Prediction of cerebral venous thrombosis with a new clinical score and D-dimer levels

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Abstract
Objective
To investigate prediction of cerebral venous thrombosis (CVT) by clinical variables and D-dimer levels.

Methods
This prospective multicenter study included consecutive patients with clinically possible CVT. On admission, patients underwent clinical examination, blood sampling for D-dimers measuring (ELISA test), and magnetic resonance/CT venography. Predictive value of clinical variables and D-dimers for CVT was calculated. A clinical score to stratify patients into groups with low, moderate, or high CVT risk was established with multivariate logistic regression.

Results
CVT was confirmed in 26.2% (94 of 359) of patients by neuroimaging. The optimal estimate of clinical probability was based on 6 variables: seizure(s) at presentation (4 points), known thrombophilia (4 points), oral contraception (2 points), duration of symptoms >6 days (2 points), worst headache ever (1 point), and focal neurologic deficit at presentation (1 point) (area under the curve [AUC] 0.889). We defined 0 to 2 points as low CVT probability (negative predictive value [NPV] 94.1%). Of the 186 (51.8%) patients who had a low probability score, 11 (5.9%) had CVT. The frequency of CVT was 28.3% (34 of 120) in patients with a moderate (3–5 points) and 92.5% (49 of 53) in patients with a high (6–12 points) probability score. All low CVT probability patients with CVT had D-dimers >500 μg/L. Predictive value of D-dimers for CVT for >675 μg/L (best cutoff) vs >500 μg/L was as follows: sensitivity 77.7%, specificity, 77%, NPV 90.7%, and accuracy 72.4%, respectively. Adding the clinical score to D-dimers >500 μg/L resulted in the best CVT prediction score explored (at the cutoff ≥6 points: sensitivity 83%/specificity 86.8%/NPV 93.5%/accuracy 84.4%/AUC 0.937).

Conclusion
The proposed new clinical score in combination with D-dimers may be helpful for predicting CVT as a pretest score; none of the patients with CVT showed low clinical probability for CVT and D-dimers <500 μg/L.

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Glossary

AUC = area under the curve; CI = confidence interval; CVT = cerebral venous thrombosis; DVT = deep venous thrombosis; MRV = magnetic resonance venography; NPV = negative predictive value; PE = pulmonary embolism; PPV = positive predictive value; ROC = receiver operating characteristics.

Headache is the most frequent clinical symptom of potentially disabling and life-threatening cerebral venous thrombosis (CVT). Headache in CVT may be isolated or more frequently associated with other symptoms such as epileptic seizures, papilledema, transient or persistent focal neurologic deficits, and decreased consciousness. Because of the broad clinical spectrum of CVT mimicking numerous diseases, it is often difficult to establish the diagnosis of CVT according to symptoms and clinical findings only.1

Elevated D-dimer levels may indicate the presence of a pathologically high level of fibrin degradation products linked to thrombus formation. However, the diagnostic value of D-dimer levels in CVT is still under debate.1–6

The most reliable methods for diagnosing CVT are cerebral MRI, magnetic resonance venography (MRV), and contrast-enhanced CT.1 However, these neuroimaging methods are not always performed in the emergency setting, despite contrast-enhanced CT being widely available.

In patients with clinical possibility of deep venous thrombosis (DVT) and pulmonary embolism (PE), a diagnostic algorithm is widely used in emergency departments. As a first step, patients are classified as having a low, moderate, or high clinical probability of DVT/PE. In patients with low or moderate probability, normal D-dimer levels have been shown to reliably exclude venous thromboembolism. However, in those with elevated D-dimer levels, imaging to confirm or exclude DVT/PE is recommended. In contrast, in patients in the high probability group, normal D-dimer levels are not helpful for reliably excluding DVT/PE; thus, further investigations such as imaging are recommended in those patients.7–11

In analogy to DVT/PE, the primary aim of the present study was to develop a new clinical score for stratifying patients into groups with low, moderate, and high CVT probability and to increase the predictive value of the score for CVT by adding D-dimer levels. Furthermore, we aimed at analyzing predictive value for CVT of D-dimer levels alone. Secondary aims were to assess the overall prevalence of CVT and other diseases in patients with clinical possibility of CVT and the site of involved veins and sinus in patients with CVT.

