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Supplementary appendix

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Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study

Perry et al. (2021)

Appendix

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Venous risk factors recorded

Venous risk factors listed in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)[12] were designated 'ISCVT risk factors' and analysed separately so that a direct comparison with ISCVT could be made. These were:

- combined oral contraceptive pill or HRT
- pregnancy or recent childbirth
- thyroid disease
- dehydration
- malignancy or myeloproliferative disorder
- recent neurosurgery or head injury
- recent lumbar puncture
- Behçet syndrome or SLE
- antiphospholipid syndrome or other acquired thrombophilia
- inherited thrombophilias
- intracranial infection
- inflammatory bowel disease

However we also present data on a broader collection of known or putative venous risk factors, which in addition to the factors above included:

- obesity
- smoking
- chronic renal disease
- previous DVT or PE
- family history of venous thrombo-embolism

Staged roll-out of vaccination by age criteria in the UK during 2021

At the time of this study, most vaccination in the United Kingdom was offered according to age criteria, starting with people aged 80 and over, and then progressively working downwards through the other age groups. Up to 12th April 2021 all individuals aged 50 and over were offered vaccination and from 13th April 2021 individuals aged 45 and over were offered vaccination. The vaccine was only routinely offered to patients aged 40-45 years after 30th April 2021, which was the last date of vaccination of any of the individuals included in the present study. A minority of individuals were vaccinated using criteria other than age, such as those with a very high risk from COVID-19 and their carers, frontline health or social care workers, individuals who lived or worked in care homes and individuals with learning difficulties.

Appendix tables

		ELISA			
		Positive	Negative	Not tested	Total
Acustar HIT-IgG assay	Positive	3	0	0	3
	Negative	9	5	0	14
	Not tested	46	11	21	78
	Total	**58**	**16**	**21**	**95**

ELISA assays were Stago Asserachrom, Immucor Lifecodes or Hyphen Zymutest. Of the 21 patients not tested by either of these methods, two were tested only using a functional assay (Diapharma HITAlert), and 19 patients were not tested for anti-PF4 antibodies by any method.

Table A1: **Contingency table comparing testing for anti-PF4 antibodies using ELISA or Acustar HIT-IgG assay (an automated chemiluminescent assay), the two commonest methods used**

Patient	A	B	C	D	E	F
Sex	Male	Female	Female	Female	Female	Female
Age group (decade)	50s	50s	50s	60s	50s	50s
Vaccine given	ChAdOx1	ChAdOx1	ChAdOx1	ChAdOx1	ChAdOx1	ChAdOx1
Interval (days)	17	14	20	8	8	8
Symptoms	Headache, abdominal pain, vomiting, dysphasia	Headache, dysphasia	Headache	Headache, dysphasia, drowsiness	Headache	Headache, left facial weakness, left neglect
Admission platelet count ($x10^9$/L) NR 150-400	73	158	110	57	37	57
Lowest platelet count ($x10^9$/L) NR 150-400	73	158	110	34	24	57
Highest platelet count after treatment ($x10^9$/L) NR 150-400	259	355	223	(768*)	106	374
Admission D-dimer (μg/L) NR 220-460	6,177	4,985	370	822	119,913	29,503
Highest D-dimer (μg/L) NR 220-460	22,730	4,985	410	822	119,913	29,503
Fibrinogen (g/L) NR 1.9-4.3	2.9	2.0	2.8	2.1	0.83	2.0
Anti-PF4 IgG antibody Stago Asserachrom ELISA (OD) NR 0 - 0.238	0.827 (+ve)	0.594 (+ve)	Not done	Not done	0.177 (-ve)	0.078 (-ve)
Anti-PF4 IgG antibody Immucor Lifecodes ELISA (OD) NR 0 - 0.400	Not done	1.41 (+ve)	2.20 (+ve)	0.298 (-ve)	Not done	Not done
Anti-PF4 IgG antibody Hyphen Zymutest ELISA (OD) NR 0 - 0.239	Not done	Not done	Not done	Not done	0.082 (-ve)	0.035 (-ve)
Brain parenchyma	Haemorrhagic infarct in left temporal lobe	Left ICH	Normal	Right focal oedema	Normal	Right focal oedema. ICH
Intracranial sinuses or veins thrombosed	Left TS, SS, IJV	Left TS, SS	Right TS, SS.	Right TS, SS	Left CoVT. Left SOV, IOV	Right TS, SS, IJV
Extracranial thrombosis	Left PA. HVs, HPV, SV, SMV	None	None	HVs	None	None
Parenteral anticoagulant	SC fondaparinux	None	SC fondaparinux	SC enoxaparin	SC fondaparinux	IV argatroban
Oral anticoagulant	Apixaban	Apixaban	Warfarin	Warfarin	Dabigatran	Apixaban
Oral steroids	None	Prednisolone	Prednisolone	Prednisolone	Prednisolone	None
Plasma exchange	Yes	No	No	No	No	No
IV immunoglobulin	Yes	No	Yes	No	Yes	Yes
mRS on discharge	3	2	0	2	2	1
VITT on Starting Criteria	Yes	No	No	No	Yes	Yes

