Outcomes of patients with thromboembolic events following coronavirus disease 2019 AstraZeneca vaccination: a systematic review and meta-analysis

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AstraZeneca coronavirus disease 2019 (COVID-19) vaccinations have recently been implicated in thromboembolism formations. Our aim was to investigate the outcomes of patients with thromboembolic events following the AstraZeneca vaccine (ChAdOx1 nCoV-19, AZD1222). A literature search was performed from December 2019 to September 2021. Eligible studies must report participants older than 18 years vaccinated with AstraZeneca and outcomes of thromboembolic events. Pooled mean or proportion were analyzed using a random-effects model. A total of 45 unique studies (number of patients = 144, 64.6% women, mean age 21–68 years) were included. The most common presenting adverse events were headache (12.1%), intracerebral hemorrhage (7.5%), and hemiparesis (7%). The most common thromboembolic adverse events were cerebral venous sinus thrombosis (38.5%) and deep vein thrombosis/pulmonary embolism (21.1%). The most common radiologic finding were intracerebral hemorrhage and cerebral venous thrombosis. Laboratory findings included thrombocytopenia (75%) and hypofibrinogenemia (41%). On admission, 64 patients tested positive for PF4-Heparin ELISA assay (80%). Seventy-four patients were hospitalized with 22 being admitted to the ICU. A total of 78 patients recovered while 39 patients died. This meta-analysis presents evidence to suggest vaccine-induced immune thrombotic thrombocytopenia (VITT) following AstraZeneca vaccine. Clinical practice must, therefore, account for the possibility of VITT and subsequent embolic events in certain individuals' postvaccination with adenovirus-based COVID-19 vaccines. Serum anti-PF4 suggests diagnostic value for VITT and could subsequently inform treatment choices in such instances. *Blood Coagul Fibrinolysis* **33:90–112**

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Introduction

The first case of coronavirus was identified in Wuhan, China in early December 2019 [1]. The virus, part of the novel enveloped RNA betacoronavirus family, has been named as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease coronaviruses disease 2019 (COVID-19) [2]. Since then, COVID-19 has been declared as a pandemic affecting over 224 180 411 globally with more than 4 621 205 deaths [3]. As such, efforts have been directed to combat and manage this disease.

Currently, four companies (AstraZeneca-Oxford (Cambridge, United Kingdom) Pfizer-Biontech (New York, NY, USA and Mainz, Germany), Moderna (Cambridge, Massachusetts, USA), and Johnson and Johnson (New Brunswick, New Jersey, USA)) have manufactured vaccines that have been authorized for use in the European Union. Whilst all are yet to reach approval status, emerging data from double-blinded, randomized, controlled clinical trials have persuaded the American Food and Drug Administration (FDA) to permit emergency use authorization for the Pfizer-Biontech, Moderna and Johnson and Johnson vaccines, whilst the European Medicine Agency has permitted use of the AstraZeneca vaccine, and full FDA approval for Pfizer-Biontech vaccine. Two of these vaccines are messenger RNA-based vaccines – BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) – which encode the spike protein antigen of SARS-CoV-2, encapsulated in lipid nanoparticles [4,5]. The other two vaccines, ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson and Johnson/Janssen), are recombinant adenoviruses that encode the spike glycoprotein of SARS-CoV-2 [6].

To date, approximately 560 261 011 of vaccines have been administered in the European Union and 5.88 billion

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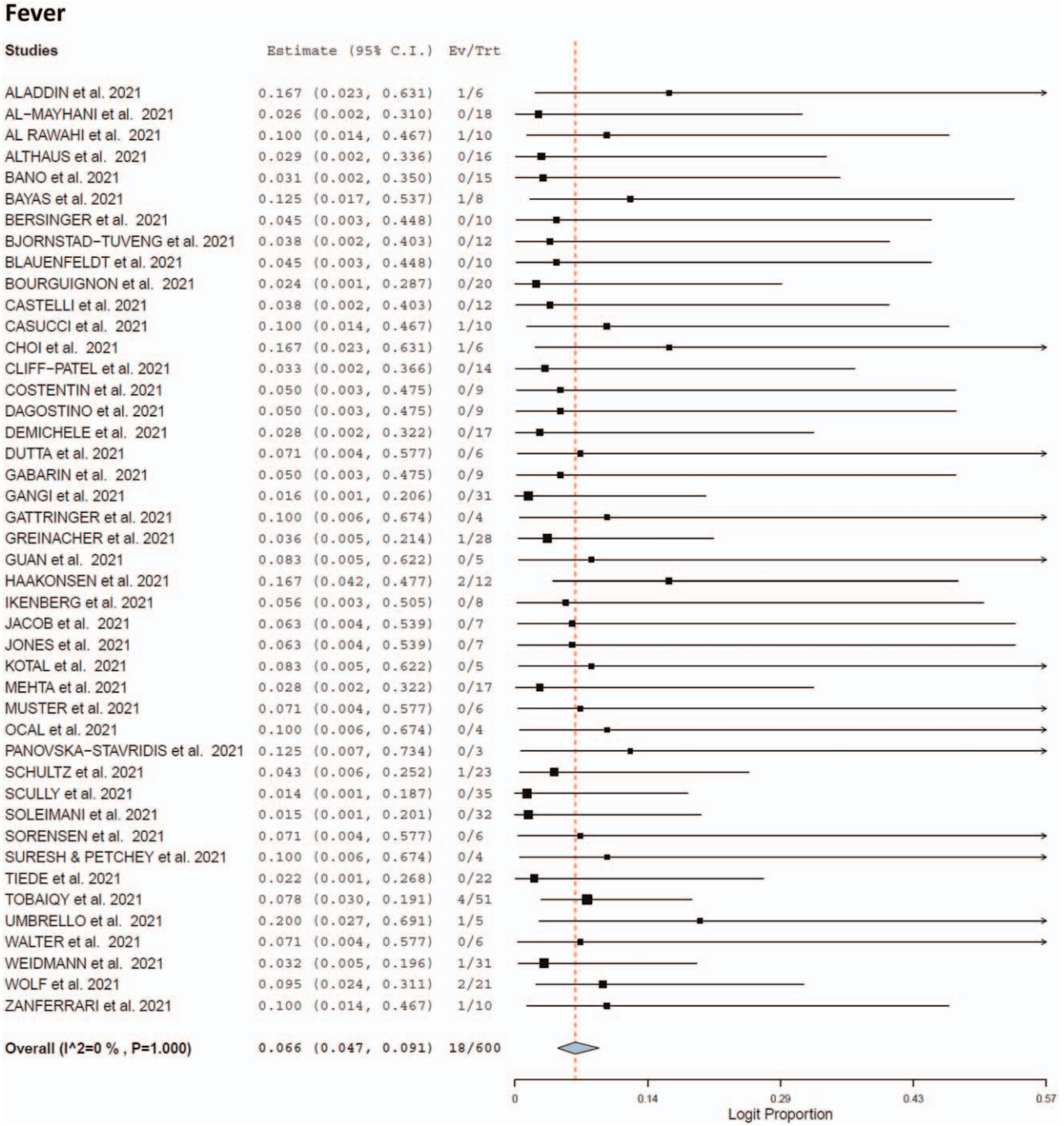
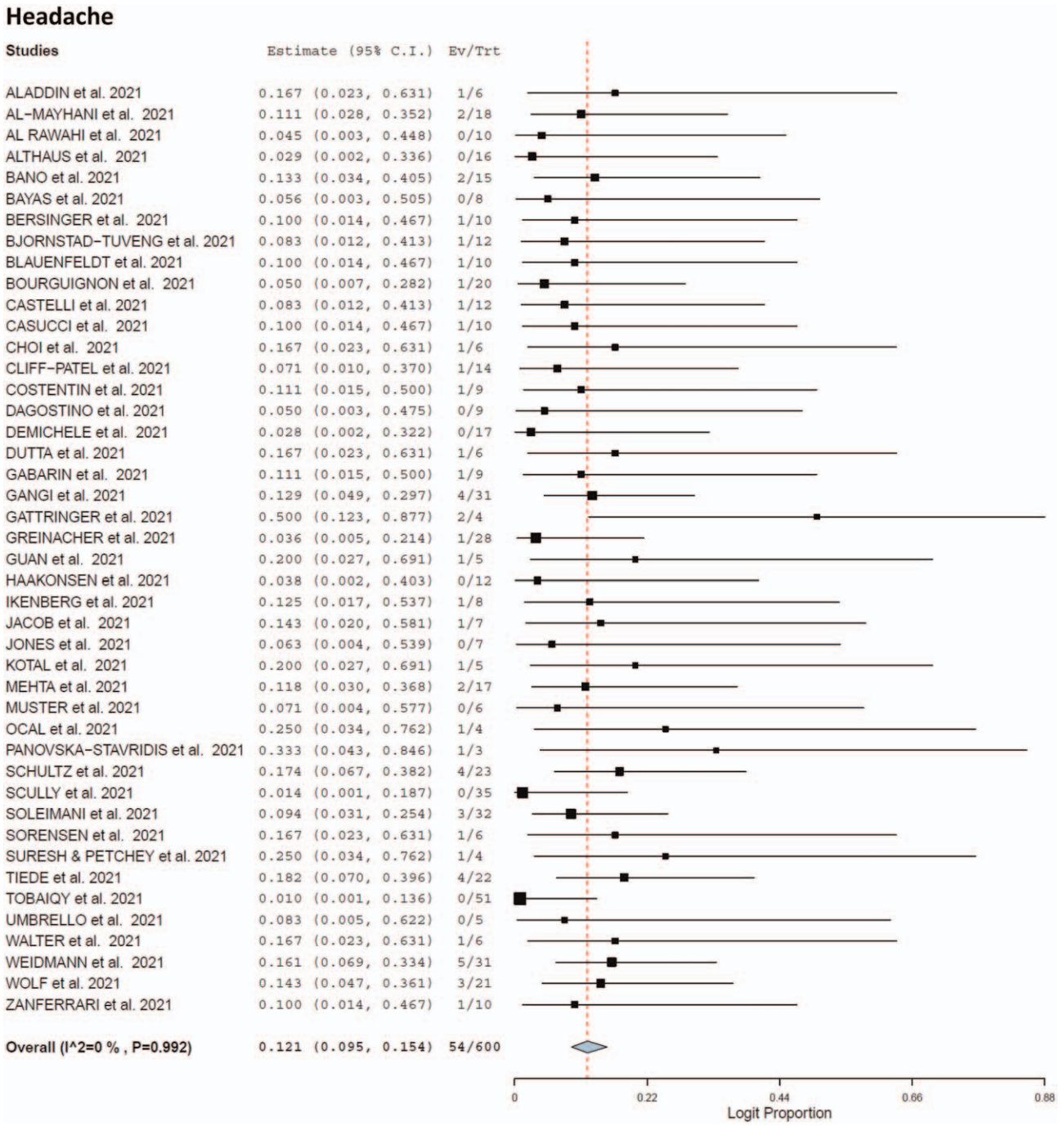
Fig. 1



Forest plot of the adverse effects at time of presentation.

around the world, roughly 25% being ChAdOx1 nCoV-19 [7]. The expedited approval for the use of the vaccines, however, does not come without its pitfalls. In mid-February 2021, many patients reported various vaccine-related side effects [8]. A study has evaluated the safety and efficacy of the ChAdOx1 nCoV-19 based on clinical trials of 23 745 individuals randomized to either AstraZeneca vaccine or control in United Kingdom, Brazil, and South Africa [9]. The results demonstrated that most prevalent adverse events included redness, pain, headache, fatigue, and malaise. Since then, the majority of the European Union decided to temporarily halt the use of the AstraZeneca vaccine amid reports of its association with increased risk of thromboembolic events along with multiple deaths.

