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Systematic Review of Individual Patient Data COVID-19 Infection and Vaccination–Associated Thrombotic Microangiopathy

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Introduction: Sporadic cases of atypical hemolytic uremic syndrome (aHUS) have been described in the literature in association with COVID-19 infection and vaccination in adults and pediatric patients. The exact mechanisms underlying COVID-19–associated thrombotic microangiopathies (TMAs) remain incompletely understood. Herein, we present a detailed meta-analysis of the clinical characteristics, outcomes, and management strategies of COVID-19–associated aHUS and thrombotic thrombocytopenic purpura (TTP).

Methods: This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses updated guidelines. PubMed was utilized for searching for case reports and series. Adverse outcome at last follow-up was defined as estimated glomerular filtration rate < 30 ml/min per 1.73 m^2 (patients with aHUS), no remission with therapy, or patient death. Data were analyzed using Wilcoxon rank and Chi-square tests.

Results: Our analysis cohort included 118 studies reporting on 170 patients. These included 84 cases of aHUS and 86 cases of TTP resulting from COVID-19 infection ($n = 92$) or vaccination ($n = 78$). Significantly more cases of aHUS were reported after infection ($n = 65$) than immunization ($n = 19$), compared to TTP, where the reverse was true ($n = 27$ and $n = 59$, respectively; $P < 0.001$). In patients with aHUS with stage 3 acute kidney injury (AKI), requirement of kidney replacement therapy (KRT) was seen in three-fourths of the cohort for a median of 15. In patients with TTP, severe COVID-19 infection ($P = 0.04$) predicted non-remission or death at last follow-up. Administration of i.v., rituximab and caplacizumab were protective ($P = 0.03$ and $P = 0.06$, respectively). Immune TTP (iTTP) was reported more often than HUS following mRNA vaccines (81% vs. 58%; $P = 0.06$).

Conclusion: COVID-19 infection and vaccination are a potential trigger for onset or relapse of aHUS and TTP, especially in patients who are not on maintenance complement inhibitors or immunosuppression.

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TMAs encompass heterogenous disorders that are uniformly characterized by ischemic multiorgan damage due to occlusive microthrombi, microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction.[1,2] Although, the majority of hemolytic uremic syndrome cases occur following gastroenteritis due to Shiga toxin producing organisms, chiefly *Escherichia coli* (STEC-HUS),[3] primary complement–mediated HUS/TMA/aHUS is associated with dysregulation of the alternative complement pathway due to genetic defects in or inhibitory autoantibodies against complement regulatory proteins.[4] TTP is caused by inherited or acquired deficiency of von Willebrand factor (vWF) protease, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13).[5] Patients with an inherited complement defect in aHUS or subclinical deficiency of ADAMTS13 in TTP often require a secondary trigger for TMA to manifest.[6] Recently, both aHUS and TTP have been reported to be triggered

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by coronavirus disease COVID-19 infection or immunization.[7,8]

Severe COVID-19 has been recognized for causing multiorgan injury, chiefly driven by aggressive inflammation, coagulopathy, cytokine storm, and dysregulated complement activation causing widespread microvascular damage including TMA, a feature shared with aHUS and TTP.[9,10] Recent studies suggest dysregulation of alternative complement pathway in the pathogenesis SARS-CoV-2 infection.[11–13] Studies have shown a qualitative and quantitative increase in vWF with relative deficiency of ADAMTS13 in COVID-19 infection.[14] Moreover, several autoimmune disorders have been shown to be associated with SARS-CoV-2 infection, including autoantibodies to ADAMTS13 causing iTTP.[15] Although the exact mechanisms underlying COVID-19–associated TMAs remain incompletely understood, the clinical characteristics, outcomes, and optimal management strategies of COVID-19–associated aHUS and TTP warrant further investigation.

COVID-19 vaccinations are available in various formulations, including mRNA, viral vector, subunit, and inactivated vaccines. As of the latest data provided by the World Health Organization and the US Centers for Disease Control and Prevention, 13.59 billion doses have been administered worldwide and nearly 676 million doses have been administered in the United States alone.[16,17] Although these vaccines have demonstrated efficacy in preventing severe illness and reducing transmission of the virus, reports of several adverse events have emerged as well. Common adverse events include mild reactions at the injection site, such as pain or redness, and transient events such as fever, fatigue, or muscle pain.[18–20] In light of these considerations, our comprehensive review and meta-analysis systematically evaluates and synthesizes available evidence on COVID-19–associated and vaccine-associated aHUS and TTP.

METHODS

The study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses updated guidelines.[21]

Eligibility Criteria

We searched PubMed for case reports and series on the occurrence of TMA following COVID-19 infection or vaccination, reported in the form of microangiopathic hemolytic anemia and thrombocytopenia, or diagnosed on kidney biopsy. Eligible study designs were cohort, case series, case reports, letters, and comments published in English language, without restriction on age or date of publication. We excluded the studies with the following features: (i) lacking extractable individual patient data, (ii) no reported ADAMTS13 level and PLASMIC score < 6 or not reported, (iii) unclear temporal association, and (iv) patients with simultaneous infectious etiology more likely to be associated with TMA (STEC-HUS).