*Platelet count after platelet transfusion. Precise ages are not given to protect the identities of the patients. ChAdOx1 first dose of ChAdOx1 (AstraZeneca) vaccine. NR normal range, OD optical density, ICH intracerebral haemorrhage, TS transverse sinus, SS sigmoid sinus, IJV internal jugular vein, CoVT cortical vein thrombosis, SOV superior ophthalmic vein, IOV inferior ophthalmic vein, HVs hepatic veins, HPV hepatic portal vein, SV splenic vein, SMV superior mesenteric vein, PA pulmonary artery.

Table A2: **Characteristics of index patients A-F referred to in the text**

	VITT (n=70)	Non-VITT (n=25)	p value (VITT vs non-VITT	ISCVT	p value (VITT vs ISCVT)
Headaches	59 (84%)	21 (84%)	1.0	553/623 (89%)	0.27
Limb weakness	34 (49%)	9 (36%)	0.28	232/624 (37%)	0.063
Nausea / vomiting	31 (44%)	6 (24%)	0.074	Not given	
Drowsiness	23 (33%)	4 (16%)	0.11	Not given	
Confusion	19 (27%)	7 (28%)	0.93	137/624 (22%)	0.32
Seizures	20 (29%)	5 (20%)	0.40	245/624 (39%)	0.081
Visual field defect	13 (19%)	4 (16%)	1.0	Not given	
Language disturbance	12 (17%)	7 (28%)	0.26	119/624 (19%)	0.70
Facial weakness	10 (14%)	0	0.06	Not given	
Limb sensory disturbance	10 (14%)	4 (16%)	1.0	Not given	
Other cortical	10 (14%)	0	1.0	Not given	
Blurred vision	10 (14%)	4 (16%)	1.0	Not given	
Limb clumsiness / ataxia	9 (13%)	3 (12%)	1.0	Not given	
Papilloedema	7 (10%)	1 (4%)	0.35	174/614 (28%)	0.0010
Diplopia or IIIrd or VIth nerve palsy	3 (4%)	1 (4%)	1.0	84/624 (13%)	0.028
Other cranial neuropathy	2 (3%)	0	1.0	Not given	
Vertigo	1 (1%)	1 (4%)	0.46	Not given	

Data compared between VITT-associated cerebral venous thrombosis and the historical cerebral venous thrombosis data set from the ISCVT[12] and between the VITT-associated and non-VITT-associated cerebral venous thrombosis patients in the present study. Variables were compared using the chi squared test.

Table A3: **Clinical features of cerebral venous thrombosis at the time of admission in patients with and without VITT**