Methods

From September 2009 to February 2016, we prospectively included consecutive adult patients (age ≥18 years) with clinical possibility of CVT who were identified at the neurologic emergency department of the University Hospitals Bern and Amsterdam and consented to participate in the study. The final sample size and inclusion period were defined by the available funding. A detailed flowchart of inclusion/exclusion is depicted in figure 1.

One or more of the following symptoms or clinical findings of <30 days’ duration had to be present, as evaluated by trained neurologists at both centers: (1) isolated unexpected headache, (2) headache associated with focal neurologic deficits, (3) headache associated with disturbed consciousness, (4) headache associated with seizure(s), or (5) unexplained papilledema. We excluded patients with anticoagulation treatment before admission or one of the following diseases 3 months before admission: DVT, PE, ischemic stroke, or myocardial infarction.

Patients underwent a complete diagnostic workup on admission. A neurologist performed a neurologic examination. Prespecified baseline characteristics, demographic data, and risk factors for CVT were recorded (table 1 and data available from Dryad, doi:10.5061/dryad.2bq83bm2).

Standard laboratory investigations included measuring of D-dimer levels, which were determined with an automated immunoenzymatic assay (VIDAS D-Dimer Exclusion II, BioMérieux, Marcy-l’Étoile, France) at the Haemostasis Research Laboratory, Department for BioMedical Research, University of Bern, Switzerland. Citrated plasma samples were collected on admission and stored frozen until laboratory analysis. The laboratory investigators were blinded to clinical and neuroimaging findings and to the patient’s diagnosis.

Diagnosis of CVT was confirmed or excluded by MRV or CT venography. If CVT was excluded by MR or CT venography, other main diagnoses were confirmed according to local guidelines and as mentioned in the electronic patient file. MRIs were acquired on 1.5T (in Bern: Siemens Magnetom Avanto, Siemens Healthcare, Erlangen, Germany; in Amsterdam: Philips Ingenia, Philips Healthcare System, Amsterdam, the Netherlands) or 3T (in Bern: Siemens Magnetom Verio; in Amsterdam: Philips Ingenia) magnetic resonance scanners, and CT images were acquired with a multidetector-row CT scanner (in Bern: Siemens Definition Edge 128 slice scanner, in Amsterdam: Siemens Sensation 64 slice scanner and Philips Brilliance 64-slice scanner). All neuroradiologic images were reviewed by neuroradiologists (2 in Bern, 1 in Amsterdam) blinded to clinical and laboratory findings.
All patients included received standard care applied by the treating physicians who followed international recommendations. Patient involvement in the study did not influence any treatment decision.

**Statistical analysis**

All baseline characteristics, demographic data, risk factors, and clinical findings were compared between the 2 groups (with vs without CVT) with the χ² test and Fisher exact test if appropriate for categorical variables and Mann-Whitney U test for continuous and ordinal variables. A 2-tailed value of p < 0.05 was considered significant. Continuous variables statistically associated with CVT were dichotomized according to the most discriminative cutoff point that was defined by the highest Youden (J) index in receiver operating characteristics (ROC) curve analysis. Odds ratios (95% confidence intervals [CIs]) for CVT for each variable were calculated in univariate logistic regression, with and without adjustment for age and sex. Variables statistically significantly associated with CVT in univariate analysis were included in a multivariate logistic regression model. From this model, nonstatistically significant variables were removed. In the final model, regression coefficients, p values, and odds ratios (95% CI) were calculated. The newly developed CVT score resulted from the variables of this final model, which were weighted according to their regression coefficients.

To predict CVT with the newly developed CVT score, we calculated positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, accuracy, and ROC curve with area under the curve (AUC) and the corresponding 95% CIs. The best cutoff was defined as the crossing point of the highest sensitivity and specificity.

The following subgroup analyses were performed: for isolated headache; for focal neurologic deficits, seizure(s), or disturbed consciousness; and for acute symptoms (<48 hours).

D-dimer levels were calculated within each probability group. To predict CVT with D-dimer levels alone and with D-dimer levels (weighted according to their regression coefficients in univariate analysis) added to our newly developed CVT score in our patient cohort, we also calculated PPV, NPV, sensitivity, specificity, accuracy, and ROC curves with the AUC and their corresponding 95% CIs. Best cutoffs were defined as the crossing point of the highest sensitivity and specificity.

Missing data were considered missing because they were incidentally missing.

All analyses were performed with SPSS version 25 (SPSS Inc, Chicago, IL).

