

Endovascular treatment of cerebral sinus thrombosis due to vaccine-induced immune thrombotic thrombocytopenia

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Abstract

Introduction: There is little data on the role of endovascular treatment (EVT) of cerebral venous sinus thrombosis (CVST) due to vaccine-induced immune thrombotic thrombocytopenia (VITT). Here, we describe clinical characteristics and outcomes of CVST-VITT patients who were treated with EVT.

Patients and methods: We report data from an international registry of patients who developed CVST within 28 days of SARS-CoV-2 vaccination, reported between 29 March 2021 and 6 March 2023. VITT was defined according to the Pavord criteria.

Results: EVT was performed in 18/136 (13%) patients with CVST-VITT (92% aspiration and/or stent retrieval, 8% local thrombolysis). Most common indications were extensive thrombosis and clinical or radiological deterioration. Compared to non-EVT patients, those receiving EVT had a higher median thrombus load (4.5 vs 3). Following EVT, local blood flow was improved in 83% (10/12, 95% confidence interval [CI] 54–96). One (6%) asymptomatic sinus perforation occurred. Eight (44%) patients treated with EVT also underwent decompressive surgery. Mortality was 50% (9/18, 95% CI 29–71) and 88% (8/9, 95% CI 25–66) of surviving EVT patients achieved functional independence with a modified Rankin Scale score of 0–2 at follow-up. In multivariable analysis, EVT was not associated with increased mortality (adjusted odds ratio, 0.66, 95% CI 0.16–2.58).

Discussion and conclusion: We describe the largest cohort of CVST-VITT patients receiving EVT. Half of the patients receiving EVT died during hospital admission, but most survivors achieved functional independence.

Keywords

Intracranial thrombosis, thrombectomy, thrombocytopenia, vaccination, venous thrombosis, COVID-19

Introduction

Cerebral venous sinus thrombosis (CVST) due to vaccine-induced immune thrombotic thrombocytopenia (VITT) is a severe adverse event after adenovirus-based SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccination.^{1–3} VITT is caused by a pathologic autoimmune response resulting in production of antibodies against platelet factor 4, which causes a highly thrombogenic state. As a consequence, CVST-VITT patients experience severe thrombosis, often at multiple sites,² and have a worse prognosis compared to patients with CVST unrelated to SARS-CoV-2 vaccination.³

In CVST unrelated to SARS-CoV-2 vaccination, the role of endovascular treatment (EVT) is uncertain. Although it seems to increase recanalization, it does not improve functional outcome and is generally not recommended as a standard treatment. Nevertheless, it is sometimes performed in severe CVST cases that do not respond to anticoagulation, and is therefore suggested as a potentially viable treatment option for a selected subgroup of CVST patients.^{4–8}

Recommended treatment for CVST-VITT consists of non-heparin anticoagulants, immunotherapy and avoidance of platelet transfusions.⁹ Nevertheless, mortality rates in CVST-VITT patients remain high.^{10,11} While the current literature suggests that EVT in CVST-VITT patients may be a safe and effective treatment option, the available evidence is anecdotal.^{12–16}

According to the literature, up to one-fifth of CVST-VITT patients undergo EVT.^{3,17} We hypothesize that because CVST-VITT is a distinct clinical entity with a significantly higher mortality and morbidity, the potential benefit of EVT might be more pronounced in this disease compared to non-VITT CVST.^{2,3,11,18} In this study, we aim to provide a descriptive analysis of clinical, laboratory, and imaging characteristics and outcomes of patients with CVST-VITT treated with EVT.

Material and methods

We used data collected between March 29, 2021 and March 6, 2023 from an international registry on patients diagnosed

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Table 1. CVST-VITT patients treated with endovascular treatment.