Fig. 1



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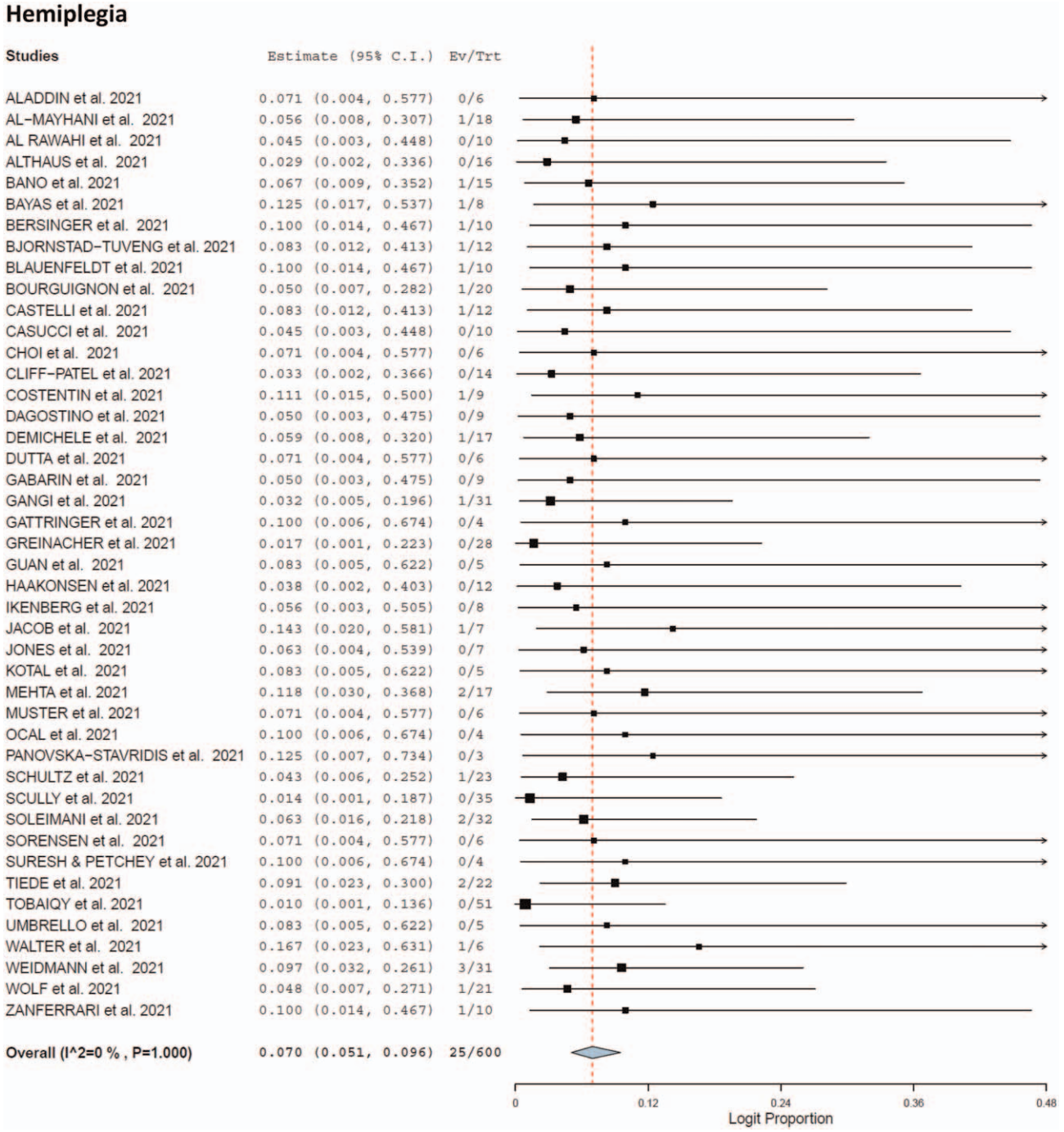
Accordingly, a retrospective study investigated reports submitted to the EudraVigilance database [10]. Following 54,571 adverse events, 28 were associated with thromboembolic events, of which were four related mortalities.

On 13 April 2021, in a joint statement, the CDC and FDA recommended to suspend the use of Johnson and Johnson vaccines as six thromboembolic events were discovered following an administration of 6.8 million doses [11]. As more individuals continue to get vaccinated, there is an urgent need to answer questions regarding the safety of the AstraZeneca vaccine specifically pertaining to its association with increased thromboembolic adverse events. Although the results available in the literature

Fig. 1



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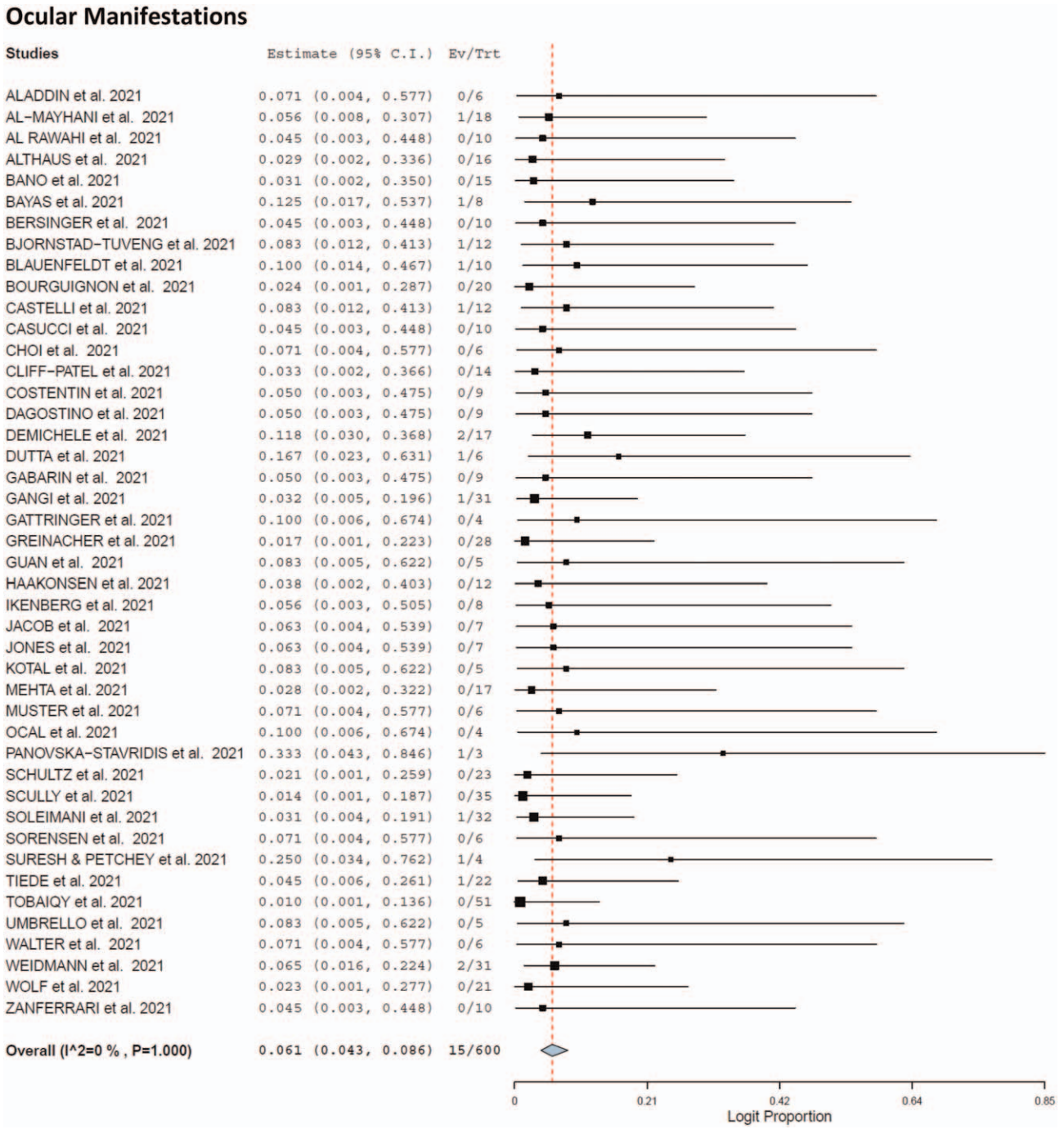
may be sparse, it is important to recognize the urgency and time-sensitivity of this issue. To date, there is no systematic review or meta-analysis that has been conducted. Therefore, this systematic review and meta-analysis aims to provide insight into the outcomes of thromboembolic events in patients following AstraZeneca Vaccine.

Methods

Search strategy and data sources

A comprehensive search of several databases from 1 December 2019, to 1 September 2021 was conducted and limited to English language only. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily,

Fig. 1



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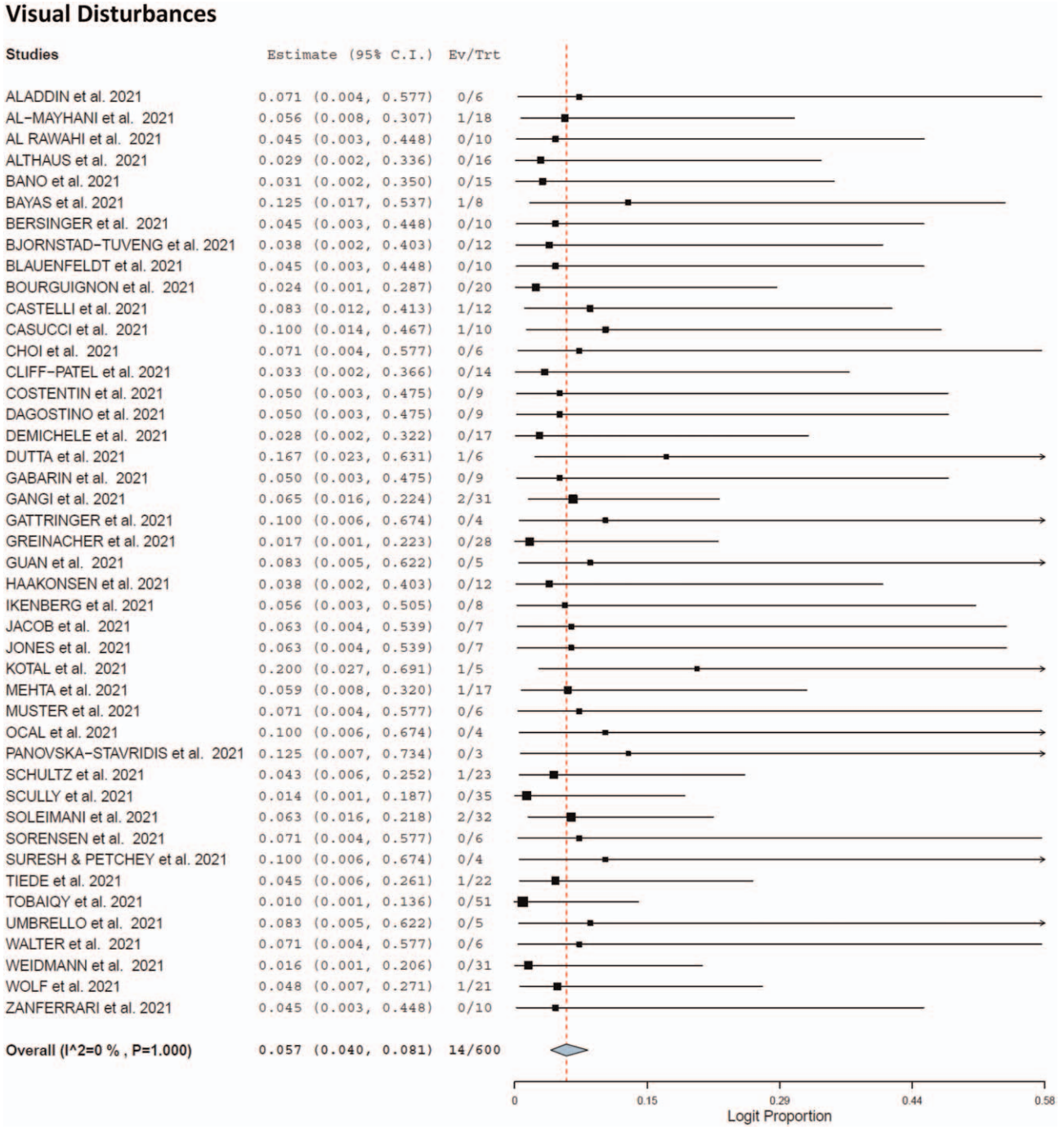
Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, PMC Preprints, and ClinicalTrials.Gov. The search strategy was designed and conducted by a medical reference librarian. Controlled vocabulary supplemented with keywords was used to search for AstraZeneca vaccine and thromboembolic events. The actual strategy listing all search terms used and how they are combined is available in Supplementary Item 1, http://links.lww.com/BCF/A119.