**Standard protocol approvals, registrations, and patient consents**

Written informed consent was obtained for all participants. The study was approved by the local ethics committee of the canton of Bern/Switzerland and by the local Academic Medical Center Ethical committee in Amsterdam/the Netherlands and registered at ClinicalTrials.gov (NCT00924859).

**Data availability**

Raw data of all patients included in this study can be made available on request to the corresponding author and after clearance by the local ethics committee.

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**Figure 1 Flowchart of inclusion/exclusion**

CVT = cerebral venous thrombosis; DVT = deep venous thrombosis; PE = pulmonary embolism.
| Table 1 Baseline characteristics, demographic data, risk factors, and clinical findings |
|-------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                         | Patients without CVT (n = 265) | Patients with CVT (n = 94) | Crude OR (95% CI) | p Value | Age-/sex-adjusted OR (95% CI) | p Value |
| Age (median, range), y | 39.7 (16.6–82.6) | 40.1 (18.2–79.5) | 1.00 (0.99–1.02) | 0.984 | 1.00 (0.99–1.02) | 0.951 |
| Sex (female), n (%) | 180 (67.9%) | 73 (77.7%) | 1.64 (0.95–2.84) | 0.077 | 1.64 (0.95–2.85) | 0.077 |
| Body mass index (median, range), kg/m² | 24.6 (15.7–45.7) | 25.2 (16.5–45.4) | 1.02 (0.98–1.07) | 0.331 | 1.02 (0.97–1.06) | 0.437 |
| Time from symptom onset to admission, median (range), d | 3 (0–120) | 6 (0–40) | 1.01 (0.99–1.03) | 0.239 | 1.01 (0.99–1.03) | 0.262 |
| Symptom duration, n (%) | | | | | | |
| >6 d | 89 (34.9) | 63 (67.7) | 3.92 (2.63–6.49) | 0.0001 | 3.88 (2.33–6.44) | 0.0001 |
| Race, n (%) | | | | | | |
| White | 220 (85.3) | 78 (85.7) | | | | |
| Nonwhite | 38 (14.7) | 13 (14.3) | | | | |
| African | 10 (3.9) | 1 (1.1) | | | | |
| Asian | 5 (1.9) | 1 (1.1) | | | | |
| Other | 23 (8.9) | 11 (12.1) | | | | |
| Headache, n (%) | 248 (95) | 86 (94.5) | 0.90 (0.31–2.60) | 0.848 | 0.90 (0.31–2.67) | 0.855 |
| Headache, worst ever, n (%) | 84 (31.7) | 50 (53.2) | 2.45 (1.51–3.96) | 0.0001 | 2.37 (1.46–3.84) | 0.0001 |
| Headache, unilateral, n (%) | 149 (56.2) | 45 (47.9) | 0.72 (0.45–1.15) | 0.163 | 0.70 (0.43–1.12) | 0.135 |
| Headache, after Valsalva, n (%) | 33 (14.3) | 19 (20.4) | 2.19 (1.15–4.17) | 0.017 | 2.18 (1.14–4.16) | 0.019 |
| Focal neurologic deficits, n (%) | 129 (49.8) | 73 (77.7) | 3.50 (2.04–6.03) | 0.0001 | 3.54 (2.05–6.12) | 0.0001 |
| Seizure(s), n (%) | 11 (4.3) | 39 (41.9) | 16.2 (7.78–33.55) | 0.0001 | 16.43 (7.86–34.35) | 0.0001 |
| Decreased consciousness, n (%) | 21 (7.9) | 23 (24.5) | 3.76 (1.97–7.20) | 0.0001 | 3.95 (2.05–7.63) | 0.0001 |
| GCS score at admission | 15 (3–15) | 15 (3–15) | 0.81 (0.71–0.92) | 0.002 | 0.81 (0.71–0.93) | 0.002 |
| Visual acuity decreased, n (%) | 45 (17.6) | 13 (13.5) | 0.85 (0.43–1.66) | 0.628 | 0.82 (0.42–1.61) | 0.564 |
| Visual positive phenomena, n (%) | 65 (25.4) | 17 (20) | 0.74 (0.40–1.34) | 0.315 | 0.72 (0.39–1.33) | 0.294 |
| Diplopia or other visual disturbance, n (%) | 29 (11.3) | 9 (10.6) | 0.93 (0.42–2.05) | 0.851 | 0.91 (0.41–2.01) | 0.806 |
| Nausea, n (%) | 120 (46.2) | 56 (60.9) | 1.82 (1.12–2.95) | 0.016 | 1.74 (1.07–2.84) | 0.027 |
| Vomitus, n (%) | 74 (28.5) | 46 (50) | 2.51 (1.54–4.10) | 0.0001 | 2.41 (1.47–3.96) | 0.0001 |
| Fever, n (%) | 21 (7.9) | 3 (3.2) | 0.38 (0.11–1.32) | 0.127 | 0.36 (0.11–1.26) | 0.109 |
| Infection, local, n (%) | 23 (8.7) | 9 (9.6) | 1.11 (0.50–2.50) | 0.794 | 1.15 (0.51–2.60) | 0.741 |
| Infection, systemic, n (%) | 18 (6.8) | 9 (9.6) | 1.45 (0.63–3.36) | 0.382 | 1.36 (0.58–3.15) | 0.478 |
| Previous CVT, n (%) | 7 (2.6) | 2 (2.1) | 0.80 (0.16–3.93) | 0.785 | 0.82 (0.17–4.03) | 0.803 |
| Previous DVT, n (%) | 10 (3.8) | 6 (6.4) | 1.74 (0.61–4.92) | 0.298 | 1.77 (0.62–5.06) | 0.289 |
| Previous PE, n (%) | 8 (3) | 6 (6.4) | 2.19 (0.74–6.49) | 0.157 | 2.20 (0.74–6.59) | 0.158 |
| Previous CVT/DVT/PE, ≥2 events, n (%) | 2 (0.8) | 3 (3.2) | 4.34 (0.71–26.36) | 0.111 | 4.67 (0.75–28.92) | 0.098 |
| Known thrombophilia, n (%) | 1 (0.4) | 10 (10.6) | 31.43 (3.97–249.13) | 0.001 | 32.79 (4.10–262.36) | 0.001 |
| Pregnancy, n (%) | 15 (5.7) | 0 | 0 (0–NA) | 0.998 | 0 (0–NA) | 0.998 |
| Recent birth (<1 y), n (%) | 6 (2.3) | 3 (3.2) | 1.42 (0.35–5.81) | 0.623 | 1.25 (0.30–5.18) | 0.757 |
| Smoking, current, n (%) | 62 (24) | 11 (11.8) | 0.42 (0.21–0.85) | 0.015 | 0.43 (0.21–0.86) | 0.018 |
Table 1 Baseline characteristics, demographic data, risk factors, and clinical findings (continued)