	EVT (n = 18)	Missing n (%)	No EVT (n = 118)
Demographic characteristics			
Women, n (%)	15 (83)	-	87 (74)
Age, in years, median (IQR)	39 (28–45)	-	45 (28–56)
SARS-CoV-2 vaccination details			
ChAdOx1 nCoV-19, n (%)	17 (94)	-	92 (78)
Sinovac, n (%)	1 (6)	-	3 (2.5)
Other, n (%)	0	-	12 (10)
Days from vaccination to CVST symptom onset, median (IQR)	8 (7–10)	-	9 (7–11)
Clinical characteristics at presentation			
Headache, n (%)	18 (100)	-	108 (92)
Focal neurological deficits, n (%)	14 (78)	-	62 (54)
Seizure, n (%)	5 (28)	-	16 (14)
Coma, n (%)	5 (35)	1 (6)	22 (20)
Second VTE at presentation	4 (27)	3 (17)	24 (21)
Laboratory values at presentation			
Platelet count ($\times 10^3/\mu\text{L}$), median (IQR)	42 (28–76)	-	55 (30–84)
D-dimer (mg FEU/L), median (IQR)	20 (11–35)	2 (11)	20 (8–28)
Fibrinogen (g/L), median (IQR)	1.5 (0.8–2.4)	2 (11)	2.1 (1.3–2.8)
Platelet Factor 4 antibodies, n (%)	13 (87)	3 (17)	83 (91)
Imaging at presentation			
Non-hemorrhagic lesion, n (%)	7 (39)	-	29 (26)
Hemorrhagic lesion, n (%)	15 (88)	1 (6)	74 (64)
Thrombus load, median (IQR)	4.5 (3–5.75)	-	3 (1.25–3)

CVST: cerebral venous sinus thrombosis; EVT: endovascular treatment; FEU: fibrinogen equivalent units; IQR: interquartile range; VITT: vaccine-induced immune thrombotic thrombocytopenia; VTE: venous thromboembolism.

with CVST after vaccination with any SARS-CoV-2 vaccine.³ Formal approval was waived by the ethics committee of Amsterdam UMC and written informed consent for the use of pseudonymized care data was obtained by the participating centers from all included subjects if required by national law and hospital regulation. Inclusion criteria for this study were radiologically or autopsy-confirmed CVST with symptom onset within 28 days after SARS-CoV-2 vaccination, and definite, probable or possible VITT according to the Pavord et al. criteria.²

We used descriptive statistics for baseline characteristics, complications and outcomes of patients treated with or without EVT. Functional outcome was rated with the modified Rankin Scale (mRS). Primary outcomes include the rate of in-hospital mortality, functional independence at follow-up (mRS 0–2) and improved blood flow of at least one treated vessel.

Thrombus load was defined as the number of affected cerebral sinus or veins.¹⁹ Improved blood flow was defined as at least partial recanalization in one or more occluded sinus/veins according to assessment of the local investigator. The indication for EVT was provided by multiple selection from one of the following reasons: widespread thrombosis, progressive thrombosis despite conventional therapy, routine procedure, and “other.” Progressive thrombosis was favored over clinical deterioration, as the latter can have multiple causes including for example, herniation,

new or enlarged lesions, seizures or systemic medical complications.

Wilson’s method was used to calculate 95% confidence intervals (CI) for main outcomes. Odds ratios (ORs) for in-hospital mortality per EVT were calculated using uni- and multivariable logistic regression models adjusted for the following pre-specified confounders in CVST-VITT: coma at presentation, intracranial hemorrhage (ICH) at presentation, baseline platelet count, immunomodulation with intravenous immunoglobulins or plasma exchange and baseline thrombus load.^{2,3,10} Confounders were chosen based on clinical plausibility. A two-sided probability value <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS statistics (version 28.0.1.0) and R (Version 4.2.1).

Results

Among 136 CVST-VITT cases reported in the registry, 18 (13%) were treated with EVT. Median age of patients receiving EVT was 39 years (interquartile range [IQR] 28–45) and 15 (83%) were female. Baseline thrombus load was higher among patients receiving EVT with a median of 4.5 sinuses affected (IQR, 3–5.75) compared to 3 (IQR 1.25–3) in those who were not treated with EVT. Further baseline characteristics are presented in Table 1.

Sixteen of 18 (89%) EVT patients had cerebral hemorrhagic lesions on pre-intervention neuroimaging and EVT was performed at a median of 18 h (IQR 7–54) after diagnosis of CVT. Prior to EVT, 10/15 (67%) were already sedated or intubated (Table 2). The most common indications for EVT were extensive thrombosis and clinical or radiological deterioration, accounting together for 17/18 (94%) cases. More specifically, the indications included extensive thrombosis in 57%, progressive thrombosis despite conventional therapy in 50%, and other reasons include clinical worsening, progressive edema and progressive hemorrhagic lesions in 7% each (Table 3). EVT was performed with direct aspiration in 10/13 (77%) and stent retrieval in 9/13 (69%), both techniques were performed in 7/13 (54%, see Figure 1 for example), while local thrombolysis was performed in 1/13 (8%). The superior sagittal sinus, transverse and sigmoid sinus were the most frequent target vessels. Concomitant treatment included anticoagulation in 17/18 (94%) and immunoglobulins in 12/18 (67%) patients. Eight (44%) patients were treated with decompressive surgery before or after EVT (Table 3).

