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ORIGINAL ARTICLE

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

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Abstract

Background and purpose: Cerebral venous sinus thrombosis due to vaccine-induced immune thrombotic thrombocytopenia (CVST-VITT) is an adverse drug reaction occurring after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. CVST-VITT patients often present with large intracerebral haemorrhages and a high proportion undergoes decompressive surgery. Clinical characteristics, therapeutic management and outcomes of CVST-VITT patients who underwent decompressive surgery are described and predictors of in-hospital mortality in these patients are explored.

Methods: 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, were used. Definite, probable and possible VITT cases, as defined by Pavord et al. (N Engl J Med 2021; 385: 1680–1689), were included.

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 amongst 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 bilaterally reactive pupils; $p = 0.023$). Postoperative imaging revealed worsening of index haemorrhagic lesion in 19 (70%) patients and new haemorrhagic lesions in 16 (59%) patients. At a 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.

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

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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations [1–5]. With high rates of coma, frequent intracerebral haemorrhages 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 the 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 US guidelines [9–12]. Although up to one-third of CVST-VITT patients undergo decompressive surgery, there are limited data about the outcomes of this treatment in this group of patients [5, 7, 13].

The clinical, laboratory and imaging characteristics, therapeutic management and outcomes of CVST-VITT patients who underwent decompressive surgery are described and predictors of mortality are explored.

METHODS

Patient selection and data collection

Details of the coronavirus disease 2019 (COVID-19) vaccination study initiated by the International Cerebral Venous Thrombosis 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 are requested to report consecutive cases from their hospitals. CVST has to be confirmed with computed tomography venography, magnetic resonance imaging, magnetic resonance venography, catheter angiography or autopsy [11, 12].

The ethical review committee of Amsterdam University Medical Centre issued a waiver of formal approval for this study. Each centre 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 to the Pavord et al. [5] definition. Given the pragmatic design of this study, all positive tests for detection of anti-platelet factor 4 (anti-PF4) antibodies, as reported by the investigators, regardless of the type of test, were accepted.

Focal neurological deficits were defined as any persistent clinical focal neurological 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 a Glasgow Coma Scale score <9. When providing the last available Glasgow Coma Scale score before surgery the last score prior to sedation was used. Thrombocytopenia was defined as a platelet count of $<150 \times 10^3/\mu l$. Severe thrombocytopenia was defined as a platelet count of $<50 \times 10^3/\mu l$.

Assessment of the imaging was done as shown by computed tomography or magnetic resonance, according to the definitions provided to the local investigators. Haemorrhagic lesion was defined as haemorrhagic infarction and/or intracerebral haematoma. Worsening of the haemorrhagic lesion was defined as enlargement of the haemorrhagic component of the index haemorrhagic 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 peri-mesencephalic cistern, effacement of all basal cisterns, ipsilateral widening of cerebellopontine angle, and 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 the 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 haematoma evacuation. Postoperative imaging was defined as postoperative computed tomography or magnetic resonance 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 the 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

Two comparison groups of non-surgical CVST-VITT patients with some similar features to the surgical CVST-VITT patients were included. 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 concomitant causes for coma be excluded in this group. The second comparison group included surgical patients from the CVST cases classified as 'unlikely VITT' per the Pavord criteria from the CVST-VITT registry.

The mortality in the comparison groups is described, but no formal statistical comparison with surgical CVST-VITT patients in coma with intracerebral haemorrhage was performed 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.). A 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

In all, 128 CVST-VITT cases were included from 84 centres in 20 countries (Table S1): 112 (88%) after ChAdOx1 nCoV-19 (Vaxzevria, previously AstraZeneca/Oxford), 10 (8%) after Ad26.COV2.S (Janssen/Johnson & Johnson), three (2%) after Sinovac and three (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).

