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ORIGINAL ARTICLE

Coma in adult cerebral venous thrombosis: The BEAST study

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Abstract

Background and purpose: Coma is an independent predictor of poor clinical outcomes in cerebral venous thrombosis (CVT). We aimed to describe the association of age, sex, and radiological characteristics of adult coma patients with CVT.

Methods: We used data from the international, multicentre prospective observational BEAST (Biorepository to Establish the Aetiology of Sinovenous Thrombosis) study. Only positively associated variables with coma with <10% missing data in univariate analysis were considered for the multivariate logistic regression model.

Results: Of the 596 adult patients with CVT (75.7% women), 53 (8.9%) patients suffered coma. Despite being a female-predominant disease, the prevalence of coma was higher among men than women (13.1% vs. 7.5%, $p = 0.04$). Transverse sinus thrombosis was least likely to be associated with coma (23.9% vs. 73.3%, $p < 0.001$). The prevalence of superior sagittal sinus thrombosis was higher among men than women in the coma sample (73.6% vs. 37.5%, $p = 0.01$). Men were significantly older than women, with a median (interquartile range) age of 51 (38.5–60) versus 40 (33–47) years in the coma ($p = 0.04$) and 44.5 (34–58) versus 37 (29–48) years in the non-coma sample ($p < 0.001$), respectively. Furthermore, an age- and superior sagittal sinus-adjusted multivariate logistic regression model found male sex (odds ratio = 1.8, 95% confidence interval [CI] = 1.0–3.4, $p = 0.04$)

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to be an independent predictor of coma in CVT, with an area under the receiver operating characteristic curve of 0.61 (95% CI = 0.52–0.68, $p = 0.01$).

Conclusions: Although CVT is a female-predominant disease, men were older and nearly twice as likely to suffer from coma than women.

KEYWORDS
cerebral venous thrombosis, characteristics, coma, CVT, predictors, women

INTRODUCTION

Cerebral venous thrombosis (CVT) is a multifactorial, female-predominant disease with a reported incidence of approximately 0.5%–1% of all strokes [1, 2]. Approximately 60%–85% of patients with CVT make a complete recovery, but the severity, permanent disability, or mortality remains high at approximately 6%–18% [3, 4]. As CVT often presents with nebulous clinical symptoms, early diagnosis and prompt medical management are challenging [2–4]. Although a Glasgow Coma Scale (GCS) score of ≤12 at hospital admission [5] and coma (GCS ≤ 8) [6] have already been identified as independent predictors of poor clinical outcome, few studies have described the details of the clinical and radiological characteristics associated with CVT-related coma. Furthermore, coma in CVT has a 2.7 times greater association with death or dependency at 6-month follow-up than in patients without coma [2–4, 6].

CVT leads to impaired venous drainage, and cerebrospinal fluid reabsorption causes a rise in cerebral blood volume and diminished cerebral perfusion, which is ultimately responsible for cytotoxic oedema, herniation, and coma [2, 3, 5]. However, superior sagittal sinus (SSS) thrombosis causes rapid and profound neurological deficits, as it drains extensive areas of the cerebral cortex, including the motor area and fibrous septa at the inferior sinus angle, aggravating the severity of SSS thrombosis [2, 4–7].

We aimed to characterize the association of age, sex, and radiological findings of adult CVT patients with coma using data from a large prospective international collaboration.

METHODS

Biorepository to Establish the Aetiology of Sinovenous Thrombosis study

We used data from the Biorepository to Establish the Aetiology of Sinovenous Thrombosis (BEAST) study, an international prospective observational study of adult (aged ≥18 years) patients with CVT recruited between the years 2000 and 2018. The detailed protocol has been published elsewhere [8], but in brief, diagnosis of CVT was confirmed by angiography, either conventional, computed tomography, or magnetic resonance venography, or dedicated venography [8]. Patients were recruited from the UK, Finland, Sweden, Greece, Italy, Portugal, Belgium, France, the Netherlands, Mexico, and the USA.