Asymptomatic sinus perforation occurred in one case (6%), and no thromboembolic complications were observed. Repeated imaging after the intervention showed improved blood flow in at least one location in 10/12 cases (83%, 95% CI 54–96), while enlarged or new hemorrhagic lesions were detected in 9/14 (64%, Table 3).

Mortality among EVT patients was high with 9/18 (50%, 95% CI 29–71) and the median mRS at discharge was 4 (IQR 4–6), which was higher than in non-EVT patients (mRS 3, IQR 1–6, $p=0.015$). All but one of the surviving EVT patients (in total 8/18, 44%, 95% CI 25–66) achieved functional independence at a median follow-up of 2.5 months (IQR 1–6 months, Figure 2). In univariable logistic regression analysis, EVT was not associated with in-hospital mortality (OR 1.74, 95% CI 0.63–4.79), which was confirmed in multivariable analysis adjusted for pre-specified prognostic factors (adjusted OR 0.66, 95% CI 0.16–2.58, Table 4).

Discussion

In our study, 13% of CVST-VITT patients underwent EVT. This rate is in line with a British cohort study also in which 13% patients were treated with EVT,¹⁷ but it is higher than in the study of Pavord et al. in which 7% were treated with EVT (personal communication).² Compared to previous anecdotal reports, the rates of technical success, complications and favorable outcomes were similar, while mortality was higher in our cohort (50% vs 27%, Supplemental Table). However, the mortality rate of 27% is lower than in CVST-VITT in general (40%)²⁰ and might be subject to reporting bias, as it is based on single cases and small cohorts up to $n=6$.

Table 2. Pre-intervention status in EVT CVST-VITT patients.

	EVT CVST-VITT (n = 18)	Missing, n (%)
Last pre-intervention clinical status		5 (28)
GCS <9, n (%)	4 (31)	
GCS 9–12, n (%)	4 (31)	
GCS 13–15, n (%)	5 (38)	
ICU admission prior to EVT, n (%)	11 (73)	3 (17)
Sedation/intubation prior to EVT, n (%)	10 (67)	3 (17)
Last pre-intervention imaging		
Hemorrhagic lesion, n (%) ^a	16 (89)	-
Intraparenchymal, n (%)	12 (80)	3 (17)
Subarachnoid, n (%)	6 (46)	3 (17)
Subdural, n (%)	2 (13)	3 (17)
Epidural, n (%)	0	3 (17)
Cerebral edema, n (%)	6 (40)	3 (17)
Midline shift, n (%)	7 (47)	3 (17)
Transtentorial herniation, n (%)	3 (20)	3 (17)
Last lab values ^a		
Platelet count ($\times 10^3/\mu\text{L}$), median (IQR)	67 (30–84)	-
D-dimer (mg FEU/L), median (IQR)	20 (7–69)	2 (11)
Fibrinogen (g/L), median (IQR)	2.2 (1.8–3.6)	4 (22)

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

^aIf not available carried forward from admission ($n=3$ for hemorrhagic lesion, D-Dimer and fibrinogen, $n=5$ for platelet count).

The most common indications for EVT in this cohort were extensive thrombosis and clinical or radiological deterioration. Therefore, it is not surprising that patients treated with EVT had a higher thrombus load compared to those who were not treated with EVT. Moreover, a median of 18 h between the diagnosis and treatment suggests that EVT was not performed as a first-line treatment but rather as an adjunct or escape treatment in deteriorating patients. This approach is consistent with the available literature: in some cases, following initial experiences with CVST-VITT patients who acutely deteriorated and died, there was a lower threshold for proceeding quickly to EVT for subsequent CVST-VITT patients.¹³

