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Title: Decompressive surgery in cerebral venous sinus thrombosis due to vaccine-induced immune thrombotic thrombocytopenia

Short title: Decompressive surgery in CVST-VITT

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](https://doi.org/10.1111/ene.15735). Please cite this article as doi: [10.1111/ene.15735](https://doi.org/10.1111/ene.15735)

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Keywords: cerebral venous thrombosis, surgery, brain death, coma, COVID-19 vaccinations

Word count: 2896

Figures: 3

Tables: 4

Supplemental Tables: 4

References: 23

ABBREVIATIONS

CVST = cerebral venous sinus thrombosis

VITT = vaccine-induced immune thrombotic thrombocytopenia

PF4 = platelet factor 4

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

ABSTRACT

Background

Cerebral venous sinus thrombosis due to vaccine-induced immune thrombotic thrombocytopenia (CVST-VITT) is an adverse drug reaction occurring after SARS-CoV-2 vaccination. CVST-VITT patients often present with large intracerebral hemorrhages and a high proportion undergoes decompressive surgery. We describe clinical characteristics, therapeutic management and outcomes of CVST-VITT patients who underwent decompressive surgery, and explore predictors of in-hospital mortality in these patients.

Methods

We used data from an ongoing international registry of patients who developed CVST within 28 days of SARS-CoV-2 vaccination, reported between 29 March 2021 and 10 May 2022. We included definite, probable and possible VITT cases, as defined by Pavord et al.

Results

Decompressive surgery was performed in 34/128 (27%) patients with CVST-VITT. In-hospital mortality was 22/34 (65%) in the surgical and 27/94 (29%) in the non-surgical group ($p < 0.001$). In all surgical cases, the cause of death was brain herniation. The highest mortality rates were found among patients with preoperative coma (17/18, 94% vs 4/14, 29% in the non-comatose; $p < 0.001$), and bilaterally absent pupillary reflexes (7/7, 100%, vs 6/9, 67% with unilaterally reactive pupil, and 4/11, 36%, with bilateral reactive pupils; $p = 0.023$). Postoperative imaging revealed worsening of index hemorrhagic lesion in 19 (70%) patients and new hemorrhagic lesions in 16 (59%)

patients. At median follow-up of 6 months, 8/10 of surgical CVST-VITT who survived admission were functionally independent.

Conclusions

Almost two thirds of surgical CVST-VITT patients died during hospital admission. Preoperative coma and bilateral absence of pupillary responses were associated with higher mortality rates. Survivors often achieved functional independence.

Word count: 250

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is the most common and most severe presentation of vaccine-induced immune thrombotic thrombocytopenia (VITT), a rare adverse drug reaction reported after SARS-CoV-2 vaccinations.¹⁻⁵ With high rates of coma, frequent intracerebral hemorrhages and often severe thrombocytopenia, CVST-VITT has a clinical picture distinct from CVST unrelated to SARS-CoV-2 vaccination.⁵⁻⁷ Despite increased disease awareness and introduction of new treatment guidelines, approximately half of CVST-VITT patients die during the initial hospital admission, mainly due to brain herniation.^{5,7,8}

Decompressive surgery is considered a life-saving intervention for patients with impending herniation as a result of CVST unrelated to vaccination, and is recommended by both the European and United States guidelines.⁹⁻¹² Although up to one third of CVST-VITT patients undergo decompressive surgery, there is limited data about the outcomes of this treatment in this group of patients.^{5,7,13}

We describe clinical, laboratory and imaging characteristics, therapeutic management and outcomes of CVST-VITT patients who underwent decompressive surgery, and explore predictors of mortality.

METHODS

Patient selection and data collection

Details of the COVID-19 vaccination study initiated by the International CVT Consortium Registry have been reported previously.⁷ Briefly, this ongoing study collects data on patients with radiologically confirmed CVST with symptom onset within 28 days of SARS-CoV-2 vaccination. Participating investigators were requested to report consecutive cases from their hospitals. CVST had to be confirmed with computed tomography venography (CTV), magnetic resonance imaging (MRI), magnetic resonance venography, catheter angiography, or autopsy.^{11,12}

The ethical review committee of Amsterdam UMC issued a waiver of formal approval for this study. Each center was responsible for obtaining local permission to carry out the study and to acquire informed consent for the use of pseudonymized care data if required by national law and hospital regulations.

A standardized case report form was used to collect detailed information on demographics, CVST risk factors, vaccination details, clinical manifestations, laboratory and imaging characteristics, surgery details, concomitant treatments, and outcomes of the post-SARS-CoV-2 vaccination CVST patients. Data were collected from a total of 150 hospitals from 26 countries and reported between 29 March 2021 and 10 May 2022.

Definitions

A case was defined as VITT when it fulfilled the criteria for a possible, probable or definite VITT according Pavord et al definition.⁵ Given the pragmatic design of this study, we accepted all positive tests for detection of anti-PF4 antibodies, as reported by the investigators, regardless of the type of test.

Focal neurological deficits were defined as any persistent clinical focal neurologic deficit described at admission, including paresis of limbs and or face, sensory loss, visual field loss, aphasia or dysarthria and ataxia. Coma was defined as Glasgow Coma Scale (GCS) score <9. When providing the last available GCS before surgery last score prior to sedation was used. Thrombocytopenia was defined as a platelet count of $<150 \times 10^3/\mu\text{L}$. Severe thrombocytopenia was defined as a platelet count of $<50 \times 10^3/\mu\text{L}$.

