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Thrombosis and thromboembolism: Brighton collaboration case definition and guidelines for data collection, analysis, and presentation of immunization safety data

Jahnavi Gollamudi [a,1,2], Sarah E. Sartain [b,1], Amir Hassan Navaei [c], Satinder Aneja [d], Pawandeep Kaur Dhawan [e], Dat Tran [f], Jyoti Joshi [g], Jane Gidudu [h], Jayakrishna Gollamudi [i], Elena Chiappini [j], Frederick Varricchio [k], Barbara Law [l], Flor M. Munoz [m,*]

[a] Department of Medicine, Section of Hematology, Baylor College of Medicine, Houston, TX, USA
[b] Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine, Houston, TX, USA
[c] Pediatric Critical Care, Transfusion Medicine & Coagulation, Pediatrics and Pathology & Immunology Departments, Texas Children's Hospital, Baylor College of Medicine, 6701 Fannin St, Suite WB110, Houston 77021, TX, USA
[d] Department of Pediatrics, School of Medical Sciences & Research, Sharda University, Gr Noida, India
[e] Independent Consultant, India[3]
[f] Oregon Health Authority, Public Health Division, Acute and Communicable Disease Prevention Section, Portland, OR, USA
[g] International Centre for Antimicrobial Resistance Solutions (ICARS), Orestads Boulevard 5, 2300 Copenhagen, Denmark
[h] Centers for Disease Control and Prevention, Atlanta, GA, USA
[i] University of Cincinnati, Cincinnati, OH, USA
[j] Meyer University Hospital, Department of Health Science, University of Florence, Florence, Italy
[k] Independent Consultant, Venice, FL, USA
[l] SPEAC, Brighton Collaboration, Independent Consultant, Vancouver, BC, Canada
[m] Department of Pediatrics, Section of Infectious Diseases, and Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, USA

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ABSTRACT

This is a Brighton Collaboration case definition of thrombosis and thromboembolism to be used in the evaluation of adverse events following immunization, and for epidemiologic studies for the assessment of background incidence or hypothesis testing. The case definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of SARS-CoV-2 vaccines. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and defined levels of certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network and by selected expert reviewers prior to submission.

1. Preamble

A thrombus is a localized hemostatic plug or blood clot in a blood vessel. Thrombosis occurs when a thrombus causes blockage in the blood vessel. This blockage can result in partial or complete blood flow obstruction either in larger vessels such as arteries or veins, or smaller vessels collectively termed as microcirculation. Deep vein thrombosis (DVT) refers to a blood clot involving non-superficial, i.e., 'deep' veins, and in this document DVT will be used to designate lower limb deep venous thrombosis. Other anatomic sites will be specified, as appropriate. Thromboembolism is an umbrella term encompassing in situ thrombus and embolus, a dislodged thrombus. Embolism most commonly occurs in the lungs and is known as pulmonary embolism (PE). Venous thromboembolism (VTE) is an umbrella term referring to DVT and PE. The epidemiology, risk factors, treatments and outcomes are globally different for VTEs and arterial thromboembolisms (ATEs), despite

* Corresponding author at: Institution: Baylor College of Medicine, USA.
E-mail address: florm@bcm.edu (F.M. Munoz).
[1] These authors contributed equally to the work presented.
[2] Current address: University of Cincinnati, Cincinnati, OH, USA.
[3] Current address: Global Medical Expert, Sanofi India, Mumbai, India.

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some overlapping risk factors and treatments. This case definition will focus on VTE, although both myocardial infarct and non-hemorrhagic stroke, if present, could meet the case definition, but a more detailed description of arterial thromboembolism is beyond the scope of this document.

Although there are standardized definitions for thrombosis and thromboembolism for research and clinical purposes, there are currently no definitions for these as adverse events of special interest which would enable data to be compared across trials and surveillance systems, and thus facilitate interpretation and promotion of scientific understanding.

The purpose of this document is to provide a concise overview of the epidemiology, etiologies and diagnosis of the most common presentations of VTE, in addition to ischemic stroke and to propose a standard case definition for use in vaccine safety settings and related activities. More detailed information related to MedDRA ICD codes, background incidence rates, risk factors and data collection tools can be found in an online companion guide to this case definition (Appendix A). Thrombosis with thrombocytopenia syndrome (TTS) has been covered in a specific case definition and therefore is not included here. The most current draft of the TTS case definition (available at https://www.brightoncollaboration.us) shares many of the features of thrombosis or thromboembolism as defined here.

2. Thrombosis and thromboembolism: Incidence and risk factors

2.1. Incidence of thrombosis and thromboembolism

Thrombosis and thromboembolism (TE) can affect virtually any vessel and is a complex, multifactorial disease, involving interactions between acquired or inherited predisposition to thrombosis (e.g., thrombophilia) and environmental exposures (e.g., smoking) [1–8]. The estimated average annual incidence rate of overall venous thromboembolism (VTE) among persons of European ancestry ranges from 104 to 183 per 100 000 person-years [9–19]. In the United States (US), overall VTE incidence may be higher in African-Americans [20–22] compared with Asians [23], and Native-Americans [24]. Large epidemiological studies have estimated an age-standardized rate for ischemic stroke at 114.3 per 100 000 population (95 % CI, 108.5/100 000–122.3/100 000) [25].

The incidence of VTE increases with age, with a sharp increase in individuals aged more than 45 years old, particularly in men [8,26]. Incidence rates for VTE are moderately higher in women during childbearing years [26]. A trend for increased VTE diagnosis was reported in about 40 children's hospitals in the US [27].

2.2. Risk factors for thromboembolism

Age is an important risk factor, as indicated above. Other risk factors for VTE include smoking, atrial fibrillation, cancer and chemotherapy, congenital heart diseases, sickle cell disease, thrombophilia (inherited or acquired, e.g., Factor V Leiden mutation, protein C and S deficiency, antithrombin III deficiency, hyper-homocystinuria), estrogen-based medications (oral contraceptives or hormone replacement therapy), immobility/critically ill patients, indwelling devices, trauma/surgery, and inherited predisposition [28,29].

