus. Successful iliofemoral (IF) clot
16 removal has been shown to reduce the severity of post thrombotic syndrome (PTS). It is assumed
17 that earlier thrombus lysis is associated with better outcome. Generally, the earlier IFDVT is
18 confirmed, the earlier thrombus lysis could be performed. D-dimer levels and Wells score are
19 currently used to assess the pre-duplex probability for DVT, however, some studies indicate that
20 D-dimer value varies depending on the thrombus extent and localization. Using D-dimer and
21 other risk factors might facilitate development of a model selecting those with an increased risk
22 of IFDVT that might benefit from early referral for additional analysis and adjunctive IF
23 thrombectomy.

1 **Methods**

2 All consecutive adult patients from a retrospective cohort of STAR diagnostic center (primary
3 care) in Rotterdam suspected of DVT between September 2004 and August 2016 were assessed
4 for this retrospective study. Diagnostic workup for DVT including Wells score and D-dimer
5 were performed as well as complete duplex ultrasonography (CDUS). Patients with an objective
6 evidence of DVT were categorized according to thrombus localization using the Lower
7 Extremity Thrombolysis (LET)-classification. Logistic regression analysis was done for a model
8 predicting IFDVT. Cut-off value of the model was determined using an ROC-curve.

9 **Results**

10 A total of 3381 patients were eligible for study recruitment, of whom 489 (14.5%) had confirmed
11 DVT. We developed a multivariate model (sensitivity of 77% and specificity of 82%, area under
12 the curve (AUC)=0.90, 0.86-0.93) based on D-dimer, Wells score, age, and anticoagulation use
13 which is able to distinguish IFDVT patients from all patients suspected of DVT.

14 **Conclusions**

15 This multivariate model will adequately distinguish IFDVT among all suspected DVT patients.
16 Practically, this model could give each patient a pre-duplex risk score which could be used to
17 prioritize suspected IFDVT patients for an immediate imaging test to confirm or exclude IFDVT.
18 Further validation studies are needed to confirm potential of this prediction model for IFDVT.

19

20 **KEYWORDS:** Venous thrombosis, Fibrin fragment D-dimer, Wells score, Risk Factors

21 Iliofemoral DVT, Referral and consultation

22

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3

4

5 **Disclosure:**

6 None

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1 **Introduction**

2 Deep vein thrombosis (DVT) is a common condition that leads to a significant burden on the
3 health care system (1). More proximal (iliofemoral or higher) localization of the thrombus is
4 associated with higher risk of developing post-thrombotic complications such as pulmonary
5 embolism (PE), recurrent DVT, and post-thrombotic syndrome (PTS) (2). In patients with an
6 iliofemoral DVT (IFDVT), the risk of developing PTS despite adequate conservative treatment
7 may exceed 50% (3).

8
9 Earlier thrombus removal lowers the risk of further thrombus growth and propagation (4, 5),
10 increases patency rates (6), and lowers the likelihood of PTS (3). Catheter-directed thrombolysis
11 (CDT) in patients with IFDVT has been shown to reduce the severity of PTS as well as improve
12 quality of life (7-10), with better results observed within 14 days of the onset of symptoms (9,
13 11, 12). Therefore, early diagnosis of IFDVT has both therapeutic and prognostic implications
14 (13, 14).

15
16 Objective and timely diagnosis, and treatment of DVT are, however, frequently delayed in daily
17 practice (4, 15, 16). The problem might be even more pronounced for patients with IFDVT, due
18 to lack of pre-duplex risk score for IFDVT identification, delay in DVT identification, delay
19 regarding availability of resources (dedicated expert sonographers) in non-specialized centers,
20 and the unreliability of compression ultrasound in detecting clot in pelvic veins. A recent study
21 showed that 56 percent of symptomatic IFDVT were not promptly referred to vascular center
22 while 43% of them were proper candidates for early thrombus removal (14).

23

1 Previous studies have indicated higher D-dimer values are associated with more proximal
2 localization of thrombus (17-19). In addition to D-dimer, other DVT risk factors may be
3 associated with the extent and location of thrombus (20-22). There is, however, no specific
4 model to predict IFDVT based on risk profiles. Hence, we hypothesized that the combination of
5 D-dimer level and certain DVT risk factors may be a valuable clinical tool to develop a pre-
6 compression ultrasound (CUS) risk score for IFDVT and identify those who may benefit from
7 adjunctive advanced imaging such as CTV, MRV, or complete compression ultrasonography.
8 This study sought to assess whether the combination of some identified risk factors at
9 presentation could allow early identification of IFDVT among all patients suspected of having
10 DVT.

12 **Methods**

13 In this retrospective study, we analyzed the data of all consecutive patients with suspected DVT
14 who were referred to the STAR medical diagnostic center (primary care) in Rotterdam, the
15 Netherlands between September 2004 and August 2016. Subjects were considered suspected
16 DVT if had acute symptoms including edema, redness, and/or pain in the affected legs. Data on
17 patient demographics, clinical history, and diagnostic tests were collected from medical records.
18 Patients under the age of 18 years and those with suspected pulmonary embolism (PE) were
19 excluded. The study was approved by the medical ethics committee of Maastricht University
20 Medical Centre (METC, no. 2018-0498). In this retrospective study without any intervention,
21 obtaining the patient's signed consent was waived. All patients received standard diagnostic
22 workup for DVT including clinical assessment (Wells score and D-dimer) as well as a complete

1 duplex ultrasonography (CDUS) (23), which was performed by a nurse and an experienced
2 dedicated duplex technician, respectively.

3

4 Clinical assessment included Wells score according to the current international standard
5 guidelines for DVT diagnosis (24, 25). Plasma D-dimer levels were assessed using quantitative
6 immunoassay kits (VIDAS until 2011, 2011-2015 STA Liatest, 2016 AQT 90 radiometer). All
7 D-dimer values were converted to $\mu\text{g/L}$ FEU. Location of the thrombus was identified by a
8 CDUS of the lower limbs, which included assessment of the common femoral vein (CFV),
9 femoral vein (FV), popliteal vein (PV), calf veins, small and great saphenous veins of the
10 affected limb. The duplex protocol also evaluated flow waveforms of bilateral common femoral
11 veins with continuous, nonphasic flow, and compression B-mode for suspicion of iliac vein
12 obstruction.