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 33, IQR 15–35 vs. 19, IQR 8–21 mg/l fibrinogen equivalent units, $p = 0.002$) and lower admission fibrinogen values (1.3, IQR 1.0–2.4 vs. 2.3, IQR 1.4–2.9 g/l; $p = 0.007$). Haemorrhagic 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 seven (26%) had bilaterally fixed dilated pupils (Table 1). In 19/34 (56%) cases, severe thrombocytopenia persisted preoperatively. All surgical patients had a haemorrhagic lesion before surgery. Last imaging before the surgery revealed a midline shift amongst 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 for 32/34 (94%) patients (Table 2). Amongst those operated, 23 patients (72%) underwent decompressive craniectomy, two (6%) haematoma evacuation

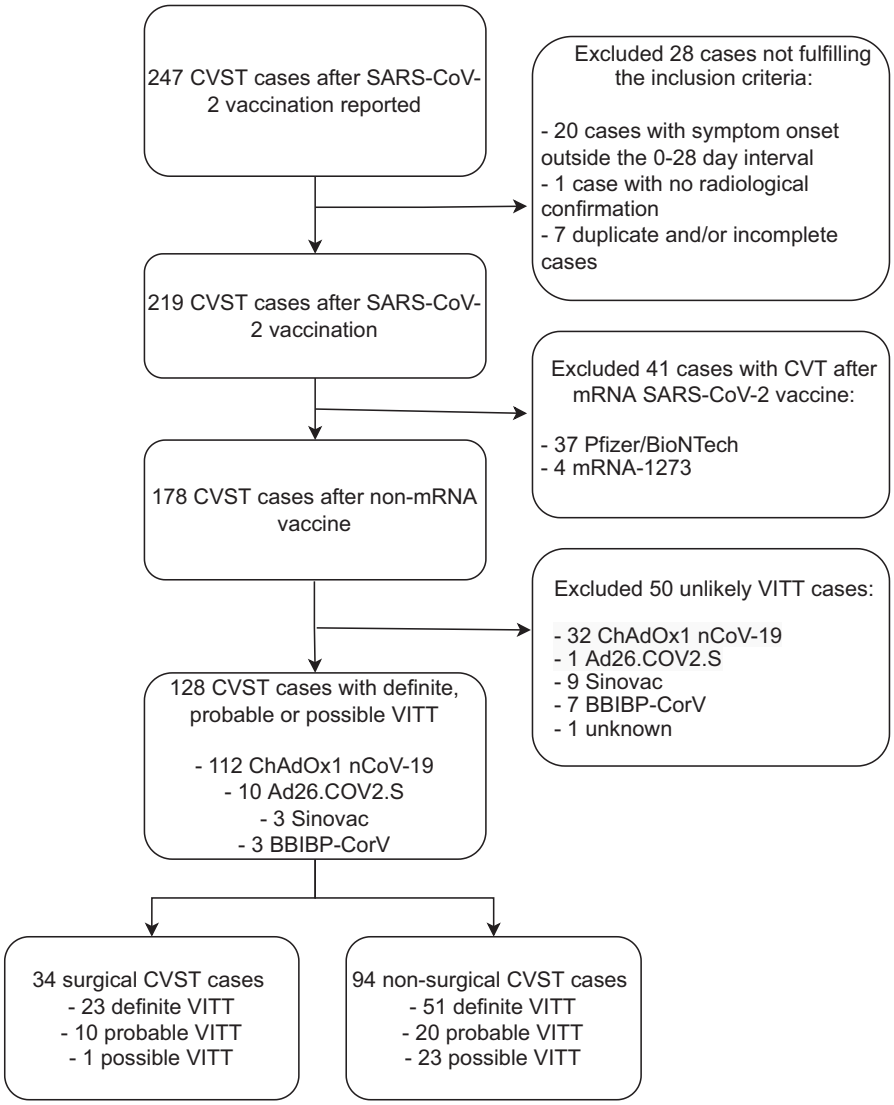

FIGURE 1 Patient selection. CVST, cerebral venous sinus thrombosis; VITT, vaccine-induced immune thrombotic thrombocytopenia.

and seven (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 six (21%) and two (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 amongst six (24%) patients the repeated imaging revealed persisting herniation. Nineteen (70%) patients suffered worsening of the haemorrhagic lesion and 16 (59%) developed a new haemorrhagic lesion. Thirteen (48%) patients suffered both worsening of the index haemorrhagic lesion and development of a new one.

Almost two-thirds of surgical patients died (22/34, 65%), whilst 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 two (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 was 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

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[a]	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 ($\times 10^3$/μl), median (IQR)	52 (26–71)	–
Platelet count $<50\times10^3$/μl, *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		
Haemorrhagic lesion, *n* (%)	34 (100)	–
Diameter of largest haemorrhagic 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 oedema		5 (15)
Less than half of the hemisphere, *n* (%)	13 (45)	–
More than half of the hemisphere, *n* (%)	16 (55)	–
Midline shift[b], *n* (%)	25/27 (93)	1 (3)
Transtentorial herniation, *n* (%)	11 (38)	5 (15)
Descending, *n* (%)	8/11 (73)	–
Ascending, *n* (%)	3/11 (27)	–

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

[a]Last assessment prior to sedation.