3. Etiology of venous thromboembolism

Thromboembolic events are multifactorial events that can be caused by patient-related factors and underlying disease states. The mechanisms involved in VTE vary depending on the type of vessel (venous vs microcirculation) and anatomical location of the vascular bed. Endothelial injury due to various causes (e.g., hypertension, inflammation, endotoxins, plaque formation, reactive oxygen radicals) is a dominant factor in the majority of thrombotic mechanisms [12]. Virchow provided a simplified explanation of pathophysiological factors for venous thromboembolisms in his famous triad [30]. It has been suggested that hypo-fibrinolysis is also a potential major contributing risk factor (Fig. 1) [31]. In arterial thrombosis, the typical initiating event is the release of atherosclerotic plaque content. Due to the shear force and speed of blood flow, platelet aggregation and subsequent activation of coagulation factors contribute to arterial thrombosis.

Thrombosis in micro vessels such as arterioles, capillaries and venules can cause significant organ injury. Various disease processes such as sepsis, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and antiphospholipid syndrome (APS) can cause microvascular thrombi. The pathophysiology can be complex, and often involves endothelial injury in small vessels leading to organ dysfunction.

3.1. Thromboembolism following infection

3.1.1. Thrombosis after acute bacterial and viral infections

Acute bacterial and viral infections are associated with a transient increased risk of VTE and microvascular thrombosis [32]. Hospitalization with infection is a strong trigger for VTE even in non-immobilized patients. VTE can occur following influenza-like illness, varicella and other infectious diseases [33–35]. Varicella infection is a known risk factor for arterial thrombosis, due to vasculopathy [35]. Data support a hypercoagulable state leading to deep vein thrombosis (DVT) and other thromboembolic sequelae following varicella-induced autoantibodies to natural anticoagulants in children as well as adults [36]. Individuals infected with human herpes viruses (DNA viruses) and HIV have an increased risk of thrombosis, which for chronic HIV infection has been reported to be up to a 10-fold increase, including the risk for cerebral venous thrombosis (CVT) [37–40]. The risk of microvascular thrombosis due to infections varies, depending on the infectious agent and severity of infection [41].

3.1.2. Thrombosis after severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection

Thrombotic complications and coagulopathy are frequent in coronavirus disease 2019 (COVID-19) [42]. The risk of VTE is 2- to 6-fold higher in patients with COVID-19 disease than in patients without, despite the use of a standard prophylaxis anticoagulation dose in patients with COVID-19. The risk for arterial thrombosis is also increased and occurs in younger individuals. Microvascular thrombi have been identified in the lung tissue of patients who died from COVID-19 [43–45]. Disseminated intravascular coagulation (DIC) has also been reported to be associated with increased mortality [46,47]. Bleeding complications are less frequent in SARS-CoV2 infection, and they are usually associated with preexisting lesions (e.g., duodenal ulcer) in the setting of coagulopathy from DIC or anticoagulation [48].

The rates of DVT and pulmonary embolism (PE) associated with COVID-19 infections differ based on differences in baseline risk, comorbidities, use of prophylactic antithrombotic agents and severity of infection. The observed risk for VTE in COVID-19 is variable across studies but remains high, particularly in intensive care unit (ICU) patients (13–31 %) [49,50]. In patients with COVID-19 infection, two unusual sites for venous thrombosis, CVT and portal vein thrombosis (PVT), have been described and they seem to develop generally within two weeks of the infection. CVT is a rare form of stroke accounting for 0.5–1 % of all strokes [51]. The incidence is about 5–16 cases per 1 million people per year and CVT

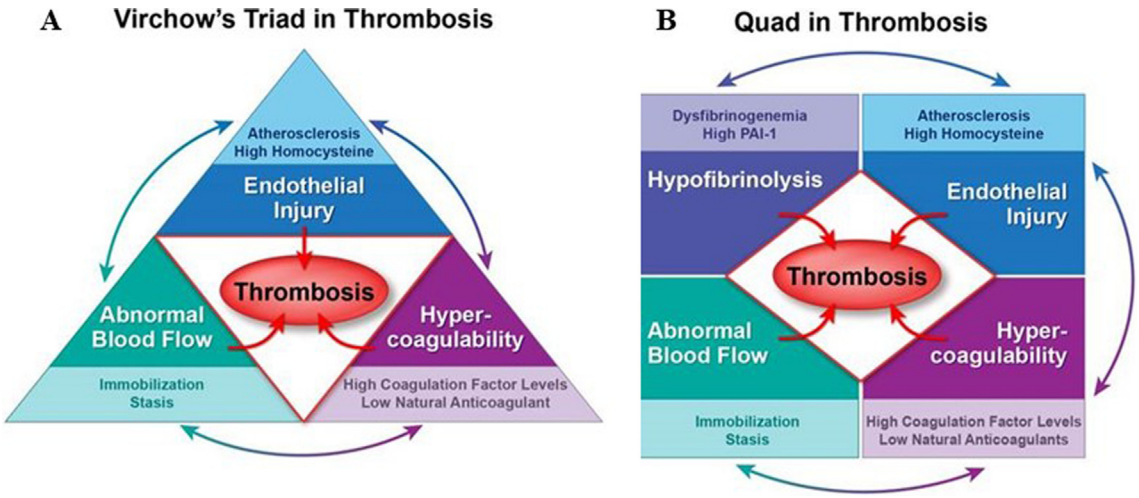

Fig. 1. Virchow proposed a triad of three key elements in the development of venous thrombosis and thromboembolism (A). Hypo-fibrinolysis can be an additional element (B); PAI-1 = plasminogen activator inhibitor 1. (This figure was reproduced/used with permission from [32], copyright, Texas Children's Hospital, 2019.).

generally occurs in patients aged less than 50 years, and predominantly in women [51–53]. The incidence of CVT in patients with COVID-19 infection is estimated to be low and seems to be more frequent in patients under the age of 30. In a recent literature review of nine studies, 14 cases were identified after COVID-19 infection [54]. The prevalence of PVT is about 1 % in the general population with an increasing prevalence in certain subgroups such as those with cirrhosis [55,56]. In a recent study, the estimated incidence of PVT following COVID-19 infection was estimated to be about 392 events per million patients [57].

