

A Systematic Review of the Epidemiology and Disease Burden of Congenital and Immune-Mediated Thrombotic Thrombocytopenic Purpura

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Abstract: Congenital (cTTP) and immune-mediated (iTTP) thrombotic thrombocytopenic purpura are serious and rare clotting disorders resulting from a deficiency in the ADAMTS13 enzyme. A systematic review was conducted using the Ovid[®] MEDLINE & Embase databases to synthesize the epidemiology and burden of cTTP and iTTP worldwide (from January 1, 2010, to February 6, 2020, with an update that covered the period January 1, 2020–February 11, 2022). Outcomes of interest were incidence and prevalence of TTP, incidence of acute episodes, mortality, burden of illness (eg complications, healthcare utilization, patient-reported outcomes) and disease management. A total of 221 eligible observational studies were included. The incidence rate of acute episodes ranged from 0.19–0.35 person-years in adult patients with cTTP, and 1.81–3.93 per million persons per year for iTTP in the general population. Triggers of acute episodes were similar for cTTP and iTTP, with pregnancy and infection the most commonly observed. Exacerbation in patients with iTTP varied widely, ranging from 2.4–63.1%. All-cause mortality was observed in 0–13.4% of patients with cTTP, across studies and follow-up periods, and in 1.1% (median follow-up: 0.4 years) to 18.8% (1 year) of patients with iTTP during acute episodes. Cardiovascular, renal, and neurological disease were common complications. TTP also led to work disturbances, feelings of anxiety and depression, and general activity impairment. TTP treatment regimens used were generally reflective of current treatment guidelines. The evidence identified describes a high patient burden, highlighting the need for effective treatment regimens leading to improvements in outcomes. Considerable evidence gaps exist, particularly for disease epidemiology, patient-reported outcomes, costs of disease management, and associated healthcare resource utilization. This review may help increase disease awareness and highlights the need for additional real-world studies, particularly in geographical regions outside the United States and Western Europe.

Keywords: thrombotic thrombocytopenic purpura, epidemiology, burden of illness, disease management, patient-reported outcomes, ADAMTS13

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy (TMA), primarily caused by a deficiency in the von Willebrand factor (VWF)-cleaving enzyme ADAMTS13 (A disintegrin and metalloproteinase with thrombospondin motifs 13).^{1–3} This deficiency can be the result of mutations in the *ADAMTS13* gene (hereditary/congenital TTP; cTTP) or, more commonly, result from ADAMTS13 autoantibodies (acquired/immune TTP; iTTP).³ An ADAMTS13 activity of <10% is required to confirm the diagnosis of TTP,^{2,4–6} and the distinction between cTTP and iTTP relies on genetic analysis and/or an anti-ADAMTS13 autoantibody assay.²

The annual incidence of TTP is estimated to range between 2–6⁴ and 3–11 cases per million persons.⁷ Recent research suggests that the diagnostic criteria for TTP should consider patients with microangiopathic hemolytic anemia and thrombocytopenia (MAHAT), without neurologic/renal abnormalities and fever (previously part of the “classic pentad” of diagnostic symptoms).^{2,3,5} Thus, estimated ranges for the annual incidence of acute TTP episodes are not adequately summarized in the literature to date. Acute episodes are considered a true medical emergency and are associated with a mortality rate of >90% if left untreated.^{2,8,9} Damage to major organs may also result in transient ischemic attack, stroke,

myocardial infarction, or acute kidney injury.^{1,10,11} Triggers for acute episodes include infections, pregnancy, autoimmune disease, blood/marrow transplant and exposure to certain medications.^{3,12,13}

The current standard of care for managing acute TTP episodes is to restore ADAMTS13 levels using plasma therapy, either by plasma infusion for cTTP or plasma exchange (PEX) for iTTP.^{3,11,14,15} Immunosuppressive or anti-CD20 therapy (eg rituximab) and anti-VWF therapy (caplacizumab) are also options for iTTP,^{3,15} while prophylaxis with regular plasma infusions has been used to prevent acute episodes in cTTP. However, TTP treatment guidelines highlight a lack of high-quality evidence supporting long-term outcomes with currently available therapy.¹⁵

Due to the rarity of TTP, the body of evidence to describe the natural history of the disease and to identify unmet needs for TTP is limited but growing. Therefore, a systematic literature review was conducted to analyze data on the epidemiology and burden of TTP worldwide in order to better inform the management of TTP and clinical decision-making. This review covers the epidemiology, patient characteristics, natural history, burden of illness, mortality, and real-world treatment of TTP.

Materials and Methods

Scope of the Review

A systematic review was conducted which covered the period from January 1, 2010, to February 6, 2020 (date of last search) (PROSPERO CRD42020172273) using methods developed by the Cochrane group and the National Academy of Medicine, formerly the Institute of Medicine of the National Academy.^{16,17} An update was conducted covering the period January 1, 2020, to February 11, 2022 (date of last search).

The systematic review was based on the PICOTS (Population, Intervention or Exposure, Comparator, Outcomes, Time Period, Setting) criteria. The target population included adult and pediatric patients with iTTP or cTTP. Intervention was the local/regional standard of care prescribed in the real-world setting and the comparator could be the local/regional standard of care (or no comparator). Outcomes of interest in the general population were incidence and prevalence of the disease; incidence of acute episodes; all-cause and TTP-related mortality; patient characteristics (age and sex distribution, race and ethnicity, comorbidities at baseline); natural history of disease (ADAMTS13 activity pre-treatment, during treatment and post-treatment, disease course, disease triggers, disease-related complications, organ damage biomarkers); burden of illness (hospital length of stay [LOS], healthcare costs, patient-reported outcomes/quality of life [PROs/QoL]); and disease management. The study setting was observational/non-interventional.

Search Strategy and Information Sources

Literature searches using the Ovid[®] MEDLINE & Embase databases were conducted to identify publications written in English. Search strategies were based on free-text keywords and thesaurus terms (ie, Medical Subject Headings [MeSH] and Emtree terms): Population of interest (iTTP and cTTP, or unspecified TTP when distinction between subtypes was not available) and parameters of interest (incidence, prevalence, mortality, relapse, age distribution, sex ratio, disease management, natural history, organ damage, complications, and burden of illness). Search strategies are detailed in [Supplementary Table 1](#). In addition, pragmatic searches were performed using Google and the Google Scholar search engines, as well as websites of learned or clinical societies and related conference proceedings (annual meetings) and relevant patient organizations ([Supplementary Table 2](#)) to identify publications not indexed in MEDLINE and Embase. The reference lists of retained publications were screened for additional relevant sources (referred to as “snowballing”).

Eligibility Criteria

The inclusion criteria consisted of observational studies (eg cohort studies, cross-sectional studies, non-comparative cohort studies [case series]) published in English that included patients with iTTP or cTTP (or unspecified TTP when distinction between subtypes was not available) either as the study population or as a sub-group analysis. Other criteria included studies that reported on outcomes of interest as defined in the PICOTS, original research articles published as full-text or conference proceedings (ie, posters, abstracts), and reviews (systematic, non-systematic, and meta-analyses

[for snowballing only]). Case reports, editorials, letters to editors, opinions, clinical trials (phase I–III), nonclinical studies, experimental studies, and studies describing preliminary results later reported as full text were excluded.

Selection of Studies

Duplicate sources were removed using automated procedures. During the first stage of the selection process, titles and/or abstracts were screened using the predefined eligibility criteria by two independent reviewers, with conflicts resolved by a third assessor. During the second stage, eligibility was confirmed by in-depth review of full texts and reasons for exclusion at this stage were documented. For studies with multiple publications, only the most recent reporting on each outcome of interest was retained.

Data Extraction and Data Synthesis

Data from relevant publications were extracted independently by two reviewers in a standardized data extraction form, with conflicts resolved by consensus or by a third assessor for completeness. Data items extracted included general study information (source, citation, publication type, geographical coverage); study methods (study period, study design, data collection method, data source); target population (population of interest [unspecified TTP, cTTP, iTTP, mixed] and targeted age); and study population (study inclusion/exclusion criteria, diagnostic criteria, number of TTP patients). The following study outcomes were also extracted: study follow-up, patient characteristics (age at first symptoms/diagnosis, sex distribution, race and ethnicity, comorbidities, biomarkers at baseline or during follow-up), and estimates of outcomes of interest.

Results of the systematic review were synthesized qualitatively and there was no pooling of estimates through a meta-analysis. A range of estimates was provided when possible, and outlying estimates were qualitatively assessed. Data for all outcomes were reported separately according to TTP type (ie, unspecified TTP, cTTP, iTTP). Risk of bias was not assessed due to the rarity of the disease.

Studies reporting outcomes have been placed into separate categories based on the type of data source used to identify TTP patients, namely registry-based studies, healthcare database studies (claims-based or integrated healthcare studies; from here on referred to as database studies) and other studies including multicenter, single-center, and survey-based studies. The separation of database studies from registry and other clinical studies was necessary due to the difference in diagnosis/identification of patients between these study types. As there is no unique International Classification of Diseases (ICD) code for TTP, research databases that use claims coding algorithms to identify cases of TTP are not based on confirmed diagnoses,¹⁸ unlike clinical studies.

Results

Search Results

Following literature searches and the removal of duplicate sources, 207 literature sources were eligible and included in the review. Pragmatic searches and snowballing yielded 14 additional relevant sources. Thus, a total of 221 references were included in the review (Figure 1; Supplementary Figure 1). The majority of studies reported on unspecified TTP (n=113) or on iTTP only (n=88), while the remaining studies reported on cTTP only (n=15) or both cTTP and iTTP (n=5). Key characteristics of the studies included in this manuscript are presented in Supplementary Table 3.