13

14 Based on the CDUS findings, thrombus location was categorized using the Lower Extremity
15 Thrombosis (LET)-classification (26). Our duplex evaluated to the point of CFV. The key to
16 LET III is identifying outflow impairment of the lower extremity due to obstruction of CFV, or
17 iliac veins (IV). We considered LET III patients as IFDVT as the term 'proximal DVT' is often
18 thought to include isolated femoropopliteal DVT. Patients were then divided in two groups. First,
19 IFDVT (LET III), which included all patients with thrombosis of CFV, with or without
20 involvement of the more caudal veins. Second was the control group, which constituted all other
21 suspected DVT patients including both non-DVT and non-IFDVT (LET I and II) patients.

22

23 Based on available items from the dataset, risk factors were analyzed included D-dimer, age, sex,

1 Wells score, family history of venous thromboembolism (VTE), anticoagulation use,
2 contraceptive use, and recent pregnancy. Based on the comparative analysis of the above risk
3 factors among the two groups, a model was generated for prediction of IFDVT. We have also
4 calculated an absolute value of D-dimer in patients with elevated Wells score (≥ 2) for prediction
5 of IFDVT.

6

7 **Model development and testing**

8 Univariate analysis was done to estimate the strength of association between IFDVT (vs. control
9 group) and baseline potential predictors listed above. The variables that presented a statistically
10 significant difference ($p < 0.1$) in univariate analysis were used in the multivariate logistic
11 regression. By testing each predictor by a change in -2 log-likelihood chi-squares, a final model
12 was found containing only statistically significant effects of predictors. All first-order
13 interactions between significant effects of these predictors were also tested. Backwards
14 elimination was employed to select the final set of risk factors that were independently
15 associated with IFDVT. We have also assessed for multicollinearity between the predictors.
16 Following development of the model, its performance was evaluated by calculating receiver
17 operating characteristic (ROC) curves, the area under the curve (AUC), its standard error, 95%
18 confidence interval, sensitivity, and specificity. The Hosmer-Lemeshow test was used for model
19 calibration, which examined how accurate the percentage of observed IFDVT matched the
20 percentage of expected IFDVT over deciles of predicted risk. A cut-off point for the model for
21 predicting IFDVT was selected from the ROC curve. Scores above the cut-off point were
22 considered high risk scores for IFDVT.

1 The risk score and the model were then applied to the study dataset to test the model
2 performance. A flowchart using risk scores and the model was developed for the number of
3 patients at each DVT stage. Based on the prediction model and risk score, the sensitivity,
4 specificity, positive predictive value (PPV), and negative predictive value (NPV) for selecting
5 those at highest risk of IFDVT in the study dataset were calculated. We also applied the existing
6 guidelines for the diagnosis of DVT to the dataset to estimate the number of DVT, and non-DVT
7 patients in the same population of the cohort from which the model was developed.

8

9 **Statistical analysis**

10 Metric data were examined for normality of distribution by the Shapiro-Wilk test and histogram
11 visualization. If continuous variables were normally distributed, means and their associated
12 standard deviations (SD) are reported. In the case of a non-normal distribution for continuous
13 variables, the median and interquartile range (IQR) was provided. Categorical data are showed in
14 terms of percentages of the number of cases within each group. To evaluate differences between
15 two groups Chi-squares, and Mann–Whitney U tests were performed where appropriate. Odds
16 ratios (OR) and log-likelihood are reported. Due to the highly skewed values of D-dimer, the 10-
17 log transformation of D-dimer was utilized. We did visual inspection on outliers for each
18 variable. We used box plots to identify outliers. We have checked both outliers and extreme
19 skewness and it did not affect the outcome of the logistic models. There was no imputation for
20 missing data. A p-value of 0.05 (two-sided) or less was considered significant in all analyses. All
21 tests were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp.,
22 Armonk, NY, USA).

23

1 Results

2 A total of 3381 consecutive subjects (2137 female, 63.3%) with suspected DVT were included in
3 this analysis. Diagnosis of DVT using CDUS was confirmed in 489 (14.5%) of patients: 92
4 (18.8% of those with DVT and 2.7% of the entire cohort) had IFDVT (mean age of $66,5 \pm 16.4$
5 years) and the remaining 3289 (mean age 60.2 ± 16.5 years) constituted the control group (397,
6 11,7% non-IFDVT, and 2892, 85.5% non-DVT). Patient characteristics are shown in table I.

7
8 In contrast to the highly-skewed distribution of original D-dimer values, a 10-log transformation
9 showed a normal distribution (Shapiro-Wilk $p=0.638$). As compared to the control group,
10 patients with IFDVT had a significantly higher 10-log transformation of D-dimer (3.6 ± 0.4 , vs.
11 2.9 ± 0.4 , OR: 23.01, $p < 0.001$) and Wells score (1.8 ± 1.2 vs. 0.7 ± 0.9 , OR: 2.17, $p < 0.001$) (table
12 II). Most of the patients (86%) had a Wells score below or equal to 1. Edema and redness were
13 the most frequent reported complaints among all of the subjects. In addition, IFDVT patients
14 were significantly older than the control group (66.6 ± 16.4 vs. 60.2 ± 16.5 , OR: 1.03, $p < 0.001$).
15 Only 12.8% of patients in IFDVT group used anticoagulation versus 23.1% in the control group
16 (OR: 0.49, $p=0.02$) at the time of the investigation (table II).

17
18 In a univariate analysis, age ($P < 0.001$), log D-dimer ($P < 0.001$), Wells score ($P < 0.001$), and
19 anticoagulation use ($P=0.02$) were found to be risk factors for IFDVT. Family history of VTE
20 ($p=0.25$), recent pregnancy ($p=0.38$), and contraceptive use ($p=0.84$) were not significantly
21 associated. Although IFDVT was numerically higher in males, the difference was not statistically
22 significant ($p=0.07$, table II).