| Risk Factor | Patients without CVT (n = 265) | Patients with CVT (n = 94) | Crude OR (95% CI) | p Value | Age-/sex-adjusted OR (95% CI) | p Value |
|-------------|-------------------------------|---------------------------|------------------|---------|-------------------------------|---------|
| Smoking, previous, n (%) | 32 (12.1) | 10 (10.6) | 0.87 (0.41–1.84) | 0.710 | 0.88 (0.41–1.88) | 0.740 |
| Malignancy, n (%) | 10 (3.8) | 9 (9.6) | 2.70 (1.06–6.87) | 0.037 | 2.69 (1.05–6.91) | 0.039 |
| Malignancy, active or previous, n (%) | 23 (8.7) | 10 (10.6) | 0.90 (0.52–1.58) | 0.721 | 0.86 (0.49–1.51) | 0.590 |
| Vasculitis or systemic inflammatory disease, n (%) | 14 (5.3) | 3 (3.2) | 0.59 (0.17–2.10) | 0.417 | 0.57 (0.16–2.04) | 0.388 |
| D-dimer levels >675 μg/L, n (%) | 357 (74–44,082) | 1,280 (155–57,137) | 1.14 (0.77–1.69) | 0.510 | 1.15 (0.78–1.70) | 0.510 |
| D-dimer levels >500 μg/L, n (%) | 89 (33.6) | 84 (89.4) | 0.87 (0.51–1.49) | 0.582 | 0.86 (0.50–1.49) | 0.582 |
| D-dimer levels >675 μg/L, n (%) | 61 (23) | 73 (77.7) | 1.16 (0.62–2.19) | 0.670 | 1.16 (0.62–2.19) | 0.670 |

Abbreviations: CI = confidence interval; CVT = cerebral venous thrombosis; DVT = deep venous thrombosis; GCS = Glasgow Coma Scale; LP = low pressure; NA = not applicable; OR = odds ratio; PE = pulmonary embolism.