[b]Amongst patients with hemispheric lesions.

(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 haemorrhagic lesion died. This was significantly higher than the mortality rate amongst surgical patients without worsening of the haemorrhagic lesion (2/8, 25%; $p = 0.033$; Table 4).

In a sensitivity analysis, it was found that the proportion of patients who received decompressive surgery was significantly higher amongst 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 amongst surgical patients did not decrease (11/19, 58% before vs. 11/15, 73% after, $p = 0.476$; Table S3).

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

Amongst 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 haemorrhage 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 amongst 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 amongst 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 haemorrhagic lesion before surgery (100%) was similar to the pre-COVID data (90%) [10]. On the other

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)	–
Haematoma evacuation only, *n* (%)	2 (6)	–
Both craniectomy and haematoma 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[a], *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)	–

Abbreviations: CVST, cerebral venous sinus thrombosis; IQR, interquartile range; VITT, vaccine-induced immune thrombotic thrombocytopenia.

[a]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 h of surgery	27 (84)	2 (6)
Persistent midline shift[a]	16 (70)	8 (24)
Worsening of the index haemorrhagic lesion	19 (70)	7 (21)
New haemorrhagic 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 haematoma	1 (3)	–
Seizures	2 (6)	–
Infection[b]	4 (12)	–
Systemic venous thromboembolism[c]	3 (9)	–
In-hospital mortality	22 (65)[d]	–
Death ≤24 h of diagnosis	3/22 (14)	–
Death within >24 and ≤72 h of diagnosis	10/22 (45)	–
Death >72 h of diagnosis	9/22 (41)	–

Abbreviations: CVST, cerebral venous sinus thrombosis; VITT, vaccine-induced immune thrombotic thrombocytopenia.

[a]Amongst patients with hemispheric lesions.

[b]Pneumonia ($n = 2$), ventriculitis ($n = 1$), unknown ($n = 1$).

[c]Portal and hepatic vein thrombosis ($n = 1$), soleal deep vein thrombosis ($n = 1$), unknown ($n = 1$).

[d]In all cases due to brain herniation.

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]. Whilst information is not available on whether indication for surgery was more liberal, the time interval between diagnosis and surgery and the proportions of types of surgical approaches (craniectomy or haematoma 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 haemorrhage rate at admission—but can also be a consequence of clinical deterioration before the surgery and/or postoperative complications.

A high rate of postoperative worsening of index haemorrhagic lesions was found in more than two-thirds of the surgical patients, and the development of new haemorrhagic lesions was observed in