1 We have checked the correlation between the four predictors in the final models and the highest
2 correlation was between log D-dimer and wells score (0.284, supplemental table I). Variance
3 inflation factor was below 1.18 in all final predictors. So multicollinearity did not affect the data.
4

5 There were missing data from 322 patients for D-dimer and 30 patients for Wells scores in the
6 dataset (table I). The multivariate model (table III) for the predicted probability of IFDVT was
7 developed based on four independent risk factors including log D-dimer, Wells score,
8 anticoagulation use, and age (model sensitivity: 77%, specificity: 82%, AUC=0.90, 0.86-0.93,
9 figure 1). The multivariate model was generated from data of 2962 patients whose four variables
10 included in the final model were available (not missing) for the analysis. There was a statistically
11 significant correlation between log-D-dimer, age, and Wells score and the risk of IFDVT (table
12 III). The use of anticoagulation appears to be protective against IFDVT. A discrimination and
13 calibration of model are reported in figure 1 and supplemental table II, respectively (AUC=0.90,
14 95% CI 0.86-0.93, Hosmer-Lemeshow test=8.14; P=0.42).
15

16 A cut-off point of 0.016 of the ROC curve which had sensitivity, specificity, PPV and, NPV of
17 90%, 59%, 8%, and 99%, respectively was chosen to detect patients with IFDVT in the study
18 dataset (table IV). By applying the risk score and the model as well as existing guidelines for the
19 diagnosis of DVT to the same population of study dataset, we estimated the number of DVT, and
20 non-DVT patients (figure 2). Figure 2A shows the number of patients at each stage of current
21 DVT diagnosis flowchart if the study population had gone through the conventional approach for
22 DVT diagnosis. Applying our model to predict IFDVT in the study dataset, 849/2962 patients
23 (29%) showed high risk score of having IFDVT (figure 2B).

1
2 Among 556 patients with elevated Wells score (≥ 2), an absolute value of D-dimer 1360 ($\mu\text{g/L}$)
3 had sensitivity 85%, specificity 64%, NPV 98 %, and PPV 18% to identify IFDVTs
4 (supplemental figure 1). Additionally we tested the accuracy of the model to distinguish between
5 IFDVT and other types of DVTs in our cohort. The proposed risk score had the sensitivity of
6 90%, specificity 28%, NPV of 92%, and PPV 21% to distinguish IFDVT from other types of
7 DVT in our cohort.

8
9 The risk prediction formula, which could be integrated in an online based calculator is showed in
10 table III. Basically, by the formula, following data entry on D-dimer, Wells score, age, and
11 whether patients use anticoagulation or not ,subsequently, it will provide a risk score that predict
12 highly likely IFDVTs among all suspected DVTs.

14 **Discussion:**

15 In this study, a model consisting of four predictive factors showed high sensitivity and specificity
16 for identification of patients at risk for IFDVT (77% and 82%, respectively) among all suspected
17 DVT patients. This study confirmed D-dimer, the Wells score, and age as independent risk
18 factors for IFDVT with the use of anticoagulation at presentation being protective. Using a
19 proposed model in the formula (table III) that can be integrated in an online calculator tool, a
20 pre-duplex risk score can be assigned to subjects suspected of having DVT to prioritize those at a
21 higher risk of IFDVT for receiving immediate confirmatory imaging and initiation of therapy, if
22 necessary.

23

1 Similar to previous reports of association between D-dimer level and DVT location (17-19), our
2 analysis also demonstrated that among assessed factors, D-dimer had the strongest association
3 with IFDVT (OR:15.93, 95%CI: 9.07-27.97, table III). Albeshri et al. suggested that D-dimer
4 above 700 ng/ml or higher was more likely to be associated with high proximal DVT (19). Thus,
5 in unilateral DVT, it seems that higher thrombus localization and larger clot burden is associated
6 with more fibrin degradation and subsequently higher levels of D-dimer.

7 Additionally, our results not only support the correlation between D-dimer and DVT location,
8 but are also in line with other studies showing the association of other factors with the extent and
9 location of thrombus (20-22). In a study by Rahiminejad et al (22), 5% of DVT patients had low
10 Wells score and negative D-dimer when initially assessed. Thus, they suggested other risk
11 factors to be included in the diagnosis. On a follow up evaluation, they observed that if patients
12 with negative D-dimer and low Wells score had no other risk factors such as long flight, oral
13 contraceptive pills, previous DVT, and pregnancy history, proximal DVT could be excluded
14 without any additional ultrasonography (US) (22). Proximal DVT was highly likely to present
15 with higher age, male sex, cancer, and pregnancy (21). The association of IFDVT with age was
16 also observed in our study but pregnancy had no influence on the thrombus localization. The risk
17 of IFDVT was numerically higher in males as well, though not statistically significant ($p=0.07$).

18 One possible explanation could be that our sample size was not large enough to detect these
19 changes compared to Barco et al. which had 24,911 patients. Moreover, in a multivariate
20 analysis, Spencer et al. reported that proximal DVT was associated with higher age and previous
21 VTE but not with sex (20). Their findings are in agreement with our results, although we
22 assessed previous VTE as a factor included in the Wells score.

23

1 A successful early diagnosis of VTE and thus early appropriate treatment can decrease morbidity
2 and mortality (27, 28). Generally, in IFDVT the sooner the intervention, the better the expected
3 clinical outcome (29). As mentioned earlier, however, there are several limitations in the
4 management pathway for patients with IFDVT, including a lack of specific criteria or pre-duplex
5 risk score for IFDVT, delay in DVT identification, and delay due to insufficient resources in
6 non-specialized centers. CDUS is the most common imaging modality in practice for DVT
7 confirmation and localization. In the current standard flowchart for DVT diagnosis (25) (figure
8 2A), all suspected DVT patients with likely clinical probability (Wells scores ≥ 2) and those who
9 had unlikely clinical probability but with an elevated D-dimer could be considered for a CDUS.
10 However, since there are no specific criteria for prioritizing these patients for CDUS, those who
11 are at a higher risk of IFDVT might not receive CDUS in time to institute appropriate early
12 treatment (figure 2A). Moreover, there is a delay in objective DVT (15) and IFDVT diagnosis
13 (14), and treatment onset (4, 14, 15), thus measures to improve the timing of diagnosis are
14 crucial specifically for early identification of IFDVT.