Results

Between September 2009 and February 2016, 383 adults were included in this study. We excluded 24 patients because of missing or clotted blood samples or because of withdrawal from the study, resulting in 359 patients for the final analysis. The overall frequency of CVT in our cohort confirmed by neuroimaging in patients with clinical possibility of CVT was 26.2% (94 of 359 patients). Baseline characteristics, demographic data, risk factors, and clinical findings are given in table 1; the overall frequency of other diseases in patients with clinical possibility of CVT and neuroimaging findings and the site of involved veins and sinus in patients with CVT are shown in table 2.

The optimal estimate of clinical CVT probability turned out to be based on 6 variables that defined the final CVT score (AUC 0.889, 95% CI 0.847–0.930) with a score range of 0 to 14 points: any (focal and/or generalized) seizure(s) at presentation (4 points), known thrombophilia (including any hematologic disease known to be associated with increased tendency of coagulation) (4 points), oral contraception (2 points), duration of symptoms >6 days (2 points), worst headache ever (patient reported) (1 point), and focal neurologic deficit at presentation (1 point) (figure 2). Zero to 2 points best identified patients with low CVT probability (NPV 94.1%). Of the 186 (51.8%) patients with a low probability score, 11 (5.9%) had CVT. Three to 5 points defined the moderate-probability group. One hundred twenty (33.4%) had a moderate probability score, of whom 34 (28.3%) had CVT. Six to 14 points defined the high-probability group (7–14 points: PPV and specificity 100% for CVT). Fifty-three (14.8%) patients had a high probability score, of whom 49 (92.5%) had CVT; 2 had tension headache, 1 had idiopathic intracranial hypertension, and 1 had an ischemic stroke. At the
| No-CVT, other main diagnosis            | Patients without CVT (n = 265), n (%) | Patients with CVT (n = 94), n (%) | p Value |
|----------------------------------------|--------------------------------------|----------------------------------|---------|
| Emergency unit CT imaging              | 90 (34)                              | 60 (63.8)                        | 0.0001  |
| Emergency unit MRI                     | 172 (64.9)                           | 37 (39.4)                        | 0.0001  |
| Venous ischemia                        | 0                                    | 17 (18.1)                        | 0.0001  |
| Venous bleeding                        | 0                                    | 39 (41.5)                        | 0.0001  |
| Intracerebral hemorrhage               | 12 (4.5)                             | 2 (2.1)                          | 0.302   |
| Subarachnoid hemorrhage                | 9 (3.4)                              | 16 (17)                          | 0.0001  |
| Subdural hemorrhage                    | 4 (1.5)                              | 1 (1.1)                          | 0.744   |
| Epidural hemorrhage                    | 1 (0.4)                              | 0                                | 0.551   |
| Ischemia without bleeding              | 10 (3.8)                             | 6 (6.4)                          | 0.303   |

**Location of thrombosis**

| Location of thrombosis                  | Patients without CVT (n = 265), n (%) | Patients with CVT (n = 94), n (%) | p Value |
|-----------------------------------------|--------------------------------------|----------------------------------|---------|
| Sinus sagitai superior                  | NA                                   | 54 (57.4)                        | NA      |
| Right sinus transversus                 | 48 (51.1)                            |                                  |         |
| Left sinus transversus                  | 47 (50)                              |                                  |         |
| Right sinus sigmoideus                  | 32 (34)                              |                                  |         |
| Left sinus sigmoideus                   | 38 (40.4)                            |                                  |         |
| Sinus rectus                            | 24 (25.5)                            |                                  |         |
| Cortical veins                          | 12 (12.8)                            |                                  |         |
| Deep veins                              | 19 (20.2)                            |                                  |         |
| Cerebellar veins                        | 3 (3.2)                              |                                  |         |
| Right jugular vein                      | 17 (18.1)                            |                                  |         |
| Left jugular vein                       | 22 (23.4)                            |                                  |         |

**No CVT, other main diagnosis**

| No-CVT, other main diagnosis            | Patients without CVT (n = 265), n (%) | Patients with CVT (n = 94), n (%) | p Value |
|----------------------------------------|--------------------------------------|----------------------------------|---------|
| Meningitis/encephalitis/cerebral abscess | 15 (5.7)                             | NA                               | NA      |
| Other local infection                  | 6 (2.3)                              |                                  |         |
| Systemic infection                     | 18 (6.8)                             |                                  |         |
| Cerebral tumor                         | 6 (2.3)                              |                                  |         |
| Ischemic stroke                        | 11 (4.2)                             |                                  |         |
| Apoplex of hypophysis                  | 1 (0.4)                              |                                  |         |
| Vessel dissection                      | 2 (0.8)                              |                                  |         |
| Hypertensive crisis                    | 5 (1.9)                              |                                  |         |
| Intracerebral hemorrhage               | 8 (3)                                |                                  |         |