Assessment of the imaging was done as shown by CT or MR, according to the definitions provided to the local investigators. Hemorrhagic lesion was defined as hemorrhagic infarction and/or intracerebral hematoma. Worsening of the hemorrhagic lesion was defined as enlargement of the hemorrhagic component of the index hemorrhagic lesion. Measurement of the midline shift was defined as a maximal shift of the falx cerebri or of the septum pellucidum measured at the level of the pineal gland or the lateral ventricles. Evidence of descending transtentorial herniation included any of: medial displacement of the uncus and para-hippocampal gyrus of the temporal lobe, medial displacement of the temporal horn of the lateral ventricle, ipsilateral widening of the perimesencephalic cistern, effacement of all basal cisterns, ipsilateral widening of cerebellopontine angle, asymmetrical inferior midbrain displacement.¹⁴ Evidence of ascending transtentorial herniation by a posterior fossa lesion causing superior displacement of the superior parts of the cerebellum included any of: flattening or obliteration of the quadrigeminal or the superior cerebellar, bilateral compression of the posterior aspect of the midbrain and hydrocephalus.¹⁵ Thrombus load was scored by adding thrombosed sinuses and/or veins as described in the literature.¹⁶

Treatment according to recommendations was defined based on literature and included immunotherapy (intravenous immunoglobulin, intravenous/oral steroids or plasmapheresis), non-heparin anticoagulants and avoidance of platelet transfusions, unless required for surgery.^{17,18}

A threshold date of 28 March 2021 was used for analysis on temporal trends in outcomes, as on this date the first scientific paper with treatment recommendations on VITT was published.¹

Decompressive surgery was defined as hemicraniectomy, posterior fossa decompression, and/or hematoma evacuation.

Postoperative imaging was defined as postoperative CT or MR performed within 72 hours of surgery.

Postoperative complications were defined as surgical, medical or neurological complications occurring within 30 days after the surgery, which were life-threatening or could result in death, persistent or significant disability, or prolongation of hospitalization.

Functional outcome was defined using modified Rankin Scale (mRS) score: complete recovery (mRS score 0-1), independence (mRS score 0-2), dependence (mRS score 3-5), severe dependence (mRS score 4-5) and death (mRS score 6).¹⁹

Comparison groups

We included two comparison groups of non-surgical CVST-VITT patients with some similar features to the surgical CVST-VITT patients. The first comparison group was composed of non-surgical CVST-VITT patients presenting with coma and intracranial bleeding on baseline imaging. Neuroimaging was not collected as part of the

pragmatic CVST-VITT registry and thus there is no imaging information regarding presence or absence of malignant mass effect in this group, nor could we exclude concomitant causes for coma in this group. The second comparison group included surgical patients from the CVST cases classified as “unlikely VITT” per Pavord criteria from the CVST-VITT registry.

We describe the mortality in the comparison groups, but did not perform any formal statistical comparison with surgical CVST-VITT patients in coma with intracerebral hemorrhage, because of low numbers, imbalance of baseline variables and high likelihood of confounding by indication.

Analyses were performed with IBM SPSS Statistics for Windows, version 28.0.1.0 (IBM Corp., Armonk, N.Y., USA). P-value of less than 0.05 was considered significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

RESULTS

We included 128 CVST-VITT cases from 84 centers in 20 countries (Table S1, Supplemental material): 112 (88%) after ChAdOx1 nCoV-19 (Vaxzevria, previously AstraZeneca/Oxford), 10 (8%) after Ad26.COV2.S (Janssen/Johnson&Johnson), 3 (2%) after Sinovac and 3 (2%) after BBIBP-CorV (Sinopharm) (Figure 1). Patients were diagnosed with CVST between 3 March 2021 and 18 March 2022. VITT was classified as definite in 74 (58%), probable in 30 (23%), and possible in 24 (19%) cases. Decompressive surgery was performed in 34/128 (27%) patients with CVST-VITT.

Surgical CVST-VITT patients had a median age of 45 years (interquartile range [IQR] 30-54), and 26 (76%) were women. Median time between vaccination and reported symptom onset was 8 days (IQR 7-10). Eight (24%) cases presented comatose, and 19 (56%) had severe thrombocytopenia at admission. All these five characteristics were similar between the surgical and non-surgical CVST-VITT patients (Table S2, Supplemental material).

Patients undergoing surgery differed from non-surgical patients in several aspects. Compared to non-surgical patients, surgical patients more often had focal neurological deficits at presentation (25/34, 74% vs 47/94, 50% $p=0.041$), higher admission D-dimer values [median (IQR) 33 (15-35) vs 19 (8-21) mg FEU/L, $p=0.002$], and lower admission fibrinogen values [1.3 (1.0-2.4) vs 2.3 (1.4-2.9) g/L; $p=0.007$]. Hemorrhagic lesions on baseline imaging were more common in surgical patients than in non-surgical ones (32/34, 94% vs 53/94, 56%; $p<0.001$).

At their last preoperative assessment, 18 (56%) of surgical CVST-VITT patients were comatose and 7 (26%) had bilaterally fixed dilated pupils (Table 1). In 19/34 (56%)

cases, severe thrombocytopenia persisted preoperatively. All surgical patients had a hemorrhagic lesion before surgery. Last imaging before the surgery revealed midline shift among 25/27 (93%) patients with hemispheric lesions and signs of transtentorial herniation in 11 (38%) of all surgical patients.

Data on surgery details were available in 32/34 (94%) patients (Table 2). Among those operated, 23 patients (72%) underwent decompressive craniectomy, 2 (6%) hematoma evacuation, and 7 (22%), both. Twelve patients (38%) received additional duroplasty. Twenty-seven (84%) patients underwent anterior and/or middle cranial fossa surgery, and in 4/27 (15%) cases the surgery was bilateral. Five (16%) patients underwent posterior fossa surgery.

