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ORIGINAL ARTICLE

A scoring tool to predict mortality and dependency after cerebral venous thrombosis

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Abstract

Background and purpose: A prognostic score was developed to predict dependency and death after cerebral venous thrombosis (CVT) to identify patients for targeted therapy in future clinical trials.

Methods: Data from the International CVT Consortium were used. Patients with pre-existent functional dependency were excluded. Logistic regression was used to predict poor outcome (modified Rankin Scale score 3–6) at 6 months and Cox regression to predict 30-day and 1-year all-cause mortality. Potential predictors derived from previous studies were selected with backward stepwise selection. Coefficients were shrunk using ridge regression to adjust for optimism in internal validation.

Results: Of 1454 patients with CVT, the cumulative number of deaths was 44 (3%) and 70 (5%) for 30 days and 1 year, respectively. Of 1126 patients evaluated regarding functional outcome, 137 (12%) were dependent or dead at 6 months. From the retained predictors for both models, the SI_2NCAL_2C score was derived utilizing the following components: absence of female-sex-specific risk factor, intracerebral hemorrhage, infection of the central nervous system, neurological focal deficits, coma, age, lower level of hemoglobin (g/l), higher level of glucose (mmol/l) at admission, and cancer. C-statistics were 0.80 (95% confidence interval [CI] 0.75–0.84), 0.84 (95% CI 0.80–0.88) and 0.84 (95% CI 0.80–0.88) for the poor outcome, 30-day and 1-year mortality model, respectively. Calibration plots indicated a good model fit between predicted and observed values. The SI_2NCAL_2C score calculator is freely available at www.cerebralvenousthrombosis.com.

Conclusions: The SI_2NCAL_2C score shows adequate performance for estimating individual risk of mortality and dependency after CVT but external validation of the score is warranted.

KEYWORDS
cerebral venous thrombosis, dependency, follow-up, mortality, outcome, prognosis, risk score, stroke

INTRODUCTION

The clinical course of cerebral venous thrombosis (CVT) is heterogeneous and predicting poor outcome for individual patients is challenging. Although most patients recover without physical disability, 10%–15% of patients die or become dependent in activities of daily living [1, 2]. A simple and robust risk score to identify patients with CVT who are at high risk of dependency or death would be helpful to improve personalized treatment decisions, to prioritize which patients to monitor more closely and to guide future trials in selecting patients eligible for novel interventions.

Several risk factors that affect clinical outcome after CVT have been identified. These include age, absence of female-sex-specific risk factors, coma, intracerebral hemorrhage (ICH), thrombosis of the deep cerebral venous system, infection of the central nervous system (CNS), and cancer [1, 3–6]. Nevertheless, in everyday clinical practice, interpretation of the collective influence of these risk factors on the prognosis of an individual patient is not feasible, whilst calculation of individual risk with a statistical regression equation without a practical risk score is too intricate.

Attempts to build scores to predict outcome after CVT have suffered mainly from a limited number of outcome events [7–11]. The aim for the current study was to develop an easy-to-use prognostic risk score that utilizes clinical data which are routinely available at the diagnosis of CVT to predict individual risks of dependency or death after CVT in a large, consecutive, multicenter cohort and in accordance with international prognostic score development guidelines [12–15].

METHODS

Study population

Consecutive adult patients (≥18 years) who were diagnosed with CVT were included from the International CVT Consortium registry, which is an ongoing collaboration between CVT research groups from 14 hospitals in 13 countries. Details of the consortium have been previously described [16]. Patients were in part included retrospectively and in part prospectively. The inclusion period varied

per hospital and spanned from July 1995 to June 2021 (Appendix S1, Table S1). Patients with known disability (modified Rankin Scale [mRS] score >2) prior to the diagnosis of CVT and patients who had a missing primary outcome of interest for each respective model were excluded.