**Abbreviations:** CVT = cerebral venous thrombosis; NA = not applicable.
CVT score crossing of highest sensitivity/speciﬁcity values (sensitivity 78.7%/speciﬁcity 83%/NPV 91.7%/PPV 62.2%/ accuracy 80.5%), at 3 points, there was a cumulative missing rate of CVT of 21.3% (ﬁgure 3 and ﬁgure 4A).

The validity of D-dimer levels alone in predicting CVT in all patients is presented in ﬁgure 4B. Predictive value of D-dimers for CVT for >500 μg/L was as follows: sensitivity 89.4%/ speciﬁcity 66.4%/NPV 70.6%/PPV 48.6%/ accuracy 72.4%. At D-dimer levels >675 μg/L, crossing of highest sensitivity/ speciﬁcity was seen (sensitivity 77.7%/speciﬁcity 77%/NPV 90.7%/PPV 54.5%/accuracy 77.2%), but the best Youden index (J) at >533 μg/L was in favor of a high sensitivity rather than a high speciﬁcity. Because the latter value was close to the predeﬁned commonly used cutoff point between normal/ elevated levels in DVT/PE diagnosis, we decided to analyze the cutoff value of >500 μg/L instead of >533 μg/L in further analyses. The ROC curve of continuous D-dimer levels alone showed an AUC of 0.830 (95% CI 0.783–0.877). At cutoff D-dimer levels of >675 μg/L, 22.3% of patients with CVT were missed; at >500 μg/L, 10.6% were missed (ﬁgure 4B).

Predictive values and diagnostic accuracy for CVT if the D-dimer level cutoffs were >500 and >675 μg/L were applied to the different low, moderate, and high CVT probability groups (ﬁgure 5). All patients with CVT in the low CVT probability group had D-dimer levels >500 μg/L (NPV 100%/sensitivity 100%), but 5 patients in the moderate CVT probability group had D-dimer levels ≤500 μg/L (NPV 91.7%/sensitivity 85.3%), of whom 1 had seizure(s) at presentation, none had known thrombophilia, 2 used an oral contraception, 3 had a duration of symptoms >6 days, 3 had a worst headache ever, and 2 had focal neurologic deﬁcits at presentation. In addition, 5 patients with CVT in the high-probability group did not have D-dimer levels >500 μg/L (NPV 37.5%/sensitivity 89.8%/PPV 97.8%/speciﬁcity 75%). All but 1 patient with CVT in the low CVT probability group with a low thrombus load and a sinus cavernous clot location had D-dimer levels >675 μg/L (NPV 99.3%/sensitivity 90.9%/PPV 20%/speciﬁcity 77.1%). Ten patients in the moderate-probability group (NPV 86.8%/sensitivity 70.6%/PPV 54.5%/speciﬁcity 76.7%) and 10 in the high-probability group (NPV 23.1%/ sensitivity 79.6%/PPV 97.5%/speciﬁcity 75%) had D-dimer levels ≤675 μg/L (ﬁgure 5).

If the variables of D-dimer levels >500 or >675 μg/L (3 points each according to their regression coeﬃcients) were included as another subitem in the newly developed CVT score, the predictive value and diagnostic accuracy of a single score as such further improved (ﬁgure 4, C and D).

The CVT D-dimers (>675 μg/L) score showed crossing of highest sensitivity/speciﬁcity values at ≥5 points (sensitivity 89.4%/speciﬁcity 83%/NPV 95.7%/PPV 65.1%/accuracy 83.3%), with a cumulative CVT missing rate at that level of 10.6%. All patients with a score of 9 to 17 points had CVT (PPV 100%/speciﬁcity 100%). The ROC curve of this score showed an AUC of 0.934 (95% CI 0.906–0.961) (ﬁgure 4, C and D).