Nine surgical patients (27%) underwent concomitant endovascular treatment. Of 31 (94%) who received anticoagulation, 16 (52%) received non-heparin anticoagulation only. Twenty-nine patients (85%) were treated with immunotherapy, mostly intravenous immunoglobulin (27/29, 93%). Immunotherapy was given preoperatively in 10 (34%) patients, postoperatively in 11 (38%), both in 6 (21%), and 2 (7%) at an unknown moment. Sixteen patients (47%) received platelet transfusion before the surgery.

Information about postoperative imaging and complications was available for 32/34 (94%) patients (Table 3). In 27 (84%) patients, imaging was repeated postoperatively (Figure 2). In 16 (70%) patients with hemispheric lesions there was persistent midline shift, and among 6 (24%) patients the repeated imaging revealed persisting herniation. Nineteen (70%) patients suffered worsening of the hemorrhagic lesion and 16 (59%) developed a new hemorrhagic lesion. Thirteen (48%) patients suffered both worsening of the index hemorrhagic lesion and development of a new one.

Almost two thirds of surgical patients died (22/34, 65%), while the in-hospital mortality rate for non-surgical patients was 29% (27/94) ($p<0.001$). In all surgical patients, the reported cause of death was brain herniation.

At discharge, 7/12 (58%) surgical patients who survived the initial hospital admission, were severely dependent, and 2 (17%) were functionally independent. At follow-up, after a median of 6 months after discharge (IQR 3-10), mRS evaluations were available for 11/12 (92%) of surgical CVST-VITT patients who were alive at discharge. One patient had died after 4 months from the diagnosis due to brain herniation after a major intracerebral bleeding. Otherwise, none of the discharged surgical patients were severely dependent, and 8/10 (80%) were functionally independent (Figure 3).

Coma and pupillary response at the last preoperative assessment were associated with in-hospital death in the surgical group. The mortality rates were significantly higher in comatose than in non-comatose patients (17/18, 94% vs 4/14, 29% in the non-comatose; $p<0.001$), and in patients who presented with bilaterally fixed pupils (7/7, 100%), compared to those with a unilaterally reactive pupil (6/9, 67%) or bilaterally reactive pupils (4/11, 36%; $p=0.023$). Fourteen (74%) patients with postoperative worsening of the hemorrhagic lesion, died. This was significantly higher than the mortality rate among surgical patients without worsening of the hemorrhagic lesion (2/8, 25%; $p=0.033$) (Table 4).

In a sensitivity analysis, we found that the proportion of patients who received decompressive surgery was significantly higher among patients diagnosed before 28 March 2021 - 19/39 (49%), compared to 15/89 (17%) diagnosed after this date ($p<0.001$). Nevertheless, the percentages of patients in coma, proportions of preoperative pupillary responses and platelet counts prior to surgery were not

significantly different between the two time periods. More patients were treated with intravenous immunoglobulins and non-heparin anticoagulation after the release of management guidelines for VITT compared to before ($p=0.011$ and $p=0.037$, respectively). Nevertheless, mortality among surgical patients did not decrease (11/19, 58% before vs 11/15, 73% after, $p=0.476$) (Table S3, Supplemental material).

In our comparison group of non-surgical CVST-VITT patients, 15/94 (16%) presented with coma and with an intracerebral hemorrhagic lesion on baseline imaging. The mortality rate was 13/15 (87%, 95% CI 62-96%), which was numerally higher - but not with a statistically significant difference - compared to the surgical group with coma and intracerebral bleeding (6/8; 75%, 95% CI 41-93%)(Supplemental Table S4).

Among the CVST cases deemed unlikely to be VITT, only one patient 1/50 (2%) underwent decompressive surgery. This patient in her 30s presenting with headache without focal deficits and an intracerebral hemorrhage on baseline imaging was admitted for 81 days before she was discharged to a rehabilitation facility with mRS 5; and after 7 months she improved to mRS 3.

DISCUSSION

In our cohort, almost one-third of CVST-VITT patients underwent decompressive surgery. This is slightly higher than the rate of 19% described in the British CVST-VITT series, although only decompressive hemicraniectomy patients were counted in that cohort.¹³ The in-hospital mortality of surgical CVST-VITT patients - 22/34 (65%) - is also slightly higher than the mortality reported in the afore-mentioned study (54%).¹³ Still, these numbers are considerably higher compared to decompressive surgery and mortality rates among the CVST surgical patients described in pre-COVID-19 CVST cohorts (1-7% and 16-20%, respectively).^{9,10,20-22}

A possible explanation for the observed higher mortality among surgical CVST-VITT compared to cohorts of CVST patients treated with decompressive surgery from the pre-pandemic period, could be the more severe clinical and radiological presentation before the surgery in the former group. Nevertheless, in our study, the proportion of surgical CVST-VITT patients who were comatose preoperatively was numerically lower compared to surgical patients from the pre-COVID CVST studies (56% in CVST-VITT vs 72% in CVST unrelated to vaccination) and the percentage of CVST-VITT patients with at least one intracerebral hemorrhagic lesion before surgery (100%) was similar to the pre-COVID data (90%).¹⁰ On the other hand, CVST-VITT patients slightly more often had bilaterally fixed pupils before the surgery (26% vs 15% in CVST unrelated to vaccination) and were more likely to have a posterior fossa surgery (16% vs 4% in CVST unrelated to vaccination).¹⁰ While we do not have information on whether indication for surgery was more liberal, time interval between diagnosis and surgery and proportions of types of surgical approaches (craniectomy or hematoma evacuation) were not different from the historical cohort.¹⁰

When comparing the non-surgical and surgical CVST-VITT patients - the two groups did not differ with regard to the proportion of patients presenting in coma, the median platelet count at presentation, or the thrombus load, but the in-hospital mortality was significantly higher in the latter group. This difference could be related to poor status at baseline – reflected by high D-dimer, low fibrinogen and high intracerebral hemorrhage rate at admission – but can also be a consequence of clinical deterioration before the surgery and/or postoperative complications.

