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COVID-19 Vaccine-Associated Thrombosis With Thrombocytopenia Syndrome (TTS): A Systematic Review and Post Hoc Analysis

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Abstract

Background: A new clinical syndrome has been recognized following the COVID-19 vaccine, termed thrombosis with thrombocytopenia syndrome (TTS). The following systematic review focuses on extrapolating thrombotic risk factors, clinical manifestations, and outcomes of patients diagnosed with TTS following the COVID-19 vaccine.

Methods: We utilized the World Health Organization's criteria for a confirmed and probable case of TTS following COVID-19 vaccination and conducted a systematic review and posthoc analysis using the PRISMA 2020 statement. Data analysis was conducted using SPSS V25 for factors associated with mortality, including age, gender, anti-PF4/heparin antibodies, platelet nadir, D-dimer peak, time to event diagnosis, arterial or venous thrombi.

Results: Of the 175 studies identified, a total of 25 studies with 69 patients were included in this systematic review and post hoc analysis. Platelet nadir ($P < .001$), arterial or venous thrombi ($\chi 2 = 41.911$, $P = .05$), and chronic medical conditions ($\chi 2 = 25.507$, $P = .041$) were statistically associated with death. The ROC curve analysis yielded D-dimer (AUC = .646) and platelet nadir (AUC = .604) as excellent models for death prediction.

Conclusion: Adenoviral COVID-19 vaccines have been shown to trigger TTS, however, reports of patients having received mRNA COVID-19 vaccines are also present. Healthcare providers are recommended to maintain a high degree of suspicion among individuals who have received the COVID-19 vaccine within the last 4 weeks.

Keywords

vaccine, COVID-19, thrombosis with thrombocytopenia syndrome, TTS, vaccine-induced immune thrombotic thrombocytopenia, VITT, heparin-induced thrombocytopenia, anti-platelet factor-4

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Introduction

In February of 2021, a new clinical syndrome was documented among patients who received the ChAdOx1 nCoV-19 AstraZeneca (AZ) vaccine and similar trends were noted for the Ad26.COV2. S Johnson & Johnson (JJ) vaccines in April 2021.[1,2] Now termed "Thrombosis with thrombocytopenia syndrome" (TTS), known also as "vaccine-induced immune thrombotic thrombocytopenia" (VITT) or "vaccine-induced prothrombotic immune thrombocytopenia" (VIPIT), TTS is a clinical syndrome that has been recognized following the administration of two adenovirus vector-based vaccines, including the AD26.COV2. S JJ

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vaccine and ChAdOx1 nCoV-19 AZ vaccine.[3] Both the vaccines encode for the SARS-CoV-2 spike protein immunogen via recombinant adenoviral vectors, chimpanzee for AZ and human for JJ.[4] TTS is similar to heparin-induced thrombocytopenia (HIT), despite the absence of heparin exposure, given firstly, its clinical presentation with venous or arterial thrombosis at odd sites including cerebral venous sinus thrombosis (CVST) and splanchnic vein thrombosis, secondly, the varying degrees of thrombocytopenia, and thirdly, positive platelet factor 4 (PF-4)-dependent enzyme-linked immunosorbent assay (ELISA) independent of heparin.[5] The underlying pathophysiology is associated with IgG antibodies that recognize PF4 and activate platelets through their Fcγ receptors.[6] This is similar to the classic HIT associated with platelet-activating anti-PF4/heparin antibodies.

Estimated clinical manifestations of symptoms present 5 to 30 days following the vaccination.[7,8] Symptoms are often severe and persistent including severe headache, visual changes, altered mental status, nausea, vomiting, abdominal pain, shortness of breath, bleeding or petechial, and leg pain or swelling. So far, CVST has been reported among two adenoviral vector-based (Jenssen and AstraZeneca) vaccine recipients who are among predominantly middle-aged women. However, these demographics may be skewed and if true, would be consistent with the risk factors associated with HIT.[9] The rare clinical entity is similar to autoimmune HIT presentations, clinically identified through PF4 antibodies and mild-to-severe thrombocytopenia.[10] However, the relationship between PF4 antibodies and the clinical manifestations of TTP following vaccine administration is yet to be fully determined. While there had been a temporary pause in the administration of JJ and AZ, the rollout has been resumed with a focus on closely evaluating the risks and benefits for each COVID-19 vaccine including the close monitoring of the newly defined TTS.[11] It is unclear whether those who develop TTS have a prior history of thrombosis or associated risk factors. There is also no mechanistic association of thrombotic events centered on cerebral vessels and splanchnic circulation with TTS.[12]

The following systematic review and posthoc analysis provide insight into the pre-existing risk factors for thrombosis or immunity among patients who developed TTS for relevant therapeutic implications.