The CVT D-dimers (>500 μg/L) score showed crossing of highest sensitivity/speciﬁcity values at ≥6 points (sensitivity 83%/speciﬁcity 86.8%/NPV 95.5%/PPV 69%/accuracy 84.4%), with a cumulative CVT missing rate at that level of 17%. The NPV and sensitivity for 0 to 2 points were 100%, and no CVT was missed. All patients with a score of 9 to 17 points had CVT (PPV 100%/speciﬁcity 100%). The ROC curve of this score showed an AUC of 0.937 (95% CI 0.910–0.963) (ﬁgure 4, C and D).

Subgroup analyses for isolated headache, for focal neurologic deﬁcits and/or seizure(s) and/or disturbed consciousness, and
for acute symptoms (<48 hours) are shown in data available from Dryad (Figures 1–3, doi:10.5061/dryad.2bvq83bm2).

Discussion

This study presents a clinical prediction score that was derived from a large, prospectively collected cohort of patients with possible CVT presenting at the emergency departments of 2 tertiary care centers in 2 different countries. The newly developed clinical CVT score is based on routinely collected variables that are easily available from the patients’ history and neurologic examination. The CVT score allows emergency staff to classify patients into 3 CVT probability groups. The predictive value of the CVT score for CVT further increased by adding D-dimer levels.

The main strengths of our study are its prospective, systematic, multicenter design; its novelty in this specific field; and its relatively large sample size. One more strength supporting the clinical relevance of the score is that we considered the vast majority of known associated risk factors and clinical findings of CVT. Another strength is that we developed this CVT score by using a recommended and known method.8,13,14 First, we explicitly defined our outcome, which was CVT, diagnosed by accepted diagnostic neuroimaging methods. Second, we explicitly defined our variables used to predict CVT: stated age and sex of patients and the study sites. Third, we described the statistical modeling technique. However, the study has some limitations. We have tested neither the misclassification rate in a new and external cohort of patients nor the effects of clinical use of this score, which was retrospectively calculated from a prospective cohort, if applied prospectively. Moreover, we included consecutive patients in our analysis. However, some eligible patients may have been missed, which is reflected in the high rate of patients with CVT of one-fourth in our cohort of a majority of patients with possible CVT.1 However, another fact may have influenced the high rate of patients with CVT in our study: both the Bernese and Amsterdam University Hospitals are tertiary care centers for cerebrovascular diseases and do not represent a population-based setting. Another limitation is that, because of the lack of data in the literature, power calculation was not performed.

The subitems of the Wells and modified Geneva score for prediction of DVT and PE, respectively, are different from the most predictive CVT variables identified in our score. However, DVT and CVT are diseases with different clinical presentation and risk factors. The following collected and analyzed Wells/modified Geneva score subitems did not make it into the final model of our score: malignancy according to Wells criteria, recently bedridden >3 days, major surgery within 3 months, fracture within 1 month, age >65 years, and previous DVT/PE. We stress that patients with DVT/PE 3 months before admission were excluded from our study, which might have lowered the association of previous thromboembolism with CVT, and data on patients being recently bedridden, major surgery, and fracture were not prospectively recorded. However, these variables are not thought to be major risk factors of CVT.1

Furthermore, the Wells score and the modified Geneva score are widely used. The latter is standardized, and the Wells score involves subjective clinical judgment of whether an alternative

Figure 3 CVT score values stratifying patients into groups with low, moderate, and high CVT probability

CVT = cerebral venous thrombosis.
diagnosis is more likely than PE. In addition, this subitem weighted heavily in the score, which might therefore have caused the Wells score to be driven vastly by subjective judgment.\textsuperscript{11} Our CVT score involves subjective judgment by the patient in the subitem worst headache ever (1 point) and potentially in the subitem duration of symptoms >6 days (2 points) and subjective

![Image](https://example.com/image.png)

(A) Validity of cerebral venous thrombosis (CVT) score in predicting CVT and cumulative percentage of patients with CVT missed at various score values. (B) Validity of D-dimer levels in predicting CVT and cumulative percentage of patients with CVT missed at various D-dimer levels. (C) Validity of CVT D-dimers (>675 \(\mu g/L\)) score in predicting CVT and cumulative percentage of patients with CVT missed at various score values. (D) Validity of CVT D-dimers (>500 \(\mu g/L\)) score in predicting CVT and cumulative percentage of patients with CVT missed at various score values. ACC = accuracy; NPV = negative predictive value; PPV = positive predictive value.
clinical judgment concerning the subitem seizure(s) at presentation (4 points). Subitems involving subjective judgment might pose more difficulties by their nonobjective nature than objective subitems, especially if weighted heavily. Moreover, the subitem of thrombophilia (4 points) turned out to be strongly associated with CVT prediction. However, history of thrombophilia might not be known before thromboembolism and also not thereafter if not investigated or if investigated with delay due to initial anticoagulation. This further underlines the strength of association of this subitem; in some patients, thrombophilia might have been present without us knowing it for this analysis. Having said that, we labeled patients as having thrombophilia in case of any hematologic disease known to be associated with increased tendency of coagulation.

