Epidemiology and Administration outcomes of Thrombotic Thrombocytopenic Purpura (TTP): Review article


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ABSTRACT

Background: Fever, thrombocytopenia, hemolysis, pentad failing kidneys, anaemia, and neurological impairment has historically been used to describe bleeding as the blood syndrome “thrombotic thrombocytopenic purpura” (TTP), a type of hemolytic anaemia caused by microangiopathy. TTP is an uncommon condition, and it is unclear exactly how often it is? According to studies, incidence per million depends on where individuals live. TTP can occur in youth with congenital forms, however it mostly strikes adults over the age of 40. The two organ systems most frequently impacted by TTP are the nerve system of the body (CNS) and kidneys. Because TTP is a serious medical condition with a 90% fatality grad if untreated, prompt diagnosis is crucial. Initial therapy is effective in around 80% of patients, and post-treatment mortality is between 10% and 15%.

Objectives: The study aimed to summarize current evidences regarding epidemiology and outcomes of Thrombotic Thrombocytopenic Purpura therapy (TTP).

Methods: For article selection, the PubMed database and EBSCO Information Services were used. All articles relevant with our topic and other articles were used in our review. Other articles that were not related to this field were excluded. The data was extracted in a specific format that was reviewed by the group members.

Conclusion: Older patients had longer Immune thrombotic thrombocytopenic purpura (iTTP) episodes and died at higher rates than younger patients. iTTP patients have a considerable increase in chance of illness and demise, while receiving TPE and immunosuppressants, which necessitate the need for more potent treatments. Moreover, they are more likely to have secondary thrombotic microangiopathies than primary microangiopathies due to several causes. Depending on the origin of thrombotic microangiopathies, there are different risks associated with dialysis, neurologic and cardiac issues, and mortality. Mortality rate are low for patients who received hospital care with low rate of complications.

Keyword: Thrombocytopenic purpura (TTP), Epidemiology, Thrombocytopenia, Neurologic dysfunction.

Introduction

Fever, thrombocytopenia, hemolysis, pentad anaemia, renal failure, as well as neurological impairment has traditionally been used to describe bleeding as the blood syndrome TTP characterised by microangiopathic hemolytic anaemia in its various forms. The protease that breaks down the von
Willebrand factor ADAMTS13 is decreased or absent in TTP due to either a hereditary or acquired condition. Microthrombi are formed when ADAMTS13 levels are low, which causes end-organ ischemia and injury. This is because the big Von Willebrand factor (VWF) in multiple forms that is necessary to prevent spontaneous coagulation, cannot be inactivated by the ADAMTS13. When left unchecked, large multimers have a strong tendency to bind platelets and trigger the development of thrombi. The two organ systems most frequently impacted by TTP are the central nervous system (CNS) and kidneys. Prompt identification is essential since TTP is a medical emergency with a 90% death risk if untreated. Initial therapy is effective in about 80% of patients, and post-treatment mortality is between 10% and 15% [1, 2, 3, 6]. The history of TTP is fascinating because it demonstrates the transformation from a clinical disease to a particular syndrome with unique biological criteria: the severe lack of ADAMTS-13. The liver produces the enzyme metalloprotease as well as disintegrin called ADAMTS-13 that contains repetitions of thrombospondin type 1 that can cleave large vWF multimers. Endocrine cells discharge large-scale vWF multimers entering the bloodstream under physiological circumstances. Such multimers produce strong squeezing pressures in the blood, which, at a certain point, cause the emergence of vWF's A2 dominion. An ADAMTS recognizes well the location and gradually cut the VWF, resulting in smaller multimers with lower adhesiveness to platelets. Some variables, such as female sex, obesity, and black ethnicity, are perhaps connected to ADAMTS-13 deficiency and are regarded as danger signs with TTP [4, 5, 7]. Ninety percent of instances of iTTP manifest in adulthood. Incidence rates for adults are 1.5 to 6 million instances every year on average. Differences in the yearly incidence rate are probably caused by local demographics. In the mostly Asian countries, the incidence is 1.5 cases per million per year. The United States has 2.99 instances per million people annually, which may be related to the larger percentage of African Americans, who experience TTP at an approximately eightfold higher prevalence. In a local UK registry, the incidence rate was revealed to be six per million. Nevertheless, considering that TTP was occasionally detected clinically and not usually by ADAMTS13 testing, this may be an overestimate [8, 9, 13]. TTP is an uncommon condition, and it's unclear exactly how often it is. According to studies depending on where people live, there are between 1 and 13 incidences per million people. TTP can occur in youth with congenital forms, however it mostly strikes adults over the age of 40. TTP has a 2:1 female to male prevalence and is more frequent in women. Without therapy, TTP mortality is 90%; however, with the right care, it is reduced to 10%–15%. In infants, TTP is quite uncommon [1, 10]. The cornerstone first-line therapy for an acute episode is daily therapeutic plasma exchange (TPE). Soon after feasible, at 1.5 times the amount of plasma in the patient, it should be started. Take autoantibodies out, vWF multimers, and probably cytokines that cause inflammation when TPE supply be insufficient, according to ADAMTS-13. The treatment is administered every day as long as when the platelet count is stabilised (more than 150 x 109/L over a two-day period.) and the lactic dehydrogenase (LDH) is standard or normalised. Possibly twice-daily TPE are helpful from refractory illness. Blood transfusions on a regular basis supply ADAMTS-13 to prevent the acute episodes. This preventative strategy is employed. Patients may have different needs, and there are no established regulations to direct management [7, 11].