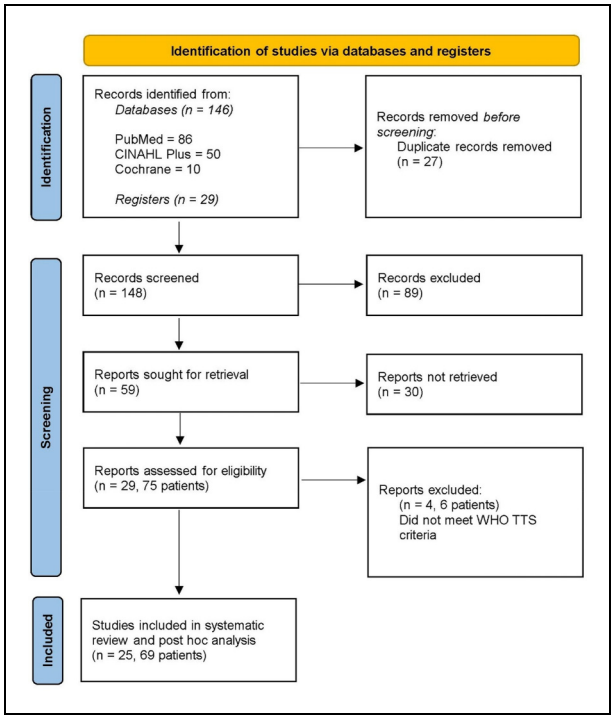

Figure 1. PRISMA flowchart.

Methodology

Search Strategy and Study Selection

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement, we conducted a systematic literature search from December 2019 through July 2021[13,14] The following keywords were used, by using the Boolean logic (and/or): thrombosis, thrombocytopenia, blood clot, DVT, embolism, VTE, clotting, covid-19, coronavirus or 2019-ncov, sars-cov-2 or cov-19, vaccines, vaccinations, immunizations. An a-priori approach was used to include the clinical studies and ensure that the outcome measures were listed systematically and continuously for the included studies.[15] The PRISMA flowchart is illustrated in Figure 1.

We included studies where patients either had confirmed or probable TTS diagnosis based on the World Health Organization's (WHO) criteria. For this analysis, we only included case series and case studies, whereas cohorts, systematic reviews, meta-analysis, letters, and editorials were excluded. Three databases were searched including PubMed, CINAHL Plus, and Cochrane, with an additional search of registers (NEJM, JAMA, BMJ). To ensure that all relevant studies were included, we screened the reference lists of included studies (umbrella review).

Eligibility Criteria

The WHO criteria for a confirmed and probable case of TTS following COVID-19 vaccination were used as listed below. These case definitions imply the absence of a better alternative explanation for the condition and are adapted from the WHO Interim Guidance for TTS.[16]

Confirmed case

- Individuals who present with thrombosis (imaging, surgical or pathological) in unusual locations (cerebral, splanchnic or multi-organ) within four weeks following vaccination with severe thrombocytopenia ($< 50 \times 10^9$/L), confirmatory peripheral smear showing reduced platelet, no evidence of platelet clumping, increased D-dimer and positive anti-PF4 antibodies;

- Positive laboratory criteria other than severe thrombocytopenia in patients with thrombosis in usual or unusual locations;
- Thrombosis in unusual locations with severe thrombocytopenia without positive laboratory markers (eg, anti-PF4 antibodies).

Probable case

- Individuals who present with thrombosis (imaging, surgical or pathological) in usual locations (pulmonary, limb veins, coronary arteries or cerebral arteries) within four weeks following vaccination with severe thrombocytopenia ($< 50 \times 10^9$/L);
- Thrombosis in unusual location with mild thrombocytopenia ($> 50 \times 10^9$/L—$< 150 \times 10^9$/L or > 50% decrease from baseline) and D-dimer > 4 mg/L.

Any study that did not meet the criteria listed above was removed.