Data collection and definitions

The study design, management and reporting of data were developed in accordance with the TRIPOD and PROBAST guidelines [12–15]. Data were extracted from the International CVT Consortium registry including admission characteristics covering demographics, laboratory investigations, imaging findings, treatment and clinical outcome using standardized case report forms. The diagnosis of CVT was confirmed with computed tomography venography, magnetic resonance imaging with magnetic resonance venography, catheter angiography or autopsy [17]. Female-sex-specific risk factors were considered as any of the following: oral contraceptive use, pregnancy, postpartum period (delivery within 12 weeks of CVT symptom onset) or hormone replacement therapy [5]. Type of CVT onset was categorized according to time from symptom onset to admission as either acute (<48 h), subacute (between 48 h and 30 days) or chronic (>30 days). Functional outcome was assessed at routine follow-up visits at 6 months using the mRS and poor clinical outcome was defined as a score of 3–6. For retrospectively included patients, mRS scores were obtained from medical records by certified adjudicators. The main reasons for choosing evaluation of functional outcome at 6 months were (i) that most patients with CVT recover and achieve a functionally stable condition within the first 6 months [1]; (ii) from the patient's point of view at admission, a perspective of 6 months is relevant for planning objectives for rehabilitation and could guide decision making regarding readjustments for activities in daily life; (iii) a majority of centers in the International CVT Consortium routinely plan follow-up visits at around 6 months including a clinical examination with assessment of functional status. Mortality was assessed at 30 days as a measurement of short-term mortality. Long-term mortality was investigated at 1 year to yield a fair balance between the influence of underlying risk factors and the CVT.

Data analysis

The models were developed using multiple imputation (predictive mean matching) for missing predictors and results were pooled from five imputed datasets. Dependency or death (mRS 3–6) at 6 months was investigated using logistic regression analysis with backward stepwise selection ($p < 0.1$). All-cause mortality up to 1 year was investigated using a Cox proportional hazard model with backward stepwise selection ($p < 0.1$) with time to death as the event of interest. Patients who did not experience the event were censored at the time of last follow-up. The potential violation of the proportional hazards assumption was assessed by visual inspection of Schoenfeld residuals.

The following candidate predictors were selected for both models based on clinical plausibility, previous studies and avoidance of potential collinearity: cancer (any malignant tumor or hematological malignancy diagnosed during hospitalization or up to 10 years prior to diagnosis of CVT), coma at admission (Glasgow Coma Scale score <9), deep cerebral venous system thrombosis (thrombosis in either the vein of Galen, the basal vein of Rosenthal, the inferior sagittal sinus or the internal cerebral veins), ICH (including hemorrhagic transformation of venous infarct, detected on admission neuroimaging), age at admission, absence of female-sex-specific risk factors at diagnosis of CVT (either oral contraceptive use, pregnancy, postpartum period [i.e., delivery within 12 weeks] or hormone replacement therapy), infection in the CNS (any infection affecting the CNS including bacterial or viral meningitis, encephalitis or invasive infections in any of the dural sinuses and/or veins), lower admission hemoglobin level (g/l), higher admission glucose level (mmol/l) and neurological focal deficits at admission (any clinical neurological focal deficit present at admission) [1, 3–6, 18, 19]. Admission hemoglobin level and admission glucose level were kept as continuous variables [12–15] as prior studies reported trends that suggested concentration-related associations with poor outcome and as dichotomization of continuous variables is not recommended by prognostic score development guidelines [4, 6, 12–15]. Anticoagulant treatment was not added as a candidate predictor due to the risk of confounding by indication. The linearity of continuous variables was assessed and adding transformations was considered depending on the improvement of model fit based on Akaike's information criterion (AIC). The type of transformation applied was dependent on characteristics of the nonlinear relationship between the predictor and the outcome. Coefficients were shrunk using ridge regression to adjust for optimism in internal validation. To identify potential multicollinearity, the variance inflation factor was calculated for each model.

Internal validation was assessed using bootstrapping with 1000 samples. Performances of the predictive models were evaluated with calibration plots for goodness of fit and C-statistics with 95% confidence intervals (CI) for discrimination. As outcome after CVT has improved over time [20], sensitivity analyses were performed by adding year of CVT diagnosis to the final predictive models. Data were analyzed with IBM SPSS Statistics 23.0 (International Business Machines Corporation) and R-statistic programming (version 4.0.3; R Foundation for Statistical Computing).

Standard protocol approvals, registrations and patient consents

Each participating center received permission from local authorities and ethics committees to collect observational data and obtained written informed patient consents when required under applicable national laws.

