Stroke

BRIEF REPORT

Outcomes of Cerebral Venous Thrombosis due to Vaccine-Induced Immune Thrombotic Thrombocytopenia After the Acute Phase

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BACKGROUND: Cerebral venous thrombosis (CVT) due to vaccine-induced immune thrombotic thrombocytopenia (VITT) is a severe condition, with high in-hospital mortality rates. Here, we report clinical outcomes of patients with CVT-VITT after SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccination who survived initial hospitalization.

METHODS: We used data from an international registry of patients who developed CVT within 28 days of SARS-CoV-2 vaccination, collected until February 10, 2022. VITT diagnosis was classified based on the Pavord criteria. Outcomes were mortality, functional independence (modified Rankin Scale score 0–2), VITT relapse, new thrombosis, and bleeding events (all after discharge from initial hospitalization).

RESULTS: Of 107 CVT-VITT cases, 43 (40%) died during initial hospitalization. Of the remaining 64 patients, follow-up data were available for 60 (94%) patients (37 definite VITT, 9 probable VITT, and 14 possible VITT). Median age was 40 years and 45/60 (75%) patients were women. Median follow-up time was 150 days (interquartile range, 94–194). Two patients died during follow-up (3% [95% CI, 1%–11%). Functional independence was achieved by 53/60 (88% [95% CI, 78%–94%]) patients. No new venous or arterial thrombotic events were reported. One patient developed a major bleeding during follow-up (fatal intracerebral bleed).

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CONCLUSIONS: In contrast to the high mortality of CVT-VITT in the acute phase, mortality among patients who survived the initial hospitalization was low, new thrombotic events did not occur, and bleeding events were rare. Approximately 9 out of 10 CVT-VITT patients who survived the acute phase were functionally independent at follow-up.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: hospitalization ■ intracranial thrombosis ■ mortality ■ thrombocytopenia ■ vaccination ■ venous thrombosis

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Nonstandard Abbreviations and Acronyms

CVT	cerebral venous thrombosis
ISCVT	International Study on Cerebral Vein and Dural Sinus Thrombosis
PF4	platelet factor 4
VITT	vaccine-induced immune thrombotic thrombocytopenia

Cerebral venous thrombosis (CVT) due to vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare adverse event of adenovirus-based SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccines.[1–3] CVT-VITT has substantially higher in-hospital mortality rates (20%–50%), compared with CVT unrelated to VITT (4%).[2–4] We aimed to report clinical and functional outcomes of patients with CVT-VITT who survived initial hospitalization.

METHODS

We used data from an international registry on CVT after COVID-19 vaccination collected until February 10, 2022. Details have been described.[3] Inclusion criteria were radiologically or autopsy-confirmed CVT and symptom onset within 28 days of any SARS-CoV-2 vaccine. The ethical review committee of Amsterdam UMC waived formal approval for this observational study. This article follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. Original data are available upon reasonable request.

VITT classification was based on the Pavord criteria[2] (Table S1). We included cases with definite, probable, or possible CVT-VITT. We excluded CVT-VITT patients who died during initial hospitalization, patients with missing follow-up data, and cases with CVT after mRNA vaccines, which do not cause VITT.[5]

We used the information from the last available visit. Outcome measures were mortality, functional independence (modified Rankin Scale score 0–2), VITT relapse after initial clinical remission, new thrombosis, and new major bleeding events according to the criteria of the International Society on Thrombosis and Haemostasis.

Clinical remission was defined as fulfilling the following criteria at any time during follow-up: (1) platelet count >150×10^9/L; (2) no clinical evidence of new or progressive ischemic organ injury; and (3) no immunomodulatory treatment for 30 days. Relapse was defined as a decrease in platelet count to <150×10^9/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury, at any time after achieving clinical remission.

We calculated 95% CI using Wilson score method for main outcomes. Analyses were performed with IBM SPSS Statistics,

Table 1. Patient Details of Initial Hospitalization

	CVT-VITT patients who survived the acute phase (N=60)
Baseline characteristics	
Age, y	40 (27–56)
Female sex	45/60 (75)
Coma	4/60 (7)
Intracerebral hemorrhage	30/60 (50)
Concomitant VTE	14/60 (23)
Laboratory data	
Platelet count nadir, x 10^9/L	47 (29–69)
Positive anti-PF4 antibodies	47/53 (89)
D-dimer level >4 mg/L FEU	51/56 (91)
Treatment data	
Anticoagulation	60/60 (100)
Heparin as first anticoagulant*	23/60 (38)
Immunomodulatory treatment	44/60 (73)
Intravenous immunoglobulin	44/60 (73)
Plasma exchange	4/60 (7)
Corticosteroids	17/60 (28)
Other	2/60 (3)
Platelet transfusion	10/60 (17)
Intensive care unit admission	37/58 (64)
Endovascular treatment	8/59 (14)
Decompressive surgery	10/59 (17)
Discharge data	
Duration hospital admission, median (IQR; range), d	14 (8–26;1–53)†
Discharge disposition	
Home	38/59 (64)
Rehabilitation center	19/59 (32)
Other hospital	2/59 (3)

Discrete data are presented as n/N (%), continuous data as median (IQR). Denominators <60 represent incomplete data points. CVT indicates cerebral venous thrombosis; FEU, fibrinogen equivalent units; IQR, interquartile range; PF4, platelet factor 4; VITT, vaccine-induced immune thrombotic thrombocytopenia; and VTE, venous thrombotic event.