Data Extraction and Synthesis

The following data were extracted from the included studies: demographic data (country, age, gender), the vaccine used and dosage, chronic medical conditions, thrombosis risk factors, presenting complaint, anti-PF4/heparin antibodies, platelet nadir, D-dimer peak, arterial or venous thrombi, time to event diagnosis and mortality. All data was inputted in a shared spreadsheet, which was extracted independently by the three authors for analysis and cumulative result interpretation (M.U.H., M.I., Z.S.). All discrepancies were resolved by the fourth and fifth authors (A.S., Z.S.) and a consensus was reached. Refer to Supplementary Table 1.

Data Analysis

The fourth and fifth authors (A.S. and Z.S.) extracted all nominal and ordinal data for analysis using SPSS V25. A bivariate analysis was conducted to assess the associations of mortality to age, gender, anti-PF4/heparin antibodies, platelet nadir (109/L), D-dimer peak (mg/L), time to event diagnosis, arterial or venous thrombi, and treatment. The factor was considered statistically significant if the *P*-value was .05 or less. Furthermore, a chi-square test of proportions was carried out to assess associations of 1) arterial or venous thrombi, 2) thrombosis risk factors, and 3) chronic medical conditions to death among the included patients. The post hoc analysis comprised of quantitative analytical measures for associations to mortality, where a ROC analysis was conducted with a value of .5 indicating a generally good model.

Role of Funding

No funding was obtained for this study.

Results

As illustrated in Figure 1, a total of 175 studies were identified, of which 148 were screened and 59 were sought for retrieval. In total, 29 studies comprising 75 patients were assessed for eligibility, where 25 studies with 69 patients were included in this systematic review and post hoc analysis. Six patients were excluded from this study as they did not meet the WHO TTS criteria.

Of 58 patients, 3 (5.17%) were from Canada, 1 (1.72%) from Denmark, 1 (1.72%) from France, 18 (31.03%) from Germany, 3 (5.17%) from Italy, 1 (1.72%) from Malaysia, 7 (12.07%) from Norway, 1 (1.72%) from Oman, 4 (6.9%) from Saudi Arabia, 4 (6.9%) from the United Kingdom, and 15 (25.86%) from the United States ($P = .165$) (Figure 2).

The results of the statistical analysis (ie, bivariate and chi-square proportion testing) are enlisted in Table 1 along with the summary details. The median age of all participants was 54, ranging from 18 to 72 ($P = .16$). There were 51 females (73.9%) in the total sample, with 80% who remained alive and 62.5% who died ($P = .059$). The most commonly administered vaccine ($N = 51$, 73.9%) was a single dose of AstraZeneca (ChAdOx1 nCoV-19), which was administered to 20 (83.3%) individuals who died ($P = .136$). Anti-PF4/heparin antibodies were present in 53 (76.8%) patients, and they were more prevalent (87.5%) in the individuals who died ($P = .416$). The median value of platelet nadir (109/L) among the entire sample was 326, ranging from 8 to 334 ($P < .001$). The median D-dimer peak (mg/L) value among the population was 140.9, ranging from 1.1 to 142 ($P = .419$). The mean ± standard deviation duration for time to event diagnosis in days was 10.4 ± 8.14 in the alive group and 7.67 ± 5.95 in the dead group ($P = .109$). The chi-square test determined that arterial or venous thrombi ($\chi 2 = 41.911$, $P = .05$) and chronic medical conditions ($\chi 2 = 25.507$, $P = .041$) led to a statistically higher likelihood of death.

The results of the ROC curve for vaccine dosage, gender, and age using death as the reference line. Similar associations were found for the area under the curve (AUC) for the vaccine type (AUC = .556), gender (AUC = .593), and age (AUC = .582). The AUC for the country was computed to be .731, suggesting that some countries of origin were strongly associated with mortality. While the ROC curve for platelet nadir, D-dimer peak was not presented in the figure, the findings were significant with the strongest associations of death to D-dimer peak (AUC = .646), suggesting that it was an excellent model for death prediction. This was closely followed by platelet nadir (AUC = .604), which is considered to be a generally good model. (Figure 3)

Discussion

To the best of our knowledge, this is the first quantitative analytical study to explore confirmed or probable TTS of cases reported in the literature. The most commonly implicated vaccine and the dose was a single dose of AstraZeneca