RESULTS

Between July 1995 and June 2021, 1540 patients with CVT were recorded in the International CVT Consortium registry. After excluding 85 patients with a history of functional dependency, 1455 patients were considered eligible for the study. For each model, patients who had a missing follow-up status were excluded, leaving 1454 patients in the mortality model development cohort and 1126 patients in the prediction of poor outcome model cohort (Figure 1). Baseline characteristics for patients included in the analyses are described in Table 1. For both models, median age was 40 years (interquartile range [IQR] 29–52) and the proportion of women was 70%. The distribution of the investigated outcomes, sex and age was comparable in prospectively and retrospectively included patients. Calculations of the variance inflation factor between variables included in each model showed values <1.4, which were hence not indicative of multicollinearity.

Model to predict 6-month dependency or death

Of 1126 patients included in the analyses for development of the model to predict poor outcome, 137 (12.2%) patients were dependent or dead (mRS 3-6) at 6 months (median follow-up time 183 days, IQR 181–184). After logistic regression with backward stepwise selection, retained predictors were age, coma, cancer, absence of any female-sex-specific risk factors, lower admission hemoglobin level (g/l), higher admission glucose level (mmol/l), focal neurological deficits and ICH at baseline. According to the AIC, transformation of age improved model fit of the logistic regression model. Thus, after square root transformation, the nonlinear relation between age and poor outcome is described as a summary of two coefficients ($-0.068*(age)+0.001*(age)^2$[2]). The final model with odds ratios and coefficients after applying shrinkage is provided in Table 2a. Assessment of calibration plots indicated adequate goodness of fit between predicted and observed values, and the C-statistic indicated good discrimination (0.80, 95% CI 0.75–0.84; Figure 2c). The risk increase by age is calculated from the two age coefficients combined (Table 3).

Model to predict 30-day and 1-year mortality

Of the 1454 patients included in the development of the model to predict mortality at 30 days and 1 year, 122 (8.4%) had died by the end of follow-up, with a median follow-up time of 365 days (IQR 113–720). The cumulative number of deaths was 44 (3.0%) and 70 (4.8%) for 30 days and 1 year, respectively. After Cox regression with backward stepwise selection, the retained predictors for mortality at 30 days and 1 year were age, coma, cancer, absence of female-sex-specific risk factors, lower admission hemoglobin level (g/l), higher admission glucose level (mmol/l), ICH, neurological focal deficits and infection in the CNS. Based on the AIC, transformations of continuous variables did not improve model fit. The final model with hazard ratios and coefficients after applying shrinkage is presented in Table 2b. The proportional hazards assumption was met indicating stable hazards over time, meaning that the model can be used to predict mortality both at 30 days and at 1 year. Calibration plots indicated adequate goodness of fit between predicted and observed values, and C-statistics to predict mortality at 30 days (0.84, 95% CI 0.80–0.88) and 1 year (0.84, 95% CI 0.80–0.88) indicated good model discrimination (Figure 2a,b).

Sensitivity analyses

When adding year of CVT diagnosis or prospective enrollment as a predictor, coefficients, adjusted odds ratios, hazard ratios and model performances did not differ significantly. Replacing the variable

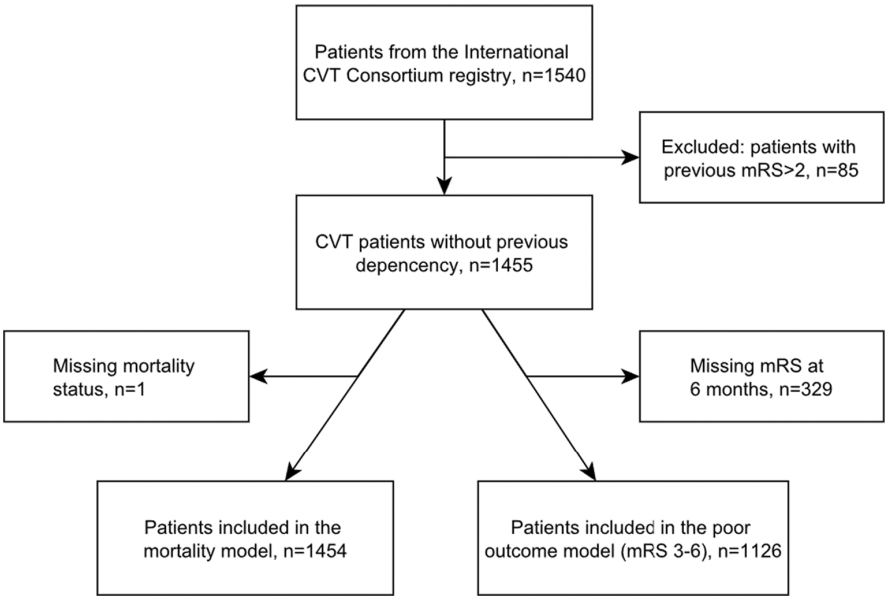

FIGURE 1 Flow chart of patient selection. CVT, cerebral venous thrombosis; mRS, modified Rankin Scale.