Eligibility criteria and quality assessment

Eligible studies must have met all the following inclusion criteria: participants must be older than 18 years

Fig. 1



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vaccinated with AstraZeneca vaccine; reports adverse events and outcomes of thromboembolic events. The methodological quality of each study was independently evaluated by two authors (R.H.M. and C.A.T.) using the methodological quality and synthesis of case series and case reports as has been previously described within the literature [12].

Statistical analysis

Means of continuous variables and rates of binary variables were pooled using the random-effects model, generic inverse variance method of DerSimonian and Laird [13]. Proportions underwent logit transformation prior to meta-analysis. The heterogeneity of effect size estimates across the studies was quantified using the Q

statistic and the I^2 index ($P < 0.10$ was considered significant). A value of I^2 of 0–25% indicates minimal heterogeneity, 26–50% moderate heterogeneity, and 51–100% substantial heterogeneity. Data analysis was performed using Open Meta analyst software (CEBM, Brown University, Providence, Rhode Island, USA).

Results

Study selection and characteristics

The initial search yielded 567 potentially relevant articles from which 45 unique studies involving 144 patients met the eligibility criteria. The details of study selection process are depicted in Supplementary Item 2, http://links.lww.com/BCF/A120. The baseline characteristics of the included studies are comprehensively described in Table 1. The mean age ranged from 21 to 68 years of which 93 patients were women.

Risk of bias

Results of the quality assessment of all included studies are shown in Supplementary Table 1, http://links.lww.com/BCF/A124. All the case series were judged to be of good quality. The patients appeared to represent the whole experience of the investigator and the exposure and outcome were adequately ascertained, and the length of follow-up was adequate.

Table 1 Baseline characteristics of included studies

Author, year	Country	Study design	Number of subjects (*n*)	Sex (male)	Sex (female)	Mean age ± SD (years)
Aladdin *et al*., 2021	Saudi Arabia	Case Report	1	0	1	36.00
Al-mayhani *et al*., 2021	UK	Case Series	3	1	2	38.33
Al rawahi *et al*., 2021	Oman	Case Report	1	1	0	64.00
Althaus *et al*., 2021	Germany	Case Series	8	3	5	39.50
Bano *et al*., 2021	UK	Case Report	3	1	2	56.00
Bayas *et al*., 2021	Germany	Case Report	1	0	1	55.00
Bersinger *et al*., 2021	France	Case Report	1	0	1	21.00
Bjornstad-tuveng *et al*., 2021	Norway	Case Report	1	0	1	NR
Blauenfeldt *et al*., 2021	Denmark	Case Report	1	0	1	60.00
Bourguignon *et al*., 2021	Canada	Case Series	3	2	1	68.00
Castelli *et al*., 2021	Italy	Case Report	1	1	0	50.00
Casucci *et al*., 2021	Italy	Case Report	1	0	1	52.00
Choi *et al*., 2021	South Korea	Case Report	1	1	0	33.00
Cliff-patel *et al*., 2021	UK	Case Series	3	3	0	40.66
Costentin *et al*., 2021	France	Case Report	1	0	1	26.00
D'agostino *et al*., 2021	Italy	Case Report	1	0	1	54.00
Demichele *et al*., 2021	Italy	Case Series	2	0	2	56.00
Dutta *et al*., 2021	India	Case Report	1	1	0	51.00
Gabarin *et al*., 2021	Canada	Case Series	2	2	0	61.50
Gangi *et al*., 2021	UK	Case Series	6	4	2	37.33
Gattringer *et al*., 2021	Austria	Case series	2	0	2	31.50
Greinacher *et al*., 2021	Germany	Case Series	11	2	9	36.00
Guan *et al*., 2021	Taiwan, ROC	Case Report	1	1	0	52.00
Haakonsen *et al*., 2021	Norway	Case Series	2	1	1	NR
Ikenberg *et al*., 2021	Germany	Case Report	1	0	1	NR
Jacob *et al*., 2021	UK	Case Report	1	0	1	39.00
Jones *et al*., 2021	Canada	Case Report	1	1	0	63.00
Kotal *et al*., 2021	India	Case Report	1	0	1	32.00
Mehta *et al*., 2021	UK	Case Series	2	2	0	28.60
Muster *et al*., 2021	Austria	Case Report	1	0	1	51.00
Ocal *et al*., 2021	Germany	Case Report	1	1	0	41.00
Panovska-stavridis *et al*., 2021	Republic of North Macedonia	Case Report	1	0	1	29.00
Schultz *et al*., 2021	Norway	Case Series	5	1	4	40.80
Scully *et al*., 2021	UK	Retrospective Study	22	9	13	43.00
Soleimani *et al*., 2021	UK	Case Series	3	1	2	44.00
Sorensen *et al*., 2021	Denmark	Case report	1	0	1	30.00
Suresh, Petchey *et al*., 2021	UK	Case Report	1	1	0	27.00
Tiede *et al*., 2021	Germany	Case Series	5	0	5	58.60
Tobaiqy *et al*., 2021	Saudi Arabia	Retrospective Descriptive Study	28	9	19	NA
Umbrello *et al*., 2021	Italy	Case Report	1	0	1	36.00
Varona *et al*., 2021	Spain	Case Report	1	1	0	47.00
Walter *et al*., 2021	Germany	Case Report	1	1	0	31.00
Weidmann *et al*., 2021	Norway	Case Series	5	0	5	41.20
Wolf *et al*., 2021	Germany	Case Series	3	0	3	34.70
Zanferrari *et al*., 2021	Italy	Case Report	1	0	1	40.00
Abou-Ismail *et al*., 2021[a]	USA	Case Report	1	1	0	48.00
Clark *et al*., 2021[a]	USA	Case Report	1	0	1	40.00
Dhoot *et al*., 2021[a]	USA	Case Report	1	1	0	24.00
Malik *et al*., 2021[a]	USA	Case Report	1	0	1	43.00
Muir *et al*., 2021[a]	USA	Case Report Correspondence	1	0	1	48.00
See *et al*., 2021[a]	USA	Case Series	12	0	12	NR

NR, not reported; SD, standard deviation. [a]Studies are Ad26.COV2.S reports.

Table 2 Clinical characteristics of included patients

Author, year	Existing comorbidities (*n*)	History of relevant disorders (*n*)	Preexisting medications (*n*)	Use of contraceptives or hormonal therapies (*n*)
Aladdin *et al.*, 2021	Diabetes (1)	0	0	0
Al-mayhani *et al.*, 2021	0	NR	NR	NR
Al rawahi *et al.*, 2021	Hyperlipidaemia (1), hypertension (1)	0	0	0
Althaus *et al.*, 2021	NR	NR	NR	NR
Bano *et al.*, 2021	Asthma (1), fibromyalgia (1), hypertension (1), obesity (1)	0	Anti-HTN agent (1)	HRT (1)
Bayas *et al.*, 2021	0	0	0	NR
Bersinger *et al.*, 2021	Chronic migraine (1)	0	0	Oral contraceptive pill (1)
Bjornstad-tuveng *et al.*, 2021	Allergy (1), iron deficiency (1)	NR	Desloratadine (1), Duroferon (1)	0
Blauenfeldt *et al.*, 2021	Hypertension (1), hypothyroidism (1),	NR	Anti-HTN agent (1), cholesterol-lowering medication (1), thyroid hormone replacements (1)	0
Bourguignon *et al.*, 2021	Diabetes (1), hypertension (1), prostate cancer (1)	Sleep apnoea (1)	Aspirin (1), heparin (1)	0
Castelli *et al.*, 2021	0	0	0	NR
Casucci *et al.*, 2021	Chronic headaches (1), Hepatitis B (1), history of breast cancer (1), ovarian cyst (1)	0	0	0
Choi *et al.*, 2021	0	0	0	0
Cliff-patel *et al.*, 2021	NR	NR	NR	NR
Costentin *et al.*, 2021	0	0	0	Oral contraceptive pill (1)
D'agostino *et al.*, 2021	Meniere's disease (1)	0	0	0
Demichele *et al.*, 2021	History of breast cancer (1), hypothyroidism (2)	NR	NR	NR
Dutta *et al.*, 2021	0	0	0	0
Gabarin *et al.*, 2021	0	NR	NR	NR
Gangi *et al.*, 2021	Asthma (1), cardiomyopathy (1), depression (2), diverticulitis (1), Guillain–Barre syndrome (1), hip arthroscopy (1), hypertension (1), PCOS (1), polycythemia (1)	0	0	Oral contraceptive pill (1)
Gattringer *et al.*, 2021	0	0	NR	NR
Greinacher *et al.*, 2021	Anticardiolipin antibodies (1), factor V Leiden (1), Von Willebrand factor (1)	NR	0	Hormonal IUD (2), oral contraceptive pill (1)
Guan *et al.*, 2021	0	NR	0	0
Haakonsen *et al.*, 2021	Hypothyroidism (1).	0	Thyroid hormone replacements (1)	0
Ikenberg *et al.*, 2021	0	0	0	0
Jacob *et al.*, 2021	0	0	0	0
Jones *et al.*, 2021	Hypertension (1), obesity (1)	0	Anti HTN medication (1)	NR
Kotal *et al.*, 2021	0	0	0	0
Mehta *et al.*, 2021	0	0	Amitriptyline (1), corticosteroids (1), ursodeoxycholic acid (1)	NA
Muster *et al.*, 2021	0	NR	NR	NR
Ocal *et al.*, 2021	NR	NR	NR	NR
Panovska-stavridis *et al.*, 2021	0	0	0	0
Schultz *et al.*, 2021	Allergy (2), asthma (1), hypertension (1)	0	Anti-HTN agent (1)	HRT (1), oral contraceptive pill (1), contraceptive vaginal ring (1)
Scully *et al.*, 2021	0	DVT (1)	0	0
Soleimani *et al.*, 2021	Bipolar disorder (1)	0	Lithium (1)	0
Sorensen *et al.*, 2021	0	0	0	Oral contraceptive pill (1)
Suresh & petchey *et al.*, 2021	0	0	0	0
Tiede *et al.*, 2021	0	NR	NR	NR
Tobaiqy *et al.*, 2021	0	NR	NR	NR
Umbrello *et al.*, 2021	0	0	NR	NR
Varona *et al.*, 2021	NR	0	NR	NR
Walter *et al.*, 2021	0	0	0	0
Weidmann *et al.*, 2021	Allergy (3), hypertension (1)	0	Anti HTN agent (1)	HRT (1), oral contraceptive pill (1), contraceptive vaginal ring (2)

Table 2 (*continued*)

Author, year	Existing comorbidities (*n*)	History of relevant disorders (*n*)	Preexisting medications (*n*)	Use of contraceptives or hormonal therapies (*n*)
Wolf *et al.*, 2021	0	0	0	0
Zanferrari *et al.*, 2021	0	0	0	0
Abou-ismail *et al.*, 2021[a]	Asthma (1)	0	0	0
Clark *et al.*, 2021[a]	0	0	0	0
Dhoot *et al.*, 2021[a]	0	0	NR	NR
Malik *et al.*, 2021[a]	Depression (1), hyperlipidaemia (1), obesity (1)	GORD (1), hyperlipidaemia (1), sleep apnoea (1)	0	0
Muir *et al.*, 2021[a]	0	NR	NR	NR
See *et al.*, 2021[a]	Hypothyroidism (1), obesity (6)	0	0	Oral Contraceptive Pill (1)

DVT, deep vein thrombosis; IUD, intrauterine device; NR, not reported. [a]Studies are Ad26.COV2.S reports.

