A clinical prediction score for upper extremity deep venous thrombosis

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Summary

It was the objective of this study to design a clinical prediction score for the diagnosis of upper extremity deep venous thrombosis (UEDVT). A score was built by multivariate logistic regression in a sample of patients hospitalized for suspicion of UEDVT (derivation sample). It was validated in a second sample in the same university hospital, then in a sample from the multicenter OPTIMEV study that included both outpatients and inpatients. In these three samples, UEDVT diagnosis was objectively confirmed by ultrasound. The derivation sample included 140 patients among whom 50 had confirmed UEDVT, the validation sample included 103 patients among whom 46 had UEDVT, and the OPTIMEV sample included 214 patients among whom 65 had UEDVT. The clinical score identified a combination of four items (venous material, localized pain, unilateral pitting edema and other diagnosis as plausible). One point was attributed to each item (positive for the first 3 and negative for the other diagnosis). A score of –1 or 0 characterized low probability patients, a score of 1 identified intermediate probability patients, and a score of 2 or 3 identified patients with high probability. Low probability score identified a prevalence of UEDVT of 12, 9 and 13%, respectively, in the derivation, validation and OPTIMEV samples. High probability score identified a prevalence of UEDVT of 70, 64 and 69% respectively. In conclusion we propose a simple score to calculate clinical probability of UEDVT. This score might be a useful test in clinical trials as well as in clinical practice.

Keywords

Venous thrombosis, upper extremity deep vein thrombosis, clinical prediction

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Introduction

Upper extremity deep venous thrombosis (UEDVT) is far less frequent than lower extremity deep venous thrombosis (LEDVT) but accounts for as much as 10% of DVT (1). However, this condition may well become more frequent because of the increasing utilization of indwelling central venous catheters, its most powerful risk factor (1). Cancer is also found in as many as 40% patients with UEDVT (2, 3). UEDVT may be complicated by pulmonary embolism (PE) in up to 20% patients (4–6). Mortality is frequent in patients with UEDVT, not associated with PE but with characteristics of the underlying patient's disease. Other significant complications of UEDVT include post- thrombotic syndrome, occurring in 25% patients with UEDVT (7, 8). UEDVT is usually suspected in case of upper limb discomfort, pain or swelling. Little is known about the importance of clinical signs or symptoms from prospective studies. Moreover, less than 50% symptomatic subjects have objectively confirmed UEDVT (9), so that calculation of clinical probability might be useful in the diagnosis strategy. This approach has been validated in

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LEDVT where clinical scores have proved to be useful, either alone or in combination with the measurement of D- dimers (10–13). For UEDVT, the calculation of clinical probability would even be more useful since D-dimers are not as sensitive in UEDVT as in LEDVT (14). Therefore we decided to develop a score for the calculation of clinical probability in patients suspected of DVT and referred to a University Hospital vascular exploration unit. Then, a validation of this score was conducted in the same hospital and in another sample from OPTIMEV, a multicenter study including both outpatients and inpatients.

Patients and methods

Study design

Standardized clinical information was reported for the patients from the derivation sample, and a clinical prediction score was built in this derivation sample. Then this score was validated in a new sample from the same hospital (validation sample). Finally the score was tested in the OPTIMEV sample that included both outpatients and hospitalized patients in a multicenter prospective study and was our external validation cohort according to the criteria from Laupacis et al. (15).

Samples

Three groups of patients were investigated. The derivation (2000–2003) and internal validation (2003–2005) groups were made up of patients hospitalized in St. André Hospital who were referred to the vascular exploration unit for suspicion of UEDVT. St. Andre hospital is an university hospital with medicine, reanimation, oncology, digestive and gynaecological surgery (17% cancer patients) (11). The external validation sample was obtained from the OPTIMEV study. OPTIMEV methods have been described previously (16). Briefly, this was a multicenter prospective study carried out by both hospital-based or registered vascular physicians in 2004 and 2005. The investigators recorded all the patients examined for suspicion of DVT in a limited time. Suspicions of DVT of lower and upper limbs were included in this study.