TABLE 1 Baseline characteristics and treatment

Clinical characteristics	Mortality model ($n = 1454$)	6-month poor outcome model ($n = 1126$)
Women, *n*/*N* (%)	1015/1454 (70)	790/1126 (70)
Age in years, median (IQR)	40 (29–52)	40 (29–52)
Prospective enrollment, *n*/*N* (%)	846/1454 (58)	588/1126 (52)
Symptom onset, *n*/*N* (%)		
Acute (<48 h)	378/1351 (28)	300/1036 (29)
Subacute (48 h to 30 days)	862/1351 (64)	648/1036 (63)
Chronic (>30 days)	111/1351 (8)	88/1036 (8)
Headache, *n*/*N* (%)	1186/1377 (86)	898/1059 (85)
Neurological focal deficits, *n*/*N* (%)	798/1397 (57)	593/1074 (55)
Mental state disturbance (GCS <15 and >9), *n*/*N* (%)	338/1430 (24)	242/1109 (22)
Coma (GCS <9), *n*/*N* (%)	74/1433 (5)	52/1109 (5)
Acute symptomatic seizure(s), *n*/*N* (%)	464/1264 (37)	345/952 (36)
Late seizures, *n*/*N* (%)	141/1091 (13)	110/810 (14)
Risk factors, *n*/*N* (%)		
Cancer	139/1454 (10)	116/1126 (10)
Previous venous thrombosis	121/1452 (8)	97/1124 (9)
Hereditary thrombophilia	215/1452 (15)	185/1125 (16)
CNS infection	54/1453 (4)	40/1126 (4)
Oral contraceptive use[a]	435/810 (54)	322/623 (52)
Pregnancy[a]	60/810 (7)	51/623 (8)
Recent delivery (<12 weeks)[a]	102/810 (13)	87/623 (14)
Hormone replacement therapy[b]	35/1015 (3)	32/790 (4)
Any female-sex-specific risk factor[c]	613/1015 (60)	469/790 (59)
Comorbidities, *n*/*N* (%)		
Severe heart disease[d]	32/1454 (2)	27/1126 (2)
Systemic inflammatory or autoimmune disease	129/1454 (9)	98/1126 (9)
Type 1 diabetes	9/1454 (<1)	7/1126 (<1)
Chronic obstructive pulmonary disease	5/1454 (<1)	4/1126 (<1)
Admission parameters, median (IQR, *n*)		
Blood glucose level (mmol/l)	6.0 (5.2–7.3, 944)	5.9 (5.1–7.2, 737)
Hemoglobin concentration (g/l)	135 (122–147, 1183)	136 (123–147, 914)
Systolic blood pressure (mmHg)	130 (120–145, 1045)	130 (120–145, 802)
Temperature	36.8 (36.4–37.2, 923)	36.8 (36.3–37.1, 724)
Imaging findings at admission, *n*/*N* (%)		
Intracerebral hemorrhage	427/1382 (31)	301/1057 (28)
Non-hemorrhagic lesion only	236/1382 (17)	190/1057 (18)
Sulcal subarachnoid hemorrhage	129/1397 (9)	100/1072 (9)
Subdural hemorrhage	41/1394 (3)	34/1069 (3)
Cerebral venous thrombus location, *n*/*N* (%)		
Superior sagittal sinus	702/1399 (50)	518/1072 (48)
Sigmoid sinus		
Sigmoid sinus, right	320/1197 (27)	236/899 (26)
Sigmoid sinus, left	401/1207 (33)	307/906 (34)

(Continues)

TABLE 1 (Continued)