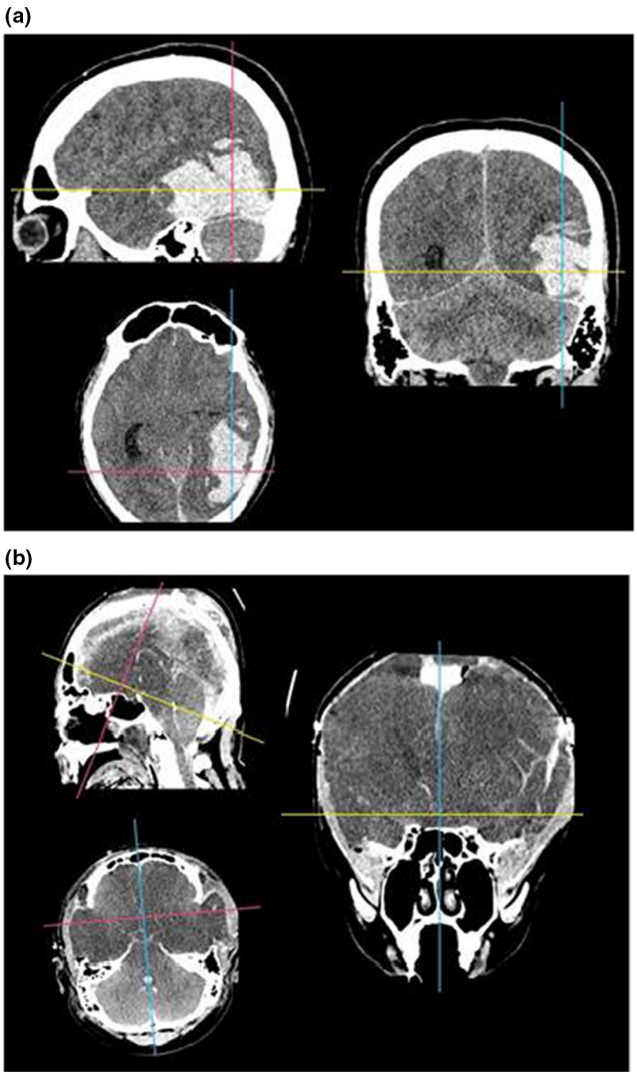

FIGURE 2 Preoperative and postoperative imaging findings in a patient with CVST-VITT. (a) Last preoperative non-contrast brain CT scan on day 11 after ChAdOx1 nCoV-19 vaccination. The patient in his 50s presented with headache, right hemiparesis and rapid deterioration of consciousness, showing left-sided intraparenchymal haemorrhage with mass effect and diffuse cerebral oedema. Last preoperative platelet count was 15×10^3/μl. (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.

approximately half of the patients. Although the literature on haemorrhagic complications of surgical CVST patients is scarce, in a small case series of pre-COVID surgical CVST patients only 4/10 (40%) had new haemorrhagic 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 the 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 favourable 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 the 5-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 centres 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, it was expected that this practice also translated to management of CVST-VITT. Thus, it is unsurprising that for the analysis of surgical CVST-VITT patients an appropriate non-surgical CVST-VITT comparison group with a comparable clinical severity is lacking. 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 versus 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. A sufficiently large surgical group with unlikely VITT was also not available for comparison, 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, a decrease in in-hospital mortality was not detected amongst 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 haemorrhagic 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 study and previous studies [13] suggest that decompressive surgery

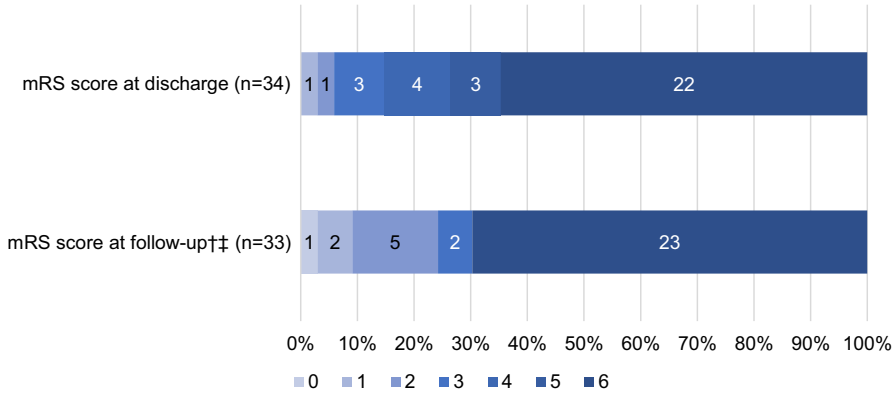

FIGURE 3 Modified Rankin Scale score of surgical CVST-VITT patients at discharge and follow-up. CVST, cerebral venous sinus thrombosis; mRS, modified Rankin Scale; VITT, vaccine-induced immune thrombotic thrombocytopenia. †Follow-up after a median of 6 months after discharge (interquartile range 3–10). ‡Missing values for 1/34 (3%) patients.

TABLE 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
$\geq 50 \times 10^3/\mu l$	9/15 (60)	–	–
$< 50 \times 10^3/\mu l$	13/19 (68)	–	–
Last preoperative imaging		–	–
Posterior fossa lesion	4/5 (80)	2 (6)	0.635
Cerebral oedema more than half of hemisphere	10/16 (63)	5 (15)	1.000
Concomitant therapies			
Preoperative intravenous immunoglobulins	7/9 (78)	–	0.439
Heparin[a] 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 haemorrhagic lesion	14/19 (74)	7 (21)	0.033
New haemorrhagic lesion	10/16 (63)	7 (21)	0.710
Persisting herniation	5/6 (83)	9 (26)	0.180

Abbreviations: CVST, cerebral venous sinus thrombosis; VITT, vaccine-induced immune thrombotic thrombocytopenia.
[a]Unfractionated heparin or low molecular weight heparin.

should not be contraindicated in CVST-VITT patients with impending herniation.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

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

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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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