The cumulative incidence rate of acute ischemic stroke was reported to be between 2 % and 3.7 % in ICU adult patients with COVID-19 infection and about 2 % in non-ICU patients [49,58,59]. The cumulative incidence rate for peripheral arterial thrombosis in patients with COVID-19 admitted to ICU was 4.4 % [60]. SARS-CoV-2 infection is reported to increase the pro-thrombotic state through various mechanisms, which can explain the extent of the thrombotic complications contributing to the severity of the disease (Fig. 2) [61].

3.2. Thrombosis and thromboembolism after vaccination

3.2.1. Venous thromboembolism following immunization

Two post-licensure monitoring studies from the US identified a possible risk of DVT and VTE following quadrivalent human papillomavirus (HPV4) vaccination based on spontaneous reports from passive surveillance systems [62,63]. More than 90 % of reported cases with VTE had other risk factors for VTE. Subsequently, a self-controlled risk interval study which included 650 000 females aged 9–26 years found no increased risk of VTE following HPV vaccination [64].

A review of vaccine adverse event reports to the Vaccine Safety Datalink database in the US concluded that there was no evidence that inactivated influenza vaccine was associated with VTE in adults aged 50 years and over, although an increased risk was found among current smokers in a post-hoc analysis [34].

3.2.2. Thrombotic thrombocytopenia syndrome

Cases of thromboembolism associated with thrombocytopenia, known as thrombotic thrombocytopenia syndrome (TTS) have occurred following vaccination with the CHaDOx1 nCov-19 (AstraZeneca) and the Ad26.COV2-S (Johnson & Johnson) vaccines with extremely low incidence [65–68]. This has also been referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT) [69]. TTS is characterized by thrombosis, often at unusual sites, mild to severe thrombocytopenia, and positive PF4 antibodies, similar to those formed in HIT, despite no recent exposure to heparin [70,71]. If TTS is not recognized or treated promptly, the outcome can be fatal.

3.2.3. Ischemic stroke following immunization

Published case reports have described ischemic stroke after influenza vaccination, potentially due to the inflammatory and immunological responses to the vaccine, although no causal relationship has been demonstrated [72–74]. An increased risk of stroke after vaccination with a live varicella vaccine is biologically plausible since natural infection is a risk factor for stroke and the vaccine mimics infection. There have been isolated case reports of ischemic stroke after varicella vaccination, but a retrospective study using data from greater than 3 million children aged 11 months to 17 years in the US Vaccine Safety Datalink reported no association between stroke and varicella vaccine in the 12 months following varicella vaccination [75]. Similarly, a population-based cohort study in Canada reported no increased risk of arterial ischemic stroke in the 12 months following varicella vaccine for children vaccinated between 11 and 23 months of age, compared with non-vaccinated children [76]. Another study reported a decrease in the risk of stroke in persons aged 66 years and above following live attenuated zoster vaccine [77].

4. Diagnosis of thrombosis and thromboembolism

4.1. Pathologic diagnosis

The definitive method for the diagnosis of thrombosis and thromboembolism is pathologic, which can include histopathology of tissue recovered by biopsy or autopsy or recovery of a thrombus by surgical or a catheterization procedure, such as thrombectomy.

4.2. Imaging modalities

When pathologic diagnosis is not possible, as is often the case, imaging modalities are crucial for the diagnosis of thrombosis and thromboembolism. More details of the appropriate imaging modalities are presented in Section 4.2 below, organized by the type of thrombus or thromboembolism. Table 1 provides a sum-