Incidence and Prevalence of TTP

Incidence

There was substantial heterogeneity in incidence estimates for unspecified TTP (n=4 studies) and iTTP (n=7 studies), with a single study reporting the incidence for cTTP (Figure 2A). The reported incidence for unspecified TTP was 8.92 per million person-years between 1996 and 2012 based on the US Oklahoma TTP-Hemolytic Uremic Syndrome [HUS] registry study,¹⁹ 3.88 cases per million new admissions between 2003 and 2013 in the UK Hospital Episode Statistics [HES] database,²⁰ 0.8 cases per million between 2011 and 2014 in a multicenter study in the UK,²¹ and 1.91 per million per year between 2012 and 2019 in a single-center study in Canada.²² The incidence for cTTP from 2005 to 2013 was 0.3 cases per million based on medical charts from a single-center study in Israel.²³ For iTTP, incidence ranged between 0.77 and 2.67 per million persons

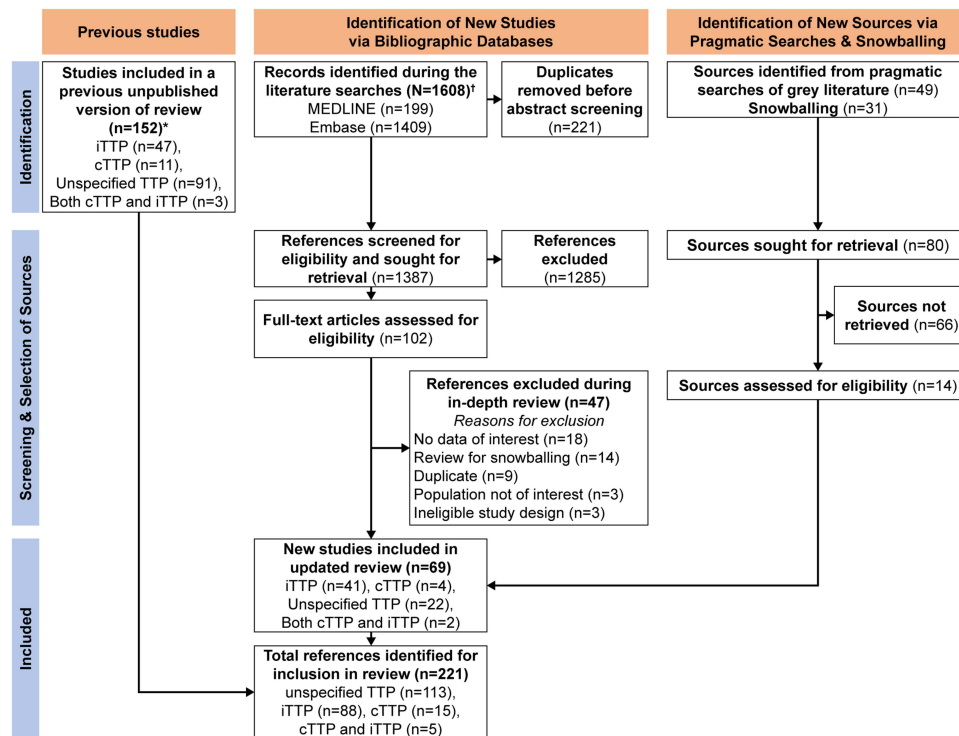


Figure 1 PRISMA flow chart for the selection of sources.

Notes: *Search period January 1, 2010–January 31, 2020 (See [Supplementary Figure 1](#)); [†]Search period January 1, 2020–February 11, 2022.

per year in European multicenter studies (assessment period: 2014–2016 in Germany, 1998–2007 in central Norway, and 2015–2017 in Spain).^{24–27} The incidence of iTTP reported in an Israeli single-center study from 2005 to 2013 was similar to that observed in Europe (2.0 per million per year).²³ In Japan, the incidence of iTTP reported in 2018 was 0.4 per million persons according to a Nara Medical University Registry study.²⁸

Prevalence

A summary of the prevalence of TTP is presented in [Figure 2B](#). Three studies reported on the prevalence of unspecified TTP.^{29–31} 13 adult-onset cases per million in a French TMA registry study,²⁹ 9.9 per million adults aged 19–64 years in the US (estimated from 2439 eligible patients among 245 million patients screened; IBM MarketScan[®] Research Database),³⁰ and 1–2.7 per million in the US (HealthCore Integrated Research Database[™]).³¹ The prevalence of cTTP varied widely across three studies, with a global prevalence of 0.4–16.7 per million persons based on the Orphanet disease information resource,³² 0.86 cases per million from the French TMA registry,³³ while a Norwegian multicenter cohort study investigating a hypothesis that central Norway may have higher cTTP prevalence than elsewhere reported 3.1 diagnosed or suspected cases per million based on the population for the whole of Norway and an outlier of 16.7 diagnosed or suspected cases per million based on the population of central Norway.²⁶ The authors hypothesized that the higher cTTP prevalence in central Norway may be associated with a high frequency of the *ADAMTS13 c.4143_4144dupA* mutation, thought to have arisen in that small area.²⁶ Six studies reported prevalence for iTTP, with estimates of 3.43 per million persons in the US (Optum-Humedica Database),³⁴ 12.99 per million persons in France (Orphanet disease information resource),³² 19 per million persons in the US (Oklahoma TTP-HUS registry),³⁵ and 19–21.44 per million per year in Spain (multicenter study).^{24,25} In the French TMA registry, one person with childhood-onset iTTP was estimated per million children.³⁶ Additional details for studies reporting the incidence and prevalence of TTP are available in [Supplementary Table 4](#).

Patient and Disease Characteristics

Patient characteristics of individuals with cTTP and iTTP are summarized in [Table 1](#).

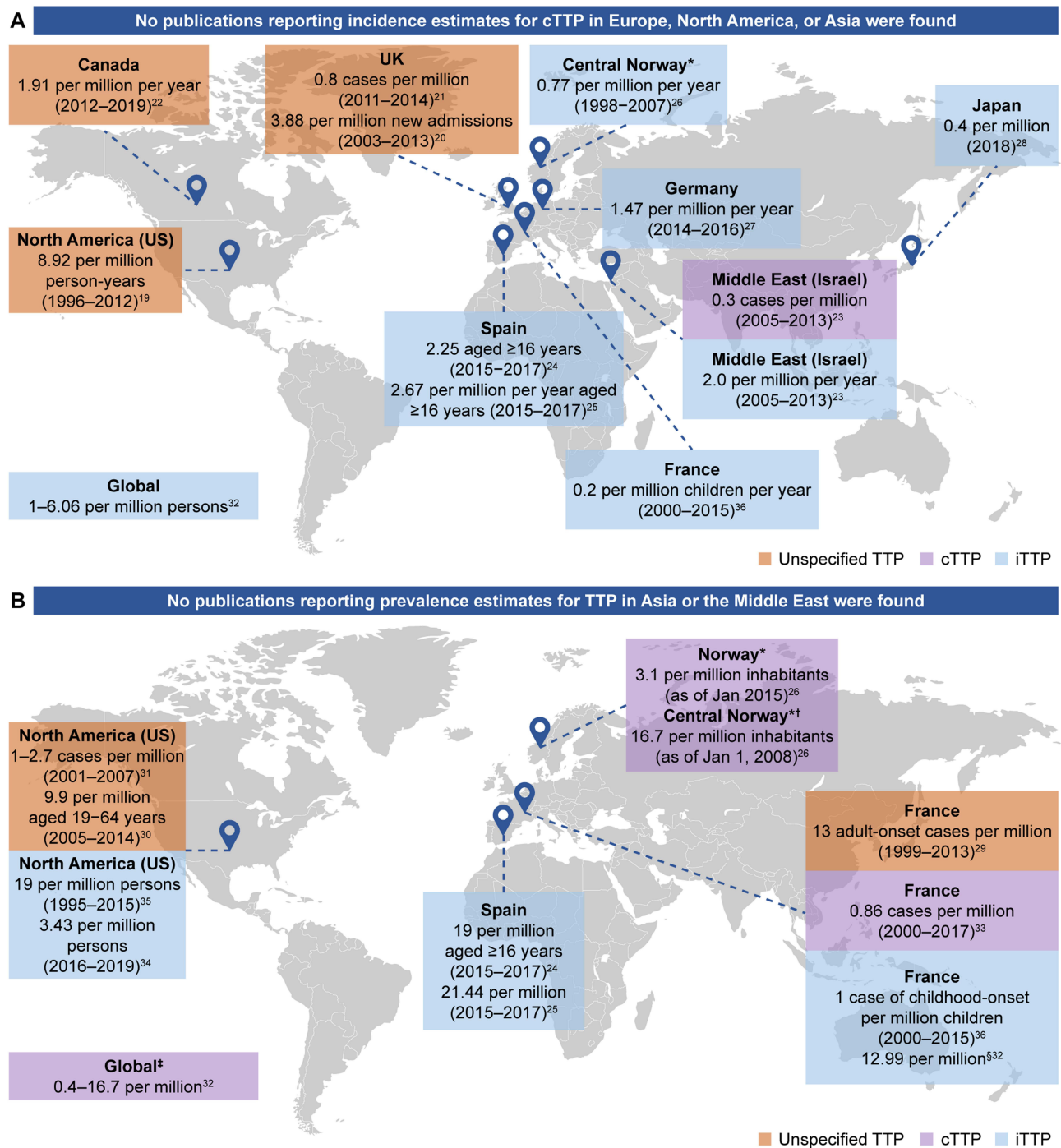


Figure 2 The incidence (A) and prevalence (B) of unspecified TTP, cTTP and iTTP.
Notes: *Considered both diagnosed or suspected cTTP cases; †Based on a study of central Norway with specific *ADAMTS13* mutations. ‡Values derived from reported data: 1 per 60,000 to 2,500,000. §Value derived from reported data: 1 per 77,000.
Abbreviations: cTTP, congenital thrombotic thrombocytopenic purpura; iTTP, immune thrombotic thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura.