Clinical characteristics	Mortality model ($n = 1454$)	6-month poor outcome model ($n = 1126$)
Transverse sinus		
Transverse sinus, right	536/1383 (39)	399/1059 (38)
Transverse sinus, left	605/1393 (43)	465/1067 (44)
Cortical vein(s)	331/1394 (24)	242/1067 (23)
Straight sinus	200/1396 (14)	144/1069 (13)
Deep cerebral venous system	147/1396 (11)	113/1069 (11)
Multiple sinuses involved (>1)	1001/1297 (77)	762/985 (77)
Treatment, *n/N* (%)		
Anticoagulation	1356/1446 (94)	1038/1120 (93)
Decompressive craniectomy	61/1395 (4)	40/1068 (4)
Hematoma evacuation	28/1322 (2)	21/1008 (2)
Endovascular treatment	71/1396 (5)	45/1069 (4)
Steroid treatment	90/1381 (7)	76/1061 (7)

Abbreviations: CNS, central nervous system; GCS, Glasgow Coma Scale; IQR, interquartile range.

[a]Percentage of women <50 years.

[b]Percentage of women.

[c]Oral contraceptive use, pregnancy, recent delivery (<12 weeks) or hormone replacement therapy.

[d]Myocardial infarction, heart failure, previous cardiac intervention or surgery, or pacemaker.

"absence of female-sex-specific risk factors" with male sex resulted in worse model performances.

Calculating individual risks with the SI_2NCAL_2C score

For ease of use in clinical practice, the combined SI_2NCAL_2C score was developed to calculate individual risk either for dependency or death at 6 months or for mortality at 30 days or at 1 year. The SI_2NCAL_2C score comprises predictors for all of the investigated outcomes (absence of female-sex-specific risk factors, ICH, infection in the CNS, neurological focal deficits, coma, age, lower level of hemoglobin at admission, higher level of blood glucose at admission and cancer). The formulas, coefficients and baseline risks are presented in Table 3. The application is freely available at www.cerebralvenousthrombosis.com, but is not intended for use in clinical practice prior to external validation.

DISCUSSION

The main results of this study are the development of two models for the prediction of dependency or death at 6 months and mortality at 30 days and 1 year after CVT. The combined SI_2NCAL_2C score shows promising performance in internal validation, in its ability to estimate individual risks for dependency and mortality for patients diagnosed with CVT. Using the proposed score and application, individual risks can easily be calculated bedside, already in the early days of admission. The proposed score comprises predictors that are widely available in routine clinical CVT care. Calculation of individual risks therefore normally requires no additional tests or examinations.

The study was designed to develop robust models to calculate individual risk of death and dependency for patients diagnosed with CVT that could easily be implemented in clinical practice. Candidate predictors were selected based on previous literature, biological plausibility and potential collinearity. Whilst the retained variables resemble previously suggested risk factors for dependency and mortality after CVT [1, 3, 4, 6], the variables predicting each outcome should be interpreted as markers rather than definite risk factors for poor outcome and mortality. Any causal relation between the variables and outcome after CVT cannot be determined from our study. Similarly, associations with the outcomes of interest cannot be ruled out for several variables that were not retained in the final models.

The predictors in the three most recently developed risk scores for estimating risks of dependency or death at 6 months (CVT risk score), dependency or death at 3 months (IN-REvASC) and mortality at 30 days (CVT-GS) are partially overlapping with predictors in SI_2NCAL_2C, including cancer and coma [7, 10, 11]. In comparison to previous models, novel predictors included in our models were absence of female-sex-specific risk factors which reportedly is a more specific risk factor for poor outcome than sex [5]. Lower hemoglobin and higher blood glucose levels at admission were indicative of poor outcome, which is in accordance with recently published data showing that anemia [6] and hyperglycemia [4] were predictive of both dependency and death. Whilst our analyses suggest linear relationships, it is possible that also severe hypoglycemia or polycythemia (as indicative of myeloproliferative neoplasm) could be predictive of poor outcome. Similar to the previous CVT risk score, our analyses indicated a nonlinear relationship between age and dependency or mortality at 6 months [7]. According to the AIC, the logistic regression model fit was improved by adding a square root transformation to the age variable, which therefore is expressed as the summarized

TABLE 2 Description of the final predictive models: (a) logistic regression model for prediction of dependency or death (mRS 3-6) at 6 months; (b) Cox proportional hazards model for prediction of mortality at 30 days and 1 year

(a)