Interestingly, we observed a shift in the employed recanalization techniques compared to those used in the Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis trial (TO-ACT), where thrombectomy was performed in 91% and 52% received local thrombolysis.⁴ In our cohort, thrombectomy was also performed in 92%, but local

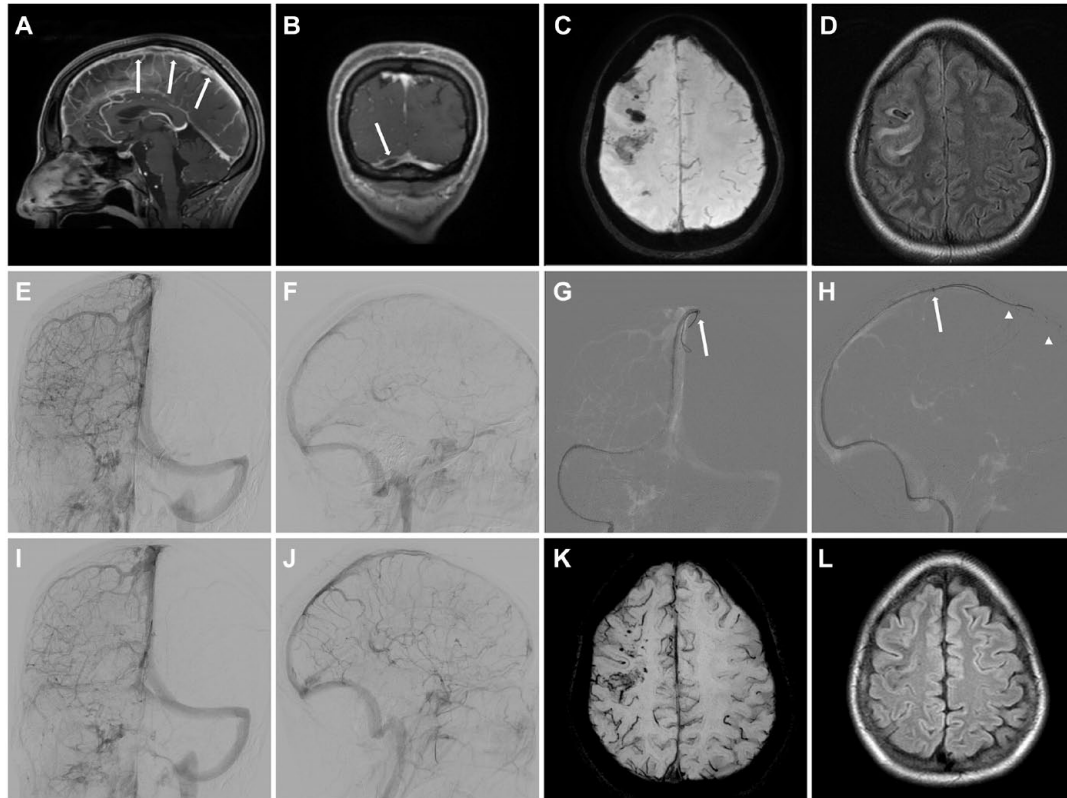


Figure 1. Presentation of an illustrative case of EVT in CVST-VITT. Female patient with extensive thrombosis of the superior sagittal sinus (SSS; arrows in (a)) and the right transverse sinus (TS; arrow in (b)) with microhemorrhages and focal edema (c and d). Digital subtraction angiography with injection of the right internal carotid artery (ICA; (e) posterior-anterior view, (f) lateral view) confirmed extensive occlusion of the SSS and right TS with missing opacification of the cortical veins. (g and h) EVT was performed by aspiration with a large-bore aspiration catheter (arrow: tip of the 6F Sofia plus, Microvention) in the SSS and simultaneous use of two stent retrievers (arrowheads: Solitaire 6/40 mm, Medtronic). Injection of the right ICA after three passes demonstrated recanalization of the SSS and right TS (i and j). MRI at 3-month follow-up showed edema resolution (k and l).

Table 3. Endovascular treatment details in CVST-VITT patients.