Age at Symptoms Onset and Age at Diagnosis

The onset of cTTP symptoms typically occurred between birth and 35 years of age.^{8,37-40} Age at cTTP diagnosis followed a similar trend. Based on International hTTP and UK TTP registry studies, cTTP was typically diagnosed between early childhood (3.5 years) and late twenties.^{8,11,37,50}

Table 1 Patient Demographic and Clinical Characteristics

Category	cTTP	iTTP
Age at symptom onset	<p>Registry studies</p> <ul style="list-style-type: none"> • Median: 4.5–4.6 years^{8,37} • 74.3% experienced any TTP-related symptom(s) at birth; 37.1% experienced a first acute episode <1 year of age³⁸ • Ranged from neonatal period to 35 years³⁹ <p>Multicenter study⁴⁰</p> <ul style="list-style-type: none"> • 53.3% during the neonatal period (<28 days) • 23.3% during the prepubescent phase (<14 years) • 6.7% at age ≥14 years 	<p>Registry studies</p> <ul style="list-style-type: none"> • Median: 41–54 years^{41–45} <p>Single-center studies</p> <ul style="list-style-type: none"> • Median in pediatric patients: 14 years⁴⁶ • Median: 41–49 years^{47,48} • Mean: 45.7 years⁴⁹
Age at diagnosis	<p>Registry studies</p> <ul style="list-style-type: none"> • Median: 16.7–18.7 years^{8,37,50} • Two peaks in presentation (median): early childhood (3.5 years) and during pregnancy in women (29 years)¹¹ <p>Single-center study²³</p> <ul style="list-style-type: none"> • Median: 27 years <p>Patient-interview study</p> <ul style="list-style-type: none"> • Mean: 27.5 years in the US⁵¹ 	<p>Registry studies</p> <ul style="list-style-type: none"> • 40–46 years (median)^{52–56} • Mean 39.4–40.7⁵⁷ • Pediatric patients – 13 years (median)^{36,38} <p>Database studies</p> <ul style="list-style-type: none"> • Median: 64 years⁵⁸ • Mean: 48.8–53.1^{59,60} <p>Single-center and multicenter studies</p> <ul style="list-style-type: none"> • Median: 33–47 years^{23,56,61–65} • Mean: 43.7–47.0 years^{66–70}
Frequent comorbidities (≥10%)	<p>Registry studies</p> <p>Cardiovascular</p> <ul style="list-style-type: none"> • Arterial thrombotic diseases^a: 28.0%–36.0%^{8,37} <p>Hepatic</p> <ul style="list-style-type: none"> • Hyperbilirubinemia in neonatal period: 25.0%–43.0%^{8,37} • Jaundice: 49.0%⁸ <p>Neurological</p> <ul style="list-style-type: none"> • Epileptic seizure, headache: 22.0%³⁷ <p>Renal</p> <ul style="list-style-type: none"> • Renal insufficiency: 25.0%–31.0%^{8,37} 	<p>Registry studies</p> <p>Autoimmune disease</p> <ul style="list-style-type: none"> • Autoimmune disease (type unspecified): 14.7%–41.9%^{41,43,54,71} • Autoimmune thyroiditis^b: 10.8%–32.0%^{41,54} • Lupus: 7.0%–13.0%^{11,54,56,72–74} <p>Cardiovascular</p> <ul style="list-style-type: none"> • Hypertension: 26.9%–60.2%^{52,56,72–74} • Obesity: 29.2%⁷³ • Dyslipidemia: 17.5%⁷³ • Hyperlipidemia: 32.6%⁷² • Atrial fibrillation: 10.5%⁷² <p>Renal</p> <ul style="list-style-type: none"> • CKD: 16.8%–28.2%^{56,72,73} <p>Other</p> <ul style="list-style-type: none"> • Diabetes: 15.4%–27.1%^{52,56,72–74} <p>Database studies</p> <p>Psychiatric</p> <ul style="list-style-type: none"> • Depression: 16.7%⁵⁹ <p>Renal</p> <ul style="list-style-type: none"> • Renal disease: 18.0%⁷⁵ <p>Other</p> <ul style="list-style-type: none"> • Diabetes: 12.5%–25.7%^{59,75} • Cancer: 11.8%–18.3%^{59,75} • Chronic pulmonary disease: 13.0%⁷⁵ • Rheumatologic disease: 10.6%⁷⁵ • Stroke/TIA: 10.4%⁵⁹ <p>Single-center and multicenter studies</p> <p>Autoimmune disease</p> <ul style="list-style-type: none"> • Autoimmune disease (type unspecified): 12.1%–24.3%^{63,64} • Systemic lupus erythematosus: 38.2%⁷⁶ • Connective tissue disease: 10.0%–14.6%^{47,76} <p>Cardiovascular</p> <ul style="list-style-type: none"> • Hypertension: 17.5%⁶⁴ <p>Psychiatric</p> <ul style="list-style-type: none"> • Psychiatric disease: 11.0%¹³ <p>Other</p> <ul style="list-style-type: none"> • Flu-like syndrome: 16.2%⁶⁴

Notes: ^aStroke, transient ischemic attack, myocardial infarction and other (not specified); ^bIncluding Hashimoto’s thyroiditis.

Abbreviations: cTTP, congenital thrombotic thrombocytopenic purpura; iTTP, immune thrombotic thrombocytopenic purpura; US, United States.

Compared with cTTP, the onset of symptoms in patients with iTTP occurred later in life, at a median age ranging between 41 (interquartile range [IQR]: 35–48) and 54 years (IQR: 37–65).^{41–44,47,48} Diagnosis of iTTP was typically confirmed at the time of symptom onset. The median age at diagnosis ranged between 33 (range: 12–64) and 64 years (IQR: 47–74).^{23,52–56,58,61–65}

Sex Distribution

There was generally a lower proportion of males than females in both adult and pediatric cTTP and iTTP populations. The proportion of males among patients with cTTP ranged from 7% to 55.6%, even though cTTP is an autosomal recessive disorder and therefore should have the same risk regardless of sex.^{11,23,37–39,75,77–80} Two UK TTP registry

studies reported that the proportion of males varied according to age at the onset of cTTP symptoms,^{11,77} with a higher proportion observed with early-onset disease (68%) compared with late-onset (7–25%). Similar to cTTP, the proportion of male patients with iTTP typically ranged from 17.0% to 50.0% across studies.^{12,23,41–48,54–56,58–63,65–69,72–76,81–106} Out-of-range estimates were found in two studies, one including patients who provided a self-reported diagnosis in a UK-based survey (2.9% male patients)¹⁰⁷ and one Italian multicenter study in which patients presented with an initial TTP episode (64.9% male patients).⁶⁴

Race and Ethnicity

Two studies using the international hTTP registry reported that White/Caucasian race was the most common among patients with cTTP (53.0–86.2%).^{8,37} For patients with iTTP in registry studies across Europe and the US (TTP, TMA, iTTP/aHUS, and US state registries), the proportion of White/Caucasian patients ranged between 21.9% and 98.0%.^{41,43,53,54,56,71–74,81,86–89} For other study types, the proportion of White/Caucasian patients reported was 61.7%⁵⁹ in the US Medicare Fee-for-Service database study, and 39.0–97.1% in single-center and multicenter studies across the US and Italy.^{48,64,93,99–101,108} In Europe, White/Caucasian iTTP patients were predominant (67.1% to 98.0%).^{41,43,48,54,64,71,81,86} Nine US-based studies reported African Americans as the predominant racial group (50.5% to 78.0%),^{46,53,56,72–74,88,89,102} while six US-based studies reported that iTTP patients were predominantly White/Caucasian (54.0% to 78.9%).^{59,87,93,100,101,108}

Comorbidities

In studies using the hTTP registry, nearly half of patients with cTTP had a history of jaundice,^{8,37} while approximately 30.0% of patients had arterial thrombotic diseases and/or renal insufficiency,^{8,37} and 22.0% had neurological disorders³⁷ (Table 1). Comorbidities observed in $\geq 10\%$ of patients with iTTP included autoimmune disease (12.1–41.9%^{41,43,54,63,64,71}), hypertension (17.5–60.2%^{52,56,64,72–74}), obesity (29.2%⁷³), diabetes (12.5–27.1%^{52,56,59,72–75}), chronic kidney disease (16.8–28.2%^{56,72,73}), psychiatric disease (11.0–16.7%^{13,59}), cancer (11.8–18.3%),^{59,75} and stroke/transient ischemic attack (10.4%⁵⁹). Estimates were consistent across registry studies [n=9],^{41,43,52,54,56,71–74} database studies [n=2],^{59,75} and single-center and multicenter studies [n=4].^{47,63,64,76}