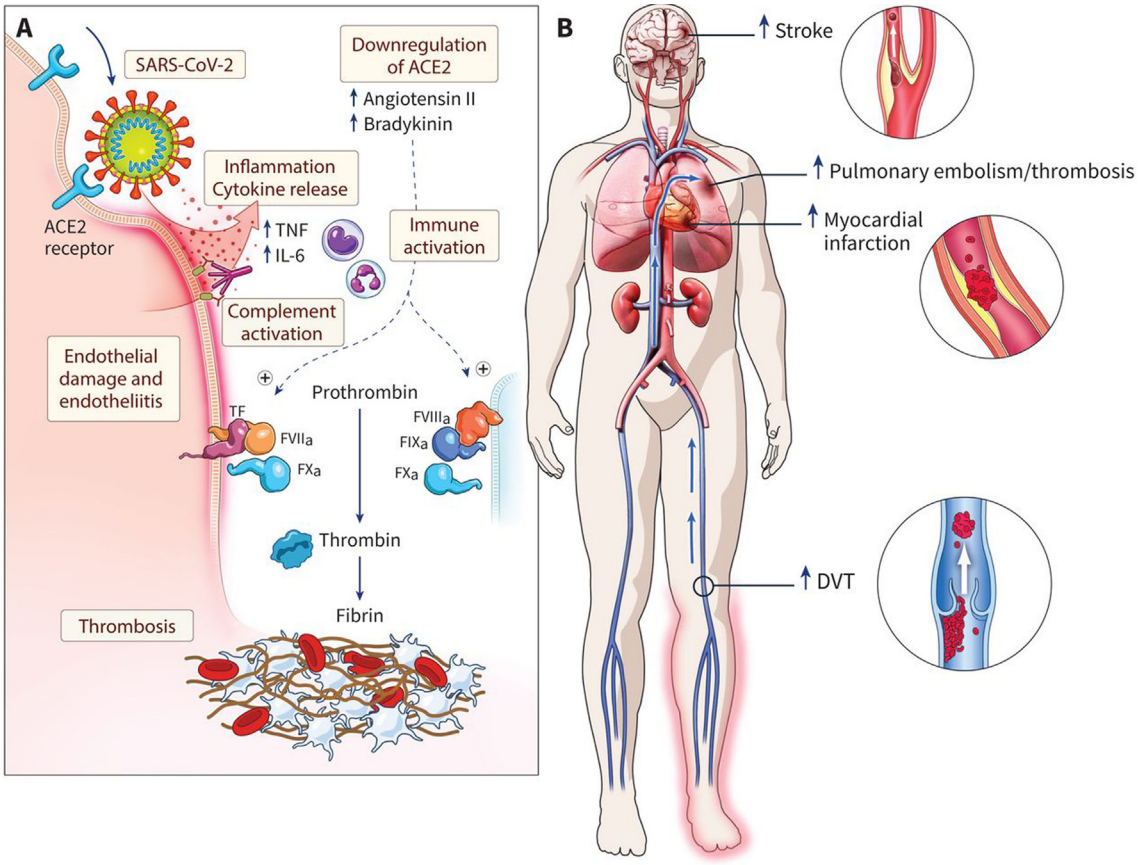

Fig. 2. Possible mechanisms for thrombosis in coronavirus disease 2019 (COVID-19) and clinical consequences. (A) Injury to the endothelium initiated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into cells via the angiotensin-converting enzyme 2 (ACE2) receptor is thought to lead to diffuse endotheliitis. The endothelial damage may result in an inflammatory host response characterized by excessive immune activation and cytokine storm, which promotes hypercoagulability and thrombosis. (B) Possible venous and arterial thrombotic complications associated with COVID19. Abbreviations DVT = deep vein thrombosis, FVIIa = factor VIIA, IL-6 = interleukin 6, PE = pulmonary embolism, TF = tissue factor, TNF = tumor necrosis factor α. Original illustration by freelance medical illustrator Gail Rudakevich. (Figure and footnote . reproduced from [63]

mary of the first line and alternative imaging tests for the diagnosis of thrombosis and thromboembolism and their limitations.

4.3. Laboratory tests for diagnosis of thromboembolism

Results from laboratory tests can provide supportive evidence for the presence of thromboembolism but there are no specific biomarkers for VTE. Only laboratory tests that have been extensively evaluated and reported in literature are included here.

Normal D-dimer levels help to rule out DVT and PE in patients with a low probability for DVT or PE but not in patients who have a high probability [78]. The D-dimer test has high sensitivity (80–100 %) but low specificity (23–63 %) [79]. Despite its widespread use as a biomarker, the D-dimer test has several limitations. There is marked variability in the methodology used, making it difficult to have a reference standard. In patients older than 50 years, an age-adjusted threshold should be used as normal D-dimer levels increase with age [79]. Troponin and B-type natriuretic peptide (BNP) are biomarkers of cardiac injury and can be used to assess the severity of PE.

4.4. Clinical scoring systems

Even when the clinical history and examination is suggestive of the presence of TE, this may be misleading. The Wells score and the revised Geneva score are commonly-used scoring systems to estimate the probability of VTE and guide the choice of investigation [80,81].

4.5. Site specific considerations

4.5.1. Diagnosis of lower limb deep vein thrombosis (DVT)

4.5.1.1. Ultrasonography. Compression ultrasonography is the first-line imaging test for the diagnosis of patients presenting with clinically suspected DVT [82]. The criteria for acute DVT include non-compressibility of the vein in combination with at least one of the following: enlarged vein, hypoechoic vein lumen, or the absence of significant collateral veins. Although this test is relatively frequently available, the results are highly operator-dependent and this method has poor sensitivity for distal DVT.

4.5.1.2. Contrast catheter venography. Contrast catheter tomography venography is the historic and de facto first line imaging technique for the diagnosis of DVT as it visualizes both distal and proximal veins of the lower extremities. The criteria for acute DVT are a complete or partial central filling defect. Acute DVT should be differentiated from chronic DVT which is suggested by thick eccentric walls, recanalization, and calcification. Concerns about radiation exposure and the technological advances in ultrasound have contributed to compression ultrasonography now being considered the first choice for imaging [83].

Table 1
First line and alternate techniques for diagnosing thrombosis and thromboembolism, by location.

Location	First line technique	Limitations of first line technique	Alternate technique(s)	Limitations of alternate technique
Deep vein thrombosis	Compression ultrasonography with and without doppler (sensitivity 94.2%: specificity 93.8% for proximal DVT, 63.5% for distal DVT)	Results are operator-dependent Poor sensitivity for diagnosing distal DVT	Contrast catheter venographyMR venographyCT venography	Invasive, time-consuming and radiation exposure
Pulmonary embolism	CT pulmonary angiography (sensitivity 83%; specificity 96%)		1. V/Q scan (may be preferred over CT pulmonary angiography if renal failure, hypersensitive to contrast medium, or pregnant)	1. Some radiation exposure
			2. Contrast-enhanced MR angiography (sensitivity varies by embolus location: proximal 97.77-100%; segmental 68-91.7%; sub-segmental 21.4-33.3%)	2. Requires hemodynamic stability and ability to hold breath for 13-17 seconds
			3. Angiography (digital-subtraction or conventional)	3. Requires IV contrast administration and ability to hold breath for ≥20 seconds
Stroke and ischemic stroke	Non-ontrast CT (sensitivity 64%, specificity 85% for identifying infarction within 6 hours of presentation) – can distinguish ischemic stroke from intracranial bleed	Cannot differentiate viable from irreversibly damaged brain tissue Insensitive for detecting small cortical/subcortical infarctions, especially in posterior fossa	1. CT angiography (92-100% sensitivity, 82-100% specificity for detecting large vessel stenosis 2. MRI (91% sensitivity) 3. MR angiography (86-97% sensitivity, 62-91% specificity to identify large vessel stenosis)	1. Requires IV contrast administration so can't be used in allergic or renal failure patients 2 and 3. Cannot be used in patients with pacemakers, metallic implants, severe claustrophobia or contraindications to contrast agents (allergy, renal failure)
Cerebral venous thrombosis	Contrast-enhanced MR venography (83% sensitivity, 100% specificity)		CT venography	Only a small study to support the use of this technique
Portal vein thrombosis	Abdominal ultrasound with Doppler (sensitivity and specificity range between 60 and 100%)		1. CT scan with contrast 2. MRI	
Microcirculation thrombosis			Pathologic diagnosis based on biopsy or autopsy samples	

CT – computed tomography; V/Q – ventilation/perfusion; MR – magnetic resonance.