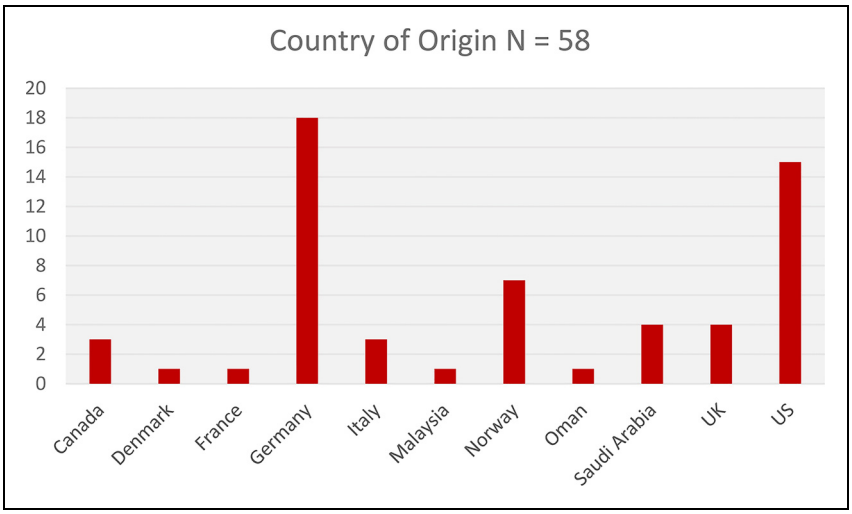

Figure 2. The country of origin for 58 patients. UK = United Kingdom, US = United States.

(ChAdOx1 nCoV-19) among 73.9% ($n = 51$) of the included patients. Other vaccines and doses were one dose of Janssen (Ad26.COV2.S) ($n = 12$, 17.4%), one dose of Pfizer/BioNTech (BNT162b2) ($n = 2$, 2.9%), two doses of Pfizer/BioNTech (BNT162b2) ($n = 2$, 2.9%), and two doses of Moderna (mRNA-1273) ($n = 1$, 1.4%) vaccines. Since March 2021, two vaccines that have been associated with TTS are the ChAdOx1 nCoV-19 (Oxford-AstraZeneca, also known as Vaxzevria) and AD26.COV2.S (Johnson & Johnson) vaccines.

Plausible mechanistic links have been evaluated between both these adenovirus-vectored vaccines and TTS.[17] Adenovirus-based COVID-19 vaccines have demonstrated thrombogenic potential with various mechanistic models being considered.[18] TTS has been identified as a result of breached immune tolerance and autoantibodies to PF-4. The underlying pathophysiology of TTS is similar to that of spontaneous HIT syndrome associated with heparin-independent platelet-activating anti-PF4 antibodies.[19] However, in the case of TTS, it may be suspected that the polyanions substituting for heparin may include immunogenic complexes present in the adenoviral-vectored COVID-19 vaccine. The contributory mechanisms are unclear but the vaccine components such as viral proteins of free DNA may bind to PF4 resulting in a neoantigen.[20] The post-vaccination antibodies are hypothesized, therefore, to be formed against PF4 as a consequence of the immune stimulation.

However, our findings suggest that mRNA vaccine recipients receiving first or second doses of BNT162b2 (Pfizer/BioNTech) and second doses of mRNA-1273 (Moderna) vaccines were also noted to develop TTS, albeit less commonly reported thus far. In both types of vaccinations (eg mRNA and adenovirus vector vaccines), our analysis suggested similar presentations of increased incidence of cerebral venous sinus thrombosis (CVST), concurrent thromboses in select patients, thrombocytopenia, elevated d-dimer, anti-platelet 4 antibodies (anti-PF4), and associated mortality.

We identified 69 patients with a median age of 54 [18 to 72] years and 73.9% females ($n = 51$). Our findings gain support from the literature regarding the AstraZeneca vaccine of a higher prevalence in women and patients aged < 60 years within 2 weeks of first vaccine dose.[21] According to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), as of June 27, 2021, 479 cases of suspected TTS were identified from EU/EEA countries of which 100 were fatal, with an incidence of 9.3 per million doses of AstraZeneca vaccine administered.[22] TTS cases in the US as reported by the Center for Disease Control and Prevention (CDC) followed trends already observed in European cases with women younger than 60 years and no diagnosed thrombophilia,[17,23] supporting our analytical findings of no further risk with underlying thrombotic risk factors (eg thrombophilia, contraceptive pill use).