Incidence of Acute Episodes and Triggers

Incidence of Acute Episodes

A limited number of studies reported incidence of acute episodes in unspecified TTP (n=1),¹⁰⁹ cTTP (n=4),^{8,37,110,111} and iTTP (n=4)^{25,27,34,35} (Supplementary Table 5). Definitions of acute episodes were either missing^{110,111} or varied between studies due to different data sources and methods.^{8,25,27,34,35,37,109,110} The reported incidence of acute TTP episodes was 14.9 per 100,000 adult hospitalizations per year according to a US National Inpatient Sample database study.¹⁰⁹ Incidence rates of acute episodes/person-years in the International hTTP registry study were 0.19–0.35 in adult cTTP patients^{37,110} and 0.77 for cTTP patients aged ≤ 18 years.¹¹¹ Between 2006 and 2017, the median number of episodes per year was 0.10 per patient (range: 0.02–8.91).⁸ The incidence of acute episodes in cTTP was higher in females compared with males, in patients aged < 10 years than in those aged ≥ 10 years, and in those who did not receive plasma prophylaxis^{37,111} (Supplementary Table 6). For iTTP, the reported annual incidence of acute episodes was 1.81 per million persons in the US Optum-Humedica database,³⁴ 2.10 per million persons in a German multicenter study,²⁷ 3.10 per million persons in the Oklahoma TTP-HUS registry,³⁵ and 3.93 per million persons in individuals aged > 16 years from a Spanish multicenter nationwide survey.²⁵

Triggers of TTP Episodes

Triggers of acute episodes were similar for cTTP and iTTP, with pregnancy and infection being the most commonly observed.^{8,11,12,35,37,42,50,64,69,103} In patients with iTTP, surgery^{12,64,103} and medication/drug use (including antidepressants, anti-inflammatories, oral contraceptives, anti-epileptics, clopidogrel, vaccination, and recreational drugs [cocaine])^{12,13,64,69} were other reported triggers of acute episodes.

Incidence of Relapsed Episodes, Relapse Rate, Exacerbation, and Refractory Disease

Incidence of Relapsed Episodes/Relapse Rate

For cTTP, 55.6% of patients experienced a relapse during follow-up (unknown period) in a study using the International and Milan HUS TTP registry³⁹ and 83.3% of patients (with recurrent episodes leading to diagnosis) relapsed between 1998 and 2007 in a Norwegian multicenter study.²⁶ During a mean follow-up of 2.8 years (IQR: 1.6–4.9 years), 0.4 episodes/year (IQR: 0.1–1.05) were recorded in the International hTTP registry between 2012 and 2016.¹¹⁰

For iTTP, the incidence of relapse ranged widely (9.4% to 48.6%) across studies that used a similar definition.^{34,36,41,42,55,65,82,84,89,90,112–114} Estimates did not vary according to the type of data source (registry, administrative claims database, medical chart review). Heterogeneity across studies can be explained through methodological differences (ie, sample size, follow-up period, definitions of relapse, eligibility criteria) and clinical management of iTTP during acute episodes and during follow-up (type of treatment and treatment setting [on-demand, prophylaxis], etc).^{64,67,81,82,86,103,115} For instance, relapse was observed in 1.1% of iTTP patients treated with a triplet regimen in France (PEX, immunosuppression with corticosteroids and rituximab, and caplacizumab; French TMA registry study),⁸¹ and 3.5% of patients receiving caplacizumab plus other approved treatment per physicians' decision in the UK (UK TTP registry).⁸⁶ In another single-center study in China, the low incidence of relapse (5.3%) was due to the short assessment period (1 month post-discharge).¹⁰³ In a meta-analysis of relapse in patients receiving rituximab or conventional treatment (primarily of PEX and corticosteroids), the incidence of relapse in patients receiving only rituximab as an acute or preemptive treatment was 15.8% and 13.9%, respectively, while 58.5% of patients who did not receive preemptive treatment relapsed.¹¹⁵

The cumulative incidence of relapse was found to increase over time.⁶⁷ At 24, 48, 72, and 120 months post-treatment initiation, the cumulative incidence was lower in patients treated with either rituximab or cyclophosphamide in addition to PEX and steroids (n=28) compared with those treated only with PEX and steroids (n=10), according to a single-center study in the US (2010–2019).⁶⁷

Incidence of Refractory TTP Disease

Data on refractory cTTP were lacking in the literature. Specifically, two TMA registry studies reported very different estimates among iTTP patients of 1.1% (French TMA registry)⁸¹ and 30.1% (US Thrombotic Microangiopathy [USTMA] registry).⁸⁹ The lower incidence of refractory iTTP may be due to patients receiving aggressive therapy with combination treatment (intensive frontline triplet regimen of therapeutic PEX, immunosuppression with corticosteroids and rituximab, and caplacizumab).⁸¹ Refractory disease was reported in 12.5–17.9% of patients included in single-center and multicenter studies.^{12,25,63}

Incidence of Exacerbation

No data were found on the incidence of exacerbation in patients with cTTP. For patients with iTTP, incidence of exacerbation varied widely, ranging from 2.4% to 63.1%.^{12,25,34,36,59,63,64,74,81,86,94,102,116,117} Incidence of exacerbation appeared to depend on treatment, with lower estimates observed in patients receiving a combination of PEX, corticosteroids, rituximab, and caplacizumab (2.4%⁸⁶ and 3.3%⁸¹). According to study type, estimates ranged between 24.7% and 46.7% in two studies based on the French TMA registry and the Alabama registry,^{36,74} while a lower range of 12.5% to 17.2%^{34,59} was reported in database studies. A wider range of 13.6% to 63.1% was observed across single-center and multicenter studies.^{12,25,63,94,102,116,117}

Disease Biomarkers – Change in ADAMTS13 Levels or Activity

No data were found on change in disease biomarkers in cTTP patients. However, a number of registry and single-center and multicenter studies reported on ADAMTS13 levels or activity in patients with iTTP, at diagnosis/first acute episode, during remission, and at relapse.^{36,73,82,84–86,94,116,118}

In patients presenting with ADAMTS13 activity <10% at diagnosis or relapse in an Italian hematology department, all had normal ADAMTS13 activity (>50%) after treatment with PEX.⁹⁴ Similarly, in a study of the UK TTP registry study, ADAMTS13 levels increased considerably after PEX and caplacizumab treatment in patients after a confirmed

diagnosis of acute TTP.⁸⁶ In patients who survived ≥ 30 days after preemptive rituximab, ADAMTS13 activity was detectable in $>80\%$ of patients at Day 30 and at 3 months post-treatment.⁸² However, at 6 months, ADAMTS13 was undetectable in most patients. In patients with child- and adolescent-onset iTTP who survived their initial episode, all had detectable ADAMTS13 activity ($>40\%$ of normal) at remission.³⁶

A strong association between the decline in ADAMTS13 activity and the occurrence of relapse was found in patients with iTTP.^{84,116} An Italian multicenter study found that a combination of anti-ADAMTS13 antibodies levels ≥ 20 U/L and ADAMTS13 activity $<20\%$ strongly predicted relapse during remission ($P=0.0004$).¹¹⁶ In the Prospective Observational Registry for iTTP in Germany, 44.9% of patients had a persisting normal ADAMTS13 activity ($\geq 50\%$) during remission; 55.1% of patients had ADAMTS13 activity of $<50\%$ at least once, and 18.6% of those had continuous activity of $<10\%$ without relapse.⁸⁴ Of patients who relapsed, 77.8% had an ADAMTS13 activity of $<2\%$ before relapse. In another study based on the same registry, 70% of patients in remission had normal ADAMTS13 activity ($\geq 50\%$) at enrollment, with 4% of patients experiencing a rapid decline from $>80\%$ to $<1\%$ at 3 months after study enrollment, and 2% experiencing a slow decline from $>100\%$ to 4.6% at 4.5 months after study enrollment.⁸⁵ In patients with a history of iTTP investigated for ADAMTS13 activity every 3 months,¹¹⁸ 10.3% experienced persistent severe ADAMTS13 deficiency in remission and 10.3% experienced subsequent severe ADAMTS13 deficiency after a median follow-up of 17 months.

Disease Complications

Overall, in patients with iTTP or cTTP, frequently reported complications (affecting $\geq 10\%$ of patients) included cardiovascular, neurological, and renal disease (Table 2). Disease complications for cTTP were reported in two studies using the UK TTP registry. Short-term disease complications during acute episodes included stroke and transient ischemic attack, observed in 24.7% of patients,¹¹ while persistent cognitive symptoms (a long-term complication) were observed in 33.3% of patients at a median follow-up of 33 months.¹¹⁹ These results were consistent with findings from a review of published case reports in which major morbidities consisted of stroke/transient ischemic attack (38.9%), end-stage kidney disease (25.9%), and neurological abnormalities (11.1%) at a median follow-up of 10 years in patients who survived an initial episode¹²⁰ (Supplementary Table 7). Other observed complications include neonatal hyperbilirubinemia (43%),³⁷ arterial thrombotic disease (36%),³⁷ renal insufficiency (31%),³⁷ ≥ 1 arterial thromboembolic event (transient ischemic attack, stroke, myocardial infarction; 25.3%),⁵⁰ neurological disorders (22%),³⁷ and miscarriage/stillbirth (11.0%).¹¹

For iTTP, frequently reported short-term disease complications include acute kidney injury (91%),⁶⁸ neurological events (36%⁶⁸ and 47.4%⁶²), stroke or transient ischemic attack (39.5%),⁶² altered mental state (15.8%),⁶² and seizure (15.8%).⁶² Several long-term complications were observed 2 to 8 years after iTTP diagnosis, including persistent neurological impairment (26.1–60.0%),^{46,48,119} major cardiovascular events (28.6%),⁷² hypertension after surviving initial iTTP episode (24.2%),⁵² and stroke (13.1–18.2%).^{72,73}