	VITT (n=70)	Non-VITT (n=25)	p value (VITT vs non-VITT)	ISCVT	p value (VITT vs ISCVT)
Sinuses / veins occluded					
Superior sagittal sinus	43 (61%)	12 (48%)	0.24	313/624 (50%)	0.074
Left transverse sinus	33 (47%)	11 (44%)	0.79	279/624 (45%)	0.70
Right transverse sinus	31 (44%)	9 (36%)	0.47	257/624 (41%)	0.62
Left sigmoid sinus	25 (36%)	9 (36%)	0.98	Not given	
Right sigmoid sinus	25 (36%)	7 (28%)	0.48	Not given	
Cortical veins	14 (20%)	7 (28%)	0.41	107/623 (17%)	0.55
Deep venous system	10 (14%)	1 (4%)	0.28	68/622 (11%)	0.40
Straight sinus	11 (16%)	1 (4%)	0.17	112/623 (18%)	0.64
Inferior sagittal sinus	5 (7%)	2 (8%)	1.0	Not given	
Cavernous sinus	3 (4%)	0	0.56	8/623 (1%)	0.057
Internal jugular veins	26 (37%)	8 (32%)	0.65	74/624 (12%)	<0.0001
Median number of sinuses or veins thrombosed (IQR)	3 (2-4)	2 (2-3)	0.041	Not given	
Brain parenchyma involvement					
Any infarct or haemorrhage	44 (63%)	14 (56%)	0.55	392/624 (63%)	1.0
Any infarcts	14 (20%)	4 (16%)	0.66	290/623 (47%)	<0.0001
Multiple infarcts	10 (14%)	0	0.046	Not given	
Any haemorrhages	41 (59%)	10 (40%)	0.11	245/622 (39%)	0.0020
Multiple haemorrhages	23 (33%)	3 (12%)	0.045	Not given	
Extracranial thromboses					
Any extracranial thrombosis	31 (44%)	1 (4%)	0.0003		
Pulmonary embolism	14 (20%)	1 (4%)	0.11		
Hepatic portal vein thrombosis	13 (19%)	0	0.018		
Deep vein thrombosis in leg	6 (9%)	0	0.34		
Arterial limb ischaemia	4 (6%)	0	0.57		
Superior mesenteric vein thrombosis	4 (6%)	0	0.57		
Myocardial infarction	2 (3%)	0	1.0		
Splenic vein thrombosis	2 (3%)	0	1.0		
Hepatic vein thrombosis	1 (1%)	1 (4%)	0.46		
Arterial ischaemic stroke	2 (3%)	0	0.34		

Data compared between the VITT-associated cerebral venous thrombosis and non-VITT cerebral venous thrombosis in the present study and between VITT-associated cerebral venous thrombosis and the historical cerebral venous thrombosis data set from the ISCVT[12]. Categorical variables were compared using chi squared test (or Fisher's exact test if fewer than 5 patients in any one category); continuous variables were compared using Mann-Whitney U test.

Table A4: **Sites of thrombosis and brain parenchyma involvement in VITT and non-VITT groups**

	Dead or dependent	Alive and independent	p value
Number of VITT cases	33	37	
Demographics			
Median age (IQR)	52 (34-58)	46 (30-51)	0.12
Female	19 (58%)	20/37 (54%)	0.77
Male	14 (42%)	17/37 (46%)	
Clinical assessment			
History of malignancy	2 (6%)	0 (0%)	0.22
Median admission GCS (IQR)	14 (12-15)	15 (15-15)	<0.0001
Blood biomarkers			
Median platelets (IQR)	34 (22-67)	50 (34-80)	0.078
Median D-dimers (IQR)*	12895 (8826-36125)	16280 (5096-29692)	0.17
Median fibrinogen (IQR)	1.8 (1.0-2.7)	1.7 (1.0-2.5)	0.45
Anti-PF4 antibody positive	26/26 (100%)	32/34 (94%)	0.21
Neuroradiological biomarkers			
Cerebral infarction	7 (21%)	7 (19%)	1.0
Any cerebral haemorrhage	27 (82%)	14 (38%)	0.0002
Multiple cerebral haemorrhages	17 (52%)	6 (16%)	0.0017
Median veins thrombosed (IQR)	3 (3-4)	3 (2-4)	0.19
Thrombosis of deep veins	5 (15%)	5 (14%)	1.0

Results are those which were obtained on admission or as close as possible to admission. For categorical variables, the proportion of patients with the characteristic is shown, followed by the percentage in parenthesis. For continuous variables, the median is shown with the interquartile range (IQR) in parenthesis. *D-dimer result was available in 27 of 33 dead or dependent patients and 35 of 37 alive and independent patients.