Clinical characteristics

The clinical characteristics of the patients are shown in Table 2. Among the overall population, some patients had at least one coexisting illness; frequently reported illnesses included pollen allergy ($n=6$), hypothyroidism ($n=4$) hypertension ($n=8$), asthma ($n=3$), diabetes ($n=2$), and neurologic disorders ($n=2$). One patient had comorbidity of Von Willebrand Disease, factor V Leiden thrombophilia, and anticardiolipin antibodies [14]. One patient had a relevant history of deep vein thrombosis (DVT) [15]. Sixteen patients were on pre-existing medication prior to presentation. Some common medications included antihypertension agents [16,17] and thyroid hormone replacement agents [16,18]. The use of contraceptive methods was indicated in 15 patients. Specifically, seven patients were on the contraceptive pill [14,15,17], three patients were on hormone replacement therapy, two on hormonal intrauterine device (IUD) [14], and three patients on contraceptive vaginal ring [17] (Supplementary Item 3: http://links.lww.com/BCF/A121; Supplementary Item 4: http://links.lww.com/BCF/A122; Supplementary Item 5: http://links.lww.com/BCF/A123).

Radiological and laboratory findings

Table 3 shows the radiologic and laboratory findings on admission. The most common imaging performed were CT ($n=114$) and MRI ($n=38$). The most common radiologic findings were intracranial hemorrhage and cerebral venous sinus thrombosis.

On admission, the pooled mean platelet count was 63 373.552/μl (95% CI 4 3420.560–83 326.543, $I^2=97.35\%$). The pooled mean international normalized ratio was 1.187 (95% CI 1.127–1.247, $I^2=56.78\%$). Thrombocytopenia was present in one hundred and four patients with a pooled proportion of 75% (95% CI 0.648–0.831, $I^2=11.99\%$). Hypofibrinogenemia was present in 24 patients with a pooled proportion of 41% (95% CI 0.217–0.636, $I^2=46.87\%$). The pooled mean d-dimer was 21 789.399 ng/ml (95% CI 15 188.467 28 390.330, $I^2=69.82\%$). The pooled mean aPTT was 25.157 s (95% CI 17.014–33.299, $I^2=98.94\%$). The pooled mean fibrinogen was 173 613 mg/dl (95% CI 146.691–200.535, $I^2=65.57\%$). The pooled mean C-reactive protein was 43.653 mg/l (95% CI 4.364–82.942; $I^2=95.05\%$).

On admission, 53 patients of 57 had a clinical diagnosis of vaccine-induced thrombocytopenia (77%; 95% CI 0.652–0.856; $I^2=0\%$). On admission, 64 patients tested positive for platelet factor 4-Heparin ELISA assay (80%; 95% CI 0.692–0.877; $I^2=0\%$). Additionally, the pooled mean rate of platelet factor 4-heparin ELISA was 1.792 optic density (95% CI 0.070–3.513; $I^2=99.33\%$). Moreover, the pooled mean rate of lifecodes PF4 IgG assay was 2.592 optic density (95% CI 1.829–3.354; $I^2=95.63\%$).

Outcomes of reported adverse events

The pooled mean of time to onset of first adverse event following vaccination was 8.468 days (95% CI 7.486–9.451; $I^2=79.42\%$) ranging from 0 to 20 days. A total of 604 adverse events were reported, 223 of which were thromboembolic events. Out of 223 thromboembolic events, 70 were central venous sinus thrombosis (CVST), 67 were pulmonary embolism (PE)/DVT, and the rest were classified as other thromboembolic events. The pooled rate of CVST was 38.5% (95% CI 0.309–0.466, $I^2=6.54\%$). The rate of PE/DVT was 21.1% (95% CI 0.168–0.255, $I^2=0\%$). Seventy-two patients presented to the Emergency Room following an adverse event with a pooled rate of 73.1% (95% CI 0.617–0.820, $I^2=0\%$). Seventy-four patients were hospitalized, of which 22 were admitted to the ICU. The pooled rate of patients hospitalized was 80% (95% CI 0.708–0.868, $I^2=0\%$) and pooled rate of ICU admission was 44.1% (95% CI 0.310–0.582, $I^2=0\%$). The pooled mean of time to hospitalization after vaccination was 10.065 days (95% CI 8.275–11.856, $I^2=57.93\%$).

Patients received various treatment modalities over the course of their stay. Twenty-one patients received platelet transfusions with a pooled rate of 34.5% (95% CI 0.251–0.452, $I^2=0\%$). Nineteen patients were treated with a craniectomy with a pooled rate of 33.5% (95% CI 0.244–0.441, $I^2=0\%$). Ten patients received low-molecular-weight heparin (LMWH) with a pooled rate of 24.6% (95% CI 0.171–0.340, $I^2=0\%$), whereas 12 patients

Table 3 Radiologic and laboratory findings on admission

Author, year	Imaging conducted (*n*)	Major MRI findings (*n*)	Major CT findings (*n*)	Thrombocytopenia (*n*)	Hypofibrinogenemia (*n*)	Mean platelet count (per μl) ± SD	Mean Prothrombin time (INR) ± SD	Mean aPTT (sec) ± SD	Mean Fibrinogen (mg/dl)	Mean D-dimer (ng/ml) ± SD
Aladdin *et al.*, 2021	Brain CT (1)	NA	NR	1	NR	NR	45.00	98.00	NR	NR
Al-mayhani *et al.*, 2021	CT (2), CTA (2), MRI (2), CT venogram (1)	PE (1), CVST (1), hepatic vein thrombosis (1), jugular vein thrombosis (1), iliac vein thrombosis (1), MCA occlusion (1)	MCA occlusion (2), portal vein thrombosis (1), internal carotid artery occlusion (1), CVST (1)	NR	NR	40 333.00 ± 28 290.00	NR	NR	NR	23 073.33 ± 11418.24
Al rawahi *et al.*, 2021	TTE (1), CTA abdomen (1), CTA pelvis (1), ECG (1), CXR (1), CT head with CT arteriogram and CT venogram (1)	NA	Descending aorta thrombi (1), PE (1), renal vein thrombosis with renal infarction (1), bilateral adrenal gland hemorrhage (1)	1	NR	20 000.00	13.00	49.20	400.00	36 900.00
Althaus *et al.*, 2021	NR	NR	NR	8	NR	44 000.00 ± 29 800.00	NR	27.56 ± 7.80	180.00	18 000.00 ± 12 300.00
Bano *et al.*, 2021	CTPA (1), CT venogram (1), CT head (1)	NA	PE (1), CVST (1), internal jugular vein thrombosis (1),subarachnoid hemorrhage (1)	3	NR	23 333.00 ± 2082.00	NR	NR	149.70	20 959.00 ± 23 391.00
Bayas *et al.*, 2021	MRI (1)	SOVT (1), ischemic stroke (1)	NA	1	NR	NR	NR	NR	NR	NR
Bersinger *et al.*, 2021	CT head (1), CT (1)	NA	CVST (1), jugular vein thrombosis (1), PE (1), splanchnic vein thrombosis (1), external iliac vein thrombosis (1)	1	NR	61 000.00	NR	NR	NR	NR
Bjornstad-tuveng *et al.*, 2021	CT head (1), CTA (1), transcranial Doppler (1)	NA	Intracranial Haemorrhage (1), Oedema (1)	1	NR	37 000.00	NR	27.00	220.00	NR
Blauenfeldt *et al.*, 2021	CT abdomen (1), MRI (1), CT head (1), MR angiography (1)	MCA infarction (1), internal carotid artery occlusion (1)	Adrenal hemorrhage (1), subscapular renal hematoma (1), oedema (1)	1	NR	118 000.00	NR	NA	NA	NA
Bourguignon *et al.*, 2021	CTA (1), US (1)	NA	NA	NR	NR	NR	NR	NR	NR	NR
Castelli *et al.*, 2021	CT head (1), CTA (1)	NA	Intracranial hemorrhage (1), CVST (1)	1	1	20 000.00	NR	26.80	98.00	NR
Casucci *et al.*, 2021	Echocardiography (1), Doppler US (1), CT head (1), CT (1), MRA (1)	Transverse sinus hypoplasia (1)	NR	NR	NR	77 000.00	15.00	28.00	100.00	8298.00
Choi *et al.*, 2021	Non-enhanced CT head (1), MRI venogram (1),	CVST (1)	Parietal lobe subcortical hematoma (1) subarachnoid hemorrhage (1)	1	1	14 000.00	14.00	28.00	77.00	NR
Cliff-patel *et al.*, 2021	CT (2), US (1), CT venogram (1), CTPA (2)	NA	Pyelonephritis (1), PE (3), renal vein thrombus (1), DVT (1)	3	NR	NR	NR	NR	NR	NR
Costentin *et al.*, 2021	MRI (1), CT (1), cervical CTA (1), transesophageal echocardiography (1)	Acute ischemic stroke	Haemorrhagic infarction (1), PE (1), portal vein thrombosis (1)	1	NR	57 000.00	NR	NR	NR	NR

Table 3 (*continued*)

Author, year	Imaging conducted (*n*)	Major MRI findings (*n*)	Major CT findings (*n*)	Thrombocytopenia (*n*)	Hypofibrinogenemia (*n*)	Mean platelet count (per μl) ± SD	Mean Prothrombin time (INR) ± SD	Mean aPTT (sec) ± SD	Mean Fibrinogen (mg/dl)	Mean D-dimer (ng/ml) ± SD
D'agostino *et al.*, 2021	CT head (2), MRA (1), brain MRI (1), CTA (2)	CVST (1), ischemic cerebral artery and pontine branch lesions (1)	Intracranial Haemorrhage (1), aortic arch thrombus (1), CVST (1), splanchnic vein defects (1), adrenal hemorrhage (1), ischemic stroke (1), oedema (1)	1	0	NR	NR	41.00	NR	NR
Demichele *et al.*, 2021	MRI (1), whole body CT (2), TTE (2), transcranial color Doppler US (1), thorax CT (1), abdominal US (1), CT head (2), CTA (1), perfusion CT (1)	MCA occlusion (2)	Internal Carotid artery occlusion (1), MCA occlusion (1), PE (2), portal vein thrombosis (2), intrahepatic branch thrombosis (1), bilateral MCA Infarct with uncal herniation (1), RDS (1)	2	NR	44 500.00 ± 30 400.00	NR	NR	286.00	5441.00
Dutta *et al.*, 2021	MRI (1), MRI venography (1)	CVST (1)	NA	0	NR	NR	NR	NR	NR	NR
Gabarin *et al.*, 2021	Doppler US (2), CT chest (1), echocardiograph (1), CT Venography (1)	NA	PE (1)	NR	NR	109 500.00 ± 9192.39	NR	NR	NR	NR
Gangi *et al.*, 2021	angiogram (1), CTPA (2), non-contrast head CT (4), CT venography (5), brain MRI (1), abdominal US (2), CT abdomen (2), CT pelvis (2), CT chest (1), echocardiogram (1)	Venous infarct (1)	PE (2), atrial appendage thrombus (1), CVST (4), pulmonary infarct (1), splanchnic vein thrombosis (2), internal iliac artery thrombosis (1), temporal cortical venous hemorrhage (1)	6	NR	59 167.00 ± 46 602.00	NR	NR	188	20 396.00 ± 26 205.23
Gattringer *et al.*, 2021	CT head (1), CTPA (1), brain MRI (2)	CVST (1), cortical veins thrombosis (1)	Unremarkable (2)	2	NR	32 500.00 ± 4950.00	NR	NR	62.00	14 200.00
Greinacher *et al.*, 2021	CT (1)	NA	Portal vein thrombosis (1), PE (1)	11	4	35 300.00 ± 33 865.91	NR	42.30 ± 13.52	191.50	36 080.00 ± 59 739.40
Guan *et al.*, 2021	Nonenhanced CT (1), CT venogram (1)	NA	CVST (1), Internal jugular vein thrombosis (1)	1	NR	99 000.00	NR	NR	NR	NR
Haakonsen *et al.*, 2021	MRI (1)	Unremarkable (1)	NA	NR	NR	318 500.00 ± 21 920.00	NR	NR	NR	NA
Ikenberg *et al.*, 2021	MRI (3)	Unremarkable (1), CVST (1), intracranial hemorrhage (1)	NA	1	NR	97 000.00	NR	NR	NR	NR
Jacob *et al.*, 2021	CT head (3), CTA (1), CTA neck (1)	NA	MCA occlusion, internal carotid artery thrombosis (1)	1	NR	66 000.00	NR	NR	NR	NR
Jones *et al.*, 2021	CTA (1)	NA	PE (1), infrarenal aortic thrombus (1)	1	NR	36 000.00	NR	NR	140	NR
Kotal *et al.*, 2021	MRI (1), CT venogram (1), CT head (1)	Parietal hemorrhage (1) oedema (1)	Parietal lobe hematoma (1)	NR	NR	120 000.00	NR	NR	NR	1105.00
Mehta *et al.*, 2021	CT (2)	NA	CVST (2)	2	2	24 500.00 ± 7778.20	NR	NR	135.00	NR
Muster *et al.*, 2021	CTA (1), MRI venography (1), CT venography (1)	Internal iliac vein thrombosis (1)	PE (1), IVC Thrombosis (1)	1	NR	37 000.00	NR	NR	220.00	34 000.00