Clinical chart record

Standardized clinical information included the following: sex, bed rest for more than three days, upper limb paralysis or immobilization, surgery in the last three weeks, previous venous thromboembolism, thrombophilia, cancer, venous material (presence of central venous catheter or pacemaker), unilateral enlargement of upper limb, pitting edema of upper limb, superficial vein dilation of upper limb, localized pain along deep veins, unilateral warmth, other diagnosis at least as plausible as UEDVT. The other diagnoses were considered to be haematoma, erysipela, cellulites, lymphangitis, upper limb superficial venous thrombosis. The clinical chart was completed by the physician who asked for the ultrasound exploration, often a junior one, in the derivation and validation studies, and by the vascular physician who performed ultrasound in the OPTIMEV study.

Ultrasound

UEDVT was diagnosed after ultrasound using B-mode compression ultrasound and colour Doppler. Both limbs were systematically examined, and the radial, ulnar, brachial, axillary, subclavian and internal jugular veins were evaluated. The gold standard for the diagnosis of UEDVT has been considered for a long time to be contrast venography. However, this type of exploration is now rarely performed because it is invasive, expensive and can result in morbidity. The standard approach to diagnosis of UEDVT is now ultrasonography (3, 5, 17). This is the only method used in the recent large series of patients with UEDVT (1, 6). Limited validation of ultrasound has been performed by Prandoni et al. who found a 96.3% sensitivity and a 93.5% specificity in 58 patients (5).

Follow up was not available from derivation and internal validation study, but in the external validation study, for each patient and two controls for one patient, a research assistant gathered follow-up information at three months, one year and then yearly for five years. At this time, inclusions have been stopped in OPTIMEV. The sonographer was blinded from clinical evaluation in the derivation and internal validation samples, but not in the external validation sample where the sonographer made the clinical evaluation. A standardised case report was used for clinical chart and for ultrasound in all samples.

Ethics

The development of our score in the derivation sample was a retrospective study using our routine standardized clinical chart, the internal validation sample was a prospective study using the same routine clinical chart. In our hospital, patients are routinely informed at entry that clinical information might be anonymously used for research purposes. According to French law, no written informed consent is required since no specific examination was performed in these studies. For the external validation sample, a positive advice was obtained from the Commission Consultative du Traitement de l'Information en Recherche dans le domaine de la Santé de la CNIL (CCTIR).

Statistical analysis

The frequency of clinical items was compared between the patients with or without thrombosis in the derivation sample (Fisher's exact test when expected values were below 5, or Chi^2-test otherwise). All items which were statistically associated to the risk of DVT ($p<0.10$) were entered in a logistic regression model. Using a downward modelling approach, we removed all the items which were not independently associated with the risk of DVT ($p<0.05$) to obtain the final model. The score was calculated by giving one point to each item that proved to be associated to UEDVT in the multivariate model to keep the score as simple as possible. This score was validated prospectively in a sample from the same institution (validation sample) and in a large multicenter sample including outpatients and inpatients. ROC curves were built from the three samples (Fig. 1). SAS 8.2 software was used for statistical analysis.

Results

Derivation sample

One hundred seventy-one patients were referred to the St. André hospital vascular exploration unit between 2000 and 2003 for UEDVT suspicion. Data were completed for 140 patients who