The European and US cases both identified positive heparin-PF4 antibody ELISA tests without prior use of heparin, suggesting autoimmune HIT as a plausible mechanism, similar to our findings.[16] In our exploratory analysis, the overall number of patients who tested positive for heparin-PF4 antibodies was higher among patients who had died (87.5% vs 71.1%). In the initial European CVST reports, 88% of the patients had positive HIT antibody tests which were not observed in the US cases (11%).[1,24,25] The lack of standardization by different laboratories may have resulted in the noted discrepancies.[26] However, the insight of current TTS cases following COVID-19 vaccination is still developing, requiring further investigations into the development of TTS following both adenovirus-vector and mRNA vaccines.

Other factors found in our analysis that were associated with the highest mortality following TTS diagnosis include chronic medical conditions (eg, comorbidities, obesity, and hypothyroidism). Independent case series were reported initially in the *New England Journal of Medicine* among patients who received the ChAdOx1 nCoV-19 AstraZeneca vaccine, and patients were healthy at the time of vaccination.[8,25,27] Underlying comorbidities, though not reported as contributors to the severity of TTS so far, are expected

Table 1. Summary of results and associations to mortality trends.

	Total sample ($N = 69$)	Alive ($N = 45$)	Dead ($N = 24$)	p-value
Age	54 [18 to 72]; $N = 47$	54 [18 to 72] ($N = 32$)	45 [24 to 69]; $N = 15$	$P = .16$
Female	51 (73.9%)	36 (80%)	15 (62.5%)	$P = .059$
Vaccine type				$P = .136$
1 dose of AstraZeneca (ChAdOx1 nCoV-19) vaccine	51 (73.9%)	31 (68.9%)	20 (83.3%)	
1 dose of Pfizer/BioNTech (BNT162b2) vaccine	2 (2.9%)	2 (4.4%)	-	
2 doses of Pfizer/BioNTech (BNT162b2) vaccine	2 (2.9%)	2 (4.4%)	-	
1 dose of Janssen (Ad26.COV2.S) vaccine	12 (17.4%)	9 (20%)	3 (12.5%)	
2 doses of Moderna (mRNA-1273) vaccine	1 (1.4%)	2 (4.4%)	1 (4.2%)	
2 doses, name not specified	1 (1.4%)	1 (2.2%)	-	
Anti-PF4/heparin antibodies (+)	53 (76.8%)	32 (71.1%)	21 (87.5%)	$P = .416$
Platelet nadir (10^9 /L)	326 (8-334); $N = 65$	326 (8-334); $N = 43$	86 (8-94); $N = 22$	$P < .001$*
D-dimer peak (mg/L)	140.9 (1.1-142); $N = 28$	115.7 (1.8-117.5); $N = 23$	140.9 (1.1-142); $N = 5$	$P = .419$
Time to event diagnosis	9.45 ± 7.52	10.4 ± 8.14	7.67 ± 5.95	$P = .109$
Arterial or venous thrombi	CVST = 47 (68.1%) PE = 20 (29%) Thrombosis = 18 (26.1%) DVT = 12 (17.4%)	CVST = 27 (60%) PE = 15 (33.3%) Thrombosis = 14 (31.1%) DVT = 11 (24.4%)	CVST = 20 (83.3%) PE = 5 (20.8%) Thrombosis = 4 (16.7%) DVT = 1 (4.2%)	$P = .05$*
Thrombosis risk factors	Combined OCP = 5 (7.3%) Factor mutation = 5 (7.3%) Smoking = 5 (7.3%)	Combined OCP use = 3 (6.6%) Factor II mutation = 1 (2.2%) Factor V Leiden mutation = 1 (2.2%) Smoking = 3 (6.6%)	Combined OCP = 2 (8.3%) Contraceptive vaginal ring = 2 (8.3%) HRT use = 1 (4.2%) Smoking = 2 (8.3%) Factor V Leiden mutation = 2 (8.3%) Factor XIII deficiency = 1 (4.2%) Heterozygous MTHFR C677T, folate deficiency = 1 (4.2%)	$P = .137$
Chronic medical conditions	Obesity = 11 (15.9%) HTN = 4 (5.8%) Type 2 DM = 3 (4.4%) Hypothyroidism = 3 (4.4%) CAD = 2 (2.9%)	Obesity = 9 (20%) HTN = 4 (8.8%) Type 2 DM = 4 (8.8%) Hypothyroidism = 2 (4.4%) CAD = 1 (2.2%)	Obesity = 2 (8.3%) HTN = 3 (12.5%) Type 2 DM = 1 (4.2%) Hypothyroidism = 1 (4.2%) CAD = 1 (4.2%)	$P = .041$*
Treatment	Apixaban = 3 (4.4%) Argatroban = 6 (8.7%) Danaparoid = 3 (4.4%) Eculizumab = 2 (2.9%) Fibrinogen substitute = 2 (2.9%) Heparin = 18 (26.1%) IVIG = 25 (36.2%) LMWH = 16 (23.2%) Non-heparin anti-coagulation = 4 (5.8%) Steroids = 7 (10.1%) UFH = 5 (7.3%)	Apixaban = 3 (6.6%) Argatroban = 6 (13.3%) Danaparoid = 3 (6.6%) Eculizumab = 2 (4.4%) Fibrinogen substitute = 2 (4.4%) Heparin = 11 (24.4%) IVIG = 18 (40%) LMWH = 11 (24.4%) Non-heparin anti-coagulation = 4 (4.4%) Steroids = 3 (6.6%) UFH = 3 (6.6%)	Dabigatran = 1 (4.2%) Heparin = 7 (29.2%) IVIG = 7 (29.2%) LMWH = 5 (20.8%) Platelet transfusion = 7 (29.2%) Steroids = 4 (16.6%) UFH = 2 (8.3%)	$P = .082$