Prognostic variable	Model coefficients	Odds ratios and 95% confidence intervals
Age[a]		
Age_1	−0.068	0.94 (0.88–1.00)
Age_2	0.001	1.001 (1.000–1.002)
Coma	1.440	4.22 (2.17–8.21)
Cancer	0.901	2.46 (1.46–4.16)
Absence of female-sex-specific risk factors	0.642	1.90 (1.12–3.21)
Admission glucose level (mmol/l)	0.130	1.14 (1.04–1.25)
Admission hemoglobin concentration (g/l)	−0.013	0.99 (0.977–0.997)
Neurological focal deficits	1.004	2.73 (1.68–4.44)
Intracerebral hemorrhage	0.604	1.83 (1.20–2.78)

(b)

Prognostic variable	Model coefficients	Hazard ratios and 95% confidence intervals
Age	0.019	1.02 (1.01–1.03)
Coma	0.827	2.29 (1.60–3.27)
Cancer	1.271	3.57 (2.74–4.64)
Absence of female-sex-specific risk factors	0.372	1.45 (1.24–1.70)
Admission glucose level (mmol/l)	0.050	1.05 (1.00–1.10)
Admission hemoglobin concentration (g/l)	−0.006	0.99 (0.990–0.998)
Neurological focal deficits	0.232	1.26 (1.07–1.49)
Intracerebral hemorrhage	0.217	1.24 (1.04–1.49)
Infection in the CNS	0.521	1.68 (1.10–2.57)

Abbreviations: CNS, central nervous system; mRS, modified Rankin Scale.

[a]According to the Akaike information criterion, square root transformation of the variable age improved model fit. The summarized risk increase by age is calculated from the two transformed age coefficients combined ($-0.068^*(age)+0.001^*(age)^2$).

risk of age_1 and age_2. Continuous variables (age, hemoglobin, glucose) were not dichotomized as prior studies reported trends which suggested concentration-related associations rather than a fixed clinically relevant cut-off value for poor outcome [4, 6]. Futher, dichotomization of continuous variables is not recommended in prognostic score development guidelines [12–15].

Initially, we hypothesized that predictors for mortality at 30 days would differ from predictors for mortality at 1 year as mortality in the acute phase is typically influenced by consequences and the severity of CVT, whilst the influence of underlying risk factors for CVT are likely to increase over time and be more determinative of long-term mortality [3]. Time periods were chosen to enable evaluation of early death (30 days) and relatively long-term death whilst balancing influences from non-CVT related sources (1 year). However, for all variables, no violation against the proportional hazards assumption was found, indicating that the influences on increased risk of death were relatively stable during the 1-year observation period after onset of CVT. Therefore, it was possible to utilize the model as a whole for prediction of mortality at 30 days and at 1 year and thereby increase the statistical power.

Whilst the previous scores' points were rounded from hazard and odds ratios [7–11], the proposed score maintains the exact coefficients which increases the accuracy in prediction of individual risks. Nevertheless, as the underlying equations are complicated, the SI_2NCAL_2C score consequently necessitates a specific online calculator or application for implementation in clinical practice. Direct comparisons with previously developed risk scores in our cohort were not performed as internal and external validations are not adequately comparable. Guidelines for development of prognostic risk scores generally recommend not introducing probability thresholds based on data from the development cohort because of risk of bias as the whole range of predicted probabilities is not fully utilized. To evade data-driven bias, thresholds should be based on clinical relevance [15]. For patients with CVT, clinically relevant cut-offs for probability of mortality and dependency may vary depending on the specific clinical setting and risk of the intended intervention. Future studies are warranted for external evaluation and comparison of available risk scores' performances for predicting outcome after CVT.

The study's strengths are (i) the SI_2NCAL_2C score was developed from a large patient cohort with a relatively high number of outcome events, and participants from 13 different countries, which increases the generalizability; (ii) the included parameters are clearly defined, available in routine hospital CVT care, and are therefore easy to collect, require no extra test or cost and are likely to possess high interobserver agreement values; (iii) the ability to calculate different outcomes from one combined calculator and (iv) the model performances in internal validation were promising.

Several limitations for this study are acknowledged. First and most importantly, the risk of overestimation of model performances is apparent as the models were developed and then validated in the same cohort. The rationale behind this strategy was to maximize the statistical power and accuracy in the development stage, in accordance with recommendations from international guidelines [12–15]. To compensate for potential overestimation, shrinkage of the model coefficients was applied, and the performance was evaluated in bootstrapped samples of the cohort. However, prior to pending external validation of the score, one should be cautious when generalizing the results and the score is not yet suitable for use in clinical practice. Secondly, the data originate from a registry which includes both retrospectively and prospectively recruited patients. However, inclusion of all patients substantially increased the number of events and thereby the statistical power of the analysis.