Methods
Research plan: A thorough examination of the available data on epidemiology, the after-treatment results of thrombotic thrombocytopenic purpura (TTP) are regarded as a reliable technique for recognising and synthesizing the peer-reviewed literature in this field in order to develop a coherent plan for empirical study that incorporates existing knowledge. Only an interpretation could be made from the qualitative material in this review. Additionally, an analysis of qualitative information seeks conclusions that have importance, individualised needs, to guide a research strategy. Utilising qualitative synthesis techniques, when it is feasible, include and interpret the data from the publications that are provided. The review strives to provide additional interpretive information beyond the simple collection of accessible data insights into the epidemiology as well as treatment of TTP results as well as identifying areas where additional study is needed [12].

Criteria for study eligibility: Peer-reviewed qualitative research were included in the review. Qualitative research using many methodologies and studies that had a relevant qualitative component passed the inclusion screening. Studies that have been carried out in the last 20 years with English language were included. The researches that have been published between October 2012 and October 2022 are considered for the review to ensure the currency.
Study Inclusion and Exclusion criterion: The articles were chosen for the project based on their relevancy, English and a ten-year time limit were taken into consideration. All other articles that don't focus primarily on one of these subjects, studies that involved repeat or review procedures were not included. No studies that weren't available in English were included in the review. Articles from publications, books, conference abstracts, or other types of literature that simply provided qualitative data were also disregarded.

Search technique: MedLine headings (MeSH) and restricted vocabulary were combined in a systematic search technique to find peer-reviewed literature on epidemiology as well as administration outcomes with TTP. The databases were from MedLine, Scopus, PubMed (Elsevier), Google Scholar and EbscoHost. We only looked at results from October 2012 and October 2022.

Selection of study: It was demonstrated using the ENTREQ criteria for reporting qualitative systematic reviews. To help removing duplicates, at first, the Endnote library was filled with all of the retrieved studies. Once the duplicates have been eliminated, the Endnote library was distributed between the two reviewers so they could independently check the titles and abstracts of the articles, based on the requirements for eligibility. The research that the two reviewers have decided upon underwent a full-text examination. A third reviewer settled any differences between the two reviewers. The whole texts of all qualifying studies were examined by the two reviewers independently. In the event that the two reviewers' opinions diverge, through conversation with the third reviewer, agreement was sought on the points of disagreement. Finally, for the final framework synthesis, the complete texts of all relevant research that satisfied the inclusion criteria were kept.