4.5.1.3. Alternative techniques. MR venography (MRV) is a noninvasive alternative to contrast catheter venography. In a recent systematic review, MRV was reported to have a pooled sensitivity of 91.5 % (95 % CI: 87.5 %; 94.5 %) and a pooled specificity of 94.8 % (95 % CI: 92.6 %–96.5 %) [84]. When evaluating for proximal DVT, MRV is as sensitive and specific as US or contrast catheter venography. Advantages of MRV include identification of external causes of venous compression and evaluation of veins above the inguinal ligament, as in one study where 20 % of DVTs were located in the pelvic veins [85]. CT venography (CTV) can also be used to diagnose DVT and has advantages similar to those of MRV. In a systematic review CTV was reported to have a pooled sensitivity of 95.9 % (95 % CI: 93.0 %; 97.8 %) and a pooled specificity of 95.2 % (95 % CI: 93.6 %–96.5 %) for diagnosing proximal DVT, which is comparable to US [86]. However, exposure to radiation makes this less preferable compared with MRV, when US is non-conclusive.

4.5.2. Diagnosis of pulmonary embolism

4.5.2.1. CT pulmonary angiography. Chest CT pulmonary angiography (CTPA) is the current first line imaging for the diagnosis of PE. In the Prospective Investigation of Pulmonary Embolism Diagnosis 2 (PIOPED II) study, its sensitivity and specificity for PE were 83 % and 96 %, respectively [87]. Its findings for acute PE include a central filling defect within a vessel surrounded by contrast material, eccentric or mural filling defect rendering an acute angle with a vessel wall or complete occlusion of a dilated vessel by a filling defect. This imaging test can also provide evidence of right heart strain, clot burden, and lung vasculature as well as significant additional information related to alternate diagnoses, which is a clear advantage over ventilation-perfusion (V/Q) scans.

4.5.2.2. Ventilation-perfusion scanning. V/Q scanning was widely used for PE diagnosis before the widespread availability of CTPA. Although V/Q scanning uses radioactive materials, the level of exposure to radiation is low. The V/Q scan result provides the probability of PE as high, intermediate, low or normal scan, where a normal scan essentially excludes a diagnosis of PE [88,89]. V/Q scan may be a preferred modality of diagnosis in patients with renal failure or with history of hypersensitivity to contrast medium. Its use in pregnant women has been debated because V/Q scan involves lower maternal radiation but higher fetal radiation whereas the opposite is true for CTPA, however ACR recommends either CTPA or V/Q scan to be the first line for pregnant women [90,91].

4.5.2.3. Contrast-enhanced magnetic resonance angiography. Pulmonary contrast-enhanced magnetic resonance angiography is an effective alternative tool for PE diagnosis but has limitations as patients need to be hemodynamically stable and to hold their breath for 13 to 17 s. Current magnetic resonance imaging technology demonstrates high specificity and high sensitivity for proximal PE but has limited sensitivity for distal PE [92].

4.5.2.4. Digital subtraction angiography and conventional angiography. Digital subtraction angiography and conventional angiography are two of the historical techniques for PE diagnosis. They have been largely replaced by modern CTPA. Both techniques require intravenous administration of contrast agents and patients must hold their breath for up to 20 s or more, which is not ideal when patients are already dyspneic from a PE [93,94].

4.5.2.5. Supportive modalities for diagnosis of pulmonary embolism.

4.5.2.5.1. Chest radiography. Chest radiography should not be used

Table 2
Summary of clinical syndromes that should be differentiated from most common thrombosis and thromboembolism.

Clinical thrombotic syndrome (examples of non-specific symptoms)	Possible alternative etiologies	
	General categories	**Specific diagnoses**
DVT [116–119](calf **pain**, redness, increased warmth, ankle **edem**a)	Physical trauma	• Calf muscle or Achilles tendon tear • Calf muscle hematoma • Fracture of tibia or fibula
	Cardiovascular disorder	• AV fistula and congenital vascular abnormalities; • External compression of major veins • Vasculitis
	Other conditions	• Ruptured Bakers cyst, • Cellulitis • Lymphatic obstruction • Dependent edema, • Heart failure • Septic arthritis, • Cirrhosis, • Nephrotic syndrome • Compartment syndrome
Pulmonary embolism [120–133](chest **pain**)	Respiratory conditions	• Pneumothorax or pneumomediastinum) • Pneumonia • Acute bronchitis • Acute exacerbation of asthma, COPD or chronic lung disease
	Cardiac injury	• Acute coronary syndrome • Acute HF • Dissecting or rupturing aortic aneurysm • Unstable angina / MI • Pericarditis
	Musculoskeletal chest pain	• Costochondritis
	Gastroesophageal reflux disease (GERD) Esophageal spasm, Peptic ulcer disease Toxic/metabolic disturbances	
Stroke [134–141] (**headache**)	Conditions causing dizziness, disturbed balance	• Hypoglycemia • Drug and alcoholic toxicity • Syncope • Labryinthine disorders: Vertigo, Meniere's, labrynthitis
	Neurologic conditions	• Seizure • Migraine with aura • Demyelination (MS) • Peripheral neuropathies (Bell's palsy) • Spinal epidural hematoma • Primary or secondary central nervous system malignancy • Detached retina • Ocular palsy.
	Systemic or local infection	
	Cardiac/major vessel injury	CNS abscess, encephalitis, sepsis

routinely for the diagnosis of PE as it is neither sensitive nor specific for PE. However, the presence of a wedge-shaped opacity indicative of infarct, pleural effusion, or prominent proximal pulmonary artery with reduction in peripheral vessel markings would be suggestive of PE [95,96].

4.5.2.5.2. Electrocardiogram. Electrocardiogram (ECG) is not a diagnostic tool for PE but it can provide corroborative evidence. The most common ECG signs for PE are sinus tachycardia, atrial fibrillation, or signs of right heart strain, e.g., anterior precordial *T*-wave inversions, and either inferior or anterior precordial ST-segment elevation [97].

4.5.2.5.3. Transthoracic echocardiography. Transthoracic echocardiography is not a diagnostic tool for PE, but it can provide corroborative evidence for right heart strain due to PE echocardiography. The structure and function of the right ventricle and the pulmonary arterial pressure can be assessed. Right ventricular abnormalities can include right heart dilation, tricuspid regurgitation, interventricular septal compression and right ventricular hypokinesia [98,99].