Table 3 (*continued*)

Author, year	Imaging conducted (*n*)	Major MRI findings (*n*)	Major CT findings (*n*)	Thrombocytopenia (*n*)	Hypofibrinogenemia (*n*)	Mean platelet count (per μl) ± SD	Mean Prothrombin time (INR) ± SD	Mean aPTT (sec) ± SD	Mean Fibrinogen (mg/dl)	Mean D-dimer (ng/ml) ± SD
Ocal *et al.*, 2021	CT head (1), CTA (1), CT thorax (1), CT abdomen (1)	NA	PE (1), splanchnic vein thrombosis (1)	1	NR	64 000.00	NR	NR	NR	42 028.00
Panovska-stavridis *et al.*, 2021	CT head (1), contrast-enhanced MRI (1)	SOVT (1)	Unremarkable (1)	1	NR	18 000.00	NR	NR	250.00	35 712.00
Schultz *et al.*, 2021	CT head (2), CT venography (3), CT abdomen (1), MRI (1)	Compromised thoracic vertebrae/ basivertebral venous drainage (1)	CVST (4) intracranial hemorrhage, (2) oedema (2), splanchnic vein Thrombosis (1), SVC constituents thrombosis (1)	5	3	27 000.00 ± 24474.48	NR	27.00 ± 2.83	152.00	13 000.00
Scully *et al.*, 2021	NR	NR	Portal vein thrombosis (2), aortic thrombosis (1)	21	12	46 571.00 ± 32 727.00	13.41 ± 1.17	29.35 ± 5.34	192.72	33 547.00 ± 22532.00
Soleimani *et al.*, 2021	CT head (2), CTA (1), CT abdomen (1), brain MRI (1), MRI venography (1), CT Whole (1)	CVST (1), intracranial hemorrhage (1)	Intracranial hemorrhage (2), CVST (2), PE (2), hepatic vein thrombosis (1), oedema (2), cerebral herniation (1)	2	NR	96 667.00 ± 134 526.00	14.80 ± 0.30	14.80 ± 0.30	196.70	32 057.00 ± 10211.60
Sorensen *et al.*, 2021	Noncontrast CT scan (1), MRI head (1) MR venogram (1), CTPA (1), CTA abdominal (1), CT venography (1)	Unremarkable (1)	Portal vein thrombosis (1), CVST (1)	1	NR	57 000.00	NR	NR	NR	NR
Suresh, Petchey *et al.*, 2021	Head CT (2), CT venogram (1)	NA	CVST (1)	1	NR	90 000.00	12.90	27.50	194.00	340 71.00
Tiede *et al.*, 2021	CTA (3), CT HEAD (2), BRAIN MRI (2), MR angiography (1)	CVST (1)	Intracranial hemorrhage (2), CVST (1), aortic arch thrombosis (1), splanchnic vein thrombosis (1)	5	NR	49 200.00 ± 36 190.00	NR	NR	227.50	22 400.00
Tobaiqy *et al.*, 2021	NR	NR	NR	4	1	NR	NR	NR	NR	NR
Umbrello *et al.*, 2021	CXR (1), abdominal CT (1), trans-hepatic portal vein venography (1), mesenteric angiography (1)	NA	Splanchnic vein thrombosis (1)	1	NR	133 000.00	NR	NR	501.00	NR
Varona *et al.*, 2021	CT (1), MRI (1)	CVST (1), Bilateral Adrenal Haemorrhage (1)	CVST (1)	1	NR	103 000.00	NR	NR	NR	20 506.00
Walter *et al.*, 2021	MRI (1), catheter angiography (1), CT (1), CTA (1), US (1), transesophageal echocardiography (1)	MCA occlusion (1)	Brain infarction (1)	0	NR	217 000.00	NR	27.50	270.00	11 000.00

Table 3 (*continued*)

Author, year	Imaging conducted (*n*)	Major MRI findings (*n*)	Major CT findings (*n*)	Thrombocytopenia (*n*)	Hypofibrinogenemia (*n*)	Mean platelet count (per μl) ± SD	Mean Prothrombin time (INR) ± SD	Mean aPTT (sec) ± SD	Mean Fibrinogen (mg/dl)	Mean D-dimer (ng/ml) ± SD
Weidmann *et al.*, 2021	Cerebral CT (9), cerebral CT with venography (1), MRI venography (3), CTPA (1), abdominal CT (1), abdominal US (1)	CVST (3), cortical vein thrombosis (2)	Subarachnoid hemorrhage (4), cerebellar hemorrhage (3), temporo-occipital hemorrhage (1), parenchymal hemorrhage (2), herniation (3), lobar hemorrhage (1), CVST (2), cortical vein thrombosis (1), PE (1), uterine vein thrombosis (1)	5	NR	31 600.00 ± 22 600.00	NR	27.40 ± 2.50	134.00	14 600.00 ± 2300.00
Wolf *et al.*, 2021	MRI (2), digital subtraction angiography (DSA) (3)	Intracranial hemorrhage (2), CVST (3), oedema (1)	NA	3	0	75667.00 ± 16010.00	NR	NR	NR	9170.00 ± 11806.00
Zanferrari *et al.*, 2021	CT head (1), brain MRI (1)	CVST (1)	Intracranial hemorrhage (1)	1	NR	NA	NR	NR	NR	27 546.00
Abou-ismail *et al.*, 2021[b]	Venous duplex ultrasound (1), CT scan (1), MR venography (1), MR angiography (1)	NA	PE (1)	1	NR	74 000.00	12.70	31.80	254.00	15 109.00
Clark *et al.*, 2021[b]	CT (1)	NA	CVST (1), PE (1)	1	NR	20 000.00	16.00	26.40	149.00	27 150.00
Dhoot *et al.*, 2021[b]	Contrast CT (2), brain MRI (1), intravascular US guidance with intracardiac echocardiography (1)	Unremarkable (1)	Portal vein thrombosis (1), superior mesenteric vein thrombosis (1), splenic vein thrombosis (1)	1	NR	66 000.00	NR	31.00	225.00	5250.00
Malik *et al.*, 2021[b]	CTA (2), MRI (1), Doppler US (1), CTPA (1), brain MRI (1), CT head (1)	None	CVST (1), PE (1), Carotid Artery Thrombosis (1)	1	NR	21000.00	12.20	26.40	142.00	35 200.00
Muir *et al.*, 2021[b]	CT (1), CT head (1), MRI (1), MRA (1), CTA (1)	CVST (1), intracranial hemorrhage (1)	CVST (1), splanchnic vein thrombosis (1)	1	1	NA	NR	41.00	NA	NA
See *et al.*, 2021[b]	CT (12)	NA	CVST (12)	12	NR	45 750.00 ± 40 636.86	NR	25.32 ± 8.77	159.33	24 928.00 ± 32 542.75

Author, year	Mean Asserachrom HPIA IgG Assay (OD) ± SD	Mean Lifecodes PF4 IgG Assay (OD) ± SD	PF4-heparin ELISA (OD) ± SD	HemosIL AcuStar HIT IgG Assay (n)	Functional HIT Assay (*n*)	PF4-heparin ELISA Ab (*n*)
Aladdin *et al.*, 2021	NR	NR	NR	NR	NR	NR
Al-mayhani *et al.*, 2021	NR	NR	NR	NR	NR	Positive (3)
Al rawahi *et al.*, 2021	NA	NR	NR	NR	NR	NR
Althaus *et al.*, 2021	NR	2.59 ± 0.64	0.17 ± 0.07	NR	NR	Positive (8)
Bano *et al.*, 2021	NR	NR	2.64 ± 0.22	NR	NR	Positive (3)
Bayas *et al.*, 2021	NR	NR	NR	NR	NR	Negative (1)
Bersinger *et al.*, 2021	0	NR	NR	NR	NR	NR
Bjornstad-tuveng *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Blauenfeldt *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Bourguignon *et al.*, 2021	NR	NR	NR	NR	NR	NR

(*continued*)

Author, year	Mean Asserachrom HPIA IgG Assay (OD) ± SD	Mean Lifecodes PF4 IgG Assay (OD) ± SD	PF4-heparin ELISA (OD) ± SD	HemosIL AcuStar HIT IgG Assay (n)	Functional HIT Assay (*n*)	PF4-heparin ELISA Ab (*n*)
Castelli *et al.*, 2021	NR	NR	NR	NR	NR	NR
Casucci *et al.*, 2021	NR	NR	NR	NR	NR	NR
Choi *et al.*, 2021	NR	0.72	NR	NR	NR	NR
Cliff-patel *et al.*, 2021	NR	NR	1.35	NR	NR	Positive (3)
Costentin *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
D'agostino *et al.*, 2021	NR	NR	NR	NR	NR	NR
Demichele *et al.*, 2021	NR	1.48 ± 0.27	NR	NR	NR	NR
Dutta *et al.*, 2021	NR	NR	NR	NR	NR	Negative (1)
Gabarin *et al.*, 2021	NR	NR	1.71 ± 1.02	NR	NR	Positive (2)
Gangi *et al.*, 2021	NR	NR	2.65 ± 0.60	NR	NR	Positive (6)
Gattringer *et al.*, 2021	NR	NR	NR	NR	NR	NR
Greinacher *et al.*, 2021	NR	NR	NR	NR	NR	Positive (9)
Guan *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Haakonsen *et al.*, 2021	NR	NR	NR	NR	NR	NR
Ikenberg *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Jacob *et al.*, 2021	NR	2.45	NR	Negative (1)	NR	NR
Jones *et al.*, 2021	NR	NR	NR	Negative (1)	NR	Positive (1)
Kotal *et al.*, 2021	NR	NR	NR	NR	NR	NR
Mehta *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Muster *et al.*, 2021	NR	NR	NR	NR	NR	NR
Ocal *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Panovska-stavridis *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Schultz *et al.*, 2021	NR	3.48 ± 0.34	NR	NR	NR	Positive (5)
Scully *et al.*, 2021	0.57	2.06 ± 0.71	NR	NR (14), Negative (8)	Positive (5), Negative (2), NR (15)	NR
Soleimani *et al.*, 2021	NR	NR	NR	Negative (1)	NR	Positive (2)
Sorensen *et al.*, 2021	NR	2.20	NR	NR	NR	Positive (1)
Suresh & etchey *et al.*, 2021	NR	NR	3.12	NR	NR	Positive (1)
Tiede *et al.*, 2021	NR	NR	NR	NR	NR	Positive (5)
Tobaiqy *et al.*, 2021	NR	NR	NR	NR	NR	NR
Umbrello *et al.*, 2021	NR	NR	2.50	NR	NR	Positive (1)
Varona *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Walter *et al.*, 2021	NR	NR	NR	NR	NR	Positive (1)
Weidmann *et al.*, 2021	NR	3.34 ± 0.46	NR	NR	NR	NR
Wolf *et al.*, 2021	NR	NR	NR	NR	NR	Positive (3)
Zanferrari *et al.*, 2021	NR	NR	2.59	NR	NR	Positive (1)
Abou-ismail *et al.*, 2021[a]	NR	NR	3.32	NR	NR	Positive (1)
Clark *et al.*, 2021[a]	NR	NR	NR	Negative (1)	NR	Positive (1)
Dhoot *et al.*, 2021[a]	NR	NR	2.47	NR	NR	Positive (1)
Malik *et al.*, 2021[a]	NR	NR	2.70	NR	NR	Positive (1)
Muir *et al.*, 2021[a]	NR	NR	2.55	NR	NR	Negative (1)
See *et al.*, 2021[a]	NR	NR	2.25 ± 0.612	NR	NR	Positive (11)

Ab, antibody; CT, computed tomography; CTA, computed tomography angiography; CVST, cerebral venous sinus thrombosis; DSA, digital subtraction angiography; HIT, heparin-induced thrombocytopenia; MCA, middle cerebral artery; MRA, magnetic resonance angiography; NA, no association; NR, not reported; OD, optical density; PE, pulmonary embolism; PF4, platelet factor 4; RDS, respiratory distress syndrome; SD, standard deviation; SOVT, superior ophthalmic vein thrombosis. [a] Studies are Ad26.COV2.S reports. [b] Values reported for one participant only within study.

received heparin with a pooled rate of 25.2% (95% CI 0.179–0.343, $I^2 = 0\%$). Lastly, nine patients were treated with a thrombectomy with a pooled rate of 22.7% (95% CI 0.157–0.317; $I^2 = 0\%$). In terms of medications, patients were treated with direct thrombin inhibitors (32.5%; 95% CI 0.236–0.428; $I^2 = 1.85\%$), factor Xa inhibitors (22.1%; 95% CI 0.153–0.309; $I^2 = 0\%$), aspirin (20.3%; 95% CI 0.136–0.292; $I^2 = 0\%$), and antibiotics (21.1%; 95% CI 0.142–0.302; $I^2 = 0\%$).