Sources and Search Strategy

Systematic literature search was conducted on PubMed from inception until October 25, 2023, using a comprehensive search strategy incorporating the following search terms: "thrombotic thrombocytopenic purpura", "immune TTP", "congenital TTP", "ADAMTS-13", "hemolytic uremic syndrome" or "thrombotic microangiopathy" and "COVID-19", "SARS-CoV-2", "coronavirus", "novel coronavirus", "vaccination" or "vaccine" (see Supplementary Materials). In addition, we checked the references of all included studies, systematic reviews, and metanalyses.[22–26] The search was updated on March 18, 2024. Two reviewers (PM and PK) independently screened the abstracts for eligibility, and conflicts, if any, were independently reviewed and resolved by discussion with a third author (RR). Full text screening was performed independently (PM and PK).

Definitions

We defined TTP based on severe deficiency (<10%) in ADAMTS13 activity, or presence of anti-ADAMTS antibodies with borderline deficiency in ADAMTS activity (10%–20%). Other reports of TMA were classified as HUS based on the fulfillment of the triad of microangiopathic hemolytic anemia, thrombocytopenia, and AKI. aHUS were further classified based on whether underlying significant genetic or autoimmune etiology of alternative complement dysregulation were identified (primary complement–mediated HUS triggered by COVID-19), absent (COVID-associated HUS), or not evaluated (unclassified). Outcomes were classified in terms of estimated glomerular filtration rate, stage 2 hypertension, and proteinuria (>2+ on dipstick) in patients with HUS. In patients with TTP, outcomes were defined in terms of clinical response, clinical remission, biochemical remission, and exacerbation or relapse, defined as follows: (i) clinical response: sustained platelet count $\geq 150 \times 109$/L and lactate dehydrogenase $<$ 1.5 times upper limit of normal without new or progressive ischemic organ injury, (ii) clinical remission: sustained clinical response without plasma exchanges (PEX) or anti-vWF therapy for $\geq$30 days, (iii) biochemical remission: ADAMTS13 activity above lower limit of normal, (iv) exacerbation: after a clinical response and before a clinical remission, platelet count decreases to $<150 \times$ 109/L, with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of

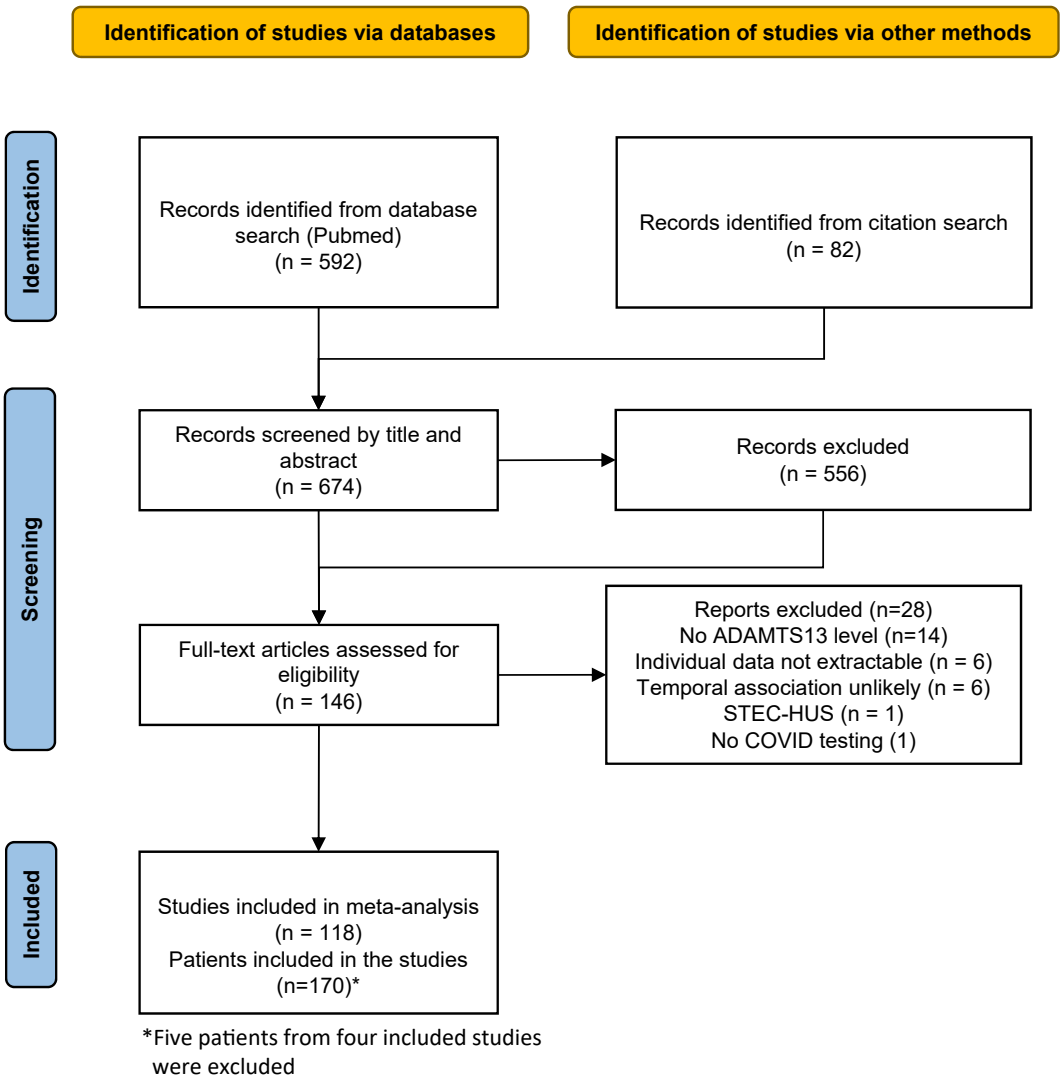

Figure 1. Flowchart depicting data collection method. STEC-HUS, Shiga Toxin-Producing Escherichia coli Hemolytic Uremic Syndrome.