4.5.3. Diagnosis of cerebral venous thrombosis

Magnetic resonance venography (MRV) is a useful tool for central venous thrombosis diagnosis. Although various techniques exist, contrast-enhanced MRV has high sensitivity and specificity (83 % and 100 %, respectively) [100,101]. [102]. If contrast cannot be used, magnetic resonance venography without contrast can be used. CT venography is another possible tool for diagnosing cerebral venous thrombosis, but this is based on a small study in which 3 reviewers reviewed the results for 13 patients and 20 controls.

4.5.4. Diagnosis of portal vein thrombosis

An abdominal ultrasound with Doppler is often the investigation of choice to detect portal vein thrombosis with a sensitivity and specificity ranging between 60 % and 100 % [103]. CT scan with contrast and MRI are are extensively used as a first-line option in higher-income countries to diagnose portal vein thrombosis [104].

4.5.5. Microcirculation thrombosis

Microvascular thrombosis is difficult to detect and requires high clinical suspicion. Definitive diagnosis can be made through pathological studies such as organ biopsies. Imaging modalities are not useful for the diagnosis of microcirculatory thrombosis. Laboratory tests suggestive of microcirculatory thrombosis include markers of hemolysis, e.g., high lactate dehydrogenase, elevated unconjugated bilirubin, high reticulocyte count, low haptoglobin and elevated free plasma hemoglobin, and markers of microangiopathy, e.g., such as anemia, thrombocytopenia and presence of schistocytes in peripheral blood smears. Microcirculation thrombosis may lead

to organ dysfunction or damage and can therefore present as laboratory abnormalities related to that organ, e.g., elevated creatinine for renal dysfunction [105].

4.5.6. Diagnosis of stroke and ischemic stroke

4.5.6.1. Magnetic resonance imaging. Brain magnetic resonance imaging (MRI) protocols for acute ischemic stroke include T1- and T2-weighted sequences, fluid attenuated inversion recovery (FLAIR) sequence, perfusion-weighted imaging (PWI), and diffusion weighted imaging (DWI) [106]. The sensitivity for DWI is 91 % compared with 61 % for non-contrast CT [107]. The combination of DWI and PWI is often used to evaluate the extent of irreversible tissue damage and therefore inform decision about reperfusion strategies [108,109]. Similar to CT, an MR angiography can be performed to identify large vessel stenosis with a sensitivity of 86 % to 97 % and specificity of 62 % to 91 % [110]. The major disadvantages of MRI are that it is not suitable for patients with severe claustrophobia, and it cannot be used in patients with pacemakers, metallic implants, or contraindications to MR contrast agents.

4.5.6.2. Non-contrast computed tomography. Non-contrast CT remains the most common first-line imaging tool used in the diagnosis of acute stroke [111]. It can be used to distinguish intracranial hemorrhage from ischemic stroke, thereby enabling specific interventions, such as reperfusion strategies, to be initiated. This tool can identify early signs of infarction (within six hour of presentation) with a specificity of 85 % and a sensitivity of 64 % and can also identify thrombosis in vessels [112,113]. However, it cannot be used to differentiate reliably between viable brain tissue and irreversibly damaged brain tissue, which limits its usefulness in patients with unknown time of symptom onset. It is also relatively insensitive for detection of acute or small cortical or subcortical infarctions, especially in the posterior fossa [114].

CT angiography and CT perfusion imaging are important modes of contrast CT. CTA enables the intracranial vasculature to be visualized, and it can identify the exact location and extent of vascular occlusion. For example, it has a sensitivity of 92 % to 100 % and a specificity of 82 % to 100 % to detect large vessel stenosis [110]. However, it requires administration of a contrast agent and, therefore, cannot be used in patients with contrast allergies and abnormal renal function.

5. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation

The Brighton Collaboration *Thrombosis and Thromboembolism Working Group* was formed in September 2020 following the process described on the Brighton Collaboration website [115]. The group members included clinical, public health, pharmacovigilance and vaccine safety experts. A literature search was performed using established databases and search engines. The Working Group met regularly to review the results from the literature search and develop the case definition and guidelines based on expert consensus supported by evidence in the reviewed published literature.

5.1. Rationale for selected decisions about the case definition of thrombosis and thromboembolism as an adverse event following immunization

The case definition of thrombosis and thromboembolism is shown in Table 3. The working group agreed that it was important to consider and distinguish the arterial system from the venous system for this case definition.

The case definition was formulated using three levels of diagnostic certainty with Level 1 being highly specific. As maximum specificity usually means a loss of sensitivity, two additional diagnostic levels were included in the definition, offering a stepwise increased sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. This approach should ensure that all cases of thrombosis and thromboembolism can be captured with a level of certainty of between 1 and 3. These levels of certainty reflect the diagnostic certainty and should not be misunderstood as reflecting different grades of clinical severity (Appendix A. Supplementary material).

5.2. Rationale for individual criteria or decision made related to the case definition

5.2.1. Clinical presentation

The Working Group agreed that DVT, and PE represent typical venous events, and that stroke and myocardial infarction represent typical arterial events. While rarer than DVT and PE, there are several other recognized venous thrombosis syndromes involving abdominal veins, cerebral veins, cerebral venous sinuses and retinal veins. As an AESI, thrombosis and thromboembolism may be actively ascertained in the setting of research projects (e.g., to measure population-based incidence or to test for a causal association with a vaccine) and also may be the subject of passively generated adverse event reports submitted to pharmacovigilance systems. Both settings could involve medical diagnoses of specific thrombosis or thromboembolism syndromes, such as DVT, PE, CVT or ischemic stroke or could involve a list of non-specific symptoms and signs that were part of the clinical illness. The Working Group agreed that both should be included in the definition but only at a lower degree of certainty (i.e. Level 2 or 3) since clinical symptoms may support the diagnosis of thrombosis or thromboembolism, but are insufficient to support a Level 1 of diagnostic certainty in the case definition.

General non-specific signs and symptoms vary depending on the location of the event and may include swelling, localized pain, shortness of breath or neurologic abnormalities. A full list is given in Table 3.

5.2.2. Pathologic and histopathologic findings

When available, pathologic and histopathologic findings of thrombosis or thromboembolism in tissue biopsy or autopsy evaluation provide a definitive diagnosis, and are considered sufficient to achieve a Level 1 of diagnostic certainty. However, pathologic and histopathologic findings are not always available and a definitive diagnosis can be established in their absence.