15
16 Furthermore, dedicated expert sonographers needed for accurate diagnosis of IFDVT are not
17 usually available in non-specialized centers leading to delayed objective diagnosis of IFDVT.
18 Additionally, these non-specialized medical centers may initially perform the 2-point CUS which
19 is unable to detect all high-risk IFDVTs. However, by using IFDVT risk score, it was possible to
20 prioritize 849/2962 (29%) potential IFDVT patients for having immediate imaging (figure 2B).
21 The risk score has high sensitivity (90%) and high NVP (99%) with a low PPV (8%) which
22 could be used as an exclusion score (table IV). This multivariate model will thus be a useful tool
23 to assess the likelihood of IFDVT, especially when a timely CDUS is not possible. This score

1 could be used to prioritize those at a higher risk of IFDVT for immediate CDUS or other
2 imaging tools in specialized centers while other patients could be followed without unnecessary
3 haste. However, a detailed physical examination and an accurate history of suspected DVT
4 patient should not be underestimated.

5 **Limitations:**

6 There are several limitations of this study. First, it is a retrospective study whose data such as
7 medical history, variables, and clinical characteristics are limited to available medical records
8 from a single diagnostic center. There is no clear explanation for the relatively high number of
9 patients on anticoagulation at the time of investigation (753/3381, 22.3%). History of VTE was
10 present in 17.4% (590/3381) of patients while 162/590 were on anticoagulation, which is
11 comparable to an age-matched group of patients as in this analysis. Since the mean age of the
12 study population was 60 years old, presence of other comorbidities not captured in the dataset
13 such as cardiac conditions may explain the need for anticoagulation in the remainder of the
14 cohort. Our observations were based on 3381 suspected DVT patients referred to a diagnostic
15 center and hence they may not be generalizable to all office-based practices. There was also no
16 data regarding the types of anticoagulation used by patients. All patients had acute symptoms,
17 though, the duration of reported symptoms by the patients was not clear. Next, although the types
18 of D-dimer kits used during the study period were not the same, all were able to quantify D-
19 dimer levels and be reported in $\mu\text{g/L}$ FEU. Another possible limitation was that MRV or CTV
20 was not used to confirm the diagnosis. Thrombus localization was done with LET classification
21 which is not generally used, though it has been previously validated (26). To address the research
22 question of selecting IFDVTs among all suspected DVTs, we have pooled the data of DVT (LET
23 I, LET II) and non-DVT patients as control group which diluted the variables of DVT subjects.

1 We could not directly compare our prediction model with existing guidelines since current
2 guidelines are designed to detect DVT and not solely IFDVT. Univariately age was significantly
3 correlated ($p < 0.001$) with IFDVT. Although the p-value for age ($p < 0.054$) in the multivariate
4 model was slightly above the significance level, ($p < 0.05$), we believe age should still be included
5 in the final model. However, external validation should be performed before using the model in
6 practice. Another limitation was that there were some missing variables from a few patients
7 which affected the total number of patients included in our final model. Moreover, there were
8 several technicians and staff involved in the diagnostic approach such as Wells score and CDUS
9 assessments during the ten-year period of the cohort which may pose questions of inter-observer
10 variability. Finally, we have included all first episode DVTs and those with recurrent DVT in the
11 analysis, so the generalizability of our results for daily practice requires additional evaluation.

12

13 **Conclusions:**

14 We present a model consisting of D-dimer, Wells score, age, and anticoagulation use which is
15 able to predict IFDVT patients with high sensitivity and specificity. This model could aid in
16 prioritization of those at a higher risk of IFDVT for having a prompt imaging diagnosis and
17 potential treatment among all suspected DVT patients. Furthermore, multi-center large sample
18 studies are required to validate our findings.

19

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23

1 References:

- 2 1. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden
3 of incident venous thromboembolism in the United States: A review of estimated attributable
4 healthcare costs. *Thromb Res.* 2016;137:3-10.
- 5 2. Kahn SR. The post-thrombotic syndrome. *Hematology Am Soc Hematol Educ Program.*
6 2016;2016(1):413-8.
- 7 3. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, et al. Determinants and
8 time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern*
9 *Med.* 2008;149(10):698-707.
- 10 4. Spacil J, Svobodova J. Does the time from symptoms onset to treatment impact further
11 development of vein thrombosis in the leg? *Vnitr Lek.* 2018;64(10):911-5.
- 12 5. Czaplicki C, Albadawi H, Partovi S, Gandhi RT, Quencer K, Deipolyi AR, et al. Can
13 thrombus age guide thrombolytic therapy? *Cardiovasc Diagn Ther.* 2017;7(Suppl 3):S186-S96.
- 14 6. Kavala AA, Turkyilmaz S. Long-term results of additional thrombolytic therapy in
15 patients with acute deep vein thrombosis treated with pharmacomechanical thromboaspiration: A
16 comparative study. *Turk Gogus Kalp Damar Cerrahisi Derg.* 2018;26(4):579-87.
- 17 7. Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ, et al.
18 Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. *N Engl J*
19 *Med.* 2017;377(23):2240-52.
- 20 8. Kahn SR, Julian JA, Kearon C, Gu CS, Cohen DJ, Magnuson EA, et al. Quality of life
21 after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis.
22 *J Vasc Surg Venous Lymphat Disord.* 2020;8(1):8-23 e18.