Ethical clearance

The BEAST study obtained ethical clearance from the UK (Ref 04/Q0401/40) and all participating institutional review boards. Informed written consent was obtained for all patients, and data were encrypted.

Study variables

A GCS score of ≤8 at presentation was defined as coma [9], with patients dichotomized into coma (GCS ≤ 8) and non-coma (GCS = 9–15) populations. Sociodemographic variables, age at CVT onset, sex, and radiological characteristics of CVT (cerebral infarction, cerebral haemorrhage, and affected sinuses and veins) were compared between coma and non-coma groups. Concomitant cortical vein thrombosis means simultaneous thrombosis of ≥1 major venous sinus and cortical veins. The primary study endpoint was to determine the clinical and radiological characteristics of coma patients with CVT.

Statistical analysis

We used SPSS v28.0 software for statistical analysis. We used univariate analysis to ascertain the risk patterns in the BEAST dataset. Study variables with <10% missing data and having a significant ($p < 0.05$) positive association with coma in the univariate analysis were included in a multivariate logistic regression model to determine the independent predictors of coma. Additionally, the accuracy of the coma prediction model was confirmed by the area under the receiver operating characteristic (AUROC) curve and cross-validated by the positive predictive value (PPV) and negative predictive value (NPV).

Quality assessment

Data quality assessment was performed with Little's Missing Completely at Random (MCAR) test and compared the age and sex distribution of coma patients between missing and nonmissing datasets. Multicollinearity among independent variables was also measured with the variance inflation factor (VIF) value and the collinearity tolerance, where VIF > 10 or tolerance < 0.1 represents

the presence of significant multicollinearity that needed to be optimized. $p < 0.05$ was considered statistically significant.

RESULTS

The study analysed 596 patients with CVT (coma: $n = 53$, 8.9%, median [interquartile range (IQR)] age = 41 [33–51] years; non-coma: $n = 543$, 91.1%, 39 [30–49] years). Although women were more prevalent (75.7%) in the dataset, the frequency of men in the coma group was higher than in the noncoma group (35.8% vs. 23.2%, $p = 0.04$). The coma group had a higher occurrence of cerebral infarction ($p < 0.04$), cerebral haemorrhage ($p < 0.001$), and thrombosis of concomitant cortical veins ($p < 0.001$) and jugular veins ($p < 0.01$) compared to patients in the non-coma population. Conversely, coma patients had a lower frequency of thrombosis of the transverse sinus (23.9% vs. 73.3%, $p < 0.001$) compared to non-coma patients (Table 1).

Furthermore, men were significantly older than women in both coma (11 years, $p = 0.04$) and non-coma (7.5 years, $p < 0.001$) samples: 51 (IQR = 38.5–60) versus 40 (IQR = 33–47) and 44.5 (IQR = 34–58) vs. 37 (IQR = 29–48) years. Men with CVT coma were 6.5 years older than men in the CVT non-coma samples (Table 1). Additionally, coma prevalence was significantly higher among men than women (13.1% vs. 7.5%, $p = 0.04$; Table S1). In the coma group, SSS thrombosis was significantly higher among men than women (73.6% vs. 37.5%, $p = 0.01$; Table S2).

An age- and SSS-adjusted multivariate logistic regression (LR) model found that male sex (odds ratio = 1.8, 95% confidence interval [CI] = 1.0–3.4, $p = 0.04$) is an independent predictor of coma in CVT (Table 2). The AUROC curve was 0.61 (95% CI = 0.52–0.68, $p = 0.01$), with a sensitivity of 35.8% and specificity of 76.8% (Figure S1). Furthermore, the PPV and NPV of coma were 13.1% and 92.5%,

TABLE 2 Age- and superior sagittal sinus-adjusted multivariate logistic regression model for predictors of coma in cerebral venous thrombosis.

Variables	OR	95% CI	*p*
Gender (men)	1.87	1.01–3.49	0.04
Age (years)	1.01	0.98–1.02	0.62
Superior sagittal sinus (yes)	0.91	0.50–1.61	0.74

Note: Variable(s) entered: age, gender, superior sagittal sinus, infarction, haemorrhage, jugular veins, and concomitant cortical veins.