	EVT CVST-VITT (n = 18)	Missing n (%)
Hours between diagnosis and EVT, median (IQR)	18 (7–54)	4 (22)
Indication for EVT (more than 1 possible)		4 (22)
Routine for CVST, n (%)	1 (7)	
Extensive thrombosis, n (%)	8 (57)	
Progressive thrombosis despite conventional therapy, n (%)	7 (50)	
Other, n (%)	3 (21) ^a	
Location of endovascular treatment		4 (22)
Superior sagittal sinus, n (%)	9 (64)	
Transverse sinus, n (%)	12 (86) ^b	
Sigmoid sinus, n (%)	10 (71)	
Straight sinus, n (%)	1 (6)	
Jugular vein, n (%)	6 (43)	
Type of endovascular treatment (more than 1 possible)		5 (28)
Aspiration, n (%)	10 (77)	
Stent retriever, n (%)	9 (69)	
Local thrombolysis, n (%)	1 (8)	

(Continued)

Table 3. (Continued)

	EVT CVST-VITT (n=18)	Missing n (%)
Concomitant treatment		
Anticoagulation initiated, n (%)	17 (94)	-
Pre-EVT, n (%)	11/17 (65)	
Post-EVT, n (%)	2/17 (12)	
Unknown sequence, n (%)	4/17 (24)	
Intravenous immunoglobulins, n (%)	12 (67)	-
Pre-EVT, n (%)	6/12 (50)	
Post-EVT, n (%)	5/12 (42)	
Unknown sequence, n (%)	1/12 (8)	
Decompressive surgery, n (%)	8 (44)	-
Pre-EVT, n (%)	2/8 (25)	
Post-EVT, n (%)	5/8 (68)	
Unknown sequence, n (%)	1/8 (13)	
Platelet transfusions, n (%)	3 (17)	-
Complication within 72 h	7 (47)	3 (17)
Perforation of vein/sinus, n (%)	1 (6)	-
Thromboembolic complication, n (%)	0	
Brain herniation, n (%)	5 (33)	-
Imaging repeated post-intervention, n (%)	14 (93)	3 (17)
Increased thrombosis, n (%)	0	4 (22)
Improved blood flow, n (%)	10 (83)	6 (33)
Improved blood flow according to localization		
Superior sagittal sinus, n (%)	8/9 (89)	-
Transverse sinus, n (%)	8/12 (67)	2 (14)
Sigmoid sinus, n (%)	6/9 (67)	1 (10)
Straight sinus, n (%)	1/1 (100)	-
Jugular vein, n (%)	2/4 (50)	2 (33)
Enlarged or new hemorrhagic lesions on first imaging after EVT	9 (64)	4 (22)

CVST: cerebral venous sinus thrombosis; EVT: endovascular treatment; IQR: interquartile range; VITT: vaccine-induced immune thrombotic thrombocytopenia.

^aClinical worsening (n = 1), progressive edema (n = 1), progressive hemorrhagic lesions (n = 1).

^bBilateral involvement in two cases (14%).

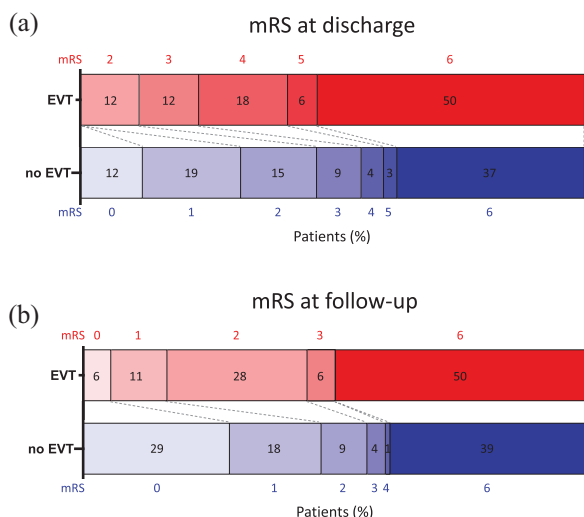


Figure 2. Functional outcome of CVST-VITT patients with versus without EVT. (a and b) Functional outcome (modified Rankin Scale, mRS) of CVST-VITT patients with versus without endovascular treatment (EVT).

thrombolysis in only 8%. While the optimal endovascular treatment approach is unknown, the observed shift might be in response to the assumed high bleeding risk as CVST-VITT had high rates (89%) of hemorrhagic lesions and low platelet counts.⁵ However, while TO-ACT recruited from 2011 to 2016, increasing experience among neurointerventionalists with thrombectomy techniques and improvement of devices following the publication of the 2015 stroke trials might also contribute to the observed preference.^{4,21}

On repeated imaging, 83% of CVST-VITT patients treated with EVT had recanalization of at least one treated vessel. While characterization of venous recanalization remains challenging to measure, this outcome seems comparable to the one achieved in studies of EVT for CVST before the pandemic.⁶ Unfortunately, there are no previous studies on early recanalization in CVST-VITT treated with anticoagulation and we did not gather recanalization data in non-EVT CVST-VITT patients.