Extraction of data: Two reviewers independently retrieved data from qualifying research into a specialised data collection platform. The third review author double-checked and verified the extracted articles. First author’s name and publishing year were among the study characteristics that were gathered as well as the time frame for data collection and the area where the study was carried out. Specific study information, such as the study's population and design, the sample size, sampling techniques, and data gathering techniques were recorded. Results of thrombosis epidemiology and management systematically of thrombocytopenic purpura (TTP) were found.

Synthesis and evaluation of data: Data analysis was done without the use of any software. The data were organised by theme by the reviewers, who then provided the themes as an analysis table (chart). The studies were mirrored in the table's columns and rows. Its associated themes allowed us to compare study results across various themes and subthemes.

Interpreting and mapping: Charts were utilised by the reviewers to map the breadth and nature of the phenomena and identify the ideas that had been identified. To assist make the results more understandable, our assessment looked at connections between the themes. According to the review's objectives and emergent themes, we mapped and evaluated the data.

Results

Figure (1) showed the selection and identification of studies. A total of 286 studies were found after searching the aforementioned databases, which were then used for title screening. 198 among these were included for the abstract review, it resulted in 52 articles being excluded. The full texts of the remaining 146 publications were examined. Due to differences in the research' objectives, 137 papers were excluded following the full-text revision and 7 were enrolled for final data extraction (Table 1). In Adeyemi et al. [14] study, 3.43/million recorded cases of iTTP were reported annually overall at this time, and 1.81/million of those cases were episodes. 86% of them got rituximab and 59% in addition to corticosteroids. 17% of patients experienced exacerbations, 11% relapsed, and 34% experienced any number of thromboembolic incidents. Over the study period, mortality rates were 14% (41/302) 25% for all patients with an iTTP diagnosis, as well as those who have experienced one or more iTTP episodes. However, in a study conducted by Page et al. [15], ten patients (13%) passed away, two before completing a plasma exchange (PEX) and complications during PEX were responsible for three of the deaths. PEX treatments were reduced necessary. Also few relapses happened for patients who presented after we started administering rituximab in certain individuals. In comparison with their first episodes, patients who had their first relapse had greater platelet counts, levels of lactic dehydrogenase, hematocrits, and required fewer PEX doses. According to Bayer et al. [16], 33 out of 564 individuals (about 6%), including 18 thrombotic thrombocytopenic purpura, 18 individuals with atypical hemolytic and uremic syndrome have thrombotic microangiopathies as its major pathologies. Within 531 out of 564 patients (94%), secondary thrombotic microangiopathies were
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Studies identified through database screening (n= 286)

Studies Identified from other sources (n=0)

Studies after duplicates removed (n= 198)

Studies screened (n= 198)

Studies excluded (n= 52)

Full studies assessed for eligibility (n =146)

Full studies excluded (n=137)

Studied included in the qualitative analysis (n=7)

Figure 1: The study designs
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Table 1: Author, country, year of publication, methodology and outcome.