- 1 9. Comerota AJ, Kearon C, Gu CS, Julian JA, Goldhaber SZ, Kahn SR, et al. Endovascular
2 Thrombus Removal for Acute Iliofemoral Deep Vein Thrombosis. *Circulation*.
3 2019;139(9):1162-73.
- 4 10. Enden T, Haig Y, Klow NE, Slagsvold CE, Sandvik L, Ghanima W, et al. Long-term
5 outcome after additional catheter-directed thrombolysis versus standard treatment for acute
6 iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*.
7 2012;379(9810):31-8.
- 8 11. Meissner MH, Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, et al.
9 Early thrombus removal strategies for acute deep venous thrombosis: clinical practice guidelines
10 of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*.
11 2012;55(5):1449-62.
- 12 12. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing.
13 National Institute for Health and Care Excellence: Clinical Guidelines. London 2020.
- 14 13. Wittens CHA, Black SA. The future of iliofemoral deep vein thrombosis treatment. *J*
15 *Vasc Surg Venous Lymphat Disord*. 2019;7(6):771-2.
- 16 14. Khan K, Li M, Erridge S, Chidambaram S, Chiew K, Pay L, et al. The management and
17 referral of iliofemoral deep venous thrombosis in North West London. *J Vasc Surg Venous*
18 *Lymphat Disord*. 2020;8(2):182-6.
- 19 15. Ageno W, Agnelli G, Imberti D, Moia M, Palareti G, Pistelli R, et al. Factors associated
20 with the timing of diagnosis of venous thromboembolism: results from the MASTER registry.
21 *Thromb Res*. 2008;121(6):751-6.
- 22 16. Elliott CG, Goldhaber SZ, Jensen RL. Delays in diagnosis of deep vein thrombosis and
23 pulmonary embolism. *Chest*. 2005;128(5):3372-6.

- 1 17. Ceriotti C, Vanini A, Giusto L, Zuliani G. Correlation between Deep Vein Thrombosis
2 Location and D-Dimer Values: A Pilot Study. *Journal of Vascular Medicine & Surgery*.
3 2014;2:1-3.
- 4 18. Mousa AY, Broce M, De Wit D, Baskharoun M, Abu-Halimah S, Yacoub M, et al.
5 Appropriate Use of Venous Imaging and Analysis of the D-Dimer/Clinical Probability Testing
6 Paradigm in the Diagnosis and Location of Deep Venous Thrombosis. *Ann Vasc Surg*.
7 2018;50:21-9.
- 8 19. Albeshri H, Kaminski B, Mattin M, Fish J, Kaspe G, Lurie F. D-Dimer Level and
9 Location of the Deep Venous Thrombosis. *Journal of Vascular Surgery: Venous and Lymphatic*
10 *Disorders*. 2018;6(2):293.
- 11 20. Spencer FA, Kroll A, Lessard D, Emery C, Glushchenko AV, Pacifico L, et al. Isolated
12 calf deep vein thrombosis in the community setting: the Worcester Venous Thromboembolism
13 study. *J Thromb Thrombolysis*. 2012;33(3):211-7.
- 14 21. Barco S, Klok FA, Mahe I, Marchena PJ, Ballaz A, Rubio CM, et al. Impact of sex, age,
15 and risk factors for venous thromboembolism on the initial presentation of first isolated
16 symptomatic acute deep vein thrombosis. *Thromb Res*. 2019;173:166-71.
- 17 22. Rahiminejad M, Rastogi A, Prabhudesai S, Mcclinton D, MacCallum P, Platton S, et al.
18 Evaluating the Use of a Negative D-Dimer and Modified Low Wells Score in Excluding above
19 Knee Deep Venous Thrombosis in an Outpatient Population, Assessing Need for Diagnostic
20 Ultrasound. *ISRN Radiology*. 2014;2014:1-5.
- 21 23. Needleman L, Cronan JJ, Lilly MP, Merli GJ, Adhikari S, Hertzberg BS, et al.
22 Ultrasound for Lower Extremity Deep Venous Thrombosis: Multidisciplinary Recommendations

- 1 From the Society of Radiologists in Ultrasound Consensus Conference. *Circulation*.
2 2018;137(14):1505-15.
- 3 24. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of
4 D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-
5 35.
- 6 25. Mazzolai L, Aboyans V, Ageno W, Agnelli G, Alatri A, Bauersachs R, et al. Diagnosis
7 and management of acute deep vein thrombosis: a joint consensus document from the European
8 Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary
9 circulation and right ventricular function. *Eur Heart J*. 2018;39(47):4208-18.
- 10 26. Strijkers RH, Arnoldussen CW, Wittens CH. Validation of the LET classification.
11 *Phlebology*. 2015;30(1 Suppl):14-9.
- 12 27. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public
13 health concern. *Am J Prev Med*. 2010;38(4 Suppl):S495-501.
- 14 28. Comerota AJ, Paolini D. Treatment of acute iliofemoral deep venous thrombosis: a
15 strategy of thrombus removal. *Eur J Vasc Endovasc Surg*. 2007;33(3):351-60; discussion 61-2.
- 16 29. Foegh P, Jensen LP, Klitfod L, Broholm R, Baekgaard N. Editor's Choice - Factors
17 Associated with Long-Term Outcome in 191 Patients with Ilio-Femoral DVT Treated With
18 Catheter-Directed Thrombolysis. *Eur J Vasc Endovasc Surg*. 2017;53(3):419-24.
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Journal Pre-proof

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Tables:

Characteristics	IFDVT group	Control group		p-value
	92 (2.7%)	3289 (97.3%)		
	IFDVT	Non-IFDVT	Non-DVT	
Subcategory, n (%)	(LET III)	(LET I, II)		
	92 (2.7)	397 (11.7)	2892 (85.5)	
Sex, female, n (%)	50 (54.3)	201 (50.8)	1886 (65.3)	.07
Age, years, mean (SD)	66.5 (16.4)	56.5 (16.3)	60.7 (16.4)	<.001
D-dimer level ($\mu\text{g/L}$ FEU), median (IQR)	3205 (1528-6023)	2099 (963-4009)	587 (296-1113)	<.001
missing, n (%)	12 (13.0)	36 (9.1)	274 (9.5)	-
Log D-dimer level, mean (SD)	3.6 (0.4)	3.4 (0.4)	2.8 (0.4)	<.001
missing, n (%)	12 (13.0)	36 (9.1)	274 (9.5)	-
Wells score, mean (SD)	1.8 (1.2)	1.1 (1.0)	0.6 (0.9)	<.001
Wells score, n (%) ≤ 1 : DVT Unlikely	42 (45.7)	284 (71.5)	2469 (85.4)	-
≥ 2 : DVT Likely	47 (51.1)	109 (27.5)	400 (13.8)	-
missing, n (%)	3 (3.3)	4 (1.0)	23 (0.8)	-
Wells score factors, n (%)				-
Active cancers	9 (10)	16 (4.1)	71 (2.5)	<.001
Immobilization (paralysis, plaster cast)	4 (4.4)	12 (3.0)	50 (1.7)	.09
Bed rest or recent surgery	11 (12)	37 (9.3)	165 (5.7)	.02
Localized pain over vein tract	20 (22.7)	59 (15.8)	215 (7.7)	<.001
missing, n (%)	2 (2.7)	21 (6.2)	77 (3.6)	-

Entirely swollen leg	25 (27.8)	31 (7.9)	185 (6.5)	<.001
Pitting edema (symptomatic leg)	53 (70.7)	156 (46.7)	1213 (49.6)	<.001
missing, n (%)	17 (18.5)	63 (15.9)	445 (15.4)	-
Calf swelling>3cm larger than asymptomatic leg	32 (34.8)	62 (15.6)	273 (9.4)	<.001
Enhanced visible veins of the leg	7 (8.4)	11 (3.0)	85 (3.2)	.008
missing, n (%)	9 (9.8)	30 (7.6)	206 (7.1)	-
Previous episode of VTE	29 (32.2)	104 (26.5)	457 (15.9)	<.001
Alternative diagnosis, n (%)				-
Varicosis	6 (6.5)	18 (4.5)	185 (6.4)	.81
Primary lymphedema	51 (55.4)	176 (44.6)	1330 (47.4)	.11
Bakers' cyst	0 (0)	0 (0)	75 (10.9)	-
Hematoma	0 (0)	7 (1.8)	208 (7.2)	-
Swollen lymph nodes	1 (1.1)	5 (1.3)	92 (3.2)	.92
PTS	0 (0)	0 (0)	5 (0.2)	-
Lipoma	0 (0)	0 (0)	2 (0.1)	-
Other	0 (0)	1 (0.3)	1 (0.1)	-
Other risk factors, n (%)				
Family history of VTE	22 (26.5)	109 (28.9)	550 (20.1)	.24
missing, n (%)	9 (9.8)	20 (5.0)	150 (5.2)	-
Use of contraceptive	5 (10.4)	59 (27.7)	159 (9.3)	.84
missing, n (%)	44 (47.8)	184 (46.3)	1184 (40.9)	-
Redness of the investigated leg	30 (3.6)	122 (32.9)	860 (31.4)	.43

missing, n (%)	8 (8.7)	26 (6.5)	157 (5.4)	-
Anticoagulation use at time of investigation	11 (12.8)	43 (11.2)	699 (24.7)	.02
missing, n (%)	6 (6.5)	14 (3.5)	60 (2.1)	-
Pregnant or recent pregnancy (up to 6weeks)	0 (0)	2 (2.8)	18 (2.5)	.53
missing, n (%)	77 (83.7)	326 (82.1)	2184 (75.5)	-

DVT, deep vein thrombosis; IFDVT, iliofemoral DVT; SD, standard deviation; n, number; IQR, interquartile range; FEU, fibrinogen equivalent units; LET, lower extremity thrombosis; VTE, venous thromboembolism; PTS, post thrombotic syndrome.

Active cancer is defined as a cancer not received potentially curative treatment, or when there is evidence that treatment has not been curative (e.g., recurrent or progressive disease), or when treatment is ongoing.

Table II. Univariate analysis of having IFDVT using possible risk factors such as age, sex, 10 log of D-dimer, Wells score, VTE family history, anticoagulation use, recent pregnancy, and contraceptive use.

Risk factor	Number	IFDVT group	Control group	OR	95% C.I.	p-value
		92 (2.7%)	3289 (97.3%)			
Age, mean (SD)	3381	66.5 (16.4)	60.2 (16.5)	1.03	1.01-1.04	<.001*
Sex, female, n (%)	3375	50 (54.4)	2087 (63.6)	0.68	0.45-1.04	.07*
Log D-dimer, mean (SD)	3059	3.6 (0.4)	2.9 (0.4)	23.0	13.77-38.46	<.001*
Wells score, mean (SD)	3351	1.8 (1.2)	0.69 (0.9)	2.17	1.85-2.54	<.001*
Family history of VTE, n (%)	3302	22 (26.5)	659 (21.1)	1.35	0.82-2.21	.25
Anticoagulation use, n (%)	3301	11 (12.8)	742 (23.1)	0.49	0.29-0.93	.02*
Pregnant or recent pregnancy, n (%)	794	0 (0)	20 (0.6)	0.97	0.96-0.99	.38

Use of contraceptive, n	1969	5 (10.4)	218 (11.4)	0.91	0.36-	
(%)					2.32	.84

number of patients with available data. IFDVT, iliofemoral deep vein thrombosis ; OR, odds ratio; C.I, confidence interval; SD, standard deviation; n, number; VTE, venous thromboembolism; * statistically significant

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Table III. Multivariate model to predict IFDVT

Risk factor	Log Odds	S.E.	p-value	OR	95% C.I.		Change in -2 Log Likelihood	Sig. of the Change
Log D-dimer	2.77	0.29	<.001	15.93	9.07	27.97	100.87	<.001
Age	0.02	0.01	.057	1.02	1.00	1.03	3.72	.054
Wells score	0.55	0.11	<.001	1.73	1.41	2.13	25.38	<.001
Anticoagulation use	-0.85	0.39	.027	0.43	0.20	0.91	5.63	.018
Constant	-14.53	1.16	.000	0.00				

IFDVT, iliofemoral deep vein thrombosis; S.E., standard error; OR, odds-ratios; C.I., confidence interval; SD, standard deviation; n, number.