Mortality

For cTTP, the rate of all-cause mortality in registry-based studies included no deaths in a pediatric study ($N=35$)³ and ranged from 4.8% (during 371 person-years of prospective follow-up; $N=87$) to 6.8% (median 8.3 year follow-up; $N=73$) in other populations with a defined follow-up period (no age definition).^{11,37,110} Causes of death consisted of stroke (80.0%) and cancer unrelated to TTP (20.0%) in one UK TTP registry study,¹¹ and sudden death due to unknown cause (55.6%), cerebral infarction (11.1%), sepsis (11.1%), uremia (11.1%), and suicide (11.1%) in a Japanese cTTP registry survey-based study.⁷⁸

Overall, the rate of all-cause mortality during or following acute episodes among patients with iTTP ranged from 1.1% (median follow-up: 0.4 years) to 18.8% (1 year).^{12,35,42,45,63,64,73,74,81,82,90,122} Three US and French database studies reported 30-day mortality between 7.4% and 21.0% after index hospitalization with standard treatment,^{59,71,91} while two US retrospective multicenter studies reported 90-day mortality between 5.5% and 7.3% (with all of the 7.3% of deaths actually occurring within the 30 days after presentation).^{93,108} Mortality differences between studies should be interpreted with caution due to differences in populations and study designs. In a meta-analysis reporting all-cause mortality among patients with acute episodes (initial or

Table 2 Short- and Long-Term Complications

Reference (Study Type, Study Period)	Patients (N) Duration of Follow-up	Disease-Related Complications
cTTP		
<i>Short-term complications (at presentation or following diagnosis)</i>		
Alwan, 2019 ¹¹ (Registry, 2003–2018)	73 Median: 8.3 years (range: 0.9–40.2)	<u>Cardiovascular</u> ● Stroke: 19% (n=14) ● Transient ischemic attack: 8% (n=6)
<i>Long-term complications (Range 2.75–10 years)</i>		
Alwan, 2020 ¹⁹ (Registry, 2005–2019)	12 Median: 33 months (range: 2–130) ^a	● Persistent cognitive symptoms ^b : 33.3% (n=4) ● Neurocognitive compromise (in those tested): 75% (n=3)
Borogovac, 2022 ¹²⁰ (Literature review, 2001–2020)	226 Median: 10 years (range: 1–47) ^c	Initial major morbidity among 217 patients: 33.6% (n=73) Subsequent major morbidity in 54 patients who survived initial comorbidity: 68.5% (n=37)
<i>Unknown assessment time</i>		
Sakai, 2021 ⁷⁸ (Registry, Apr–Sep 2020)	55 NR	Any persistent organ damage: ● FFP prophylaxis: 39.0% (n=16) ● FFP on-demand: 0%
Tarasco, 2021 ³⁷ (Registry, 2018–2019)	87 Median: 4.2 years (range: 0.01–15)	Possible cTTP-related comorbidities at enrollment ^d : <u>Cardiovascular</u> ● Arterial thrombotic disease: 36% (n=30) ● Venous thrombotic disease: 3.6% (n=3) <u>Hepatic</u> ● Neonatal hyperbilirubinemia: 43% (n=36) <u>Neurological</u> ● Neurologic disorders: 22% (n=18) <u>Renal</u> ● Renal insufficiency: 31% (n=26)
Alwan, 2019 ¹¹ (Registry, 2003–2018)	73 Median: 8.3 years (range: 0.9–40.2)	Medically significant complications: <u>Cardiovascular</u> ● Stroke/transient ischemic attack: 24.7% (n=18) ● Pulmonary hemorrhage: 1.4% (n=1) <u>Other</u> ● Miscarriage/stillbirth: 11.0% (n=8) ● Third-trimester pregnancy complications excluding miscarriage: 5.5% (n=4) ● Visual defects: 4.1% (n=3) ● Facial palsy: 2.7% (n=2) ● Retinal vein thrombosis: 1.4% (n=1) ● Seizures: 1.4% (n=1)
Mansouri, 2015 ⁵⁰ (Registry, 2015) ^e	83 NR	● ≥1 arterial thromboembolic event (transient ischemic attack, stroke, myocardial infarction): 25.3% (n=21) ● Venous thromboembolism: 1.2% (n=1)
Rurali, 2015 ³⁹ (Registry, 1996–2013)	18 NR	At last follow-up: ● Chronic kidney disease: 27.8% (n=5)
iTTP		
<i>Short-term complications (defined per publication)</i>		

(Continued)

Table 2 (Continued).

Reference (Study Type, Study Period)	Patients (N) Duration of Follow-up	Disease-Related Complications
Pollissard, 2021 ⁵⁹ (Database, 2010–2018)	2279 (aged ≥18 years) 20.7–31.7 months	During index hospital stay: <u>Cardiovascular</u> ● Stroke or myocardial infarction: 9.9% (n=226)
Pascual-Izquierdo, 2021 ²⁵ (Multicenter cross-sectional study, 2015–2017)	329 NR	After hospital admission for first episodes or relapsed episodes of iTTP (exact timing not specified): <u>Cardiovascular</u> ● Arterial thrombosis: 1.0% (n=2) ● Venous thrombosis: 1.0% (n=2) ● High blood pressure: 0.5% (n=1) <u>Other</u> ● Plasma allergy: 18.1% (n=35) ● Thrombosis of central venous catheter: 4.6% (n=9)
Renaud, 2021 ⁶² (Single-center cohort study, 2005–2020)	38 NR	At presentation with first iTTP episode: <u>Neurological</u> ● Neurological event within one week after hospital evaluation: 47.4% (n=18) ● Altered mental status: 15.8% (n=6) ● Neurological sequelae at discharge: 5.3% (n=2) <u>Cardiovascular</u> ● Stroke or transient ischemic attack: 39.5% (n=15) <u>Other</u> ● Seizure: 15.8% (n=6)
Ramachandran, 2020 ⁶⁸ (Single-center cohort study, 2014–2019)	10 NR	At hospital presentation: ● Neurological complications: 36% ● Acute kidney injury: 91%
Huang, 2021 ⁶⁹ (Single-center cohort study, 2013–2017)	55 NR	During the hospital stay: ● Mean sequential organ failure assessment score was significantly higher in non-survivors (mean score: 12.1 [SD: 3.3]) than in survivors (7.7 [2.1])
<i>Long-term complications (median follow-up 33 months to 8 years where reported)</i>		
Joly, 2016 ³⁶ (Registry, 1999–2017)	41 (child-onset and adolescent-onset iTTP) Median 8 (range 1–16) years	In patients who survived their first iTTP episode: <u>Renal</u> ● Impaired renal function: 4.9% (n=2) <u>Other</u> ● Hemiparesis: 4.9% (n=2) ● Deafness: 4.9% (n=2) ● Blindness: 4.9% (n=2)
Mancini, 2020 ⁴² (Registry, 2002–2018)	153 Median 4.9 (95% CI: 3.7–6.1) years	In patients followed after their first iTTP episode: ● Cancer: 2.0% (n=3)
Alwan, 2020 ¹¹⁹ (Registry, 2005–2019)	119 Median 33 (range 2–130) months	iTTP patients presenting with neurological symptoms: ● Underwent neuropsychology assessment (due to self-reported persistent cognitive symptoms): 26.1% (n=31)
Upreti, 2019 ⁷³ (Registry, 1995–2018)	170 Median (IQR): 3.08 (0.66– 7.79) years	In patients treated with PEX: <u>Cardiovascular</u> ● Stroke unrelated to an acute iTTP episode (ie, occurring during remission after recovery from iTTP): 2.57 per 100 patient-years (prevalence was 13.1% [n=18]) ● Median time from first iTTP diagnosis to stroke (IQR) was 2.8 (0.8–10.0) years

(Continued)

Table 2 (Continued).