*Unfractionated heparin or low-molecular weight heparin.

†Three missing values.

version 28.0.1.0, RStudio version 1.3.1093 and R version 4.0.3 using the Hmisc package.

RESULTS

Of 208 reported cases, 107 had CVT-VITT. In total, 43 (40%) died during initial hospitalization (Figure S1 and Table S2). Of the remaining 64 patients, follow-up data were available for 60 (94%) patients: 37 (62%) with definite VITT, 9 (15%) probable VITT, and 14 (23%) possible VITT.

Median age was 40 years (interquartile range, 27–56) and 45/60 (75%) patients were women (Table 1). Median follow-up time was 150 days (interquartile range, 94–194, Table 2). Two patients died during follow-up (3% [95% CI, 1%–11%]): one due to a new intracerebral hemorrhage and one of unknown causes (details in Table S3). The latter patient had a new thrombocytopenia during readmission for a COVID-19 infection, fulfilling the criteria for a VITT relapse. No other relapses or bleeding events were reported. No new venous or arterial thrombotic events were reported in any patient. Hospital readmission occurred in 9/54 (17%) cases, 4 of which were for a planned cranioplasty following decompressive hemicraniectomy (Table 2).

Functional independence was achieved by 53/60 (88% [95% CI, 78%–94%]) patients at follow-up, compared with 41/58 (71% [95% CI, 58%–81%]) at hospital discharge (Figure and Figure S2). Overall, 21/40 (53%) patients had returned to work or school at follow-up.

Platelet count at follow-up was available for 39/60 (65%) patients, details of which are provided in Figure S3. At least one D-dimer value at follow-up was available for 27/60 (45%) CVT-VITT patients. D-dimer levels declined from >4 mg/L in the acute phase to ≤0.5 mg/L at follow-up in 19/27 (70%) patients (Figure S4).

Table 2. Outcomes of Patients Who Survived the Acute Phase of CVT-VITT

	CVT-VITT patients who survived the acute phase (N=60)
Clinical events	
Time from diagnosis to follow-up, d	150 (94-194)*
New VTE	0/59
New ATE	0/57
Major bleeding event	1/55 (2)
Hospital readmission	9/54 (17)†
Treatment	
Anticoagulant treatment ongoing at last follow-up	44/53 (83)
Outcomes	
Clinical remission achieved	41/53 (77)
Relapse after remission	1/35 (3)
Mortality	2/60 (3)
Returned to work or school	21/40 (53)

Discrete data are presented as n/N (%), continuous data as median (IQR). Denominators <60 represent incomplete data points. ATE indicates arterial thrombotic event; CVT, cerebral venous thrombosis; IQR, interquartile range; VITT, vaccine-induced immune thrombotic thrombocytopenia; and VTE, venous thrombotic event.

*Two missing values. In all cases, date of follow-up was after discharge.

†Reason readmission (multiple possible): COVID-19 infection (1), cranioplasty (4), encephalopathy (1), headache (1), hepatitis (1), increased intracranial pressure (1), infection (1), inflammatory bowel disease (1), progression of brain metastases (1), and urinary tract infection (1).

DISCUSSION

This study indicates that—in sharp contrast to the high mortality rate during the acute phase—mortality of patients with CVT-VITT who survive initial hospitalization is low and new thrombotic and bleeding events rarely occur after discharge. Almost 90% of patients who survived the acute phase were functionally independent at follow-up and half of the patients had returned to work and/or school. One VITT relapse was reported, although not all patients had achieved clinical remission of VITT at follow-up.

The proportion of patients in our study who were functionally independent at follow-up is comparable to the proportion of patients with long-term functional independence after CVT not related to VITT, as reported in the ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis; 88% versus 89%, respectively).[4] The low number of adverse outcomes in surviving CVT-VITT patients may be explained by the fact that anti-PF4 (platelet factor 4) antibodies, which cause VITT,[1] are transient.[6] With the disappearance of the anti-PF4 antibodies, the triggering factor for VITT may have resolved.