Seventy-eight patients recovered following adverse event [recovery rate 57.2%; 95% CI 0.481–0.658, $I^2 = 0\%$) whereas 39 patients died following adverse event [mortality rate 35%; 95% CI 0.270–0.440, $I^2 = 0\%$). The cause of death of the patients was unknown. As shown in Table 4 and Fig. 1), headache (12.1%; 95% CI 0.095–0.154, $I^2 = 0\%$), intracerebral hemorrhage (7.5%, 95% CI 0.056–0.102, $I^2 = 0\%$), hemiplegia (7%; 95% CI 0.051–0.096, $I^2 = 0\%$), fever (6.6%; 95% CI 0.047–0.091, $I^2 = 0\%$), congestive edema (5.3%; 95% CI 0.036–0.075, $I^2 = 0\%$), visual impairment (5.7%; 95% CI 0.040–0.081, $I^2 = 0\%$), and ocular manifestations (6.1%; 95% CI 0.043–0.086; $I^2 = 0\%$) were the most common reported adverse events following vaccination after first dose.

Johnson and Johnson

Six studies demonstrated thromboembolic events following Johnson and Johnson vaccination [19,20]. Seventeen patients were included in total, of which 15 were girls. The mean age of patients was 40.6 years (range: 24–48 years). Eleven patients had preexisting comorbidities, seven of which had obesity, one had asthma, one had depression, one had hyperlipidemia, and one of which had hypothyroidism [20]. Seventeen of the patients presented and were admitted to the emergency room with thrombocytopenia. One of these patients had fibrinogenemia. Four patients were clinically diagnosed with vaccine-induced thrombocytopenia. There were 15 thromboembolic events of CVST. Moreover, out of the 17 patients who presented,15 patients out of 16 tested positive for antibody PF4-Heparin. Of the entire cohort, patients presented with 122 adverse events, of which 38 were thromboembolic events. Of the 38 thromboembolic events, 15 were CVST events and 10 were PE/DVT events, 6 were splanchnic events, and the rest were other thromboembolic events. Out of recorded reporting for 11 of these patients, 3 died and 8 recovered [20]. The baseline and clinical characteristics, radiological and laboratory findings, and outcomes of reported adverse events are reported alongside the AstraZeneca studies within Tables 1–4, respectively.

Discussion

The aim of this systematic review and meta-analysis was to investigate outcomes of thromboembolic events in patients following AstraZeneca vaccine. Forty-five AstraZeneca studies reporting on thromboembolism as an adverse event post vaccination were included, with six Johnson and Johnson studies. Within this meta-analysis, the following has been supported regarding AstraZeneca vaccine and thromboembolic events: under 60-year-olds have been the predominant age group reporting adverse events; the female sex appears to experience more adverse events than male sex; thrombocytopenia and hypofibrinogenemia appear as consistent findings in studies that report laboratory results; PF4 antibodies appear commonly present within patient serum whenever investigated. To the authors' knowledge, this is the most recent meta-analysis to describe thromboembolism adverse events following AstraZeneca vaccine. In turn, this study may assist clinical practice in determining adenovirus COVID-19 vaccine eligibility and management.

Recently, it has become evident that adenovirus-based vector vaccines may cause autoimmune thrombosis similar to heparin-induced thrombocytopenia (HIT) [21]. This phenomenon has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT) because of its shared serological profile of high antibodies to platelet factor 4 PF4–polyanion complexes, as well as clinical presentations to that of HIT in which platelet disruption leads to thrombosis development [14,17,21,22]. Clinical findings of thrombocytopenia and hypofibrinogenemia can, therefore, support suspicions of VITT, with the current meta-analysis finding thrombocytopenia prevalent in 75% of all patients who had data reported, and hypofibrinogenemia in 41%. Quantifying the estimated frequency of VITT from the included studies remains difficult, as the novel phenomenon was unknown to authors of earlier studies, with unclear guidelines for diagnosis. Now, in diagnosing VITT, guidance from the American Heart Association/American Stroke Association Stroke Council suggests complete blood counts with a peripheral smear, coagulation studies with prothrombin time, partial thromboplastin time, fibrinogen, D-dimer, and PF4 antibody ELISA [15,23]. Results of this current meta-analysis support these suggestions as included AstraZeneca studies conducting these analyses found ELISA anti-PF4 to be positive in 80% of patients tested, with corresponding abnormal patient serum samples and prolonged coagulation values (Table 3).

Upon VITT, patients have been described to present with CVST or with other arterial or venous clots [21]. The pathophysiology for thrombus formation has been previously described in detail, with the conclusion that cellular positive feedback signaling results in a hypercoagulable state post adenoviral vaccination [24]. Autoantibodies are also generated despite no heparin exposure, leading to theories of an unidentified polyanion in the adenoviral vaccine itself or infected cells causing binding to PF4 [24]. Considering this mechanism, and that prior

Table 4 Reported adverse events following vaccination and common treatment modalities

Author, year	Mean onset time of first AE post vaccination (days) ± SD	Presenting AE (*n*)	Total number of thromboembolic events[a]	Thromboembolic events (*n*)	ER admission (*n*)	ICU admission (*n*)	Hospitalization (*n*)	Mean time to hospitalization post vaccination (days) ± SD	Mortality
Aladdin *et al.*, 2021	14.00	Fever (1), headache (1), limb weakness (1), seizures (1), vomiting (1)	1	CVST (1)	1	1	1	NR	1
Al-mayhani *et al.*, 2021	13.00 ± 7.55	headache (2), speech/mouth-related issues (1), limb weakness (2), visual impairment (2), drowsiness (1), facial weakness (1), confusion (1)	9	Carotid artery thrombosis (1), cerebral artery thrombosis (2), CVST (1), iliac or femoral vein thrombosis (1), jugular vein thrombosis (1), PE (1), splanchnic vein thrombosis (2)	NR	NR	NR	NR	1
Al rawahi *et al.*, 2021	7.00	Fever (1), lethargy (1), malaise (1), abdominal pain (1), altered mental status (1), somnolence (1)	3	Aortic thrombosis (1), PE (1), renal vein thrombosis (1)	1	NR	1	7.00	0
Althaus *et al.*, 2021	10.40 ± 5.24	Ecchymosis/bruising/petechiae/erythema (3)	13	CVST (5), DVT (1), PE (4), thrombosis in other unspecified organs (3)	NR	NR	8	NR	3
Bano *et al.*, 2021	10.67 ± 2.52	Dyspnea (1), pain in extremities (1), headache (2), facial weakness (1), hemiparesis (1), speech/mouth-related issues (1)	4	CVST (2), PE (1), jugular vein thrombosis (1)	3	NR	3	13.33 ± 3.05	2
Bayas *et al.*, 2021	1.00	Fever (1), DIPLOPIA (1)	1	SOVT (1)	0	NR	1	10.00	0
Bersinger *et al.*, 2021	9.00	Headache (1), seizure (1)	5	CVST (1), iliac or femoral vein thrombosis (1), jugular vein thrombosis (1), PE (1), splanchnic vein Thrombosis (1)	1	1	1	14.00	NA
Bjornstad-tuveng *et al.*, 2021	7.00	Headache (1), lethargic (1), speech/mouth-related issues (1), unstable walking (1)	2	CVST (1), PE (1)	0	1	1	10.00	1
Blauenfeldt *et al.*, 2021	NR	Headache (1), abdominal pain (1), adrenal hemorrhage (1), subcapsular renal hematoma (1)	1	Carotid artery thrombosis (1)	1	1	1	7.00	1
Bourguignon *et al.*, 2021	12.33 ± 5.51	Pain in extremities (2), cramping (1), dyspnea (1), headache (1), confusion (1), weakness (1)	12	Aortic thrombus (1), carotid artery thrombosis (1), celiac artery thrombus (1), CVST (1), DVT (2), jugular vein thrombosis (1), peripheral artery thrombosis (2), PE (2), splanchnic vein thrombosis (1)	3	1	3	14.67 ± 8.33	0
Castelli *et al.*, 2021	7.00	Headache (1), speech/mouth-related issues (1), loss of lower limb strength (1), unstable walking (1), visual impairment (1)	1	CVST (1)	1	1	1	11.00	1

Table 4 (*continued*)

Author, year	Mean onset time of first AE post vaccination (days) ± SD	Presenting AE (*n*)	Total number of thromboembolic events[a]	Thromboembolic events (*n*)	ER admission (*n*)	ICU admission (*n*)	Hospitalization (*n*)	Mean time to hospitalization post vaccination (days) ± SD	Mortality
Casucci *et al.*, 2021	0	Headache (1), photophobia (1), nausea (1), chills (1), fever (1), myalgia (1), arthralgia (1), fatigue (1)	1	Disseminated intravascular coagulation (1)	0	0	1	15.00	0
Choi *et al.*, 2021	NR	Headache (1), tingling (1), vomiting (1), altered mental status (1), fever (1)	1	CVST (1)	1	1	1	12.00	1
Cliff-patel *et al.*, 2021	13.00 ± 5.72	Back pain (2), hematuria (1), headache (1), pain in extremities (1) loss of lower limb strength (1), dyspnea (1), chest pain (1)	5	DVT (1), PE (3), renal vein thrombosis (1)	NR	NR	3	15.33 ± 9.00	NA
Costentin *et al.*, 2021	3.00	Nausea (1), muscle ache (1), body ache (1), fatigue (1), headache (1)	2	PE (1), splanchnic vein thrombosis (1)	1	1	1	7.00	NR
D'agostino *et al.*, 2021	NR	Acute cerebrovascular accident (1)	4	Aortic arch (1), carotid artery thrombosis (1), CVST (1), Splanchnic vein thrombosis (1)	1	1	1	12.00	1
Demichele *et al.*, 2021	8.00 ± 1.41	Hemiplegia (1), ocular-related issues (2), speech/mouth-related issues (1), abdominal Pain (1)	9	Cerebral artery thrombosis (1), carotid artery thrombosis (3), PE (2), splanchnic vein thrombosis (3)	2	NR	2	NR	1
Dutta *et al.*, 2021	6.00	Headache (1), visual impairment (1), vomiting (1), ocular-related issues (1)	1	CVST (1)	NR	0	1	14.00	0
Gabarin *et al.*, 2021	19.50 ± 16.26	Leg swelling (1), erythema (1), headache (1), dyspnea (1), cough (1), hemoptysis (1)	3	DVT (2), PE (1)	1	0	1, NR (1)	16.00	0
Gangi *et al.*, 2021	10.33 ± 8.38	Myocardial Infarction (1), headache (4), visual impairment/photophobia (2), dyspnea (1), hemoptysis (1), chest pain (2), abdominal pain (1), ocular-related issues (1), nausea (1)	10	Coronary artery thrombosis (1), CVST (4), iliac artery thrombosis (1), PE (2), pelvic artery thrombosis (1), splanchnic vein thrombosis (1)	6	1	6	16.17 ± 8.06	0
Gattringer *et al.*, 2021	7.00 ± 1.41	Headache (2)	2	CVST (2)	2	0	2	10.00 ± 2.83	0
Greinacher *et al.*, 2021	9.30 ± 3.35	Chills (1), fever (1), nausea (1), epigastric discomfort (1), fatigue (1), myalgia (1), headache (1)	21	Aortoiliac thrombosis (1), CVST (9), PE (3), splanchnic vein thrombosis (3), iliac or femoral vein thrombosis (1), inter-ventricular thrombosis (1), IVC thrombosis (1), multiple organ thrombosis (1), widespread microvascular thrombosis (1)	NR	1	NR	NR	6
Guan *et al.*, 2021	5	Headache (1), nausea (1), neck pain (1)	2	CVST (2), Jugular vein thrombosis (1)	1	0	1	10.00	0
Haakonsen *et al.*, 2021	NR	Fever (2), chills (2), arthralgia (1), fatigue (1)	2	DVT (2)	0	0	0	NA	0