Reference (Study Type, Study Period)	Patients (N) Duration of Follow-up	Disease-Related Complications
Han, 2015 ¹²¹ (Registry, 1995–2013)	52 NR	Patients who recovered from TTP and underwent cognitive impairment over 11 years ^f : <ul style="list-style-type: none"> ● Results for immediate ($p=0.0124$) and delayed memory ($p=0.0228$) in 2014 were significantly worse vs results from 2006 ($n=15$) ● Other cognitive components such as attention, language, and visuospatial components did not significantly differ between 2006 and 2014
Little, 2017 ⁵² (Registry, 1995–2015)	78 Median 6.4 years	<ul style="list-style-type: none"> ● Chronic kidney disease: 6.4% ($n=4$; of which, 40% had mild CKD) <ul style="list-style-type: none"> ○ Of these patients, other conditions included: pre-existing hypertension ($n=2$), diabetes ($n=1$), diabetes and hypertension ($n=1$) ● After surviving an initial TTP episode ($n=66$), 24.2% ($n=16$) developed hypertension
Brodsky, 2021 ⁷² (Registry, 1995–2020)	181 Median 7.6 years	During clinical remission: <ul style="list-style-type: none"> ● Major cardiovascular event: 28.6% ($n=43$) <ul style="list-style-type: none"> ○ Stroke: 18.2% ($n=33$) ○ Non-fatal myocardial infarction: 6.6% ($n=12$) ○ Cardiac revascularization: 4.9% ($n=9$) ○ Fatal myocardial infarction: 0.6% ($n=1$)
Pollissard, 2021 ⁵⁹ (Database, 2010–2018)	2279 Mean 25.1 months	Incidence rates of post-discharge complications (per 100 person-years): <ul style="list-style-type: none"> ● <u>Cardiovascular</u>: 14.4 <ul style="list-style-type: none"> ○ Hypertension: 10.0 ○ Heart failure: 7.4 ○ Cerebrovascular events: 5.3 ○ Stroke or transient ischemic attack: 3.4 ○ Deep vein thrombosis: 1.2 ○ Myocardial infarction: 1.2 ● <u>Metabolic conditions and renal impairment</u>: 12.8 <ul style="list-style-type: none"> ○ Diabetes: 5.3 ○ Renal disease: 7.2 ● <u>Neurological</u> <ul style="list-style-type: none"> ○ Cognitive and physical impairment: 8.3 ○ Mental health conditions: 8.1 ○ Schizophrenia: 4.8 ○ Depression: 4.0 ○ Anxiety disorder/post-traumatic stress disorder: 3.9 ○ Dementia: 3.6 ○ Seizures/epilepsy: 1.5 ● <u>Other</u> <ul style="list-style-type: none"> ○ Fatigue: 4.7 ○ Fever: 4.6 ○ Dizziness/accidents/falls (emergency admissions for contusions, breaks, hematomas): 4.2 ○ Focal deficits: 2.3 ○ Pain or discomfort: 1.1 ○ Pulmonary embolism: 0.8 ○ Urticaria: 0.7 ○ Coma: 0.6 ○ Anemia: 11.3
Tiscia, 2021 ⁶⁴ (Multicenter cohort study, 2013–2021)	74 Median 60 months	Patients with first iTTP episode: <ul style="list-style-type: none"> ● Ischemic stroke (3 years after episode): 1.1% ($n=1$) ● Autoimmune disease^g: 3.4% ($n=4$)

(Continued)

Table 2 (Continued).

Reference (Study Type, Study Period)	Patients (N) Duration of Follow-up	Disease-Related Complications
Pascual-Izquierdo, 2021 ²⁵ (Multicenter cross-sectional survey, 2015–2017)	193 (aged ≥16 years) NR	After resolution of acute episodes: <u>Cardiovascular</u> • Cardiovascular complications: 0.5% (n=1) <u>Neurological</u> • Central neurological complications: 2.1% (n=4) • Psychiatric complications: 2.1% (n=4) <u>Renal</u> • Renal complications: 0.5% (n=1) <u>Other</u> • Avascular hip necrosis: 1.0% (n=2) • Peripheral polyneuropathy: 0.5% (n=1) • Hepatitis E virus infection: 0.5% (n=1)
Riva, 2020 ⁴⁸ (Single-center cross-sectional study, 2015–2016)	35 Median 36 months	After last acute episode, in remission phase: • Persisting subjective neurological impairment: 48.6% (n=17) • Significantly poorer scores according to neuropsychological tests were observed in iTTP patients vs the general population: ○ Direct memory (mean difference: -5.87 [95% CI: -8.57, -3.17]) ○ Deferred memory (mean difference: -1.67 [95% CI: -2.32, -1.02]) ○ Focused attention (mean difference: -10.63 [95% CI: -15.81, -5.44]) ○ Sustained and divided attention (mean difference: 65.09 [95% CI: 47.23, 82.94]) • No differences in neuropsychological assessments were found between patients with ADAMTS13 levels <45% compared with those with levels ≥45% during remission
Graciaa, 2020 ⁴⁶ (Single-center cohort study, 2001–2009)	15 (aged ≤19 years) NR	Patients presenting at hospital with iTTP: • Persistent or worse neurologic complaints 6 to 8 months following disease onset: 60% (n=9)

Notes: ^aTime from acute TTP episode to neuropsychology assessment; ^bEvaluated using the following cognitive domains: premorbid optimal level of functioning (National Adult Reading Test), current general intellectual functioning (Wechsler Adult Intelligence Scale [WAIS]-III Verbal or Performance Scale IQ), verbal and non-verbal memory, naming, perception, frontal executive function and speed of information processing; ^cFollow-up of surviving patients with major morbidities (n=54); ^dIncluding potential cTTP-related complications resulting from previous episodes. ^eYear of publication; ^fTest (Repeatable Battery for Assessment of Neuropsychological Status [RBANS]); ^gSjogren syndrome, undifferentiated connective tissue disease and autoimmune hypothyroidism.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease cTTP, congenital thrombotic thrombocytopenic purpura; FFP, fresh frozen plasma; IQR, interquartile range; iTTP, immune thrombotic thrombocytopenic purpura; NR, not reported; PEX, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

relapse), pooled, unweighted mortality was 3.0% and 10.7% of patients treated with rituximab or conventional treatment, respectively.¹¹⁵ Mortality data from studies with no reported follow-up are presented in [Supplementary Table 8](#).

Reported TTP-related mortality ranged from 0.9% to 13.3%, regardless of study type and type of episode (initial or acute).^{12,13,45,54,63,64,86,90,112,114,122–124} Frequently reported causes of death included relapse/exacerbation of TTP (1.5–77.8%);^{56,71,73,106,122} cardiovascular events (1.4–27.6%);^{56,73,116} infection (10.5–13.8%);^{56,69} and TTP refractory to PEX (2.6–88.9%).^{62,74,106,125} Variation in study type and type of episode may have contributed to the wide estimate ranges for cause of death.

Disease Burden

Patient-Reported Outcomes

cTTP had an extensive negative impact on all areas of quality of life, including daily activities such as the ability to work and/or study, mental health (specifically feelings of anxiety and depression), financial distress, and mood swings according to a single-center study conducted in the US.⁵¹ Patients also had low confidence, experienced anger and frustration, and felt burdened by treatment. Similar to cTTP, patients with iTTP reported issues with daily life, including

difficulties with work or school activities^{36,48,107} as well as with family or social interactions.³⁶ Patients with iTTP also suffer from feelings of anxiety,^{48,107} depression,^{48,107,121} and cognitive impairment.^{101,107}

Costs

A limited number of studies report on costs associated with TTP. In the US, the total mean costs associated with TTP were estimated at USD 236,278 (standard deviation [SD]: 8439) in survivors and USD 784,606 (SD: 151,799) in non-survivors, based on the Kids' Inpatient Database and the National Inpatient Sample study between 2003 and 2014.¹²⁶ According to the IBM MarketScan[®] research database, between 2005 and 2014, the total median costs per TTP patient admission were USD 42,593 (IQR: 18,904–110,424).³⁰ Based on a single-center study from China (2009–2018), inpatient median costs were higher in patients treated with PEX (24,965, range: 3305–137,685) than in those treated with plasmapheresis (22,829, range: 4197–57,185), although the currency was not reported.¹²⁷

No data on costs associated with cTTP were found. However, among patients with iTTP in Japan, median total cost per patient was USD 40,897 (IQR: 24,204–64,012) based on the Japanese Diagnosis Procedure Combination inpatient database between 2010 and 2017.⁵⁸ In a study of the US Medicare Fee-for-Service database and Inovalon MORE2 registry database (2010–2018), mean costs associated with index hospitalization (based on ICD codes for thrombotic microangiopathy and therapeutic plasma exchange) were USD 15,587.50 (SD: 13,227.75) and median costs after index hospitalization were USD 3243.25 per month over a mean follow-up of 25.1 months.⁵⁹

Healthcare Resource Utilization (HCRU)

Studies reporting hospital LOS for patients with iTTP were identified ([Supplementary Box 1](#)). The mean hospital LOS per admission ranged from 12 to 20 days,^{13,25,59,68,108} while the median hospital LOS per admission ranged from 12 to 19 days in TTP-HUS, TMA, and TTP registry studies;^{35,81,86} 20 to 45 days per admission in the Japanese Diagnosis Procedure Combination inpatient database and French national hospital discharge database;^{58,60} and 9 to 28 days per admission across single-center and multicenter studies.^{12,24,62,64} Patients remained in the intensive care unit (ICU) for a mean duration of 8.3 days in a study using the US Medicare Fee-For-Service and Inovalon MORE2[®] databases⁵⁹ and 5.5 days in a multicenter study in Spain.²⁵ The median ICU LOS was 8 days in a French national hospital discharge database⁶⁰ and 4 to 7 days in single-center and multicenter studies.^{24,62}

Disease Management

The most frequently cited therapies for the management of cTTP were regular plasma prophylaxis and on-demand plasma infusion^{8,26,37,38} ([Box 1](#)). For iTTP, PEX, corticosteroids, or rituximab were commonly prescribed as on-demand therapy.^{25,43,49,62,64,69,76,81,88,90,92,93,105,106}

Box 1 Treatment Patterns of on-Demand and Prophylaxis Therapy

cTTP
Prophylaxis therapy
<p>Registry studies</p> <ul style="list-style-type: none"> ● Regular prophylactic treatment was initiated in 67.1% of 73 patients age ≥16 years¹¹ ● Most patients were treated with regular plasma prophylaxis: 57%,³⁷ 70.9%⁸ <ul style="list-style-type: none"> ○ 80.0% in child-onset and adolescent-onset population³⁸ ● FFP was utilized in 41.1%,¹¹ 55.6%,³⁹ and 74.5%⁷⁸ of patients <p>Multicenter study</p> <p>45.5% were treated with regular plasma prophylaxis²⁶</p>

(Continued)

Box 1 (Continued).