We found a high rate of postoperative worsening of index hemorrhagic lesions seen in more than two thirds of the surgical patients, and development of new hemorrhagic lesions observed in approximately half of the patients. Although the literature on hemorrhagic complications of surgical CVST patients is scarce, in a small case series of pre-COVID surgical CVST patients, only 4/10 (40%) had new hemorrhagic lesions at postoperative imaging, and this was also associated with poor outcome.²²

Within the surgical CVST-VITT patient group, those in coma and with bilaterally fixed pupils had worse vital outcomes postoperatively. Severe thrombocytopenia before surgery was not significantly associated with mortality, but this result may have been influenced by preoperative platelet transfusion in half of surgical CVST-VITT patients.

At discharge, 94% of surgical CVST-VITT patients were dependent or dead. This is in line with the finding from a British series, where all patients who underwent decompressive surgery were dependent or dead.¹³ In our cohort, at follow-up, 80% of surgical CVST-VITT patients who were alive at discharge were functionally independent. This indicates that the prognosis is favorable in patients who survive until discharge. This proportion is in line with our previous report on outcomes of CVST-VITT patients in the acute phase of their presentation. At five-month follow-up, almost

90% had regained functional independence.^{10,22,23} Nevertheless, due to the limited size of this substudy cohort, these numbers should be interpreted with caution.

In addition to modest sample size, retrospective retrieval of information for some variables and lack of uniformity of the criteria to decide to perform surgery, another limitation of this study is that imaging and clinical outcomes were not centrally adjudicated. However, the cohort included patients from multiple centers from several countries across a wide geographical area, which should result in a high external validity of the results. Also, all included patients fulfilled criteria for VITT, thus reinforcing the internal validity of the findings.

Given that decompressive surgery is standard-of-care practice for patients with CVST without VITT who have malignant mass effect, we would expect that this practice also translated to management of CVST-VITT. Thus, it is unsurprising that for the analysis of surgical CVST-VITT patients we lack an appropriate non-surgical CVST-VITT comparison group with a comparable clinical severity. Mortality in the non-surgical CVST-VITT comatose patients with intracerebral bleeding was numerically higher than in the surgical cases, with wide and overlapping confidence intervals. The interpretation of the comparison of surgical vs. non-surgical patients is limited, because of low numbers, bias by indication (e.g. patients with imminent herniation being operated on, surgery being avoided on moribund patients and those in a very bad systemic condition), imbalance on baseline variables between the two groups and residual confounding. We also did not have a sufficiently large surgical group with unlikely VITT to compare to, as in our registry only one CVST patient with unlikely VITT underwent decompressive surgery. Lastly, several included cases were diagnosed before 28 March 2021, when there was less awareness and experience in

management of CVST-VITT. However, in the sensitivity analysis, we did not detect a decrease in in-hospital mortality among patients diagnosed after 28 March 2021.

In conclusion, CVST-VITT patients who underwent decompressive surgery had a much higher mortality than historical non-VITT CVST surgical patients. Surgical CVST-VITT patients suffered more postoperative intracerebral bleeding complications. Preoperative coma, bilateral absence of the pupillary response and postoperative worsening of the hemorrhagic lesions were major predictors of in-hospital mortality. Nevertheless, 35% of CVST-VITT patients survived after decompressive surgery and 80% of the survivors were functionally independent at follow-up. The information from our and previous studies¹³ suggest that decompressive surgery should not be contraindicated in CVST-VITT patients with impending herniation.

Data Availability Statement

The data that support the findings of this study are available from j.coutinho@amsterdamumc.nl upon reasonable request.

Acknowledgements

The authors would like to thank all patients and their families who agreed for use of their data for research purposes.

Funding

This research was funded by The Netherlands Organization for Health Research and Development (ZonMw, grant number 10430072110005) and the Dr. C.J. Vaillant Foundation. The funding organizations had no role in gathering, analyzing, or interpreting the data.

Conflict of interest

KK, FJB, DM, JPz, JZ, AA, MBP, SC, AD, VD, TG, FG, ESK, ZM, JFP, SS, AM, MSK, KJ, BZ, SA have nothing to disclose.

DAS reports travel support from Boehringer Ingelheim, DSMB participation for the SECRET trial, advisory board participation for AstraZeneca and membership in the ESO Executive Committee.

CC received speaker honoraria from Boehringer Ingelheim, personal fees for advisory board participation from AstraZeneca and Biogen, and personal fees from Biogen and Bristol Myers Squibb.

TSF received study medication from Bayer Canada and personal fees from HLS Therapeutics.

MS received speakers' honoraria/consulting fees from Bayer

MWn reports research grants from the South-Eastern Norway Regional Health Authority and ownership of stock Biontech/Pfizer.