stopping PEX or anti-vWF therapy, and (v) relapse: after a clinical remission, platelet count decreases to $<150 \times 109$/L, with or without clinical evidence of new ischemic organ injury and presence of ADAMTS13 deficiency.[27]

Statistical Analysis

Data were summarized as median (interquartile range) and number (percentage), as appropriate, and analyzed using R version 4.3.2. (R Core Team 2021). Tests for significance were Wilcoxon rank sum tests and Chi-square tests. Adverse outcomes at last follow-up were defined as estimated glomerular filtration rate <30 ml/min per 1.73 m^2 (patients with aHUS), no remission with therapy (patients with TTP), or patient death. Determinants of adverse outcome were estimated as hazard ratios using Cox proportional model in univariate analysis. Survival time was censored at last available follow-up, death, or adverse outcome (defined above). Two tailed $P < 0.05$ was considered significant.

RESULTS

Of 592 relevant studies identified, 474 were excluded by reading the title, abstract, and full text independently. Finally, 118 studies reporting on 170 patients were included (Figure 1). These included 84 cases of HUS and 86 cases of TTP resulting from COVID-19 infection ($n = 92$) or vaccination ($n = 78$). Significantly more cases of aHUS were reported after infection ($n = 65$) than immunization ($n = 19$), compared to TTP where the reverse was true ($n = 27$ and $n = 59$, respectively; $P < 0.001$).

COVID Infection–Associated TMA

Patient Characteristics

Patients Presenting With aHUS. The median age of presentation in 65 COVID-19 infection–associated HUS was 32.0 years; 17 cases (26.2%) were reported in children. Clinical and laboratory characteristics are detailed in Table 1. Potential triggers of aHUS were

Table 1. Clinical and biochemical characteristics of patients with COVID-19 infection- or COVID-19 vaccine–associated hemolytic uremic syndrome (HUS)

Characteristics	Presentation as HUS		P
	Infection associated, $n = 65$	Vaccine associated, $n = 19$	
Age, yr	32 (14.0–46.0)	48.0 (34.5–55.5)	0.05
≤18	17 (26.2)	2 (10.5)	
19–39	11 (16.9)	2 (10.5)	
40–59	24 (36.9)	6 (31.6)	
≥60	13 (20.0)	9 (47.4)	
Male	35 (53.8)	7 (36.8)	0.19
Comorbidity	33 (50.8)	7 (36.8)	0.28
Severe COVID	12 (18.5)		
Days to onset from infection/vaccine[a]	7.0 (3.0–10.0)	5.0 (2.0–8.5)	0.59
Lowest hemoglobin, g/dl	7.5 (6.4–9.3)	8.5 (7.5–9.1)	0.32
Lowest platelets, /μl	50.0 (19.0–88.0)	60.7 (35.0–109.3)	0.45
Peak LDH, IU/l	1383.0 (833.0–2844.0)	811.0 (551.8–1268.0)	0.06
Nephrotic range proteinuria[a]	18 (50.0)	5 (55.6)	0.99
Stage 2 hypertension (new onset)	27 (44.3)	3 (15.8)	0.03
Extrarenal complications	15 (23.1)	3 (15.8)	0.75
Low serum C3[b]	20 (38.5)	6 (54.5)	0.34
Elevated sC5b-9[c]	19 (76.0)	-	
Significant complement defect[d]	17 (48.6)	9 (81.8)	0.08
Therapy			
Requirement of KRT	50 (76.9)	8 (42.1)	0.004
Plasma exchange (PEX)	32 (50.0)	10 (52.6)	0.84
Eculizumab	35 (54.7)	10 (52.6)	0.87
Days to eculizumab from onset	7.5 (4.3–13.0)	6.5 (1.0–14.3)	0.49
Outcome at last follow-up	*n = 62*	*n = 19*	
Estimated GFR ≥60 ml/min per 1.73 m^2			
Without significant proteinuria	24 (38.7)	13 (68.4)	0.02
With hypertension stage 2 or proteinuria ≥2+	6 (9.7)	1 (5.3)	0.99
Estimated GFR 30–59 ml/min per 1.73 m^2	11 (17.7)	1 (5.3)	0.28
Estimated GFR <30 ml/min per 1.73 m^2; patient death[e]	21 (33.9)	4 (21.1)	0.29

GFR, glomerular filtration rate; KRT, kidney replacement therapy; LDH, lactate dehydrogenase.
[a]Information on proteinuria available in 37 patients.
[b]Information of serum C3 available in 52 and 11 patients, respectively in both groups.
[c]Information of serum sC5b-9 available in 25 patients.
[d]Pathogenic or likely pathogenic genetic defect in complement regulatory genes or anti-factor H antibodies (tested in 35 and 11 patients the 2 groups).
[e]Includes 3 patients' deaths.

simultaneously present with COVID-19 in 10 patients (15.3%) and included solid organ transplant ($n = 1$) and calcineurin inhibitors ($n = 4$); chemotherapy including gemcitabine ($n = 3$), chronic hepatitis B ($n = 1$), and pregnancy ($n = 1$).