The model is generated based on 2962 patients whose data for these 4 variables of final model were available.

The probability of IFDVT is calculated as $p = \exp(L) / (1 + \exp(L))$, where $L = -14.53 + 0.02 \cdot \text{age} + 2.77 \cdot \log \text{D-dimer} + -0.85 \cdot \text{Anticoagulation [coded 0/1]} + 0.55 \cdot \text{Wells score}$.

The cut off point for IFDVT is 0.016 (sensitivity 90% and NPV 99%).

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Table IV. Accuracy of the risk score model for “early IFDVT” identification through current DVT diagnosis flowchart.

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		IFDVT	Control group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
The model and risk score	<i>Risk score</i> ≥ 0.016 IFDVT likely n=849	66	783	90	59	8	99
	IFDVT	<hr/>					
	Risk score < 0.016 IFDVT unlikely n=1137	7	1130				

n, number; IFDVT, iliofemoral deep vein thrombosis; PPV, positive predictive value; NPV, negative predictive value.

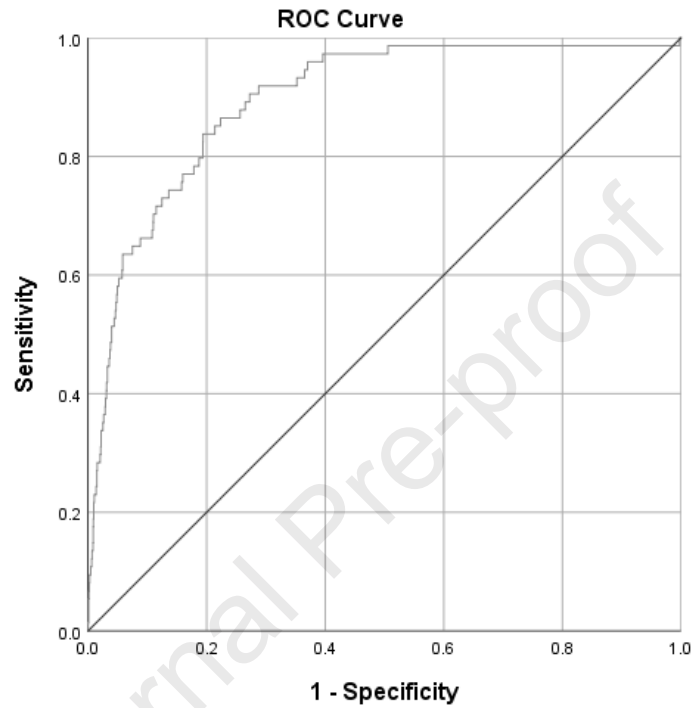
1 Figure

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10 Figure 1: Area Under the Curve of predicted probability of being in IFDVT
11 vs. control group using the risk score

Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic	95%	Confidence
			Interval	Lower Bound	Upper Bound
.895	.018	.000	.860	.931	

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a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure

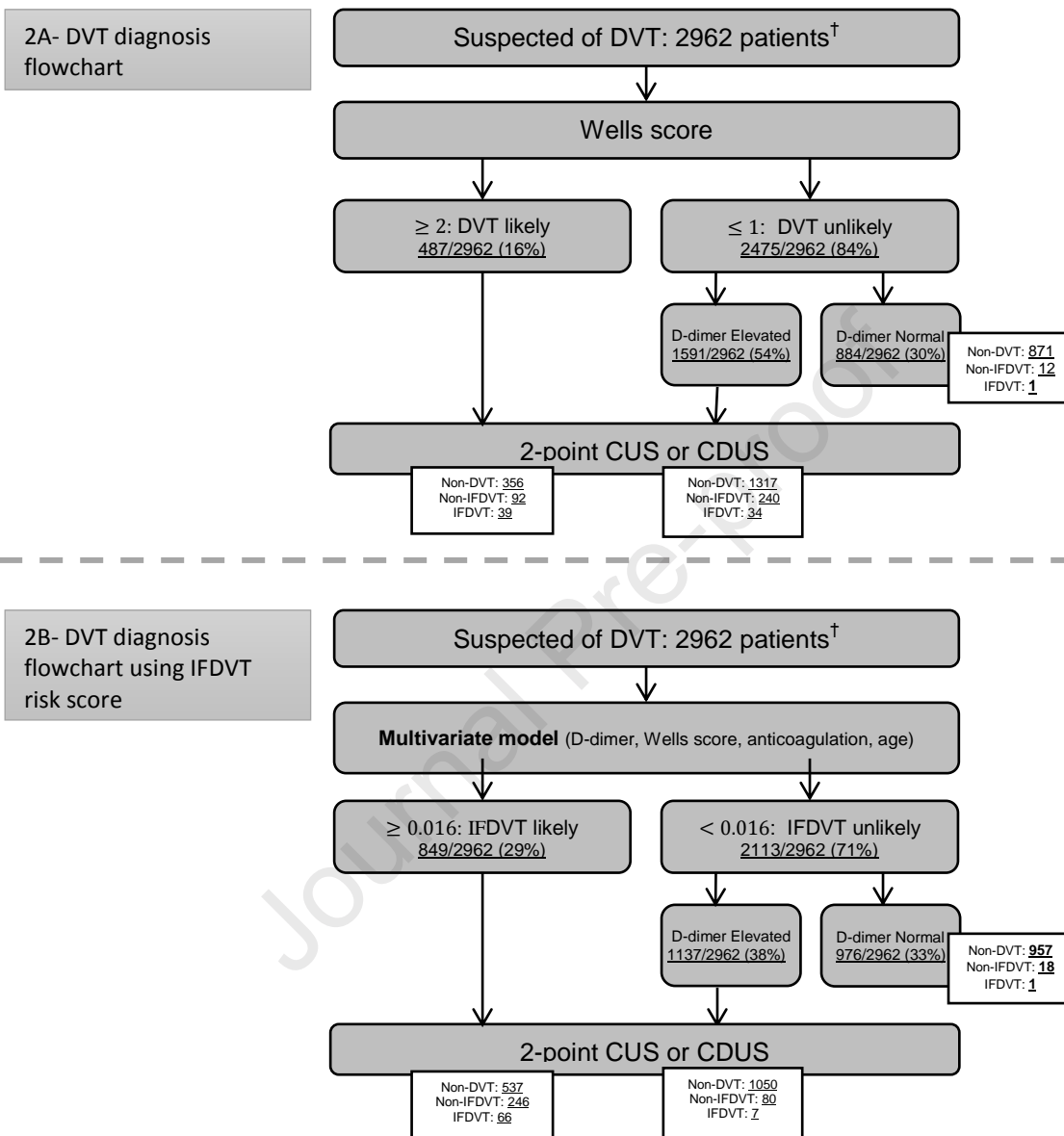


Figure 2A. If all suspected DVT subjects in the study had gone through the current standard flowchart for DVT diagnosis [25], the number of our patients at each stage is showed in the boxes.

Figure 2B. The number of patients at each stage of DVT diagnosis flowchart when using the IFDVT risk score.

DVT, deep vein thrombosis; IFDVT, iliofemoral DVT; CDUS, complete duplex ultrasound; CUS, compression ultrasound; NPV, negative predictive value. [†] The same proportion of patients.

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1 **Supplementary**

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Supplemental Table I. Correlations between the final predictors.					
		Wells score	Age	10log of D-dimer	Anticoagulation
Wells score	Pearson Correlation	1	.087**	.249**	.087**
	Sig. (2-tailed)		<.001	<.001	<.001
	N	3351	3351	3031	3279
Age	Pearson Correlation	.087**	1	.284**	.272**
	Sig. (2-tailed)	<.001		<.001	<.001
	N	3351	3381	3059	3301
10log of D-dimer	Pearson Correlation	.249**	.284**	1	-.012
	Sig. (2-tailed)	<.001	<.001		.50
	N	3031	3059	3059	2982
Anticoagulation	Pearson Correlation	.087**	.272**	-0,012	1
	Sig. (2-tailed)	<.001	<.001	.50	
	N	3279	3301	2982	3301

** . Correlation is significant at the 0.01 level (2-tailed).

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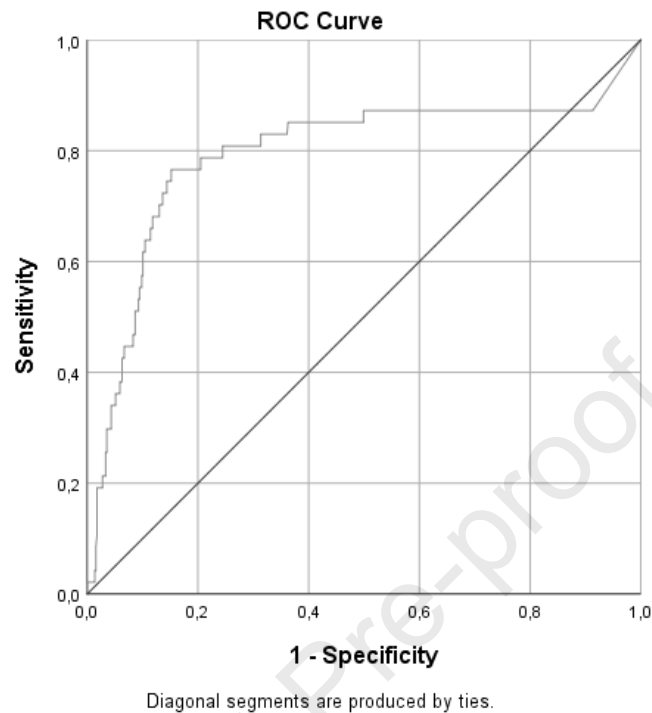
Supplemental Table II. Contingency Table for Hosmer and Lemeshow Test

Step		Control group		IFDVT		Total
		Observed	Expected	Observed	Expected	
1	1	295	295.770	1	.230	296
	2	296	295.495	0	.505	296
	3	296	295.194	0	.806	296
	4	296	294.840	0	1.160	296
	5	295	294.349	1	1.651	296
	6	295	293.571	1	2.429	296
	7	292	292.366	4	3.634	296
	8	287	290.206	9	5.794	296
	9	286	285.052	10	10.948	296
	10	250	251.156	48	46.844	298

Chi-square:8.135; df: 8; p value:0.420;
IFDVT; iliofemoral DVTs

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1 Supplemental figure

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Supplemental figure 1: Area Under the Curve of predicted probability of being in IFDVT vs. control group in elevated Wells score using absolute D-dimer value

Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic	95%	Confidence
			Interval	Lower Bound	Upper Bound
.794	.045	.000	.706	.881	

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

1 **Legends for figures.**

2 Figure 1. Area Under the Curve of predicted probability of being in IFDVT vs. control group.

3

4 Figure 2A. If all suspected DVT subjects in the study had gone through the current standard
5 flowchart for DVT diagnosis [25], the number of our patients at each stage is showed in the
6 boxes.

7

8 Figure 2B. The number of patients at each stage of DVT diagnosis flowchart when using the
9 IFDVT risk score.

10

11 **Legends for tables.**

12 Table I. Patient characteristics of IFDVT and control groups.

13

14 Table II. Univariate analysis of having IFDVT using possible risk factors such as age, sex, 10 log
15 of D-dimer, Wells score, VTE family history, anticoagulation use, recent pregnancy, and
16 contraceptive use.

17

18 Table III. Multivariate model to predict IFDVT.

19

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21 DVT diagnosis flowchart.