<p>On-demand therapy</p> <p>Registry studies</p> <ul style="list-style-type: none"> ● 29.1% of patients were treated with on-demand plasma therapy (hereditary TTP Registry⁸) ● On-demand FFP: 25.5%,⁷⁸ 61.3%,³⁷ and 100%³⁹ ● On-demand treatment (FFP for age ≥16 years, intermediate purity factor VIII concentrate for age <16 years): 12.3%¹¹ <p>Database-based studies</p> <p>Exchange transfusion during neonatal period: 45.5%²⁶</p>
<p>iTTP</p>
<p>Prophylaxis therapy</p> <p>Registry studies</p> <p>Products used among patients who received immunosuppressive treatment pre-emptively:⁸⁸</p> <ul style="list-style-type: none"> ● Corticosteroids: 53.8% ● Rituximab: 30.8% ● Others (Not reported): 15.4% <p>Multicenter study</p> <p>Maintenance treatment with rituximab during remission (patients aged ≥16 years):²⁵</p> <ul style="list-style-type: none"> ● Initial episode: 3.1% of 128 episodes ● Relapsing episode: 16.9% of 65 episodes
<p>On-demand therapy</p> <p>Registry studies</p> <p>First-line treatments used to treat first or relapsing TTP episodes:</p> <ul style="list-style-type: none"> ● PEX (87.4–100%)^{43,81} <ul style="list-style-type: none"> ○ 92.9% (patients aged ≥12 years)⁹⁰ ○ Median number of PEX sessions ranged from 14 (in patients who had the onset of the acute episode at ≥65 years of age) and 11 (patients aged <65)⁴³ ○ Median duration of PEX treatment: 5 days (range, 4–7) to 7 days^{81,86} ● Corticosteroids (82.5–98.8%)^{43,81,86} <ul style="list-style-type: none"> ○ 95.3% (patients aged ≥12 years)⁹⁰ <p>Rituximab treatment usage:</p> <ul style="list-style-type: none"> ● To treat acute episodes: 20.3%–63.3%^{43,83,88,90} ● Commonly used as a second-line treatment in refractory or exacerbated patients^{88,90} <p>Caplacizumab treatment usage:</p> <ul style="list-style-type: none"> ● Median duration: 33–36 days^{81,83} <p>Other additional treatments included:</p> <ul style="list-style-type: none"> ● Cyclosporine: 4.7%⁹⁰ ● Cyclophosphamide: 1.2%,⁸⁶ 2.2%,⁸¹ and 13.0%⁹⁰ ● Bortezomib: 0.6%⁸¹ and 5.9%⁸⁶ ● Vincristine: 1.7%⁸¹ and 6.5%⁹⁰ <p>Single-center and multicenter studies</p> <ul style="list-style-type: none"> ● PEX range: 89.1%–100%^{49,62,64,69,76,93,105} <ul style="list-style-type: none"> ○ Median number of PEX sessions ranged from 6 to 15^{62,64,69,83,93} ○ Mean duration of PEX treatment: 16.2 days²⁵ ● Corticosteroids: de novo (97.7%) and relapsing (92.3%)²⁵ <p>Rituximab treatment usage:</p> <ul style="list-style-type: none"> ● To treat acute episodes: 20.2%–48.4%^{64,69,93,105,106} ● More frequently administered among relapsing episodes (41.5%) than initial episodes (14.1%) when used as first-line treatment²⁵ ● Commonly used as a second-line treatment in refractory or exacerbated patients^{25,92} <p>Caplacizumab treatment usage:</p> <ul style="list-style-type: none"> ● 10.5% of patients with a first acute iTTP episode (2005–2020) treated with caplacizumab⁶² ● 2.6% of patients who experienced their first episode (2013–2021) received caplacizumab and/or vincristine⁶⁴ ● Median duration (2018–2019): 34 days (range, 2–211)⁴⁹ <p>Other additional treatments included:</p> <ul style="list-style-type: none"> ● Cyclosporine: 1.5%²⁵ ● Cyclophosphamide: 1.5% (de novo) and 3.0% (relapse)²⁵ and 4.0%⁹³ ● Bortezomib: 1.0%,⁹³ and 1.5% (de novo and relapse)²⁵ ● Vincristine: 0.8%⁹³ and 3.1% (de novo)²⁵

Abbreviations: cTTP, congenital thrombotic thrombocytopenic purpura; FFP, fresh frozen plasma; iTTP, immune thrombotic thrombocytopenic purpura; PEX, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

Prophylaxis Treatment

For cTTP, plasma infusion prophylaxis was administered to prevent the occurrence of TTP episodes in 41.1% to 80.0% of patients across all study types.^{8,11,26,37–39,78} For the prophylactic treatment of iTTP, 53.8% and 30.8% of patients received corticosteroids or rituximab, respectively, in a USTMA registry study,⁸⁸ while rituximab was used for remission maintenance in 3.1% and 16.9% of the initial and relapsing episodes, respectively, in a Spanish multicenter study.²⁵

On-Demand Therapy

A greater number of studies reporting data on on-demand treatment for managing acute TTP episodes were identified for iTTP compared with cTTP (Box 1). The proportion of patients with cTTP receiving on-demand therapy with fresh frozen plasma (FFP) ranged from 25.5% to 100% across all study types.^{8,26,39,75,78} For patients with iTTP, 87.4% to 100% of patients received on-demand treatment with PEX,^{43,49,62,64,69,76,81,93,105} 82.5% to 98.8% received corticosteroids,^{25,43,81,86,90} and 20.2% to 63.3% received rituximab.^{43,64,69,83,88,90,93,105,106} Other treatments used for iTTP included caplacizumab,^{49,62,64,81,83} cyclosporine,^{25,90} cyclophosphamide,^{25,81,86,90,93} bortezomib,^{25,81,86,93} and vincristine,^{25,49,64,81,90,93} with a low rate of use (<15%) reported for most of these versus PEX, corticosteroid, or rituximab as on-demand treatments.

Post-Discharge Clinical Management for Patients with iTTP

Data in the literature indicate a lack of standardized post-discharge practices.^{12,73,81,84} In registry studies, ADAMTS13 monitoring was conducted weekly during a follow-up period of 127 days after PEX administration (French TMA registry)⁸¹ or every 3 months post-discharge (78.2% of patients had ≥ 2 visits with median time between visits of 91 days; German TTP registry).⁸⁴ In a Johns Hopkins TMA registry study, 30.6% of patients were tested for ADAMTS13 activity at least 3 months following an acute episode (median number of measurements during remission: 3 [range:1–18]).⁷³ A single-center study reported ADAMTS13 measurement frequency every 3–6 months in 62.5% of episodes and every 12–14 months in 37.5% of episodes, with a median of five measurements per patient.¹²

Discussion

This systematic review provides an overview of the burden of TTP, a rare and serious condition defined by acute and relapsed episodes that is associated with significant mortality if appropriate treatment is not provided in a timely manner. Furthermore, TTP is associated with serious comorbidities in addition to short- and long-term complications, and exerts a substantial negative impact on patient QoL, daily activities, and mental health.

Although there was heterogeneity in reported prevalence estimates, epidemiological evidence highlights the rarity of TTP.^{19,21,22,24–28} There were substantial geographical disparities across reports for unspecified TTP, including a large difference in prevalence estimates between France (13 cases per million)²⁹ and the US (1–2.7 cases per million).³¹ The majority of cTTP estimates from Global, French and Norwegian studies, were very low (0.4, 0.86, and 3.1 cases per million, respectively).^{26,32,33} However, there was one prevalence estimate for cTTP in central Norway that was a noticeable outlier (16.7 cases per million).²⁶ This was based on a single study in central Norway, which had a hypothesis that the region may have a higher cTTP prevalence than elsewhere, possibly related to the high reported frequency of the *ADAMTS13 c.4143_4144dupA* mutation, and the inclusion of diagnosed or suspected cTTP cases. In addition, methods for case identification may have influenced the estimates reported for Norway, with a systematic case-finding strategy used for central Norway but not the whole country. The estimated prevalence for the whole country was 3.1 cases per million.²⁶ iTTP prevalence estimates were also heterogeneous but low (3.43 in the US³⁴ to 21.44 per million in Spain²⁵). Overall, these data suggest that cTTP and iTTP meet the criteria for ultra-rare conditions (prevalence of less than one case per 50,000 individuals).¹²⁸

The International Society on Thrombosis and Haemostasis (ISTH) diagnostic guidelines cite the annual incidence of TTP as 2–6 per million individuals,⁴ while unspecified TTP studies identified by this review reported an incidence rate ranging from 0.8 cases per million to 8.92 cases per million person-years.^{19–22} Due to finding only one study with cTTP incidence (0.3 cases per million),²³ comparisons with iTTP are limited. The wide range found in population-based estimates may be explained by variations in reported population size, parameters for defining the disease, and the time periods in which the studies were conducted (Supplementary Table 4).