Table A5: **Admission characteristics in patients with VITT-associated cerebral venous thrombosis according to whether or not they were dead or dependent (mRS 3-6) at the end of their admission**

	Died	Survived	p value
Number of VITT cases	20	50	
Demographics			
Median age (IQR)	50 (26)	47 (22)	1.0
Female	12/20 (60%)	27/50 (54%)	0.65
Male	8/20 (40%)	23/50 (46%)	
Clinical assessment			
History of malignancy	1/20 (5%)	1/50 (2%)	0.49
Median admission GCS (IQR)	14 (13-15)	15 (15-15)	<0.0001
Blood biomarkers			
Median lowest platelets (IQR)	30 (21-54)	51 (33-75)	0.034
Median highest D-dimers (IQR)	14172 (10000-35000)	15830 (6050-31301))	0.16
Median admission fibrinogen (IQR)	1.7 (1.1-2.3)	1.7 (1.0-2.5)	0.46
Anti-PF4 antibody positive	14/14 (100%)	44/46 (96%)	0.43
Neuroradiological biomarkers			
Cerebral infarction	4/20 (20%)	10/50 (20%)	1.0
Any cerebral haemorrhage	15/20 (75%)	26/50 (52%)	0.078
Multiple cerebral haemorrhages	13/20 (65%)	10/50 (20%)	0.0003
Median veins thrombosed (IQR)	3 (1)	3 (2)	0.20
Thrombosis of deep veins	2/20 (10%)	8/50 (16%)	0.71

Results are those which were obtained on admission or as close as possible to admission. For categorical variables, the proportion of patients with the characteristic is shown, followed by the percentage in parenthesis. For continuous variables, the median is shown with the interquartile range (IQR) in parenthesis.

Table A6: **Admission characteristics in patients with VITT-associated cerebral venous thrombosis who died during admission or who survived and were discharged**

	Numbers of patients treated / not treated	Number of patients that died (%)	p value
Pharmacological			
Any anticoagulation	..	..	<0.0001
Yes	60	11 (18%)	..
No	10	9 (90%)	..
Heparin/LMWH	..	..	0.53
Yes	16	3 (19%)	..
No	54	17 (31%)	..
Non-heparin parenteral anticoagulant	..	..	0.0020
Yes	50	9 (18%)	..
No	20	11 (55%)	..
Direct oral anticoagulant	..	..	0.0001
Yes	22	0 (0%)	..
No	48	20 (42%)	..
Corticosteroid	..	..	0.034
Yes	51	11 (22%)	..
No	19	9 (47%)	..
Anticonvulsant	..	..	0.060
Yes	26	22 (85%)	..
No	44	28 (64%)	..
Fibrinogen replacement	..	..	0.051
Yes	15	1 (7%)	..
No	55	19 (35%)	..
Intravenous immunoglobulin	..	..	0.080
Yes	55	13 (24%)	..
No	15	7 (47%)	..
Plasma exchange	..	..	0.13
Yes	16	2 (13%)	..
No	54	18 (33%)	..
Platelet transfusion	..	..	0.0073
Yes	25	12 (48%)	..
No	45	8 (18%)	..
Invasive			
Endovascular management	..	..	0.71
Yes	9	3 (33%)	..
No	61	17 (28%)	..
Intracranial pressure monitor	..	..	0.12
Yes	13	6 (46%)	..
No	57	14 (25%)	..
Decompressive hemicraniectomy	..	..	0.025
Yes	13	7 (54%)	..
No	57	13 (23%)	..

P values are for chi squared tests comparing the proportion of patients who died during admission, in patients treated compared with those not treated.