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 1 Baseline characteristics of study population ($N = 596$).

Variables	Sample, $N = 596$, *n/N* (%)	Coma, $n = 53$, *n/N* (%)	Non-coma, $n = 543$, *n/N* (%)	*p*
Age, years, median [IQR]	596/596 (100%)	41 [33–51]	39 [30–49]	0.20
Gender				
Men	145/596 (24.3%)	19/53 (35.8%)	126/543 (23.2%)	0.04
Women	451/596 (75.7%)	34/53 (64.2%)	417/543 (76.8%)	
Radiological characteristics				
Infarction	163/545 (29.9%)	10/20 (50.0%)	153/525 (29.1%)	0.04
Haemorrhage	149/556 (26.8%)	29/45 (64.4%)	120/511 (23.5%)	<0.001
Superior sagittal sinus	307/581 (52.8%)	26/51 (51.0%)	281/530 (53.0%)	0.78
Transverse sinus	393/567 (69.3%)	11/46 (23.9%)	382/521 (73.3%)	<0.001
Straight sinus	93/570 (16.3%)	8/47 (17.0%)	85/523 (16.3%)	0.89
Deep veins	43/536 (8.0%)	4/19 (21.1%)	39/517 (7.5%)	0.057
Cerebellar venous sinus	3/530 (0.6%)	0/18 (0.0%)	3/512 (0.6%)	1.0
Cavernous sinus	13/531 (2.4%)	1/19 (5.3%)	12/512 (2.3%)	0.38
Jugular veins	136/543 (25.1%)	11/24 (45.8%)	125/519 (24.1%)	0.01
Concomitant cortical veins	81/547 (14.8%)	9/24 (37.5%)	72/523 (13.8%)	0.001
Age differences between study groups and sexes				
Age, years, median [IQR]				
Men		51 [38.5–60]	44.5 [34–58]	0.53
Women		40 [33–47]	37 [29–48]	0.52
p[a]		0.04	<0.001	-

Note: Here, n = positive case, N = available sample; *p*-value indicates the significance between coma and non-coma groups, which is reached from the chi-squared and Fisher exact tests (when sample size ≤ 5); Mann–Whitney *U*-test was utilized for median [IQR] values.

Abbreviation: IQR, interquartile range.

[a] *p*-value indicates the significance of age differences between men and women within coma and non-coma samples.

respectively. The multivariate LR model was adjusted for SSS thrombosis to mitigate the outcome bias, which was significantly higher among men than women.

The multicollinearity test demonstrated no significant correlation among independent variables, and Little's MCAR test resulted in a p-value of 0.37, $\chi^2 = 0.78$, indicating data were randomly missing. Furthermore, we conducted a quality control subgroup analysis to compare missing and nonmissing datasets and found no significant differences in the age and sex distribution of coma patients with CVT.

DISCUSSION

Using a large prospective multinational dataset, we show that overall coma prevalence is ~9% in adult patients with CVT. Despite being a female-predominant disease, men are 11 years older and nearly twice as likely to suffer from a coma, with a higher prevalence with SSS thrombosis. Conversely, coma is least likely to be associated with transverse sinus thrombosis.

In a recent study evaluating 26 patients, Arauz et al. [10] observed that approximately 81% had a low GCS of <9 at admission, and approximately 85% had SSS thromboses; however, no sex differences were observed in the study. Furthermore, a previous study [6] of 114 CVT cases found that subjects with GCS ≤ 9 had a higher likelihood of experiencing cerebral haemorrhage (80.3%), infarction (61.8%), and thrombosis of the SSS (61.8%), a result that supports our findings. Previously described associations of transverse sinus [5], SSS [5, 6, 10], deep veins [2, 5], concomitant cortical vein thrombosis [3], and cerebral haemorrhage [5, 6] with lower GCS at admission further corroborates our findings.