AC received speaker grants from Alexion Pharma, Italfarmaco and Daiichi-Sankyo

MWk reports personal fees from Bayer, Boehringer Ingelheim, and Portola/Alexion

AG received personal fees from Bayer Vital, Bristol Myers Squibb, and Daiichi Sankyo

TK received personal fees from Boehringer Ingelheim

RL reports fees paid to his institution by Boehringer Ingelheim, Genentech, Ischemaview, Medtronic and Medpass

EDM received speaker honoraria from Aguetant

JPa received personal fees from Boehringer Ingelheim, Bayer, Herantis Pharma, and Abbott and stock ownership in Vital Signum

MP received personal fees for advisory board participation from Alexion

NR received research grants from Fulbright, Harvard University and Philippe Foundation.

EL received grants from the Swedish state, Swedish Neurologic Society, Elsa and Gustav Lindh's Foundation, P-O Ahl's Foundation and Rune and Ulla Amlöv's Foundation.

AS reports a grant from Swiss Heart Foundation.

MRH received grants from the Swiss Heart Foundation and Bangerter Foundation, travel support from Bayer, personal fees for DSMB/advisory board participation from Amgen, and is a member of the ESO Board of Directors

SP received research support from BMS/Pfizer, Boehringer-Ingelheim, Daiichi Sankyo, European Union, German Federal Joint Committee Innovation Fund, and German Federal Ministry of Education and Research, Helena Laboratories and Werfen and speakers' honoraria/consulting fees from Alexion, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS/Pfizer, Daiichi Sankyo, Portola, and Werfen

MJHAK received an unrestricted Sobi grant payments to her institution. Sobi, Roche, Bristol-Myers Squibb, speakers fee.

AAZ serves as an advisory board member for Bayer and Bristol Myers Squibb and consulting fees for Boehringer Ingelheim

ABC received consulting fees from Boehringer Ingelheim

SM reports grants from Bayer, Pfizer, Boehringer Ingelheim and Daiichi Sankyo paid to her institution, and personal fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, Abbvie, Portola/Alexion, and Daiichi Sankyo paid to her institution.

TT serves as an advisory board member for Bayer, Bristol Myers Squibb, Inventiva, and Portola Pharma.

MA received personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Covidien, Daiichi Sankyo, Medtronic, Novartis, Sanofi, Pfizer, and Amgen and grants from the Swiss National Science Foundation and Swiss Heart Foundation.

JMC received grants paid to his institution from Boehringer Ingelheim and Bayer for DSMB participation by Bayer.

JMF reports fees and DSMB or Advisory Board participation for Boehringer Ingelheim and consulting fees from Bayer.

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Tables

Table 1. Preoperative status in surgical CVST-VITT patients

CVST = cerebral venous sinus thrombosis; FEU = fibrinogen equivalent units; IQR = interquartile range; VITT = vaccine-induced immune thrombotic thrombocytopenia; †last assessment prior to sedation; ‡among patients with hemispheric lesions

Table 2. Surgery details and concomitant treatments in surgical CVST-VITT patients

CVST = cerebral venous sinus thrombosis; FEU = fibrinogen equivalent units; IQR = interquartile range; VITT = vaccine-induced immune thrombotic thrombocytopenia; †intravenous immunoglobulins, plasmapheresis or intravenous/oral steroids.

Table 3. Postoperative imaging, complications and outcomes of the surgical CVST-VITT patients

CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia; †among patients with hemispheric lesions; ‡pneumonia (n=2), ventriculitis (n=1), unknown (n=1); §portal and hepatic vein thrombosis (n=1), soleal deep vein thrombosis (n=1), unknown (n=1); ¶In all cases due to brain herniation.

Table 4. Prognostic factors associated with in-hospital mortality in surgical CVST-VITT patients

CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia; [†]unfractionated heparin or low molecular weight heparin

Figures

Figure 1. Patient selection

CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia

Figure 2. Pre- and postoperative imaging findings in a patient with CVST-VITT

CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia

Figure 3. Modified Rankin Scale Score of surgical CVST-VITT patients at discharge and follow-up

CVST = cerebral venous sinus thrombosis; mRS = modified Rankin Scale; VITT = vaccine-induced immune thrombotic thrombocytopenia; [†]Follow-up after a median of 6 months after discharge (interquartile range: 3-10). [#]Missing values for 1/34 (3%) patients.

Table 1. Preoperative status in surgical CVST-VITT patients

	Surgical CVST- VITT (N=34)	Missing n (%)
Last preoperative clinical status		
Last preoperative Glasgow Coma Scale score [†]	32 (94)	2 (6)
<9, n (%)	18 (56)	-
9-14, n (%)	13 (41)	-
15, n (%)	1 (3)	-
Last preoperative pupillary response		7 (21)
Bilaterally fixed pupils, n (%)	7 (26)	-
Unilaterally fixed pupil, n (%)	9 (33)	-
Reactive pupils, n (%)	11 (41)	-
Last preoperative laboratory values		-
Platelet count ($\times 10^3/\mu\text{L}$), median (IQR)	52 (26-71)	-
Platelet count $<50 \times 10^3/\mu\text{L}$, n (%)	19 (56)	
D-dimer (mg/L FEU), median (IQR)	20 (13-35)	2 (6)
Fibrinogen (g/L), median (IQR)	1.6 (1.1-2.4)	4 (12)
Last preoperative neuroimaging		
Hemorrhagic lesion, n (%)	34 (100)	-
Diameter of largest hemorrhagic lesion (cm) - median (IQR)	6 (5-7)	4 (12)
Location of parenchymal lesions		2 (6)
Hemispheric right, n (%)	12 (35)	-
Hemispheric left, n (%)	12 (35)	-
Hemispheric bilateral, n (%)	3 (9)	-
Posterior fossa, n (%)	5 (15)	-