Comprehensive evaluation of complement genetic defects and anti-factor H (FH) autoantibodies was reported in 35 patients (53.8%) of whom pathogenic or likely pathogenic variants were reported in 10 patients (28.6%) (See Supplementary Materials) and anti-FH antibodies were reported in 8 patients (22.8%). All patients with significant complement regulatory abnormalities presented with mild symptoms of COVID-19. Kidney biopsy was performed in ($n = 25$) patients, showed TMA in all (arteriolar, $n = 12$ and glomerular, $n = 18$), in addition to collapsing focal segmental glomerulosclerosis ($n = 5$), cortical necrosis ($n = 2$), immune complex deposition, endocapillary proliferation and basement membrane duplication, and glomerulosclerosis ($n = 1$, each).

Patients Presenting With TTP. iTTP was confirmed by the presence of anti-ADAMTS13 antibodies in 22 patients; another 4 patients did not have reported antibody levels but had PLASMIC scores 6 to 7 with absence of anti-platelet 4 antibodies; 1 patient had congenital TTP (homozygous ADAMTS13 variant, NM_139025.4:c.1584+5G > A). Four patients (15%) presented with a clinical relapse of previously diagnosed iTTP; 1 patient had a biochemical relapse only and was not included in this analysis. TTP was reported chiefly in adults, in patients aged above 40 years (22, 81.5%) with an overall mean age of presentation of 46 years. As compared to patients with HUS, more patients with TTP were presented within a week of COVID-19 onset (74% vs. 52%; $P = 0.06$) and with severe symptoms with need for intensive care or ventilatory support (37% vs.18%; $P = 0.05$). All except 6 patients had positive COVID-19 polymerase chain reaction at presentation, 4 had a positive serology at presentation and in 2 patients the type of test was not characterized. Reported comorbidities and potential triggers were simultaneously present with COVID-19 in 6 (22.2%) and included autoimmune diseases, that is, Crohn's disease, lupus with antiphospholipid syndrome, and Guillain-Barre Syndrome ($n = 3$), locally advanced breast cancer ($n = 2$), and pregnancy ($n = 1$).

Therapy and Outcomes

Patients Presenting With aHUS. Patients had stage 3 AKI with requirement of KRT in almost three-fourths of the cohort for median 15.0 days. The outcomes of 62 patients at median 70 (31.5–104.8) days follow-up are shown in Table 1. In a subgroup of patients with outcomes reported beyond 90 days, 7 of 23 patients (30.4%) progressed to CKD stage 4 to 5. Of 45 patients who received therapy with eculizumab within 7.5 (4.3–13.0) days of onset of HUS, 25 (55.6%) responded completely. The baseline characteristics of patients who were treated with eculizumab were not different from patients who did not receive complement inhibitors (Supplementary Table S1).

Table 2. Clinical and biochemical characteristics of patients with COVID-19 infection– or vaccine–associated thrombotic thrombocytopenic purpura (TTP)

Characteristics	Presentation as TTP		P
	Infection associated, $n = 27$	Vaccine associated, $n = 59$	
Classification			
Acquired TTP	22 (81.5)	52 (88.1)	
Congenital TTP	1 (3.7)	1 (1.7)	
Unclassified TTP	4 (14.8)	6 (10.2)	
Age, yr	46.0 (35.0–57.0)	49.0 (31.5–61.5)	0.61
≤18	2 (7.4)	2 (3.4)	
19–39	5 (18.5)	19 (32.2)	
40–59	8 (29.6)	21 (35.6)	
≥60	12 (44.4)	17 (28.8)	
Male	11 (40.7)	27 (45.8)	0.66
Comorbidity	12 (44.4)	31 (52.5)	0.49
Severe COVID	10 (37.0)		
Days to onset from infection/vaccine[a]	7.0 (0.0–8.5)	13.0 (7.0–21.0)	<0.001
Presentation as relapse	4 (14.8)	18 (30.5)	0.12
Lowest hemoglobin, g/dl	6.7 (6.0–8.0)	8.1 (6.6–10.6)	0.03
Lowest platelets /μl	10.0 (7.0–19.5)	15.0 (10.0–35.5)	0.02
Peak LDH, IU/l	1520.0 (1,129.0–2272.0)	999.0 (645.0–1675.0)	0.02
Peak creatinine, mg/dl	1.0 (0.9–2.7)	1.1 (0.9–1.6)	0.93
Extrarenal complications	10 (37.0)	34 (57.6)	0.08
Therapy			
Plasma exchange (PEX)	24 (88.9)	54 (91.5)	0.70
Duration of PEX, days	10.5 (6.0–13.8)	8.0 (4.5–12.5)	0.27
Steroids (oral/i.v.,)	26 (96.3)	57 (96.6)	0.99
i.v., rituximab	9 (33.3)	40 (67.8)	0.003
Caplacizumab	11 (40.7)	26 (44.1)	0.77
Outcome at last follow-up	$n = 27$	$n = 58$	0.20
Complete response	16 (59.3)	23 (39.7)	0.091
Clinical remission, ADAMTS13 level <20% or unavailable	2 (7.4)	6 (10.3)	0.99
Clinical remission, ADAMTS13 level >20% but <LLN	2 (7.4)	18 (31.0)	0.02
Clinical remission, ADAMTS13 level >LLN	2 (7.4)	5 (8.6)	0.99
No remission/death	5 (18.5)	6 (10.3)	0.31
Exacerbation or relapse	5 (18.5)	10 (17.2)	0.88

LDH, lactate dehydrogenase; LLN, lower limit of normal; TTP, thrombotic thrombocytopenic purpura.