In a study on the immune type of heparin-induced thrombocytopenia, a disorder that resembles VITT,[1] 5/28 (18%) patients developed new venous or arterial thrombosis.[7] A systematic review on CVT due to heparin-induced thrombocytopenia reported full recovery in only 4/18 (22%) cases, while all other cases had neurological sequelae.[8] The higher median age of the patients with CVT due to heparin-induced thrombocytopenia may be one of the explanatory factors for the worse outcome.

This study has limitations. First, because data were collected as part of routine clinical care, duration of follow-up varied and there was no central adjudication of study outcomes. In addition, laboratory tests were often not repeated during follow-up. Second, while follow-up rate was over 90%, we cannot exclude the possibility that clinical events occurred in the 4 patients for which follow-up was missing. Third, the median time from diagnosis to follow-up was ≈5 months. In CVT not related to VITT, recovery can occur up to 1 year after diagnosis, which may indicate that the CVT-VITT patients in this study may still recover further.[4]

In summary, in contrast to the severity of CVT-VITT during the acute phase, mortality of patients who survived initial hospital admission was low and new thrombotic and bleeding events were rare. Approximately 9

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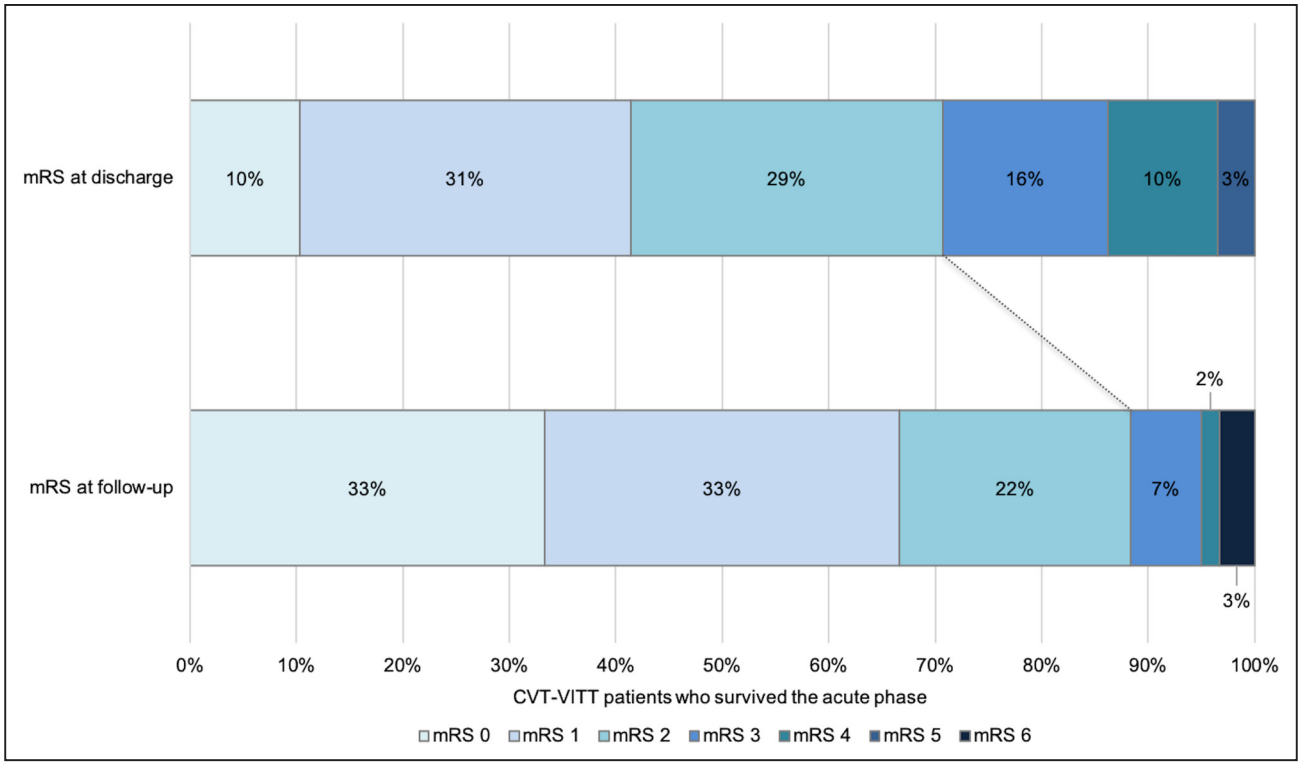

Figure. Modified Rankin Scale (mRS) score of 60 patients with cerebral venous thrombosis due to vaccine-induced immune thrombotic thrombocytopenia (CVT-VITT) who survived the acute phase, at discharge and at follow-up.
Note that CVT-VITT patients who died during initial hospitalization (43/107, 40%) are not included in the Figure. There are 2 missing mRS scores at discharge; both had mRS 0 at follow-up.

out of 10 CVT-VITT survivors were functionally independent at follow-up.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S4
Tables S1–S3
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