Post-EVT imaging revealed a subdural hematoma in one patient, presumably due to sinus perforation and

Table 4. Odds ratios for in-hospital mortality in uni- and multivariable regression models.

	Univariable OR	p	Multivariable OR	P
EVT performed	1.74 (0.63–4.79)	0.28	0.66 (0.16–2.58)	0.48
Hemorrhagic lesion	6.77 (2.75–19.33)	<0.001	5.42 (1.85–18.61)	0.004
Coma	9.56 (3.7–28.26)	<0.001	4.93 (1.59–17.15)	0.008
Platelet count ($\times 10^3/\mu\text{L}$)	0.97 (0.95–0.98)	<0.001	0.98 (0.96–0.99)	0.004
Immunomodulation	0.44 (0.21–0.91)	0.027	0.29 (0.10–0.76)	0.014
Thrombus load	1.18 (0.96–1.47)	0.13	1.17 (0.86–1.59)	0.32

EVT: endovascular treatment; OR: odds ratio.

without clinical deterioration or need for surgical intervention. This low periprocedural complication rate is in line with the findings of the TO-ACT trial, confirming the safety of the procedure.⁴ Nevertheless, in our cohort, almost two-thirds had a new or enlarged hemorrhagic lesion after EVT. In the majority of the cases, these were assessed as being unrelated to the procedure. The rate of new/enlarged hemorrhagic lesions in CVST-VITT patients not treated with EVT was also high (31/112), and extensive thrombosis increases the risk of hemorrhage. Still, an association between EVT and new/enlarged hemorrhagic lesions cannot be precluded.

In those who survived, functional outcomes of CVST-VITT patients treated with EVT were favorable. Almost 90% achieved functional independence, as was reported for CVST-VITT irrespective of EVT.²⁰ Nevertheless, half of the CVST-VITT patients treated with EVT died during the initial admission, which is similar to the mortality in patients without EVT, but significantly higher than in the EVT studies of CVST unrelated to vaccination (12%).^{4,6} This is most likely due to the greater severity of CVST-VITT in general. The worse severity of CVST-VITT compared to usual CVST can also be ascertained by comparing rates of decompressive surgery – 44% in this study versus 9% in TO-ACT.⁴

As baseline thrombus load was higher in EVT patients and EVT was mostly indicated due to refractory disease, confounding by indication contributed to the numerically higher mortality on the unadjusted Grotta bar. In univariable as well as in multivariable analysis adjusted for pre-specified severity markers, there was no association between EVT and mortality, and the aHR of 0.66 even suggests a potential survival benefit associated with EVT in CVST-VITT. However, these observations were not statistically significant, thus limiting conclusions.

In addition to the inherent constraints of an observational registry, this study has several limitations. First, some data were collected retrospectively and consequently there are variables with high rates of missing data. Second, due to restricted sample size, generalizability might be reduced and we were not able to eliminate all confounders. Third, there was no central adjudication of clinical and radiological outcomes, as the data were collected in routine clinical care.

In conclusion, we provide a descriptive analysis of CVST-VITT patients to inform clinical management of this rare disease, which might also be helpful for related conditions with thrombotic thrombocytopenia and CVST. EVT in CVST-VITT may be safe and lead to local improvement of blood flow in most cases, but the clinical benefit seems uncertain.

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Ethical approval

Formal approval was waived by the ethical review committee Amsterdam UMC for this observational study. This study was completed in accordance with the Helsinki Declaration as revised in 2013.

Informed consent

Written informed consent for the use of pseudonymized care data was obtained by the participating centers from all included subjects if required by national law and hospital regulation.

Guarantor

JMF

Contributorship

JW, KK, JZ, and JMF designed the study. JW and KK analyzed the data and wrote the first draft. JZ and JMF supervised the study. All authors were involved in patient recruitment and reviewed and edited the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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