Patients Presenting With TTP. Therapies administered to patients with TTP are shown in Table 2. Hematological remission was achieved by 22 patients (81%) by 10.5 days after onset, of which 16 were classified as complete response (5 with a subsequent exacerbation) and 6 classified as clinical remission with or without a biochemical remission (Table 2).

Mortality in patients with aHUS ($n = 3$) and TTP ($n = 5$) were reported due to septicemia and shock ($n = 2$), respiratory failure ($n = 2$), refractory status epilepticus ($n = 1$), undescribed cardiovascular event ($n = 2$), and unknown etiology ($n = 1$).

COVID Vaccine–Associated TMA

In Tables 1 and 2, we show patient characteristics of those who presented with aHUS ($n = 19$) and TTP ($n = 57$) following COVID-19 vaccination. The vaccines reported were BNT162b2 (Pfizer/BioNTech; $n = 46$), ChAdOx-1 nCoV-19 (Oxford/AstraZeneca; $n = 14$), mRNA-1273 (Moderna; $n = 11$), Ad26.COV2.S (Janssen Pharmaceuticals; $n = 2$), Sinovac/CoronaVac (Sinovac Biotech; $n = 2$), and SinoPharm (China National Pharmaceutical Group; $n = 1$). Of the vaccines used, ChAdOx1 nCoV-19 and BNT162b2 were the predominant viral vector and mRNA vaccines used in 18.4% and 60.5% patients, respectively. The most common vaccines reported were mRNA vaccines, with iTTP being reported more often than aHUS following this vaccine (81% vs. 58%; $P = 0.06$). Following the viral vector vaccine ChAdOx1 nCoV-19, proportion of reports of HUS were significantly higher than those of TTP (37% vs. 12%, respectively; $P = 0.04$). In Figure 2, we show the relative frequencies of aHUS and TTP reported after the first and subsequent vaccine doses. The case reports were either of the first (41, 53.9%), second (33, 43.4%), or third (2, 2.6%) dose of mRNA vaccines (57, 75%), viral vector vaccines (16, 21.1%), or inactivated vaccines (3, 3.9%). Proportion of cases reported were significantly higher for the first dose of viral vector vaccines compared to subsequent doses (32% vs. 8.6%, $P = 0.014$, Figure 2).

Overall, 14 of patients with aHUS (73.7%) and 16 of patients with TTP (27.1%) presented within the first week of vaccination. The onset of TTP following vaccination occurred much later (Table 2). Nine of 19 patients (47.4%) had a complete HUS evaluation that showed a known predisposing factor in all. Genetic testing revealed pathogenic variants in C3 (c.481C>T) in 6 patients (from 2 reports), CD46 (Glu179Gln/Cys94Tyr) variant and CFH (c.3096C>A) variant (1 patient each); 1 patient had cobalamin C deficiency. At-risk polymorphisms MCPggaac was reported in 5 patients and CFH-H3 haplotype in 2 patients. The disease appeared to be milder in patients following vaccination compared to that occurring after COVID-infection. In patients with aHUS, stage 2 hypertension, level of serum lactate dehydrogenase, requirement of KRT