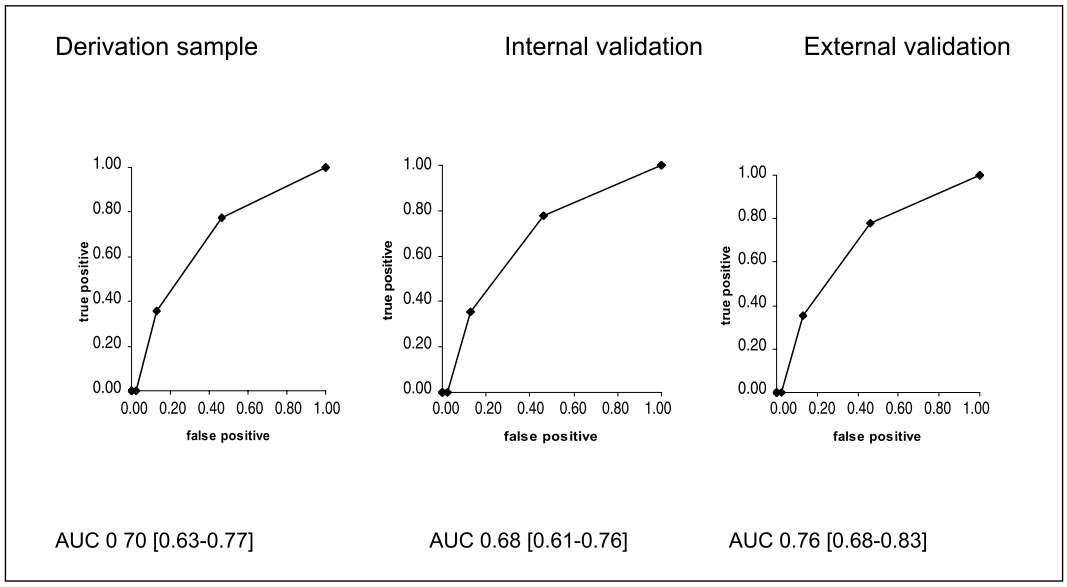

Figure 1: ROC for the clinical score in the three study samples.

constituted the derivation sample (Table 1). The 31 patients excluded from the derivation sample did not have completion of the standardized clinical chart so that we were unable to evaluate them. UEDVT was diagnosed in 50 (36%) of them, above the elbow in all cases. Those patients with a confirmed diagnosis of UEDVT more often had venous material, pitting edema or localized pain of the upper limb, and less often had alternate plausible diagnosis (Table 2). The score was developed by logistic regression with these four items by giving one point to venous material, edema or pain and by lessening one point when another diagnosis was at least as plausible as UEDVT (Table 3). None of the items in the initial model was collinear. A score of –1 or 0 gave a 12% probability of confirmed UEDVT, whereas a score of 1 found a 20% UEDVT probability, and a score of 2 or 3 gave a 70% UEDVT probability (Table 4). We considered that a score at –1 or 0 gave a low clinical probability, a score of 1 gave an intermediate probability and a score of 2 or 3 gave a high probability.

Table I: Description of the three study samples.

	Derivation sample	Internal validation	External validation
Number of patients	140	103	214
number with DVT(%)	50 (36%)	46 (45%)	65 (30%)
Male/ female (number)	73/67	49/54	85/129
Mean age years (SD)	59 (18)	60 (18)	59 (19)
outpatients	3*	3*	100
Cancerology unit	44	6	0
Reanimation unit	9	8	4
Surgery unit	9	8	11
Medicine unit	75	78	88
Liberal clinics	0	0	7

* outpatients admitted in the emergency department.

Internal validation sample

Between 2003 and 2005, 100 patients were included in the study and constituted the validation sample. UEDVT was diagnosed by ultrasound in 46% of them. The upper location of UEDVT was the subclavian vein in 38 patients (associated to internal jugular vein in 17), the internal jugular vein in two, the axillary veins in two and the brachial veins in four patients. A thoracic outlet syndrome was found in one patient.

When all the clinical items are analyzed, pain and edema were not more frequent in the patients with UEDVT while venous material was more frequent as were previous venous thromboembolism and superficial vein dilation (Table 2). However, the clinical score developed in the derivation sample predicted UEDVT in 9% of those with a clinical score of –1 or 0, 37% of those with a score of 1 and 64% of those with a score of 2 or 3.

External validation sample

The OPTIMEV study included 8,256 patients of whom 2,898 (35%) had DVT. Of these, 67% were outpatients and 33% were hospitalized. Of the 8,256 patients, 214 (2.6%) had a suspicion of UEDVT. In these 214 patients, UEDVT was confirmed by ultrasound in 65 (30%). The upper limit of thrombosis was the innominate vein in six patients, internal jugular vein in 13, subclavian in 35, axillary or brachial veins in 11 patients. Our clinical score predicted UEDVT in 13% of those classified as low probability, 38% of those classified as intermediate probability, and 69% of those classified as high probability. When we separately analysed the results of the score in the 114 inpatients (31 UEDVT) and the 100 outpatients (34 UEDVT), our score gave the following frequency of UEDVT: low probability (10% and 17%, respectively) in the in- and outpatients, intermediate probability (34% and 42%, respectively) in the in- and outpatients,

Table 2: Characteristics of the patients with or without DVT in the derivation and validation samples.