*P values are considered statistically significant if < 0.05.

to worsen prognosis as demonstrated in our analysis. Early-onset presentation (7 vs 10 days at presentation) was also associated with higher mortality risk which suggests that the first 2 weeks following vaccination is critical and the most common symptoms were persistent headache, body aches, fever, and lateralizing signs.

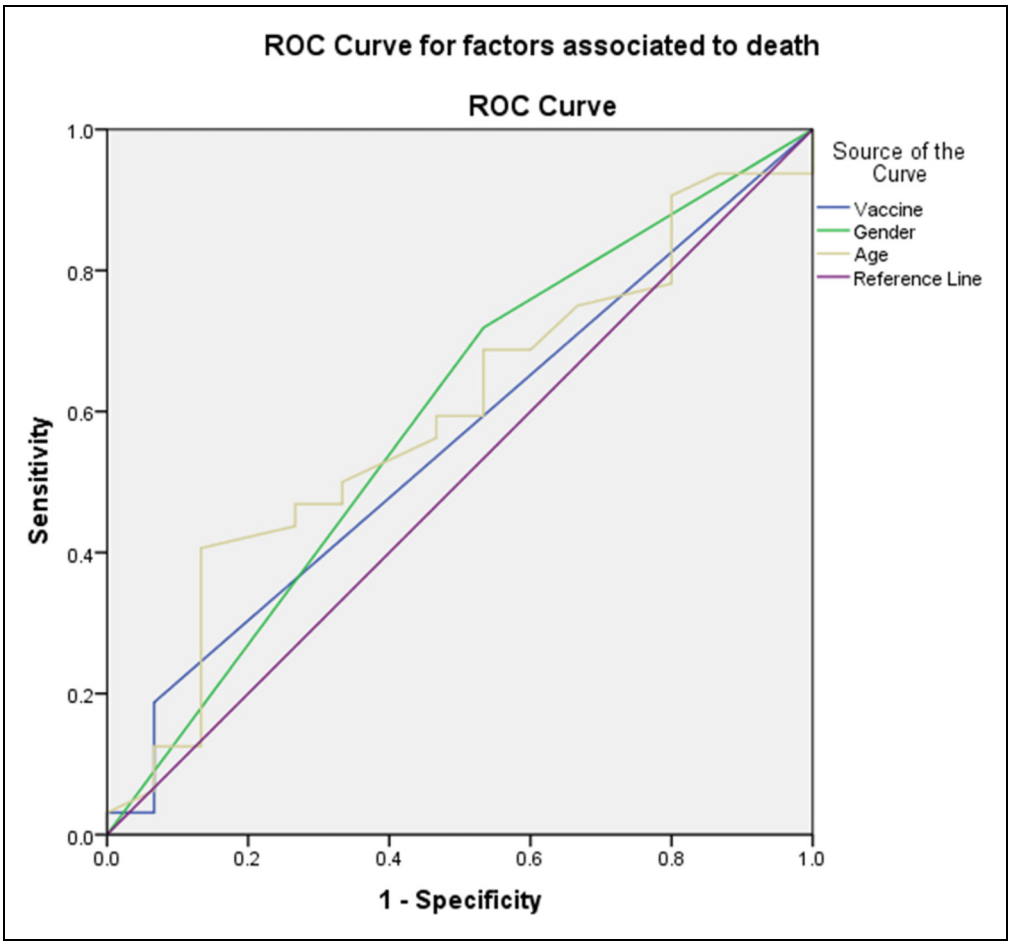

Figure 3. ROC Curve for Vaccine Dosage (in blue), Gender (in green), and Age (in yellow) associated with Death (in purple) as the reference line.

We explored cases by patient profiles and specific vaccines used; the risk denominators that cause higher mortality rates were patient-specific (eg lower age, female gender, early presentation, chronic medical conditions), and clinical (eg severe thrombocytopenia, markedly elevated d-dimer levels). The results described in this investigation show a cluster of symptoms within 1 to 2 weeks of vaccination, primarily after first dose but cases have also been identified after second dose (specifically for the Moderna mRNA vaccine). The Global Advisory Committee on Vaccine Safety (GACS) has suggested a possible link between platform-specific mechanisms associated with adenovirus vector vaccines.[28] However, our results have important implications following the identification of TTS in 4 cases who received mRNA vaccines (Pfizer/BioNTech after both first and second dose and Moderna after second dose). Our findings also gain support from expert guidelines to consider thrombi and elevated d-dimer levels with accompanied thrombocytopenia as suggestive of TTS, regardless of type or dose of vaccine administered.

The results have important implications for global vaccination efforts with speed and safety. Robust pharmacovigilance will minimize uncertainty in the medical community and the public. In patients who have developed ITP or thrombocytopenia due to other causes, a PF-4 ELISA may be utilized if there is a significant decrease in platelet count even in absence of thrombosis within the time frame of 4 to 30 days' post-vaccine as a screening measure. Importantly, there is a lack of standardization of functional platelet HIT antibody assays which may be necessary to consider when assessing TTS.[29] An adjustment of the testing methods for TTS will improve the detection and possible under-reporting of the clinical syndrome.