Size of hemispheric cerebral edema		5 (15)
Less than half of the hemisphere, n (%)	13 (45)	-
More than half of the hemisphere, n (%)	16 (55)	-
Midline shift [‡] , n (%)	25/27 (93)	1 (3)
Transtentorial herniation, n (%)	11 (38)	5 (15)
Descending, n (%)	8/11 (73)	-
Ascending, n (%)	3/11 (27)	-

CVST = cerebral venous sinus thrombosis; FEU = fibrinogen equivalent units; IQR = interquartile range; VITT = vaccine-induced immune thrombotic thrombocytopenia;

[‡]last assessment prior to sedation; [‡]among patients with hemispheric lesions

Table 2. Surgery details and concomitant treatments in surgical CVST-VITT patients

	Surgical CVST- VITT (N=34)	Missing n (%)
Timeline of surgery		-
Hours between symptom onset and surgery, median (IQR)	72 (35-132)	5 (15)
Hours between presentation and surgery, median (IQR)	21 (10-44)	2 (6)
Type of surgery		2 (6)
Decompressive craniectomy only, n (%)	23 (72)	-

Hematoma evacuation only, n (%)	2 (6)	-
Both craniectomy and hematoma evacuation, n (%)	7 (22)	-
Any of the above and duroplasty, n (%)	12 (38)	-
Location of surgery		2 (6)
Anterior and/or middle cranial fossa, n (%)	27 (84)	-
Right hemisphere only, n (%)	12/27 (44)	-
Left hemisphere only, n (%)	11/27 (41)	-
Bilateral, n (%)	4/27 (15)	-
Posterior fossa, n (%)	5 (16)	-
Maximum diameter of craniectomy (cm), median (IQR)	14 (9-16)	9 (26)
Concomitant treatments		
Endovascular treatment, n (%)	9 (27)	-
Any anticoagulation, n (%)	31 (94)	1 (3)
Heparins at any time, n (%)	15/31 (48)	-
Non-heparins only, n (%)	16/31 (52)	-
Platelet transfusions, n (%)	16 (47)	-
Immunotherapy†, n (%)	29 (85)	-
Preoperatively, n (%)	10/29 (34)	-
Postoperatively, n (%)	11/29 (38)	-
Both, n (%)	6/29 (21)	-
Unknown moment, n (%)	2/29 (7)	-

Intravenous immunoglobulins, n (%)	27 (93)	-
Preoperatively, n (%)	9/27 (33)	-
Postoperatively, n (%)	12/27 (44)	-
Both, n (%)	5/27 (19)	-
Unknown moment, n (%)	1/27 (4)	-
Mannitol or other types of osmotherapy, n (%)	20 (63)	2 (6)
Preoperatively, n (%)	5/20 (25)	-
Postoperatively, n (%)	6/20 (30)	-
Both, n (%)	9/20 (45)	-
Hyperventilation, n (%)	14 (44)	2 (6)
Preoperatively, n (%)	5/14 (36)	-
Postoperatively, n (%)	2/14 (14)	-
Both, n (%)	7/14 (50)	-

CVST = cerebral venous sinus thrombosis; FEU = fibrinogen equivalent units; IQR = interquartile range; VITT = vaccine-induced immune thrombotic thrombocytopenia; †intravenous immunoglobulins, plasmapheresis or intravenous/oral steroids.

Table 3. Postoperative imaging, complications and outcomes of the surgical CVST-VITT patients

	Surgical CVST-VITT (N=34) n (%)	Missing values n (%)
Imaging		
Imaging within 72 hours of surgery	27 (84)	2 (6)

Persistent midline shift[†]	16 (70)	8 (24)
Worsening of the index hemorrhagic lesion	19 (70)	7 (21)
New hemorrhagic lesion	16 (59)	7 (21)
Persisting herniation	6 (24)	9 (26)
Descending	5/6 (83)	-
Ascending	1/6 (17)	-
Complications		2 (6)
Subdural or epidural hematoma	1 (3)	-
Seizures	2 (6)	-
Infection [‡]	4 (12)	-
Systemic venous thromboembolism [§]	3 (9)	-
In-hospital mortality	22 (65) [¶]	-
Death within ≤24 hours of diagnosis	3/22 (14)	-
Death within >24 and ≤72 hours of diagnosis	10/22 (45)	-
Death after >72 hours of diagnosis	9/22 (41)	-

CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia; [†]among patients with hemispheric lesions; [‡]pneumonia (n=2), ventriculitis (n=1), unknown (n=1); [§]portal and hepatic vein thrombosis (n=1), soleal deep vein thrombosis (n=1), unknown (n=1); [¶]In all cases due to brain herniation.