Characteristics (%)	Derivation sample			Internal validation sample		
	Thrombosis (N=50)	No thrombosis (N=90)	P	Thrombosis (N=46)	No thrombosis (N=57)	P
Male sex	52	52	0.82	41	56	0,16
Bed rest >3 days	36	40	0.45	47	33	0.16
Paralysis or immobilization	8	7	0.27	10	7	0.51
Surgery < 4 weeks	18	8	0.14	17	5	0.059
Previous VTE	14	20	0.23	26	8	0.032
Thrombophilia	4	7	0.09	8	5	0.7
Cancer	62	56	0.96	56	47	0.43
Venous material*	66	43	0.0056	69	38	0.003
Localized pain	58	34	0.03	50	43	0;55
Unilateral enlargement	78	42	0.55	87	72	0.09
Unilateral pitting edema	70	32	0.02	80	70	0.26
Superficial vein dilation	20	20	0.96	30	10	0.013
Warmth	52	38	0.99	36	37	1
Other diagnosis	14	34	0.015	17	54	0.0002

VTE= venous thromboembolism. *venous material including catheter or access device in a subclavian or jugular vein or pacemaker.

and high probability (70% and 69%, respectively) in the in- and outpatients.

Venous material always was a CVC in the derivation and internal validation samples. In the external validation sample, there were 25 CVCs and one pacemaker. Follow-up data were available at three months in 119 (56%) out of the 214 patients. Of the 54 patients with positive ultrasound who were followed up, three recurrences were recorded (1 PE, 1 UEDVT, 1 UEDVT associated with superficial vein thrombosis of the upper limb). Of the 65 patients with negative ultrasound, no UEDVT was diagnosed in the three-month follow-up but one experienced superficial vein thrombosis. These follow-up data are useful to assess ultrasound as a good diagnosis standard in our study.

The ROC for the clinical score showed a good discriminative power in the three samples (area under the curve [AUC] between 0.68 and 0.76).

Discussion

We propose a simple four-item score for calculating the clinical probability of UEDVT. This score improved the probability of UEDVT in each sample. The prevalence of UEDVT was 36, 45 and 30% in the derivation, internal validation and external validation samples, respectively. The patients classified by our score as high probability had a prevalence of 70, 64 and 69%, respectively. The low probability patients had a prevalence of 12, 9 and 13% respectively. Then we provide a potentially useful clinical tool to help clinicians to suspect a diagnosis of UEDVT.

While clinical characteristics and risk factors for DVT have been reported in several large series, no combination of risk factors and clinical signs or symptoms has been tested so far for the diagnosis of UEDVT. While unilateral arm swelling was the strongest variable associated with thrombosis, CVC was the strongest predictor among risk factors (1, 3). Then it was not surprising that it was the only risk factor present in our model. Interestingly, most CVC-associated UEDVT are diagnosed in inpatients (68% in Joffes' prospective registry) (1). This may explain that our score seems to be somewhat less efficient in the OP-

Table 3: Independent predictors of DVT in the derivation sample.

	Regression coefficient	Odds ratio [95% CI]	P
Venous material*	1.589	4.9 [1.9–12.5]	0.0009
Localized pain	0.993	2.7 [1.2–6.3]	0.017
Unilateral pitting edema	2.163	8.7 [3.4–22.2]	<0.0001
Other diagnosis at least as plausible	–1.204	0.3 [0.1–0.8]	0.016

* venous material including catheter or access device in a subclavian or jugular vein or pacemaker.

Table 4: Prediction of DVT in the three study samples.