As with our study, the International Study on Cerebral Vein and Dural Sinus Thrombosis [2] found that 17.1% patients had thrombosis of concomitant cortical veins along with major sinuses, a result supported by others [3, 9–12]. Although we do not evaluate the pathophysiological basis of CVT coma, it seems that age [13] and thrombosis of SSS [10, 11, 14] may lead to the higher occurrence of coma in men due to impaired venous drainage and cerebrospinal fluid reabsorption, causing cytotoxic oedema, herniation, and diminished cerebral perfusion.

This study is the first report that transverse sinus thrombosis is significantly less likely to cause coma, possibly because it primarily affects the posterior parts of the brain and has a more localized impact, leading to slow onset thrombosis and less widespread neurological damage in the presence of collateral venous drainage [10–12]. In contrast, the SSS drains a more extensive area of the cerebral hemispheres, including motor areas, causing rapid and profound neurological impairment leading to coma in SSS thrombosis [11, 14, 15].

Study limitations

Several limitations need to be considered. Despite our sizable study sample size compared to other studies, the dataset for coma still remains modest. This study only evaluates adults with CVT, so our results are not generalizable to children. The patients were predominantly of European descent, so our findings may not be globally applicable to those of other ancestries. Additionally, the BEAST study was designed to primarily analyse the genetic risk factors of CVT based on the blood samples only of consenting patients; therefore, a selection bias may exist, as we excluded severe cases presenting with coma or death. Finally, we do not have data on the details of the severity of the brain injuries (size, midline shift, or herniation) or treatment outcome, which prevents us from speculating about potential differences in mortality or morbidity in the two CVT groups of coma and non-coma samples.

CONCLUSIONS

Our study shows that the prevalence of coma in adult CVT patients is ~9%. Despite CVT being a predominantly female condition, men are significantly older and have a near double likelihood of suffering from coma compared to women. Furthermore, transverse sinus thrombosis is least likely to be associated with coma.

AUTHOR CONTRIBUTIONS

Redoy Ranjan: Conceptualization; methodology; formal analysis; writing – original draft; writing – review and editing; visualization; resources. **Gie Ken-Dror:** Formal analysis; validation; writing – review and editing; methodology; supervision. **Ida Martinelli:** Formal analysis; methodology; data curation; writing – review and editing; investigation. **Elvira Grandone:** Methodology; writing – review and editing; data curation; formal analysis; investigation. **Sini Hiltunen:** Investigation; methodology; writing – review and editing; formal analysis; data curation. **Erik Lindgren:** Methodology; writing – review and editing; formal analysis; data curation. **Maurizio Margaglione:** Methodology; writing – review and editing; formal analysis; data curation. **Veronique Le Cam Duchez:** Methodology; writing – review and editing; formal analysis; data curation. **Aude Triquenot Bagan:** Data curation; writing – review and editing; methodology; formal analysis. **Marialuisa Zedde:** Methodology; writing – review and editing; formal analysis; data curation; investigation. **Nicola Giannini:** Data curation; methodology; writing – review and editing; formal analysis. **Ynte M. Ruigrok:** Methodology; investigation; writing – review and editing; formal analysis; data curation. **Bradford B. Worrall:** Methodology; investigation; writing – review and editing; formal analysis; data curation. **Jennifer J. Majersik:** Methodology; writing – review and editing; formal analysis; data curation; investigation. **Jukka Putaala:** Methodology; investigation; writing – review and editing; formal analysis; data curation. **Elena Haapaniemi:** Data curation; formal analysis; writing – review and editing; methodology. **Susanna M. Zuurbier:** Methodology; investigation; writing – review and editing; formal analysis; data curation; validation. **Matthijs C. Brouwer:** Methodology; writing – review and editing; formal analysis; data curation. **Serena M. Passamonti:** Methodology; writing – review and editing; data curation; formal analysis. **Maria**

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Ethical approval for this study was obtained from local/institutional ethics/research boards at each centre.

INFORMED CONSENT

Written informed consent was obtained from all subjects prior to recruitment.

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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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