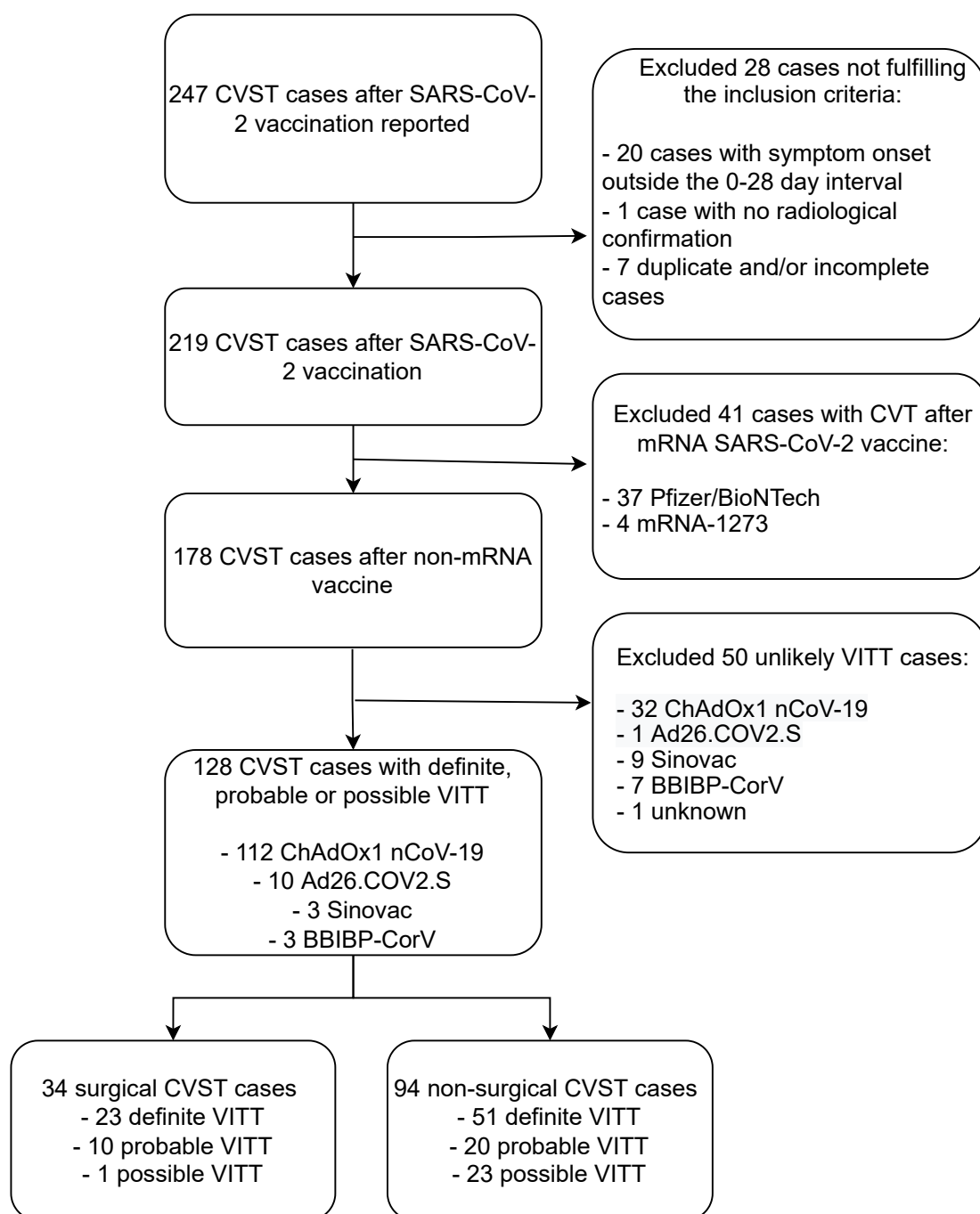
Table 4. Prognostic factors associated with in-hospital mortality in surgical CVST-VITT patients

	Died/Surgical CVST- VITT patients n/N (%)	Missing n (%)	P-value
Age at onset, in years			0.292
<50	12/21 (57)	-	-
≥50	10/13 (77)	-	-
Last preoperative Glasgow Coma Scale Score		2 (6)	<0.001
<9	17/18 (94)	-	-
≥9	4/14 (29)	-	-
Pupillary response		7 (21)	0.023
Bilaterally fixed pupils	7/7 (100)	-	-
Unilaterally reactive pupil	6/9 (67)	-	-
Reactive pupils	4/11 (36)	-	-
Last preoperative platelet counts			0.724
≥50 ×10 ³ /μL	9/15 (60)	-	-
<50 ×10 ³ /μL	13/19 (68)	-	-
Last preoperative imaging		-	-
Posterior fossa lesion	4/5 (80)	2 (6)	0.635
Cerebral edema more than half of hemisphere	10/16 (63)	5 (15)	1.000
Concomitant therapies			
Preoperative intravenous immunoglobulins	7/9 (78)	-	0.439

Heparin [†] at any time	9/15 (60)	-	0.731
Non-heparin anticoagulation only	10/16 (63)	-	1.000
Preoperative platelet transfusion	10/16 (63)	-	1.000
Postoperative status		-	
Persistent midline shift	7/16 (44)	8 (24)	0.109
Worsening of index hemorrhagic lesion	14/19 (74)	7 (21)	0.033
New hemorrhagic lesion	10/16 (63)	7 (21)	0.710
Persisting herniation	5/6 (83)	9 (26)	0.180

CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia; [†]unfractionated heparin or low molecular weight heparin