Table 4 (*continued*)

Author, year	Mean onset time of first AE post vaccination (days) ± SD	Presenting AE (*n*)	Total number of thromboembolic events[a]	Thromboembolic events (*n*)	ER admission (*n*)	ICU admission (*n*)	Hospitalization (*n*)	Mean time to hospitalization post vaccination (days) ± SD	Mortality
Ikenberg *et al.*, 2021	7.00	Headache (1), myalgia (1), chills (1)	1	CVST (1)	1	NR	1	7.00	NR
Jacob *et al.*, 2021	7.00	Fatigue (1), altered mental status (1), headache (1), nausea (1), hemiparesis (1)	2	Carotid artery thrombosis (1), cerebral artery thrombosis (1)	1	1	1	9.00	0
Jones *et al.*, 2021	20.00	Dyspnea (1), insensate (1), loss of limb strength/weakness (1), pain in extremities (1)	3	Aortic thrombosis (1), peripheral artery thrombosis (1), PE (1)	1	NR	1	25.00	0
Kotal *et al.*, 2021	0	Headache (1), loss of limb strength/weakness (1), visual impairment (1)	1	CVST (1)	NR	1	1	11.00	0
Mehta *et al.*, 2021	NR	Headache (2)	2	CVST (2)	2	NR	NR	NR	2
Muster *et al.*, 2021	8.00	Dyspnea (1), fatigue (1), cough (1)	3	Iliac or femoral vein thrombosis (1), IVC thrombosis (1), PE (1)	1	NR	1	NR	NA
Ocal *et al.*, 2021	11.00	Headache (1)	2	PE (1), Splanchnic Vein Thrombosis (1)	1	NR	1	15.00	NA
Panovska-stavridis *et al.*, 2021	9.00	Headache (1), ocular-related issues (1)	1	SOVT (1)	1	NR	1	10.00	0
Schultz *et al.*, 2021	7.20 ± 0.45	Headache (3), fever (1), comatose (including reduced consciousness) (1), back pain (1), abdominal pain (1), hemiparesis (1)	6	CVST (4), splanchnic vein thrombosis (1), svc including constituent draining vessels (1)	5	1	5	8.40 ± 1.52	3
Scully *et al.*, 2021	NR	NR	26	Aortic thrombosis (1), CVST (13), DVT (2), jugular vein thrombosis (1), multiple organ thrombosis (1), PE (5), splanchnic vein Thrombosis (3)	22	NR	NR	NR	7
Soleimani *et al.*, 2021	12.33 ± 1.69	Headache (3), hemiparesis (2), pain in extremities (1)	7	CVST (3), Jugular Vein Thrombosis (1), PE (2), Splanchnic Vein Thrombosis (1)	2	2	3	12.67 ± 5.53	0
Sorensen *et al.*, 2021	8.00	Headache (1), malaise (1), ecchymosis (1),	2	CVST (1), Splanchnic Vein Thrombosis (1)	1	NR	1	13.00	0
Suresh & petchey *et al.*, 2021	2.00	Headache (1), ocular-related issues (1), vomiting (1)	1	CVST (1)	1	NR	1	NR	1
Tiede *et al.*, 2021	8.40 ± 1.95	Headache (4), somnolence (1), speech/mouth-related issues (2), hemiparesis (2), visual impairment (1), fatigue (1), ocular-related issues (1)	6	Aortic thrombosis (1), carotid artery thrombosis (1), CVST (1), peripheral artery thrombosis (1), splanchnic vein thrombosis (1), TMA (1)	0	0	5	8.40 ± 1.96	0
Tobaiqy *et al.*, 2021	NR	NR	30	Carotid artery thrombosis (1), CVST (1), DVT (16), pelvic vein thrombosis (2), peripheral artery thrombosis (2), PE (6), thrombophlebitis (2)	NR	NR	NR	NR	3

Table 4 (*continued*)

Author, year	Mean onset time of first AE post vaccination (days) ± SD	Presenting AE (*n*)	Total number of thromboembolic events[a]	Thromboembolic events (*n*)	ER admission (*n*)	ICU admission (*n*)	Hospitalization (*n*)	Mean time to hospitalization post vaccination (days) ± SD	Mortality
Umbrello *et al.*, 2021	NR	Abdominal pain (1), fever (1), fatigue (1), arthralgia (1)	1	Splanchnic vein thrombosis (1)	1	1	1	17.00	0
Varona *et al.*, 2021	NR	NR	2	CVST (1), PE (1)	NR	NR	1	10.00	0
Walter *et al.*, 2021	8.00	Headache (1), speech/mouth-related issues (1), hemiparesis (1), fatigue (1), myalgia (1)	1	Carotid artery thrombosis (1)	1	1	NR	NR	0
Weidmann *et al.*, 2021	6.33 ± 0.58	Headaches (5), weakness (2), hemiparesis (3), numbness (2), vomiting (1), altered mental status (1), fever (1), drowsiness (1), abdominal pain (1), nausea (2), ocular-related issues (2), speech/mouth-related issues (2), bruising (1)	7	CVST (5), PE (1), pelvic vein thrombosis (1)	5	4	5	6.60 ± 3.36	4
Wolf *et al.*, 2021	5.33 ± 1.53	Shivering (1), headaches (3), fever (2), epileptic seizure (1), speech/mouth-related issues (1), hemianopia (1), somnolent (1)	3	CVST (3)	NR	NR	3	NR	0
Zanferrari *et al.*, 2021	2.00	Fever (1), headache (1), speech/mouth-related Issues (1)	1	CVST (1)	NR	NR	1	10.00	NA
Abou-ismail *et al.*, 2021[b]	11.00	Pain in extremities (1), chest pain (1)	2	DVT (1), PE (1)	1	0	1	20.00	0
Clark *et al.*, 2021[b]	5.00	Headache (1), speech/mouth-related issues (1), photophobia (1), myalgia (1), dizziness (1), petechiae (1), sinus pressure (1)	2	CVST (1), PE (1)	1	0	1	12.00	0
Dhoot *et al.*, 2021[b]	11.00	Abdominal pain (1), nausea (1), vomiting (1), decreased oral intake (1)	3	Splanchnic vein thrombosis (3)	1	1	1	21.00	0
Malik *et al.*, 2021[b]	7.00	headache (1), fever (1), myalgia (1), chills (1), dyspnea (1), lightheadedness (1)	3	Carotid artery thrombosis (1), CVST (1), PE (1)	1	0	1	10.00	0
Muir *et al.*, 2021[b]	14.00	Headache (1), malaise (1)	2	CVST (1), Splanchnic Vein Thrombosis (1)	1	NR	1	17.00	NR
See *et al.*, 2021[b]	8.00 ± 2.25	Headache (11), visual impairment/photophobia (5), hemiplegia/hemiparesis (3), vomiting (6), comatose (1), fever (3), neck pain/stiffness (3), back pain (1), abdominal pain (2), lethargy (1), myalgia (3), chills/shivering (1), nausea (5), epileptic seizure (2), aphasia (1), chest pain (1), pain in extremities (2), malaise (1)	26	CVST (12), DVT (3), jugular vein thrombosis (6), PE (3), splanchnic vein thrombosis (2)	12	10	12	NR	3

Author, year	UFH	LMWH	Fondaparinux	Direct thrombin inhibitors	Direct factor Xa Inhibitor	IVIg	Corticosteroids	Platelet transfusion	Craniectomy
Aladdin *et al.*, 2021	0	1	0	0	0	0	0	0	0
Al-mayhani *et al.*, 2021	0	0	2	0	0	3	1	1	1
Al rawahi *et al.*, 2021	0	0	1	1	0	1	1	1	0
Althaus *et al.*, 2021	NR	NR	NR	NR	NR	4	NR	NR	NR
Bano *et al.*, 2021	0	2	1	1	0	1	2	3	1
Bayas *et al.*, 2021	1	0	0	0	0	0	1	0	0
Bersinger *et al.*, 2021	1	0	1	1	0	1	0	0	1
Bjornstad-tuveng *et al.*, 2021	0	0	0	0	0	0	0	0	0
Blauenfeldt *et al.*, 2021	0	1	0	0	0	0	1	1	1
Bourguignon *et al.*, 2021	1	0	2	1	1	3	0	0	0
Castelli *et al.*, 2021	0	0	0	0	0	0	0	1	1
Casucci *et al.*, 2021	0	1	0	0	0	0	1	0	0
Choi *et al.*, 2021	0	0	0	0	0	1	1	1	0
Cliff-patel *et al.*, 2021	0	0	0	3	0	3	0	0	0
Costentin *et al.*, 2021	0	0	0	0	0	0	0	0	0
D'agostino *et al.*, 2021	0	0	0	0	0	0	0	0	0
Demichele *et al.*, 2021	0	0	1	0	0	2	2	1	1
Dutta *et al.*, 2021	0	1	0	0	0	0	0	0	0
Gabarin *et al.*, 2021	0	0	0	0	2	2	0	0	0
Gangi *et al.*, 2021	0	1	6	2	0	6	5	3	0
Gattringer *et al.*, 2021	0	0	0	4	0	2	2	0	0
Greinacher *et al.*, 2021	4	1	0	0	0	0	0	0	0
Guan *et al.*, 2021	0	0	0	0	1	0	0	0	0
Haakonsen *et al.*, 2021	0	0	0	0	2	0	0	0	0
Ikenberg *et al.*, 2021	0	0	0	1	0	1	0	0	0
Jacob *et al.*, 2021	0	0	1	1	0	1	1	1	1
Jones *et al.*, 2021	1	1	1	0	0	1	NR	1	NR
Kotal *et al.*, 2021	0	1	1	1	0	1	0	0	1
Mehta *et al.*, 2021	1	0	0	0	0	1	1	1	0
Muster *et al.*, 2021	0	1	0	1	0	0	1	0	0
Ocal *et al.*, 2021	0	0	0	1	1	1	0	0	0
Panovska-stavridis *et al.*, 2021	0	0	0	0	1	1	1	0	0
Schultz *et al.*, 2021	1	4	0	0	0	4	4	4	3
Scully *et al.*, 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Soleimani *et al.*, 2021	0	0	1	3	2	3	2	2	2
Sorensen *et al.*, 2021	0	1	1	0	0	0	0	0	0
Suresh & petchey *et al.*, 2021	0	0	0	1	0	1	1	0	1
Tiede *et al.*, 2021	1	0	0	4	0	3	0	0	2
Tobaiqy *et al.*, 2021	NR	NR	NR	NR	NR	NR	NR	NR	NR
Umbrello *et al.*, 2021	1	0	0	1	0	1	0	0	0
Varona *et al.*, 2021	0	1	1	0	0	1	1	0	0
Walter *et al.*, 2021	0	0	0	0	0	0	0	0	0
Weidmann *et al.*, 2021	0	2	0	0	0	3	3	0	3
Wolf *et al.*, 2021	0	3	0	3	0	0	0	0	0
Zanferrari *et al.*, 2021	0	1	1	0	0	1	0	0	0
Abou-ismail *et al.*, 2021[b]	0	0	0	1	2	1	1	0	0
Clark *et al.*, 2021[b]	0	0	0	1	0	1	1	0	0
Dhoot *et al.*, 2021[b]	1	0	0	1	1	1	0	0	0
Malik *et al.*, 2021[b]	0	0	1	0	1	1	0	0	0
Muir *et al.*, 2021[b]	1	0	0	0	0	1	0	0	0
See *et al.*, 2021[b]	6	0	0	4	0	7	3	4	0

AE, adverse event; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; ER, emergency room; IV, intravenous; IVC, inferior vena cava; IVIG, intravenous immunoglobulin; LMWH, low-molecular-weight heparin; NR, not reported; PE, pulmonary embolism; SD, standard deviation; SOVT, superior ophthalmic vein thrombosis; SVC, superior vena cava; UFH, unfractionated heparin. [a] Thromboembolic events were defined as thrombus presence upon imaging investigations or as stated by study authors. Different imaging of the same thrombus was considered a single thromboembolic event unless new findings were stated between the techniques. [b] Studies are Ad26.COV2.S reports.

thrombosis is not currently considered a risk factor for VITT, preemptive thrombophilia screening may not yield clinically useful information in identifying VITT susceptibility [24]. However, future studies are required to confirm this.