<table>
<thead>
<tr>
<th>Author, Publishing Year</th>
<th>Objective &amp; Methodology</th>
<th>Outcomes</th>
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<tr>
<td>Adeyemi et al. 2022 [14].</td>
<td>To evaluate the illness burden, clinical outcomes, treatment trends, and epidemiology in iTTP patients in the US. From January 2007 to December 2019, individuals having iTTP diagnosis (defined as one or more iTTP episodes or one or more verified ADAMTS13 activity less than 10%) were included in this long-term, retrospective observational analysis using the Optum-Humedica database.</td>
<td>One or more iTTP episodes were present in 46% of the 666 individuals with iTTP diagnosis. 3.43/million recorded cases of iTTP were reported annually overall at this time, and 1.81/millions of those cases were episodes. The average number of therapeutic plasma exchange (TPE) sessions were administered to patients who have experienced one or more iTTP episodes, 86% of them also received corticosteroids and 59% rituximab. 17% of patients experienced exacerbations, 11% relapsed, and 34% experienced any number of thromboembolic incidents. Over the study period, mortality rates were 14% (41/302) for those who have experienced one or more iTTP episodes and 25% for everyone who has been diagnosed with iTTP. In a cluster study, older patients had longer iTTP episodes and died at higher rates than younger patients. Patients with iTTP run a very high risk of morbidity and death while receiving TPE and immunosuppressants, highlighting the need for more potent treatments.</td>
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<td>Page et al. 2017 [15].</td>
<td>To discuss fresh findings regarding the TTP diagnosis, patient clinical features, and results from the Oklahoma Thrombotic Thrombocytopenic Purpura (TTP) Registry experience. 78 studies supported the diagnosis of TTP individuals (21%) out of 363 patients with a first onset of clinically suspected TTP, 10% each by ADAMTS13 activity and clinical characteristics. Two techniques, immunoblotting and fluorescence resonance energy transfer (FRET), were used to assess ADAMTS13 activity in each of the 363 patients (IB). 60 Patients displayed ADAMTS13 activation below 10% using equally techniques, 15 patients had it below 10% using just FRET, and 3 patients had it below 10% using only IB. Five individuals received an alternate clinical diagnosis other than TTP when ADAMTS13 activity increased by 10% in one direction. Two patients who had recurrent relapses and the typical clinical signs of TTP originally exhibited Active ADAMTS13 above 10% by both tests. 95% had no or just minor changes in serum creatinine, while 47% of patients had no or little neurologic abnormalities. Ten patients (13%) passed away, two before completing a plasma exchange (PEX); complications during PEX were responsible for three of the deaths. PEX treatments were reduced necessary also few relapses happened for patients who presented after we started administering rituximab in certain individuals. In comparison with their first episodes, patients who had their first relapse had greater platelet counts, hematocrits, lactate dehydrogenase levels, and the quantity of PEX dosages required.</td>
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<td><strong>Bayer et al. 2019 [16].</strong></td>
<td>Thrombotic microangiopathies: Their etiology and prognosis. Retrospective research was conducted between 2009 and 2014, on 564 consecutive individuals with adjudicated thrombotic microangiopathies. Researchers calculated the prevalence concerning both primary and secondary thrombotic microangiopathies, the causes of thrombotic microangiopathies, and serious hospital outcomes, such as stroke, cognitive impairment, and epilepsy, as well as acute coronary syndrome and/or sudden heart failure and major cardiovascular events. 33 out of 564 individuals (about 6%), including 18 individuals with atypical hemolytic and uremic syndrome and patients with thrombotic thrombocytopenic purpura who had primary thrombotic microangiopathies. 94% of patients (531 out of 564) with secondary thrombotic microangiopathies were discovered. 500 out of 564 cases (or 88.65%) had a cause, which included pregnancy (35%), cancer (19%), infections (33%), medicines (26%), organ transplants (17%), autoimmune illnesses (9%), Shiga toxin produced by E. coli (6%), and hypertension that is cancerous (4%). There was a higher likelihood of several causes for secondary thrombotic microangiopathies than for original thrombotic microangiopathies (57% versus 19%). 84 of the 564 patients receiving hospital care had dialysis, 11% had significant cardiovascular events, and 4% suffered neurologic problems. 58 out of 564 patients (10%) passed away, however the mortality rates varied greatly depending on the origin of the thrombotic microangiopathies.</td>
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<td><strong>Pascual-Izquierdo et al. 2021 [17].</strong></td>