Table A7: **Proportions of patients with VITT-associated cerebral venous thrombosis who died during admission, by treatment modality**

Appendix figures

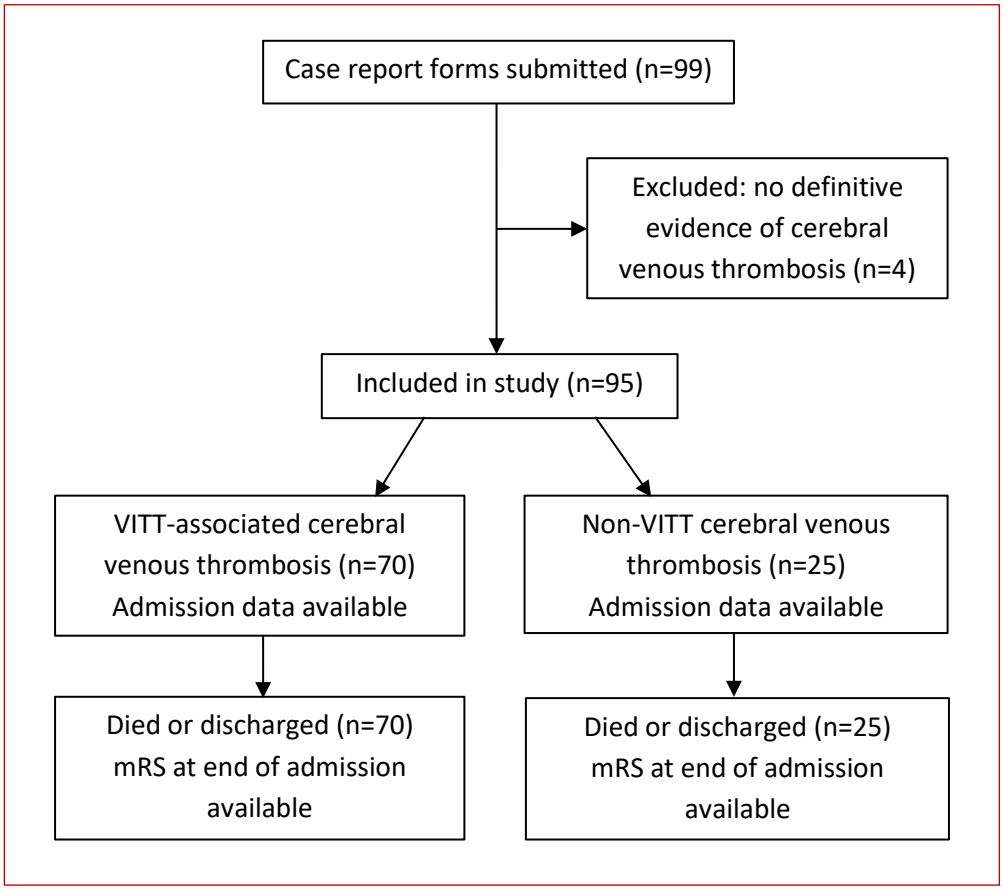

Figure A1: **Study flow diagram.**

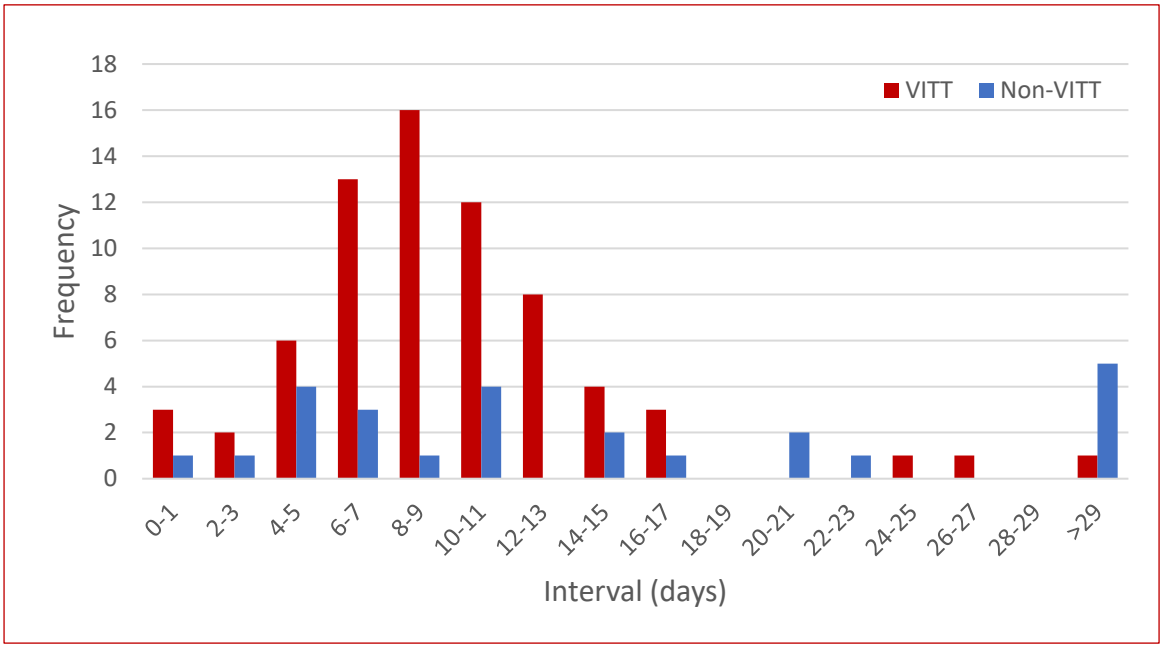

Figure A2: **Interval between vaccine date and onset of symptoms**

Data are shown for all patients with VITT (red bars) or without VITT (blue bars). For patients where a headache developed within hours of vaccination