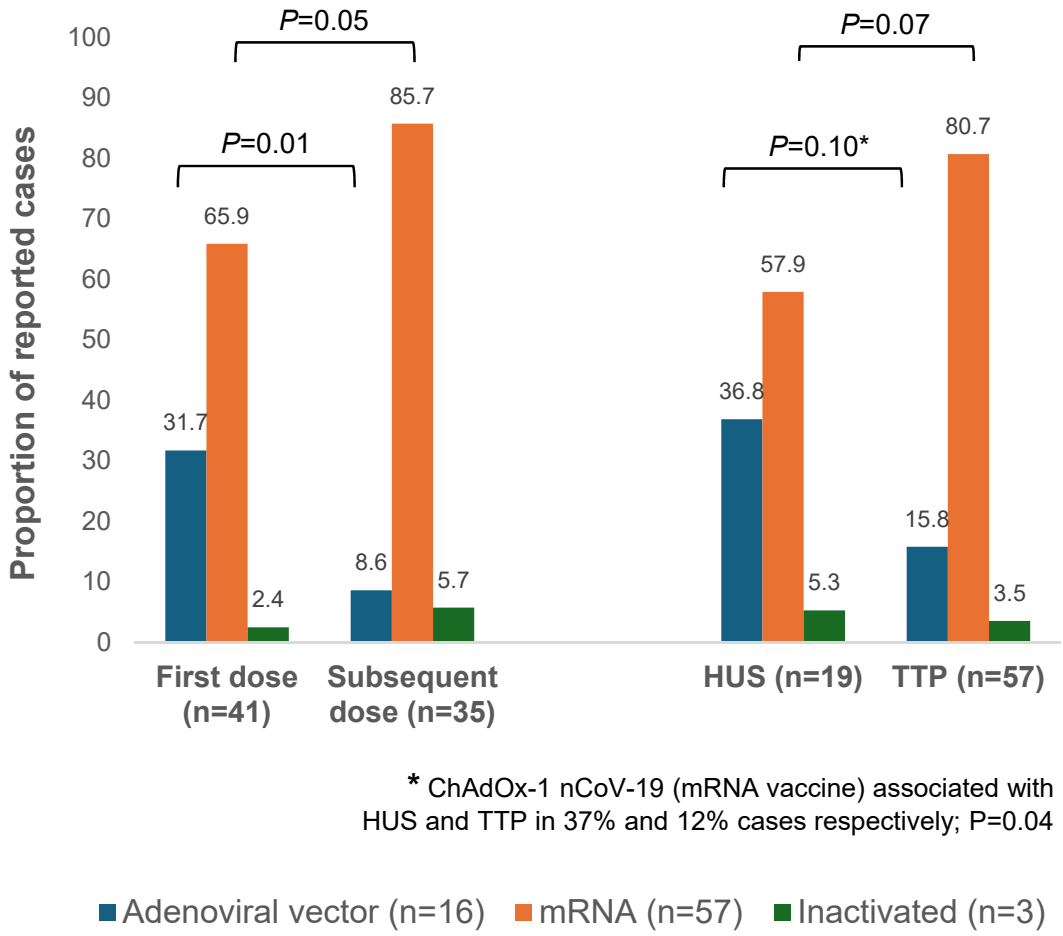

Figure 2. Frequency of aHUS and TTP reported after the first and subsequent vaccine doses. aHUS, atypical hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

were lower in vaccine-associated compared to infection-associated cases (Table 1). At 90 days of follow-up, significantly greater proportion of patients with vaccine-associated disease had an estimated glomerular filtration rate ≥ 60 ml/min per 1.73 m^2 without significant proteinuria ($P = 0.02$). Similarly, in patients with TTP, levels of hemoglobin and platelets were higher and serum lactate dehydrogenase lower in disease in vaccination-associated cases and proportion of patients with clinical remission with ADAMTS13 level >20% were significantly higher (Table 2). Therapy was like infection-associated cases, except for the expected preference against i.v., rituximab use during COVID-19 infection in TTP. The proportion of adverse outcomes were comparable in patients with aHUS and TTP following vaccination and infection (Tables 1 and 2). A total of 5 patients died during hospitalization, of which 3 deaths were attributed to sudden cardiovascular events. The disease phenotype in terms of time to onset, severity of disease and adverse outcomes were comparable following the first and subsequent doses of vaccines, on stratification by aHUS or TTP (Supplementary Table S2).

Determinants of Outcome

In patients with aHUS ($n = 84$, both infection- and vaccine-associated disease), the determinants of adverse outcome at last follow-up on univariate regression were severity of COVID-19 ($P = 0.008$), older age ($P = 0.007$) and requirement of KRT ($P = 0.03$) (Table 3). Adverse outcomes occurred in 35.3% and 11.1% of patients with or without significant complement gene or functional abnormalities, respectively ($P = 0.19$). Of patients with the above complement defects, adverse outcomes were present in 22% and 26% of patients with or without eculizumab administration, respectively ($P = 0.81$). Adverse outcomes occurred in 52% versus 22% of patients with or without reported TMA on kidney biopsy ($P = 0.006$). In patients with TTP, severe COVID-19 infection ($P = 0.04$) predicted non-remission or death at last follow-up; administration of i.v., rituximab and caplacizumab were protective ($P = 0.03$ and $P = 0.06$, respectively; Table 3).

Table 3. Determinants of adverse outcome[a] at last follow-up in patients with HUS and TTP

	Infection or vaccine associated HUS (n = 84)			Infection or vaccine associated TTP (n = 86)		
Characteristic	HR	95% CI	P-value	HR	95% CI	P -value
Age	1.04	1.01–1.06	0.007	1.02	0.99–1.06	0.17
Sex	0.81	0.33–2.21	0.74	0.70	0.20–2.39	0.57
Comorbidity	1.73	0.66–4.55	0.27	1.66	0.51–5.47	0.40
Severe COVID-19[b]	8.24	1.75–38.9	0.008	3.67	1.07–12.5	0.04
Hemoglobin	0.99	0.84–1.19	0.99	0.99	0.82–1.18	0.90
Platelet count	1.00	0.99–1.00	0.64	0.95	0.89–1.02	0.13
LDH	1.00	0.99–1.00	0.60	1.00	0.99–1.00	0.56
Nephrotic range proteinuria	1.74	0.48–6.23	0.40			
Stage 2 hypertension	1.01	0.37–2.81	0.98			
Extrarenal complications	1.51	0.53–4.29	0.44	0.71	0.21–2.33	0.57
Serum C3	1.78	0.57–5.54	0.32			
Requirement of KRT	9.0	1.19–68.0	0.03			
Plasma exchange	0.70	0.27–1.82	0.47			
Eculizumab	1.29	0.49–3.40	0.60			
i.v., rituximab				0.23	0.06–0.88	0.03
Caplacizumab				0.23	0.05–1.06	0.06
Significant genetic/ autoimmune abnormality	1.39	0.27–7.20	0.70			
Relapsing disease				0.25	0.03–1.97	0.19
Vaccine-associated	0.75	0.22–2.63	0.66	0.65	0.20–2.10	0.49

HUS, hemolytic uremic syndrome; KRT, kidney replacement therapy; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.
[a]defined by estimated glomerular filtration rate <30 ml/min per 1.73 m^2 (HUS) or absence of clinical response (TTP) or patient death.
[b]Only in patients with infection associated disease.