Determining the incidence of such a rare disease can include challenges. For example, in a US study validating administrative claims codes for TTP in the HealthCore Integrated Research Database™, the positive predictive value (PPV) of the initial claims coding algorithm used was 46% (ie, 46% of claims were assessed to have definite evidence to support TTP diagnosis), while the PPV of a refined algorithm was 72%, highlighting the difficulty of accurately confirming diagnoses used in healthcare databases.¹⁸ In our literature review, however, there did not appear to be

a trend for higher or lower incidence or prevalence reported in healthcare database studies compared with registry, single-center, or multicenter studies. Other factors that can affect the incidence and prevalence of TTP include age, and for iTTP, sex, race-ethnicity, obesity, infection and inflammation, in addition to potential genetic risk factors.^{129,130} Referral to expert centers may also impact epidemiology data, as diagnosis of rare diseases is often substantially delayed without access to specialists,¹³¹ and patients who live close to tertiary medical facilities are more likely to be accurately diagnosed than those who live further away.¹³²

Patient characteristics reported in identified studies may indicate change in practice over time and were inconsistently aligned with known risk factors. Age at diagnosis for cTTP and iTTP typically occurred around symptom onset,^{11,23,50,52,54–56,58,61–65} which appears to reflect improvements in the time required to make a clinical diagnosis. For example, during the whole enrollment period, the international hTTP registry reported a median age at cTTP diagnosis that was over 10 years later than the median age at cTTP symptom onset, but for patients diagnosed in recent years, time from symptom onset to confirmation of disease diagnosis had dropped to days or weeks with the use of ADAMTS13 activity assays.^{8,37} A female predominance was reported for both cTTP and iTTP,^{11,12,23,41–45,47,48,54–56,58,59,61–63,65–69,72–77,79,81–91,93–106} with female sex an established risk factor for iTTP.³ White race was commonly reported in patients with cTTP^{8,11,37} and those with iTTP in European studies.^{41,43,48,54,64,71,81,86} Black race is an established risk factor for iTTP,^{3,133} with a sevenfold higher incidence reported among individuals who are Black vs non-Black.¹³⁴ However, there was no predominance of Black race in patients with iTTP reported in reviewed studies, which may be influenced by differences in access to care or levels of participation in healthcare studies (such as registries).^{135–137} US-based studies reported either African American^{46,53,73,74,88,89,102} or White/Caucasian^{59,87,93,100,101,108} as the most common racial group.

Of utmost importance when considering TTP epidemiology is the incidence of acute TTP episodes, as they are associated with a substantial mortality rate.⁴ ISTH guidelines prioritize ADAMTS13 activity testing at acute TTP episodes where there is a high probability of TTP, although others have highlighted the importance of ADAMTS13 testing and treatment with appropriate therapies during remission as well as at acute episodes.^{2,138} Although the definition of an acute episode varied due to different data sources and study methods, the incidence of acute episodes was considerable and found to be consistent with relevant clinical presentations, medical events and treatment. Tarasco et al 2021 reported that the incidence of acute episodes varied by age and sex, further suggesting that age may be a driver of acute episodes, with early childhood representing a period of risk for patients with cTTP in particular.³⁷ In addition, pregnancy has been reported to precipitate TTP, with women presenting with a first acute episode of both cTTP and iTTP during pregnancy in the UK TTP registry.¹³⁹

TTP-related ADAMTS13 deficiency gives rise to acute episodes with typical MAHAT and subacute manifestations,^{5,11,110,140} which result in a variety of serious short- and long-term disease complications such as organ damage and mortality.^{4,5,110} As cardiovascular, renal, and neurocognitive disorders are common manifestations of TTP,² it may be difficult to distinguish comorbidities from disease-related complications. However, their presence contributes to the substantial disease burden for patients with TTP. Although no direct data on the management of patients with TTP with multiple comorbidities/complications were uncovered in this review, it is understood that multimorbidity results in a large economic burden on health systems and society.¹⁴¹ One of the main challenges of managing TTP is the occurrence of relapsed episodes. Relapses can occur in up to 50% of patients who survive their initial episode, and the timing may be unpredictable, occurring close to achievement of remission or months later.¹⁴² Relapse rates identified in this review ranged between 55.6% and 83.3% for cTTP^{26,39} and between 9.4% and 48.6% for iTTP.^{34,36,41,42,55,65,82,84,89,90,112–114} Variation in relapse estimates can be explained through methodological heterogeneity regarding study type, sample size, follow-up period for relapse rate assessment, patient profile, and clinical management of acute episodes (type of treatment and treatment setting [on-demand, prophylaxis], etc).^{64,65,67,82,86,103,115}

In addition to the unpredictability of relapse, refractory disease and disease exacerbations add a further degree of complexity to disease management. A strong association was found between the decline in ADAMTS13 activity and the occurrence of relapse in iTTP,⁸⁴ in keeping with known disease pathophysiology.¹⁰ International treatment guidelines acknowledge that there are practical issues around the cost, resource utilization, and patient commitment necessary for

regular ADAMTS13 monitoring during remission.¹⁵ However, given the association between ADAMTS13 activity and relapse in iTTP,⁸⁴ routine ADAMTS13 testing would be a valuable addition to current guidelines.

TTP mortality observed for both cTTP and iTTP in studies with a defined assessment/follow-up period was aligned with the generally accepted rate of between 10% and 20%, even with treatment.¹⁴³ Data on all-cause and TTP-related mortality in the current review indicate a substantial mortality burden for patients with cTTP and iTTP, with specific causes of death linked to typical consequences or complications of the disease. It is hoped that regular ADAMTS13 monitoring could help to reduce the risk of relapse and mortality, but more research in this area is needed.

Given the broad range of disease symptoms, comorbidities, and complications, it is unsurprising that studies in this review reported that both cTTP and iTTP negatively affected patient QoL, impacting everyday activities, including the ability to work and/or study^{36,48,51,107} and mental health.^{48,51,107,121} A limited number of PRO studies were identified despite the negative impact of TTP on QoL, which may be due to the rarity of the disease. Similar to what was found for other outcomes, only one study reported on QoL for cTTP, and a limited number of studies reported on costs associated with unspecified TTP (n=3) and iTTP (n=2), with the majority reporting US-based costs. Consequently, there is a need for further research on PROs and on the economic burden of TTP in different regions. Based on the evidence identified, costs associated with TTP are substantial, with an unspecified TTP admission having a total cost of USD 42,593,³⁰ for example. Owing to the limited evidence available, the main cost drivers of managing TTP remain unclear.

Different disease management approaches were documented in the literature for cTTP and iTTP, and treatment use generally reflected current ISTH treatment guidelines for TTP, which recommend plasma prophylaxis for cTTP and use of PEX, corticosteroids, or rituximab as on-demand therapy for iTTP.¹⁵ Although caplacizumab represents the first anti-VWF drug to receive a regulatory approval for the treatment of iTTP since 2018, and is now recommended for the treatment of first or relapsing acute iTTP episodes,¹⁵ few studies of this treatment were identified in the systematic review.^{49,62,64,81,83} This is likely due to the timing of approval versus studies identified in addition to challenges with the availability of caplacizumab.¹⁵ Other contributing factors may include treatment side effects, cost, requirement of cotreatments to remove the underlying autoantibodies, and the necessary clinician experience with caplacizumab use and monitoring protocols.¹⁵

A considerable variability in outcomes was reported in this review, likely resulting from differences in study inclusion criteria, research methodologies, study follow-up, and study type. Differences in disease awareness, diagnostic criteria for TTP, definitions of TTP, definitions of acute episodes, and clinical management of TTP across geographic areas and different time periods may also have contributed to the heterogeneity of the data. Some relevant sources may not have been captured in the systematic literature search, as not all studies are published in peer-reviewed journals. To mitigate this limitation, our methodology included pragmatic searches of the gray literature, as well as “snowballing”. For most outcomes, a larger body of evidence was identified in the literature for iTTP than cTTP. This is likely to be a consequence of disease epidemiology, with more than 95% of all TTP cases identified as iTTP, while the remainder are classified as cTTP.⁴ Specifically for cTTP, an ultra-rare disease, data on epidemiology, disease characteristics, and burden of disease were scarce. For TTP in general, very limited data were identified for regions other than Europe, North America (predominantly the US), and to a lesser extent, Asia. Consequently, data may be considered generalizable only to Europe and the US. The lack of data on aspects of this rare disease indicates a need for additional real-world analyses, particularly outside of Europe and the US.

Conclusion

The evidence identified in this systematic review describes a high burden of illness associated with TTP, including serious acute episodes, mortality, comorbidity, and disease-related complications, in addition to poor QoL. This review also highlights the limited data available on the epidemiology of cTTP and iTTP, PROs, costs of disease management, and associated HCRU. Substantial unmet needs remain, including effective treatment regimens leading to improvements in complications and disease-related mortality. The findings in this review may help increase disease awareness and inform decision-making for disease management and future research studies for the benefit of patients with TTP.

Abbreviations

ADAMTS13, A disintegrin and metalloproteinase with thrombospondin motifs 13; CI, confidence interval; CKD, chronic kidney disease; cTTP, congenital thrombotic thrombocytopenic purpura; FFP, fresh frozen plasma; HCRU, healthcare resource utilization; HES, Hospital Episode Statistics; HUS, Hemolytic Uremic Syndrome; ICD, International Classification of Diseases; ICU, intensive care unit; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LOS, length of stay; MAHA, microangiopathic hemolytic anemia; MeSH, Medical Subject Headings; NR, not reported; PEX, plasma exchange; PICOTS, Population, Intervention or Exposure, Comparator, Outcomes, Time Period, Setting; PPV, positive predictive value; PROs, patient-reported outcomes; QoL, quality of life; SD, standard deviation; TMA, thrombotic microangiopathy; USD, US dollar; USTMA, US Thrombotic Microangiopathy; VWF, von Willebrand factor; TTP, thrombotic thrombocytopenic purpura; UK, United Kingdom; US, United States.

Data Sharing Statement

The datasets, including the template data extraction form and data extracted from the included studies, are available upon request from Ragy Saad (ragy.saad@takeda.com) at the Global Evidence and Outcomes department at Takeda.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, or analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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