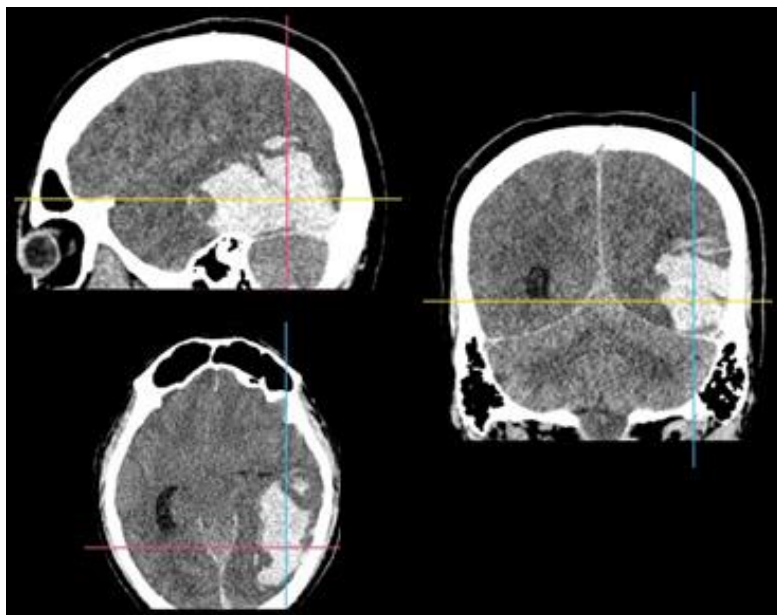
Figure 1. Patient selection



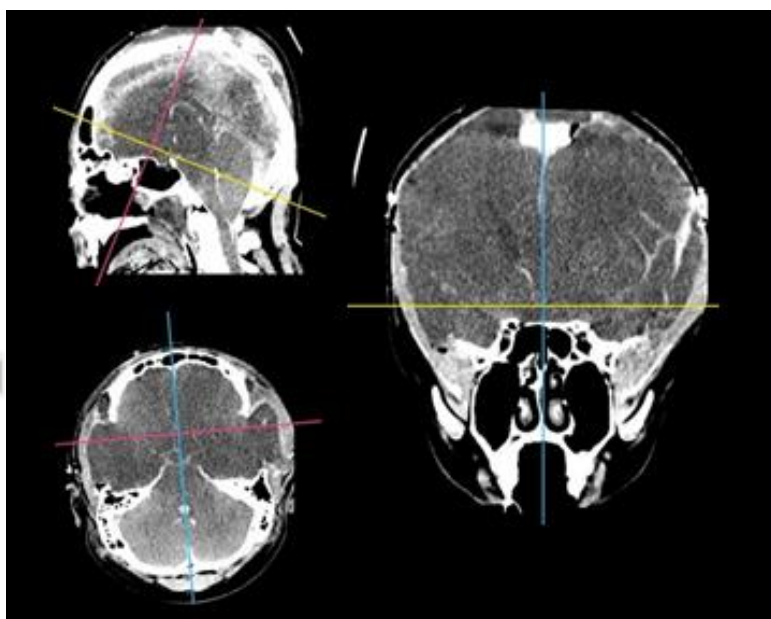
CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia

Figure 2. Pre- and postoperative imaging findings in a patient with CVST-VITT

A.



B.

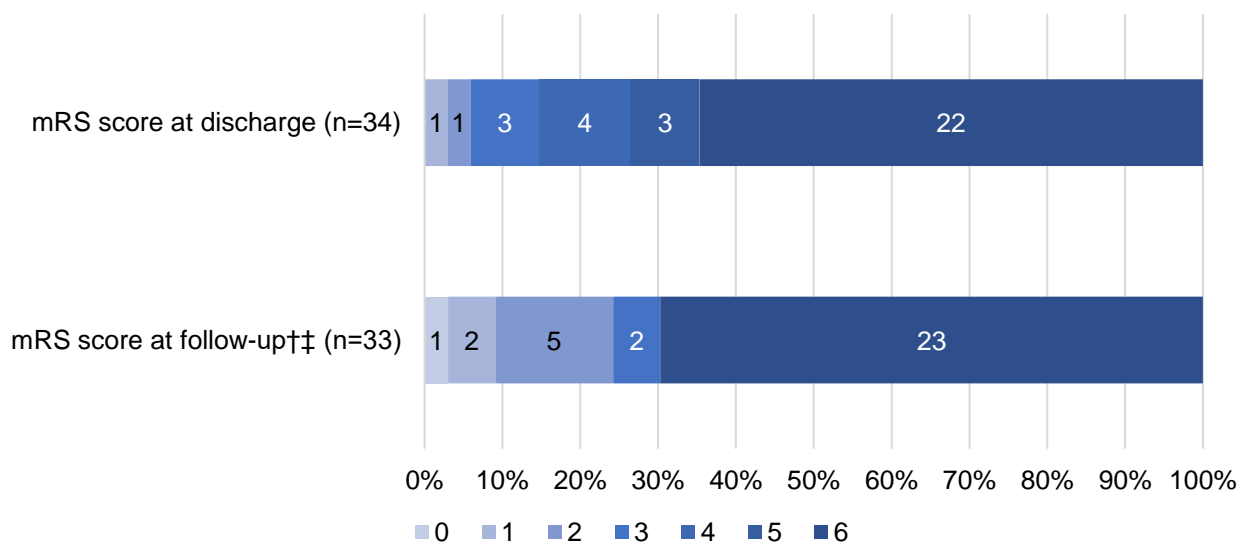


A. Last preoperative non-contrast brain CT scan on day 11 after ChAdOx1 nCoV-19 vaccination. Patient in his 50s presented with headache, right hemiparesis and rapid deterioration of consciousness, showing left-sided intraparenchymal hemorrhage with mass effect and diffuse cerebral edema. Last preoperative platelet count was $15 \times 10^3/\mu\text{L}$.

B. Postoperative non-contrast brain CT scan on day 13 after ChAdOx1 nCoV-19 vaccination and 1 day after bilateral decompressive surgery. This patient died on the same day due to brain herniation.

CT = computed tomography; CVST = cerebral venous sinus thrombosis; VITT = vaccine-induced immune thrombotic thrombocytopenia

Figure 3. Modified Rankin Scale score of surgical CVST-VITT patients at discharge and follow-up



CVST = cerebral venous sinus thrombosis; mRS = modified Rankin Scale; VITT = vaccine-induced immune thrombotic thrombocytopenia; †Follow-up after a median of 6 months after discharge (interquartile range: 3-10). ††Missing values for 1/34 (3%) patients.