DISCUSSION

Our systematic review highlights increasing recognition of COVID-19 infection–associated and vaccination–associated TMA and summarizes important findings of 170 patients with COVID-19–associated TMA. Patients with severe disease had high reported rates of severe AKI requiring KRT (37.5%), extrarenal complications (37.6%), adverse outcomes (22%), and mortality (7.2%). Notably, a considerable proportion (70%) of cases presented with only mild to moderate symptoms of COVID-19. In addition, 15.4% of cases presenting after viral clearance with negative polymerase chain reaction but positive serology suggested potential postinfectious immune-mediated mechanisms contributing to development of iTTP of anti-FH–associated HUS. Genetic testing unveiled significant complement defects in nearly half of the tested patients with HUS, all of whom presented with mild COVID-19 symptoms, indicating underlying genetic predispositions. Importantly, vaccine-associated TMAs showed distinct clinical patterns compared to infection-induced cases, with milder symptoms and higher rates of favorable outcomes. Lastly, severity of COVID-19, older age, and the requirement of KRT were identified as determinants of adverse outcomes in patients with HUS irrespective of the use of complement blockers, whereas severe COVID-19 infection predicted nonremission in or death among TTP patients, and use of rituximab or caplacizumab was protective.

The clinical characteristics of the reported cases of aHUS and TTP following COVID-19 infection and vaccination was in keeping with the known distinct characteristics of these disease entities, including the predominant occurrence in adults and common neurological manifestations in TTP, and severe AKI in patients with aHUS. aHUS are reported to be precipitated by several viral infections, including influenza A, human immunodeficiency virus, and norovirus.[28] We add to the literature by summarizing the clinical features and outcomes of 65 patients with HUS following COVID-19 infection. Genetic or autoimmune complement abnormalities were identified in 50% of our reviewed patients, consistent with the proportion of complement-mediated abnormalities reported in primary complement–mediated HUS.[1] This review shows that patients with aHUS with pathogenic or likely pathogenic variants CFH, CD46, CFI and C3, or anti-FH antibodies, with or without known at-risk polymorphisms, presented with aHUS following mild SARS-CoV-2 infection. However, it is important to note that only about one-half of studies reported complete genetic and autoimmune etiological evaluation, limiting adequate classification of patients, and highlighting the complexities of aHUS work-up, long turnaround time of genetic evaluation and need for specialized laboratories.

The reviewed studies have shown low C3 levels and elevated sC5-b levels in 38% and 76% patients tested, respectively, which is consistent with several preclinical and observational studies that suggest activation of the alternative complement pathway in the setting of COVID-19 and the correlation of biomarkers of alternative and terminal complement pathway activation, including levels of C3a, C5a, and C5b-9 with disease severity.[29] Although the exact mechanism of activation of the alternative complement pathway has not been fully elucidated, *in vitro* studies show that spike proteins of SARS-CoV-2 might competitively block cell-surface binding of FH[13] and complement-dependent killing induced by the spike protein is mitigated by addition of FH.[30] Based on these findings, several case series have shown a promising role for complement-blockers in patients with severe COVID-19.[31] Non-randomized controlled trials with eculizumab treatment in patients with severe COVID-19 showed a significant improvement in oxygenation, estimated survival, and although with a higher rate, of nosocomial infection in the eculizumab treated patients.[32] In the present review, almost 70% of patients were reported following mild COVID-19 disease, and in this cohort eculizumab

was not associated with favorable outcomes; instead, the severity of COVID-19 infection, older age, and requirement of KRT were important predictors of outcomes.

Our study highlights that COVID-19 triggered iTTP is a rare event, with 27 cases reported to-date and appear to be less common than reports of other forms of TMA following COVID-19. Patients presented early, within a week of onset of infection. We hypothesize that in such early-onset and often simultaneous presentation of iTTP, COVID-19 infection could perhaps be a trigger of occult, undiagnosed TTP rather than inducing TTP. The patients had severe disease with neurological complications in one-third of the cohort, need for prolonged PEX more than 5 days in 80%, and additional immunosuppression in one-half of the cohort. These findings may suggest a severe and refractory nature of COVID-19–associated TTP. Despite optimal management, mortality rate was 11% and 18% in patients who had exacerbations or relapse, respectively; consistent with 12% to 22% mortality and 24% to 34% relapse-rates reported in the literature on iTTP.[33–35] The hypercoagulable state conferred by COVID-19,[36] direct cytopathic injury to the endothelial cells caused by COVID-19,[36] and several reports of reduced ADAMTS13 activity[37]are multiple mechanisms that may explain the refractory nature of COVID-19-associated TTP. Although recent systematic reviews suggest an association of imbalance in the VWF-ADAMTS13 axis (endothelial inflammation with release of VWF with relative deficiency of ADAMTS13) with the severity and prognosis of COVID-19 illness,[14,37] it is interesting to note that almost two-thirds of the reviewed cohort had undetectable ADAMTS13 activity (<10%) without clinically severe COVID-19 infection.

We found that use of either rituximab or caplacizumab improved outcomes in patients with TTP. The potential risk of using i.v., rituximab during concomitant COVID-19 infection may have guided decision-making in these cases, with approximately 30% use of rituximab despite prolonged PEX requirement. Caplacizumab, a novel monoclonal therapy that inhibits the binding of vWF to platelets, has been shown to decrease rates of relapse and time to remission in randomized trials.[38,39] Our review revealed the increasing use of this strategy in 43% of patients with infection–associated and vaccine–associated TTP, with upfront use of caplacizumab without requirement of PEX in 2 patients. The present review reveals that therapy with PEX, steroids, and caplacizumab might be satisfactory during acute infection when immunosuppressive therapy might not possible.