and persisted unchanged up to cerebral venous thrombosis diagnosis, the onset of that headache was recorded as the cerebral venous thrombosis symptom onset, even though at the start it most likely had another mechanism.

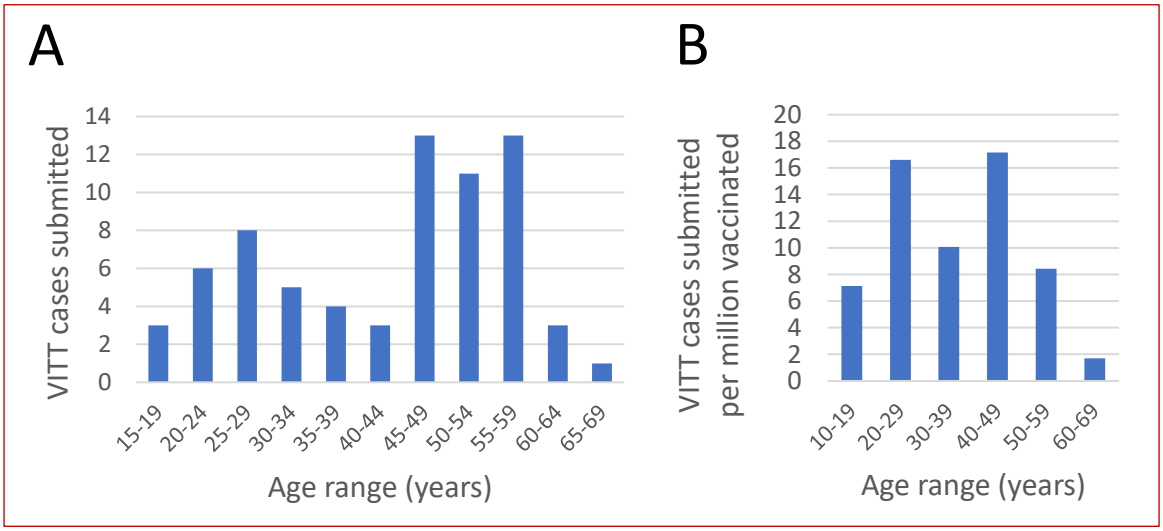

Figure A3: **Age distribution of patients with VITT-associated cerebral venous thrombosis**

A. Raw data. B. Data adjusted for numbers of patients in each age decade vaccinated in the UK extracted from the OpenSafely data set[13].