Due to ambiguity surrounding the exact mechanisms of VITT, there are no prominent risk factors for VITT with thromboembolism post vaccination other than female sex and age younger than 60 years [24], reflecting the demographics of patients included within the current study. It is, therefore, vital that clinicians take appropriate caution when administering adenovirus vaccination to this patient population. Outside of VITT-specific risk factors, standard thromboembolism risk factors of thrombophilia, pregnancy, the postpartum timeframe, and hormonal contraceptives are thought to apply in a general sense to patients receiving adenovirus vaccination [25,26]. However, limited reporting on these factors precluded investigations within this current analysis.

Out of embolic events, CVST was the most common with a pooled value of 38.5% in line with current reporting of embolism cases to EudraVigilance [27]. The high prevalence of CVST in turn largely explains the results of corresponding adverse event presentations. The main clinical syndromes seen with CVST are intracranial hypertension presenting as headache, focal deficits with hemiparesis and fluent aphasia, seizures, and venous hemorrhage [28,29], all of which were prevalent presenting adverse events within this meta-analysis. Consequently, presentation of these adverse events post vaccination should immediately guide clinical decision-making towards a diagnosis of VITT-related thromboembolism. The pooled onset of initial adverse event symptoms appearing approximately 10 days after vaccination is in line with current literature reporting a similar timeframe after receiving the first vaccine dose [23,30]. This highlights a clear delay in adverse event presentation post vaccination that clinicians must be aware of, with necessity for appropriate preemptive management after the first vaccine dose as compared with the second. Unfortunately, scarcity of literature precludes any further comment on outcomes of thromboembolic events following second dose vaccination.

AstraZeneca has not been the only COVID-19 vaccine to present with thromboembolic events, as six studies from the USA reporting embolic events following the Johnson and Johnson vaccine were included as a subgrouping within the current meta-analysis. All patients reported similar clinical pictures to that of AstraZeneca vaccine patients, in that headaches were the most common presenting adverse event, followed by thromboembolic events that saw a high prevalence of CVST. Additionally, tested patients were 93.8% positive for ELISA anti-PF4, similar to AstraZeneca reports (Table 3). Given that both AstraZeneca ChAdOx1 nCov-19 and Johnson and Johnson/Janssen Ad26.COV2.S are nonreplicating adenovirus vector–based DNA vaccines [19], it is expected that the clinical course and laboratory results would share similarities. Slight differences have been shown in delayed clinical manifestations for Ad26.COV2.S, with lower D-dimer and activated partial thromboplastin time levels [31]. However, all other clinical characteristics remain comparable [31]. Subsequently, the findings of this meta-analysis further indicate a similarity between these two vaccines in the pathogenesis of VITT leading to thromboembolic events [20].

As of now, recommended treatment for confirmed VITT according to guidelines includes the avoidance of heparin (both unfractionated heparin and LMWH) and platelet transfusions [21]. Instead, the UK's expert Hematology panel has advised anticoagulating with nonheparin-based therapies depending on the patient's drug profile and situation [24,32]. These include direct oral anticoagulants (DOACs), such as dabigatran, apixaban, rivaroxaban, edoxaban, and fondaparinux, as well as parenteral direct thrombin inhibitors (e.g. bivalirudin and argatroban) [24]. Furthermore, urgent use of high-dose intravenous immunoglobulin at rate of 1 g/kg of body weight daily for 2 days has also been suggested [21,32,33]. In delays of initiating intravenous immunoglobin, steroid administration has been advised [32], whilst in cases of declining fibrinogen levels below 1.5 g/l, fibrinogen concentrate, or cryoprecipitate should be considered [32]. These treatment modalities were largely seen within the current meta-analysis, reflecting current developing clinical practice (Table 4).

Whilst this meta-analysis reports on arising thromboembolic events, it should be noted that these cases have thus far been a rarity in opposition to the current widespread trials and live administrations, which have not yet reported such events [9,30,34,35]. At present, approximately 21 400 000 Johnson and Johnson vaccines have been administered within the USA, whilst 500 000 000 Astrazeneca vaccines have been administered within Europe. The sample size included within this meta-analysis is, therefore, miniscule in comparison to patients safely vaccinated with adenoviral-based vaccines. In addition, the risk of CVST associated with COVID-19 infection is considerably greater than that associated with vaccination [36], which should dissuade any vaccine hesitancy.

Conclusion

Considering the rapid pace at which both COVID-19 vaccine trials and adverse event outcome reporting is occurring, the limitations of this current systematic review and meta-analysis must be acknowledged. The most pressing of these is the lack of high-quality data in the included studies. Due to the urgent timeline for data extraction and the complications surrounding VITT, many cases had incomplete documentation of the epidemiological history, laboratory values, particularly about anti-PF4 levels, and outcomes including cause of

mortalities. In addition, despite pooled information providing clinical benefit, there was a reliance on case series or case reports arising within the preceding months of this meta-analysis being performed. Furthermore, vaccinated patients who were asymptomatic or had mild adverse events, and who did not require hospitalization, were not accounted for because of publication bias. This prevented calculations on true incidence rates of thromboembolism from evolving cases or discrepancies in reporting. Lastly, because of the nature of the virus and the urgent need for more studies, this meta-analysis might have missed emerging studies recently published in the literature, particularly in languages other than English.

Nevertheless, this meta-analysis presents novel evidence of VITT-related thromboembolism following AstraZeneca vaccine in certain individuals. Female individuals under 60 years of age seem as the primary group affected; however, male individuals have also been shown to be as susceptible. Further investigations are warranted into the mechanisms of potential thromboembolic formation following adenovirus vector-based DNA vaccine administration and causes for predisposition towards CVST specifically. Such elucidations may identify suitability for adenovirus vaccination and better guide clinical practice. At present, serum anti-PF4 suggests diagnostic value for VITT, and can inform treatment choices.

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Data availability statement: with publication, the data set used for this meta-analysis will be shared upon request from the study authors

Ethical approval: this systematic review and meta-analysis does not require ethical approval

Conflicts of interest

There are no conflicts of interest.

References

1 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020; **395**:497–506.
2 Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, *et al.* Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol* 2016; **24**:490–502.
3 World Health Organization. Coronavirus disease (COVID-19) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. [Accessed 12 April 2021]
4 Wang F, Kream RM, Stefano GB. An evidence based perspective on mRNA-SARS-CoV-2 vaccine development. *Med Sci Monit* 2020; **26**:e924700.
5 Zhang N-N, Li X-F, Deng Y-Q, Zhao H, Huang YJ, Yang G, *et al.* A thermostable mRNA vaccine against COVID-19. *Cell* 2020; **182**:1271.e16–1283.e16.
6 Zhu F-C, Guan X-H, Li Y-H, Huang JY, Jiang T, Hou LH, *et al.* Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2020; **396**:479–488.
7 European Commission. Available at: https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans_en#figures-on-vaccination. [Accessed 12 April 2021]
8 Kim SH, Wi YM, Yun SY, Ryu JS, Shin JM, Lee EH, *et al.* Adverse events in healthcare workers after the first dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 vaccination: a single center experience. *J Korean Med Sci* 2021; **36**:e107.
9 Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al.*, Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**:99–111.
10 Tobaiqy M, Elkout H, MacLure K. Analysis of thrombotic adverse reactions of COVID-19 AstraZeneca vaccine reported to EudraVigilance database. *Vaccines (Basel)* 2021; **9**:393.
11 Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/media/releases/2021/s0413-JJ-vaccine.html. [Accessed 13 April 2021]
12 Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018; **23**:60–63.
13 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**:177–188.
14 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *New Engl J Med* 2021; **384**:2092–2101.
15 Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, *et al.* Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021; **384**:2202–2211.
16 Blauenfeldt RA, Kristensen SR, Ernstsen SL, Kristensen CCH, Simonsen CZ, Hvas A-M. Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine. *J Thromb Haemost* 2021; **19**:1771–1775.
17 Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, *et al.* Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021; **384**:2124–2130.
18 Haakonsen HB, Nystedt A. Deep vein thrombosis more than two weeks after vaccination against COVID-19. *Tidsskr Nor Laegeforen* 2021; **141**:.
19 Muir K-L, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. *N Engl J Med* 2021; **384**:1964–1965.
20 See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, *et al.* US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. *JAMA* 2021; **325**:2448–2456.
21 Pai M, Grill A, Ivers N, Maltsev A, Miller KJ, Razak F et al on behalf of the Drugs & Biologics Clinical Practice Guidelines Working Group and the Ontario COVID-19 Science Advisory Table. Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) following AstraZeneca COVID-19 vaccination. Science Briefs of the Ontario COVID-19 Science Advisory Table. 2021.
22 Baroletti SA, Goldhaber SZ. Heparin-induced thrombocytopenia. *Circulation* 2006; **114**:e355–e356.
23 Furie KL, Cushman M, Elkind MSV, Lyden PD, Saposnik G, American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced immune thrombotic thrombocytopenia. *Stroke* 2021; **52**:2478–2482.
24 Rizk JG, Gupta A, Sardar P, *et al.* Clinical characteristics and pharmacological management of COVID-19 vaccine-induced immune thrombotic thrombocytopenia with cerebral venous sinus thrombosis: a review. *JAMA Cardiol* 2021; **6**:1451–1460.

25 Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, *et al.* First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nat Med* 2021; **27**:1290–1297.
26 Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, *et al.* Diagnosis and management of cerebral venous thrombosis. *Stroke* 2011; **42**:1158–1192.
27 AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. Available at: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood. [Accessed 13 April 2021]
28 Idiculla PS, Gurala D, Palanisamy M, Vijayakumar R, Dhandapani S, Nagarajan E. Cerebral venous thrombosis: a comprehensive review. *Eur Neurol* 2020; **83**:369–379.
29 Piazza G. Cerebral venous thrombosis. *Circulation* 2012; **125**:1704–1709.
30 Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, *et al.*, Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2020; **396**:1979–1993.
31 Hwang J, Lee SB, Lee SW, Lee MH, Koyanagi A, Jacob L, *et al.* Comparison of vaccine-induced thrombotic events between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines. *J Autoimmun* 2021; **122**:102681.
32 Suresh P, Petchey W. ChAdOx1 nCOV-19 vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis (CVST). *BMJ Case Rep* 2021; **14**:e243931.
33 Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, *et al.* Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH. *Hamostaseologie* 2021; **41**:184–189.
34 Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, *et al.*, Oxford COVID Vaccine Trial Group. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; **396**:467–478.
35 Isaacs D. The precautionary principle, the AstraZeneca COVID-19 vaccine and mixed messaging. *J Paediatr Child Health* 2021; **57**:472–473.
36 Taquet M, Husain M, Geddes JR, Luciano S, Harrison PJ. Cerebral venous thrombosis and portal vein thrombosis: A retrospective cohort study of 537,913 COVID-19 cases. *EClinicalMedicine* 2021; **39**:101061.