5.2.3. Imaging study findings

Findings from imaging tests can be used for an accurate, definitive diagnosis of a case of thrombosis or thromboembolism, and can be sufficient to achieve a Level 1 of diagnostic certainty. Depending on the location of the thrombus, various modalities are considered acceptable confirmatory tests. These include Doppler ultrasound, CT perfusion imaging, CT angiography, magnetic resonance venography or arteriography, echocardiograms, perfusion V/Q scans, and conventional or digital angiography. The choice of the appropriate modality for arterial or venous events should be based on clinical criteria, the sensitivity of the test, availability in various settings, and expertise in the interpretation of the results.

5.2.4. Laboratory findings

Abnormal laboratory results are not required for diagnostic confirmation as they can be normal in the presence of thrombotic and thromboembolic events. Coagulation markers are often obtained, but normal results do not rule out an arterial or venous thrombosis

Table 3
Case definition and Levels of diagnostic certainty for venous and arterial thrombosis and thromboembolism.

Level of certainty 1 (definitive case)

Pathologic or imaging study findings consistent with thrombosis and thromboembolism

Imaging studies include any of the following, depending on the location of the lesion
- Ultrasound – compression +/- doppler
- CT scan – contrast angiography
- MRV or MRA
- Echocardiogram
- V/Q scan
- Conventional angiography or digital subtraction angiography

OR

Procedure that confirms the presence of a thrombus e,g., thrombectomy

OR

Pathologic findings (biopsy or autopsy) consistent with thrombosis or thromboembolism

Notes:
- LOC 1 classification is independent of clinical findings or presence of risk factors.
- Most appropriate imaging test depends on the location of the lesion. Any of the tests listed may be used, as available. Echocardiogram used to detect thromboembolisms in a heart chamber or pulmonary arteries. Diagnosis is based on radiologist/expert interpretation. See Table 1 for more details

Level of certainty 2 (probable case)

Clinical presentation consistent with thrombosis or thromboembolism event, including:

Presumed diagnosis of ≥1 specific clinical syndromes, without imaging confirmation:
- DVT of lower or upper limbs; abdominal VT; cerebral venous thrombosis (CVT); cerebral venous sinus thrombosis (CVST); retinal vein thrombosis
- Pulmonary embolism (PE)
- Non-hemorrhagic stroke
- Myocardial infarction
- Other arterial thrombosis

OR

≥1 non-specific clinical signs and symptoms, including, but not limited to:
- Extremity: swelling, pain, redness, warmth, absent pulses ('DVT')
- Sudden onset of shortness of breath, pleuritic chest pain ('PE')
- Crushing central chest pain, or sudden unexpected death ('MI')
- Sudden onset headaches which could be severe and persistent; focal neurologic abnormalities, seizure; blurred vision or facial paralysis (stroke, CVT, CVST)
- Sudden painless loss of vision (retinal vein thrombosis)
- Sudden onset of acute abdominal pain (abdominal vein thrombosis)

AND

≥1 supporting imaging finding, suggestive of thrombosis or thromboembolism
- Chest radiograph suggestive of PE: wedge shaped opacity suggestive of pulmonary infarction or pleural effusion or prominent proximal pulmonary artery with reduction in peripheral vessel markings;
- Echocardiogram suggestive of PE: transthoracic echo showing right heart dilation or tricuspid regurgitation or interventricular septal compression or right ventricular hypokinesia
- Non-contrast computed tomography: similar findings as those for chest radiograph above.

AND

D-dimer, elevated above the upper limit of normal for age

AND

No alternative diagnosis

Notes:
- LOC 2 classification when the gold standard imaging study or pathologic findings are not available.
- With the exception of a D-dimer elevation above upper limit of normal for age abnormal laboratory results are not required for confirmation as results can be normal in the presence of thrombotic or thromboembolic events or abnormal in the absence of thrombosis or thromboembolism. .

Level of certainty 3 (possible case)

Clinical presentation consistent with thrombosis or thromboembolism event, including:
Presumed diagnosis of ≥1 specific clinical syndromes (same as Level 2)
OR
≥1 non-specific clinical signs and symptoms (same as Level 2)

AND
No alternative diagnosis

Notes:
- LOC 3 Lower Level of certainty based on clinical findings.
- Abnormal laboratory results are not required for confirmation as they can be normal in the presence of thrombotic or thromboembolic events.

Level 4 – Insufficient information available to confirm a possible, probable or definitive case of venous thrombosis or thromboembolism
Level 5 – Sufficient information to determine that it is NOT a case of venous thrombosis or thromboembolism
Abbreviations. CT: computed tomography; DVT: deep vein thrombosis; LOC: Level of certainty; MRA: magnetic resonance arteriography; MRV: magnetic resonance venography; V/Q: ventilation-perfusion scanning;

or thromboembolism event, except in patients with a low clinical probability. When abnormal results are obtained, an elevated D-dimer is the most specific test and can be used to support the diagnosis (Table 3 Level 2 diagnostic certainty). No other of the other coagulation markers, e.g., shortened prothrombin time (PT) or partial thromboplastin time (PTT), or elevated fibrinogen that can be associated with thrombotic events are specific. Results from coagulation markers and fibrinogen assays may be supportive in some cases, but they are less specific and thus were not included in the CD.

The working group did not include an increased international normalized ratio (INR) as it is not associated with thrombosis and could be associated with DIC or treatment interventions. Newer testing modalities, such as rotational thromboelastography (ROTEM), a viscoelasticity test, used as a marker of increased fibrinogen and platelet activity, is not used for the diagnosis of thrombosis.

5.2.5. Non-inclusion of treatment and treatment responses in the case definition

The Working Group decided against using medical treatment or treatment response in the case definition. A treatment response or its failure is not in itself diagnostic of thrombosis or thromboembolism, and may depend on variables, such as time to treatment, and other clinical parameters.