Overall, our findings demonstrate that the risk of TTS is significantly higher among young women aged 18 to 59 years and patients with comorbidities. These individuals as well as others who develop a suspicion of TTS may benefit from timely clinical detection and management.[30] However, it is important to note that these events are *very rare* with the highest incidence trends for AstraZeneca, occurring in fewer than 20.3 per million individuals aged 18 to 49 years and 10.9 per million in those aged 50 years and older, and should not discourage the use of COVID-19 vaccination.[31]

Strengths and Limitations

Certain limitations must be acknowledged. The included studies are not representative of the entire population due to TTS being a deviation from the norm. This means that the data from the included studies, while important, must be used and interpreted

with caution. We could not include cohort studies because the data could not be aligned to the post hoc analytical framework of this study. Because certain countries were represented more than others, we suspect that there has been an under-reporting of fatality reports from low- and middle-income countries.

We present pertinent trends for the thromboses communities worldwide, albeit with small sample size. The exploratory analysis presents a unique synthesis of all reported in-depth cases so far in the literature. The pertinent data collated in this study will help policymakers and clinicians to determine the persons at risk, for a cautious approach. The global representation of cases worldwide is worth noting.

Conclusion

In conclusion, adenoviral COVID-19 vaccines may trigger TTS until 4 weeks after vaccination, especially among those with prothrombotic risk factors. Clinicians ought to maintain a high degree of suspicion when recently-vaccinated individuals present with headaches or other symptoms suggestive of thrombosis. Screening with blood tests should be considered. In the case of thrombocytopenia that is not attributed to another cause, further imaging and laboratory testing may be considered. HIT testing is not highly sensitive for TTS, requiring the use of PF4 ELISA HIT testing. It is also pertinent to avoid using heparin-based products among suspected or confirmed TTS patients. Importantly, certain cases of mRNA COVID-19 vaccines have also been identified, complicating the sole implication of adenoviral COVID-19 vaccines for TTS. Public health efforts must continue focusing on early recognition and treatment of TTS while also promoting vaccination to control the COVID-19 pandemic.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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