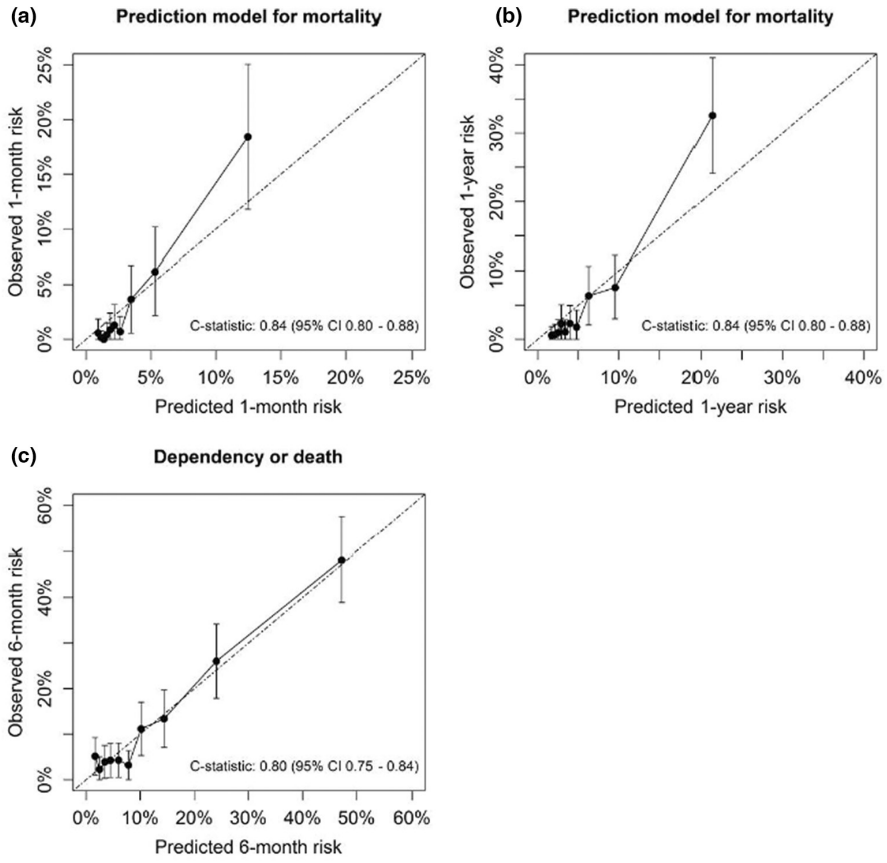

FIGURE 2 Model performances as measured by calibration plots and C-statistics. Calibration plots in 1000 bootstrap samples depicting the predicted versus observed risks according to the models predicting mortality at 30 days (a), mortality at 1 year (b) and dependency or death (modified Rankin scale 3–6) at 6 months (c). C-statistics describe the discriminative performance for each model. CI, confidence interval.

TABLE 3 SI_2NCAL_2C model to predict poor outcome or mortality after cerebral venous thrombosis

SI_2NCAL_2C prognostic variables	6-month dependency or death (mRS 3–6)	30-day mortality	1-year mortality
Absence of female-sex-specific risk factors	0.642	0.372	0.372
Intracerebral hemorrhage	0.604	0.217	0.217
Infection in the CNS	N/A	0.521	0.521
Neurological focal deficits	1.004	0.232	0.232
Coma	1.440	0.827	0.827
Age[a]	age_1 −0.068, age_2 0.001	0.019	0.019
Level of hemoglobin at admission (g/l)	−0.013	−0.006	−0.006
Level of blood glucose at admission (mmol/l)	0.130	0.050	0.050
Cancer	0.901	1.271	1.271

To calculate individual risks, the following formulas can be used:

1. 6-month dependency or death: individual risk = 1/(1 + exp[−(*A* − 1.742)]) where *A* = 0.642 (if absence of female-sex-specific risk factors) + 0.604 (if intracerebral hemorrhage) + 1.004 (if neurological focal deficits) + 1.440 (if coma) − 0.068*(age) + 0.001*$(age)^2$ − 0.013*(admission hemoglobin concentration in g/l) + 0.130*(admission glucose level in mmol/l) + 0.901 (if cancer)
2. Mortality at 30 days or at 1 year: individual risk = 1 − (1 − *B*) exp(*A* − baseline hazard) where *A* = 0.372 (if absence of female-sex-specific risk factors) + 0.217 (if intracerebral hemorrhage) + 0.521 (if infection in the CNS) + 0.232 (if neurological focal deficits) + 0.827 (if coma) + 0.019*(age) − 0.006*(admission hemoglobin concentration in g/l) + 0.050*(admission glucose in mmol/l) + 1.271 (if cancer)

$B_{30\,days}$ = 0.02362037, $B_{1\,year}$ = 0.04298228, baseline hazard = 0.898196

Note: Definition of prognostic variables. Female-sex-specific risk factor: oral contraceptive use, pregnancy, recent delivery (within 12 weeks) or hormone replacement therapy. Intracerebral hemorrhage: intracerebral hemorrhage including hemorrhagic transformation of a venous infarct, detected on the admission neuroimaging (CT or MRI). Infection in the CNS: any infection affecting the central nervous system including bacterial or viral meningitis, encephalitis or invasive infections in any of the dural sinuses and/or veins. Neurological focal deficits: any clinical focal neurological deficit present at admission. Coma: Glasgow Coma Scale score <9 points. Age: age at admission. Level of hemoglobin at admission: hemoglobin level at hospital admission (g/l). Level of blood glucose at admission: blood glucose level at hospital admission (mmol/l). Cancer: any malignant tumor at any location or hematological malignancy diagnosed during hospitalization or up to 10 years prior to diagnosis of CVT.

Abbreviations: CNS, central nervous system; CT, computed tomography; CVT, cerebral venous thrombosis; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; N/A, not applicable.

[a]According to the Akaike information criterion, square root transformation of the variable age improved model fit. The risk increase by age is calculated from the two age coefficients combined (−0.068*(age) + 0.001*$(age)^2$).

Moreover, the distribution of the investigated outcomes, sex and age was comparable in prospectively and retrospectively included patients. Thirdly, a substantial proportion of patients for the dependency or death model were excluded due to missing mRS scores at 6 months. However, for the remaining patients, multiple imputation was used to predict missing values. Thus, it was possible to include all patients with known primary outcome in the models. Finally, it was not possible to discriminate between different causes of death in our models since data were not available.

In conclusion, the combined SI_2NCAL_2C score shows promising performance in prediction of poor outcome at 6 months and mortality at 30 days and 1 year after CVT. An online calculator is freely available at www.cerebralvenousthrombosis.com. The SI_2NCAL_2C score can be used to predict individual risk of poor outcome and mortality based on parameters available in routine care and has the potential to guide future trials in identifying high-risk patients who could be eligible for novel treatments. However, an external validation of the score is warranted prior to implementation in clinical practice.

AUTHOR CONTRIBUTIONS

Study concept and design: EL, KK, MAW, MSK, TT, JMC, KJ. Major role in acquisition of data: all authors. Analysis or interpretation of data: EL, KK, MAW, JP, TT, JMC, KJ. Drafting of the manuscript: EL, KK, TT, JMC, KJ. Revision of manuscript for intellectual content, including medical writing for content: all authors.

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CONFLICT OF INTEREST STATEMENT

EL, KK, MAW, MSK, MRH, SH, DAS, MM, PC, EE, MR, ES, CGE, VA, PA, NS, SMS, SMZ, AS, MS, AA, AS, DGA, NY, MAB, MG, MA, JP, JMC and KJ report no disclosures relevant to the manuscript. TT has served/serves as an advisory board member for Bayer, Bristol Myers Squibb, Inventiva and Portola Pharma. RRL received speaker's honoraria from Boehringer Ingelheim, Pfizer, Ischema-View, Jansen, Biogen, Medtronic and Abott and advisory board honoraria from Jansen. AA has served as an advisory board member for Bristol Myers Squibb and Boehringer-Ingelheim.

DATA AVAILABILITY STATEMENT

All study data are available upon reasonable request from qualified investigators, within the boundaries of the European Union General Data Protection Regulation and applicable national laws.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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