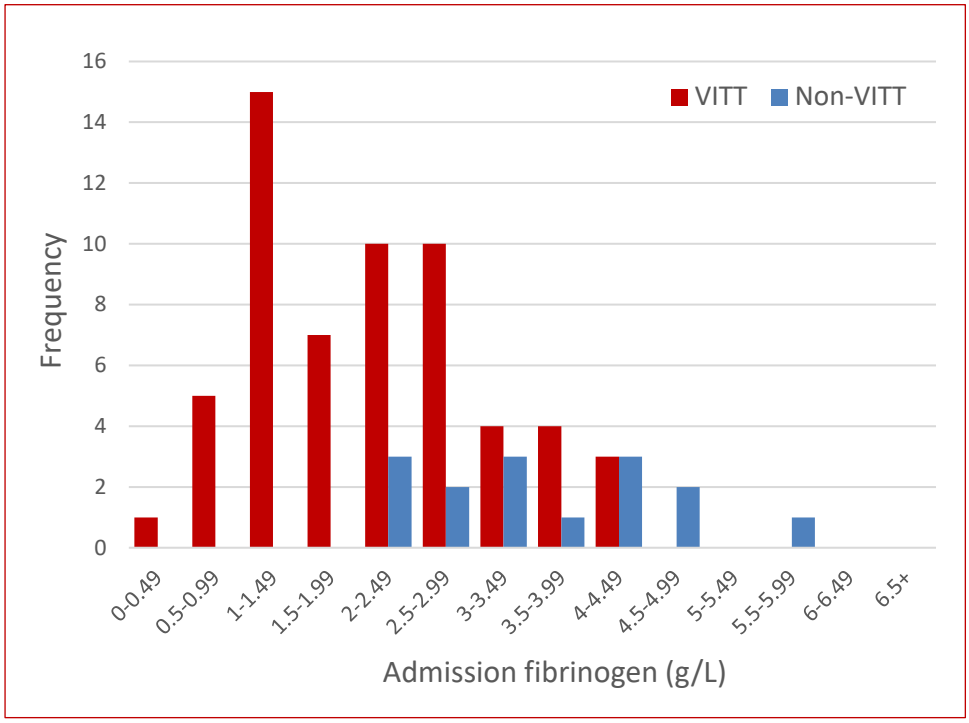

Figure A4: **Distributions of fibrinogen on admission in patients with cerebral venous thrombosis with and without VITT.**

The median fibrinogen was significantly lower in the VITT group (2.0 g/L) than in the non-VITT group (3.3 g/L, p=0.0001).

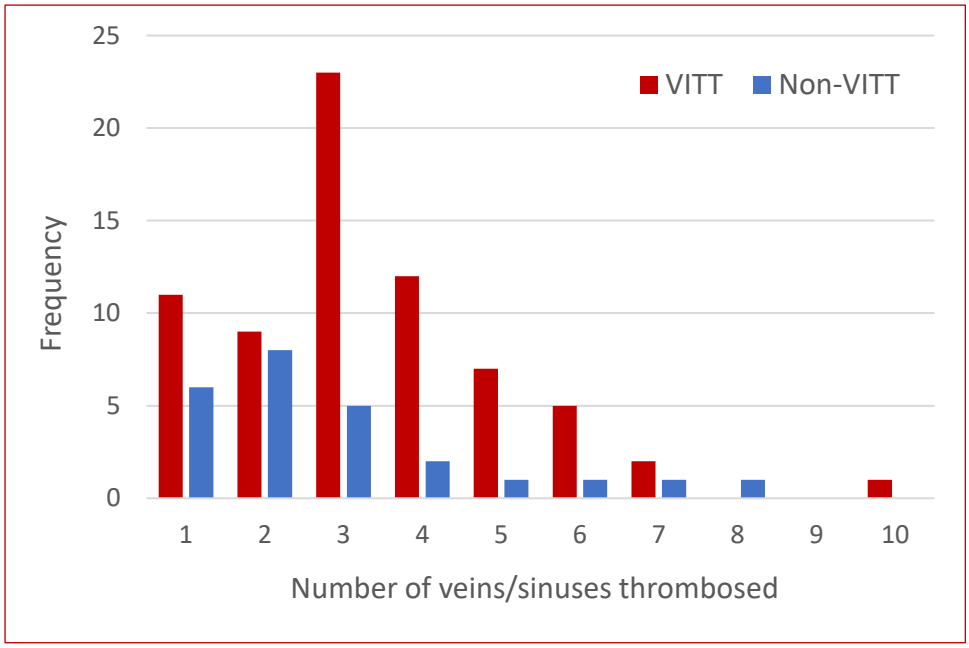

Figure A5: **Number of veins or sinuses thrombosed in the VITT and non-VITT groups**

The median number was higher in the VITT group (3) than in the non-VITT group (2, p=0.04).