Eight types of vaccines thus far have been reported to cause TMA: viral vector vaccines (Oxford/AstraZeneca), genetic vaccines using mRNA (Moderna and Pfizer/BioNTech), and inactivated vaccines (Sinovac/CoronaVac, Sinopharm). Almost three-quarters of this cohort followed mRNA vaccine administration, especially those with the occurrence of iTTP, perhaps due to the inherent immunostimulatory properties of mRNA provoking stronger antigen antibody and cellular immune responses.[40] The viral vector vaccines have a propensity to cause HUS, especially in the first dose. This higher rate of aHUS development may result from vector-specific properties and immunogenicity, potentially inducing complement activity and endothelial disruption seen in HUS. In addition, adenoviral-based COVID-19 vaccines can directly target CD46, impairing complement-regulation.[41] Other differences in the immune response kinetics and antigen presentation pathways of ChAdOx-1 CoV-19 compared to other vaccines could contribute to this differential risk of HUS over TTP. Disease symptoms across vaccine-associated aHUS and TTP were milder, and outcomes better in comparison to their infection-associated counterparts. Therapy provided for vaccine cases was mostly comparable to their infection counterparts, besides the use of i.v., rituximab seen in vaccine TTP as opposed to COVID-19 TTP.

We have shown that 59 cases presented either as relapse of iTTP (30%) or developed *de novo* anti-ADAMTS-13 antibodies following vaccination. In contrast, aHUS following COVID-19 vaccination was a rarer occurrence reported in 19 patients. The median time-to-onset of HUS was sooner than that of TTP following vaccination. This is consistent with the hypothesis that iTTP after vaccination occurs by newly formed anti-ADAMTS13 antibodies and would take at least 7 to 10 days for formation of autoreactive B-cells, plasma cell, and autoantibodies. In contrast, aHUS occurs due to accelerated activation of the alternative complement pathway, driven by localized expression of the SARS-CoV-2 spike protein in both mRNA and adenoviral-based vaccines.[42] In our reviewed reports, 8 of 9 patients of aHUS-triggered by COVID-19 vaccination (with complete evaluation) showed pathogenic complement genetic variants. Therefore, in such patients with a preexisting genetic predisposition to aHUS, the COVID-vaccine is a "second-hit" that causes overwhelming and rapid complement activation.

We present a comprehensive review and individual patient data meta-analysis to summarize clinical characteristics and outcomes of patients with COVID-19–associated TMA reported in the last 3 years of the pandemic. The review reflects a wide spectrum of patient demographics from all over the world, increasing the generalizability and relevance of our data. In addition, cases with unclear or unlikely temporal

association of COVID-19 and TMA onset were excluded, strengthening the significance of our data in the context of COVID-19. Our study does have limitations. First, during the data extraction, there was clear variability in data availability of patient baseline characteristics, onset and length of treatment, and outcome measures across the studies (Supplementary Table S3). Second, the heterogeneity of diagnostic classification of patients with HUS, primarily due to incomplete evaluation of patients in individual reports, might introduce bias in the interpretation of results. However, this reflects the real-world diagnostic challenges faced by clinicians in routine clinical practice involved in the care of patients with TMA. Third, relationship between COVID-19 vaccination or infection and TMA is temporal in all included studies, and data on the actual pathophysiological mechanism is not available. The study shows the coexistence of multiple risk factors for HUS and TTP in 15% to 22% patients, including infection, malignancy, chemotherapy, autoimmune conditions, and pregnancy, in addition to COVID-19 infection. Finally, though we showed that eculizumab use was not associated with favorable outcome, this might be misleading in the absence of long-term follow-up and comprehensive complement analysis in all patients in this cohort.

In conclusion, COVID-19 infection and vaccination are potential triggers for onset or relapse of aHUS and TTP, especially in patients who are not on maintenance complement inhibitors or immunosuppression. The study highlights the variable, but often severe presentation COVID-19–associated TMA and emphasizes the importance of a high index of suspicion for diagnosis of TMA and tailored management strategies to optimize patient outcomes. The benefits of COVID-19 vaccination exceed its potential risk. Retrospective and prospective data have shown that the risk of HUS and TTP recurrence after COVID-19 vaccination appears to be acceptable.[43–45] However, careful monitoring for clinical symptoms, blood counts, proteinuria, kidney function is required following COVID-19 vaccination to promptly diagnose and treat rare but potentially severe cases of TMA. The present review also reflects the challenges in the management of TMA, which is limited by turnaround time of investigations for comprehensive etiological evaluation, need for specialized investigations such as ADAMTS13 activity, and limited availability of complement blockers and monoclonal antibodies in certain regions of the world.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

RM conceived the original idea for the study. PK and PM contributed to the design and implementation of the research. PK contributed to the analysis of the results. RM, PM, PK, and RR participated in the writing and editing of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Search strategy (PubMed).

Details of significant genetic variants in patients with COVID associated HUS.

Table S1. Baseline characteristics in patients with COVID-19 infection triggered aHUS with or without therapy with eculizumab.

Table S2. Characteristics of vaccine-associated disease stratified by number of vaccine doses.

Table S3. Missing data in baseline characteristics in patients with aHUS and TTP included in Tables 1 and 2.

Supplementary Data Excel Sheet

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