5.2.6. Timing post immunization

It is unknown when thrombosis and thromboembolism events may occur following immunization. While a temporal association would increase the likelihood of an association between immunization and the occurrence of a thrombotic or thromboembolic event, the Working Group agreed that a definition designed to be a suitable tool for testing potentially causal relationships requires ascertainment of the outcome independent from the exposure. Further, the definition should be applicable to studies done to determine background incidence of thrombosis and thromboembolism in various populations, in which it might take a few days before diagnosis is confirmed, thus introducing a time bias due to accessibility. Therefore, to avoid this bias, a restrictive time interval from immunization to onset of thrombosis or thromboembolism is not an integral part of the case definition. Instead, where feasible, the details of this interval should be reported and assessed as described in the data collection guidelines (Appendix A. Supplementary material). The Working Group acknowledged that it may be impossible to obtain a clear timeline if the event occurred in settings outside the controlled environment of a clinical trial or hospital, particularly in rural settings and LMICs.

5.2.7. Differentiation from other (similar/associated) disorders

Levels 2 and 3 of the case definition require either the reported diagnosis of a thrombosis or thromboembolism syndrome, or one or more typical but non-specific symptoms or signs reported [116–143]. Both Level 2 and 3 also require that there is no alternate etiology that could explain the clinical illness. Table 2 provides a list of possible alternate etiologies for each of the syndromes and their associated symptoms or signs. Absence of an alternate etiology was not included as a criterion for Level 1, because this level requires proven presence of thrombus or thromboembolism by pathology, thrombus recovery or an appropriate imaging technique.

5.3. Guidelines for data collection, analysis and presentation

The case definition is accompanied by guidelines for data collection, analysis and presentation (Appendix A. Supplementary material.). Both the case definition and guidelines were developed to improve data comparability and are not intended to guide or establish criteria for management of ill infants, children, or adults.

5.4. Periodic review

As for all Brighton Collaboration case definitions and guidelines, it is planned to review the definition with its guidelines on a regular basis or as needed.

6. Case definitions for thrombosis and thromboembolism

See Table 3 and Fig. 3.

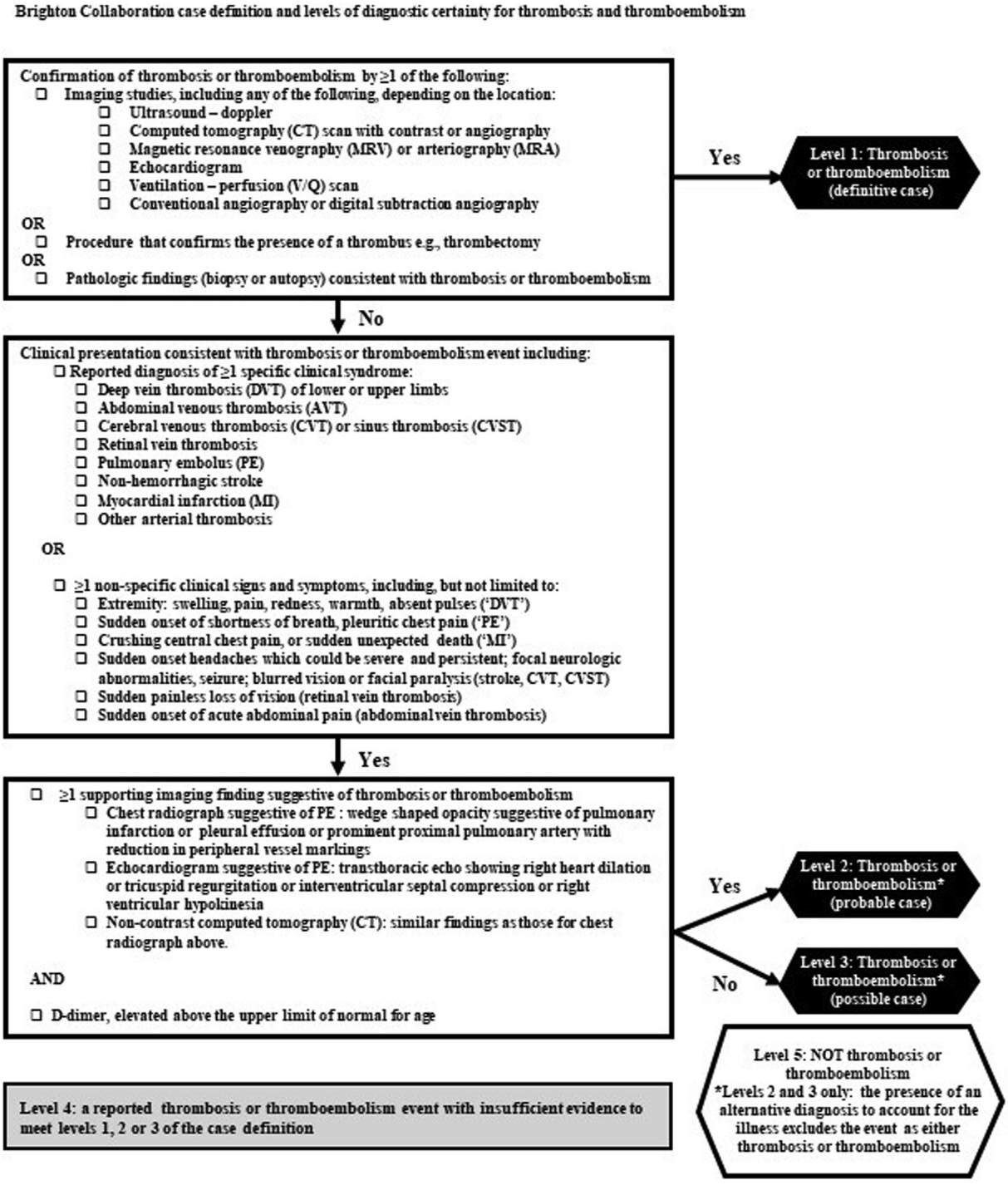

Fig. 3. Brighton Collaboration case definition and levels of diagnostic certainty for thrombosis and thromboembolism.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JG, SES, AHN, SA, K_D, DT, JJ, JD, EC, FV BL and FMM declare no conflicts of interest. PKD declares that she now works for Sanofi, India but was an independent consultant when this case definition was developed.

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Declaration of interests

JG, SES, AHN, SA, KD, DT, JJ, JD, EC, FV BL and FMM declare no conflicts of interest.

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Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization. Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of their respective institutions.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.09.001.

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