Score	Derivation sample (N= 140)	Internal validation (N=103)	External validation (N=214)
	% [95% CI] (number with thrombosis /number in level)		
≤0	12% [10–23] (4/34)	9% [0–20] (2/23)	13 % [6–19] (14/110)
1	20% [9–30] (11/56)	37% [19–55] (10/27)	38% [27–50] (26/68)
≥2	70% [57–83] (35/50)	64% [51–77] (34/53)	69% [54–85] (25/36)

TIMEV outpatients. A clinical score is most efficient in the sample where it was designed, and outpatients have less frequent CVC and probably more frequent primary UEDVT. Then a specific score for outpatients might be further developed. Cancer is a well known risk factor for UEDVT (1, 3), but most cancer patients have a CVC, so that the multivariate analysis only found CVC and not cancer to be predictive of DVT. Among clinical signs, pain and swelling are among the most common symptoms or signs. Schmittling et al. identified by multivariate analysis limb tenderness as well as CVC and malignancy as independent predictors in their retrospective study (18). As in LEDVT, another diagnosis as plausible as UEDVT was negatively associated with confirmed UEDVT. This is in accordance with Schmittling et al. who found erythema to be negatively associated with DVT (odds ratio [OR] 0.12) (18). We were surprised not to find superficial vein dilation as a predictor. Many experienced physicians consider this sign as a good clinical predictor. However, this sign was found to be associated with UEDVT in our validation sample although it was not present in the model we developed from the derivation sample. Perhaps the variability of clinical experience among the physicians who filled out the clinical chart may be an explanation, but this emphazises reproducibility of our score among all kinds of physicians, experienced or not.

One can criticize the use of ultrasound for the diagnosis of DVT but this technique has been largely accepted and is now used in most vascular exploration centers, although ultrasound has not been as widely validated in upper as in LEDVT. It is remarkable that all the large series reporting UEDVT in recent years also used ultrasound as a gold standard (1, 6, 18). Moreover we verified the sensitivity of ultrasound in the OPTIMEV sample where 95 ultrasound-negative patients were followed-up for three months with no further diagnosis of UEDVT. Our clinical score might be especially useful in defining patients with high clinical probability of UEDVT and negative ultrasound who should be further investigated by computed tomography scan.

As for LEDVT, a low clinical probability does not exclude the diagnosis of UEDVT. This score is useful for the physician to better evaluate the situation and to decide whether or not to go on explorations. A low probability score does not mean that ultrasound must not be done. Exploration may be considered as not urgent in this case and may also help the physician to decide not to do ultrasound.

The practical usefulness of scores is sometimes questioned since they may be considered difficult to remember. However, they may be used in two ways:

The first one is to improve clinical evaluation, the basis of any clinical strategy. A physician only refers patients clinically suspected to have UEDVT. The efficacy of grouping physical signs as well as risk factors and alternate diagnosis should be greater as demonstrated for LEDVT, but had not been tested so far in UEDVT. In LEDVT, scores proved to be major tools that provide help to rational evidence-based clinical thinking, integrates risk factors and differential diagnosis as well as clinical signs and symptoms. They are a good mean to teach junior physicians clinical reflection leading to the use of the score or to its assimilation for later use as implicit clinical probability. The same usefulness can be expected in UEDVT. A limitation in the external validation sample is the use of our score in patients referred by their physician. A further validation might be useful among patients seen by primary care physicians.

The second way to use the score is to include clinical probability in diagnostic strategies using D-dimer for example. Before including it in such a strategy, we had to validate our score. However, it is not certain that the combination of a clinical score with D-dimers will be as useful in UEDVT as in LEDVT, since D-dimers are less sensitive in UEDVT than in LEDVT (14). D-dimers are not useful in cancer patients who made up 50% of patients in the derivation and internal validation samples. When clinical probability is high, a therapeutic recommendation might be to start heparin treatment before the assessment of diagnosis, as now recommended for LEDVT.

Most of Laupacis' criteria for clinical rules were assessed: mathematical development of the rule, description of results, clinical sensibility, clear definition of outcomes and predictive variables, prospective validation, easy-to-use rule. Limitations of our study are methodological differences between studies in derivation and internal validation samples on the one hand, and the external validation sample where the sonographer was not blinded from the score. Another limitation is the lack of reproducibility study for the score and for its physical examination items. This limitation also exists for the LEDVT scores but should be further investigated. The effect of the use of our clinical rule on clinical outcomes should also be measured.

Conclusion

We propose a simple clinical model to predict UEDVT. This score can be used in routine but might also be included in studies on UEDVT diagnosis. Current strategies should evaluate the efficiency of magnetic resonance imaging or computed tomography to explore ultrasound-negative patients with high clinical suspicion as proposed elsewhere (3). Then such a score would be useful to identify such patients.

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