Our final CVT score resulted from the most predictive variables for CVT, and weighting was applied according to regression coefficients. Of note, few data were missing. The highest rate of missing data for the variables selected for the final score was seen for seizures (2.5%). Because data were missing incidentally, this possibly led to a loss of precision of our final CVT score, not necessarily to a biased accuracy owing to the randomness of missing data.

The frequency of patients without CVT in the low-probability group was high at 94.1% and low for patients with CVT at 5.9% and low for patients without CVT in the high-probability group at 7.5% and high for patients with CVT with 92.5%. This shows that our newly developed CVT score may be helpful as a pretest especially in combination with D-dimer levels, because none of the patients with CVT in the low-probability group had low D-dimer levels ≤500 μg/L. However, 5 patients in the moderate-probability group had D-dimer levels ≤500 μg/L. In the DVT/PE diagnosis algorithm, the Wells score and modified Geneva score are recommended for clinical probability assessment. In patients in the low DVT/PE probability group, normal D-dimer levels ≤500 μg/L have been shown to safely exclude DVT/PE, and typically, no further investigations,
especially no imaging, is required. However, D-dimer levels of >500 μg/L should prompt further investigations. The same applies to patients in the moderate DVT/PE group. However, some patients in this moderate group nevertheless are recommended to undergo further testing to safely exclude DVT/PE, especially if they are in the upper zone of the moderate group according to their score.9,11 Whether a similar approach can be applied in patients with CVT with our CVT score in the low-probability group has to be further explored. However, we would like to stress that D-dimer levels ≤500 μg/L in the moderate CVT probability group did not exclude CVT in our cohort in the applied assay, only in the low-probability group.

Besides, we were interested in the validity of D-dimer levels alone in predicting CVT. At D-dimer levels >675 μg/L (best cutoff defined as crossing of highest sensitivity/specificity), 22.3% of patients with CVT were missed; at >500 μg/L, 10.6% were missed. As previous studies have shown, some patients with CVT may have low D-dimer values, especially those with isolated headache.2–6 Our analysis showed partially better predictive values and diagnostic accuracy in the subgroup analyses than in the whole cohort, of note in patients with isolated headache (data available from Dryad, figures 1–3, doi:10.5061/dryad.2bwq83bm2).

D-dimer levels show an association with the thrombus load and clot lysis, with the acuity of symptoms, and with factors associated with high pretest probability. Another important note is that D-dimer assays are known to be highly sensitive, but their specificity is moderate to low, usually ranging between 40% and 60%, and they are often falsely positive in conditions such as malignancy, recent surgery or trauma, pregnancy or postpartum state, inflammatory process, acute illness, and renal dysfunction.15 In our study, the variety of diagnoses in patients without CVT was broad with associated elevated D-dimer levels in 89 patients, but these patients did not turn out to have high clinical score values.

In addition, we analyzed the inclusion of D-dimer levels >500 or >675 μg/L (3 points each) as a variable in the newly developed CVT score, which further improved CVT prediction and diagnostic accuracy (figure 4, C and D). At lower score values, fewer patients with CVT were missed, and all patients with a score of 9 of 17 points had CVT, especially underlining the high PPV and specificity.

We developed a clinical pretest probability CVT score for stratifying the risk of CVT among patients with possible CVT presenting to the emergency department of tertiary care hospitals; the score needs to be validated in different emergency settings. The score consists of 6 easy and weighted variables and allows the grouping of patients into low, moderate and high CVT probability groups. It might be helpful in supporting triage decisions toward a hospital with the availability of cerebral MRI, MRV, or contrast-enhanced CT and for further increasing the diagnostic value of D-dimer levels. The internal and external validation of this score, with and without D-dimer levels added to the score, its adherence, and its clinical usefulness need to be further investigated.

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| Name                      | Location                                                                 | Contribution                                                                 |
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### Appendix (continued)

| Name                        | Location                                                                 | Contribution                                                                 |
|-----------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
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