<td>Immune-mediated thrombotic thrombocytopenic purpura incidence, diagnosis, and prognosis. A cross-sectional survey of Spanish hospitals was conducted with a focus on iTTP patients under the age of 16 who had visited between 2015 and 2017 and those being followed up on prior to that time. Estimates were made for incidence, prevalence, mortality, resistance, exacerbations, and side effects from treatment, relapses, and consequences. Of the 203 occurrences recorded (138 patients with new diagnoses and 65 relapses), 193 (95.1%) were treated. The annual incidence was 2.67 cases per million people, while the annual prevalence was 21.44 patients per million people. Anti-ADAMTS13 autoantibody and ADAMTS13 activity were both assessed at the time of diagnosis in 97% and 84.3% of reported cases, respectively. The iTTP directly caused the deaths of 15 patients (7.4%), 6 of them passed away before obtaining any iTTP-specific care. 51 (26.4%) of the 193 treated episodes (or 31.1%) required at least one exacerbation, while 31 (16.1%) were resistant to plasma exchange and corticosteroids.</td>
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<td><strong>Lee et al. 2017 [19].</strong></td>
<td>Primary immune thrombocytopenia epidemiology and management: ITP patients were discovered using the database of the Korean Health Insurance Review and Assessment Service between July 2010 and June 2014. ITP was seen in 5.3 per 100,000 person-years overall. All ages, from infants to adults, and from females to men had overall incidence rate ratios of 3.8 and 1.3, respectively. 3388 patients, or 31% of the 10,814 total patients, required therapy for ITP; of these, 54% remained on medication for more than three months. In 42% of cases, corticosteroids (CS), immunoglobulin (IVIg), CS combined with IVIg, and other immunosuppressive drugs (ISA) made up the first-line of treatment. In 63% of patients after three months, CS alone was the most commonly utilised medication. Only 104 individuals had splenectomy, and after a median of one month following surgery, 51% of these patients got salvage therapy.</td>
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<td><strong>Ayoade Adeyemi et al. 2021 [19].</strong></td>
<td>This long-term retrospective observational analysis of the Optum-Humedica database included patients with aTTP diagnosis from October 2015 to December 2019 ADAMTS13 activities of 10% or at least one aTTP event must have been recorded in the database. Patients with illnesses that resemble aTTP were not included. Patients were followed up on until they lost touch, the study was over, or they passed away. 302 (45%) of the 666 individuals with aTTP diagnoses had only one episode. There were 1.81/million aTTP episodes every year, on average (based on data from 2016–2019). A mean of 16.7 TPE sessions were given to patients with 1 aTTP episode, and 59% of them utilised rituximab. Exacerbations occurred in 17% (52/302) of patients with 1 aTTP episode, whereas relapses happened in 11% (34/302). The mortality rate for all patients with aTTP diagnoses was 25% (167/666) and for patients with fewer than one episode, it was 14% (41/302). The substantial mortality and morbidity seen in this patient population, despite receiving TPE and immunosuppressants, underlines the need for more efficient therapy to enhance clinical outcomes.</td>
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<td><strong>de Louw et al. 2021 [20].</strong></td>
<td>This study analysed a huge, prospective cohort to ascertain the impact of time to first TPE, first-line rituximab use, and if mortality lowers over time, high-quality database (Marketscan) of TTP patients treated prior to caplacizumab between 2005 and 2014. 28.8% of the 1096 patients who were included in the study gotten TPE prior to day 2 in the ICU. Hospital mortality was 7.6%. (83 fatalities). The risk ratio [HR] for older age is 1.024 years old, a sepsis diagnosis (HR, 2.360), and the requirement intended for mechanical ventilation (HR, 4.103), all independently predicted mortality. TPE upon ICU admission (HR, 0.284), TPE one day following ICU hospitalisation (HR, 0.449), and early rituximab treatment (HR, 0.229) were factors that were independently linked with decreased mortality. TPE that was postponed resulted in dramatically greater expenditures. Thus, In TTP patients, early rituximab and immediate TPE are linked to increased survival.</td>
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discovered. 500 out of 564 cases (or 88.65%) had a cause, which included pregnancy (35%), cancer infections (33%) and (19%), pharmaceuticals (26%) and organ transplants (17%), autoimmune diseases (9%), E. coli's shiga toxin (6%), and, 4% have malignant hypertension. Compared to initial thrombotic microangiopathies, secondary thrombotic microangiopathies were more prevalent (57% versus 19%). 84 of the 564 patients receiving hospital care had dialysis, (11%) had significant cardiovascular events, and (4%), suffered neurologic problems. 58 out of 564 patients (10%) passed away, however the mortality rates varied greatly depending on the origin of the thrombotic microangiopathies. In Pascual-Izquierdo et al. [17] research of the 203 occurrences recorded (138 newly diagnosed cases and 65 relapses), 193 (95.1%) were treated. The annual incidence was 2.67 cases per million people, while the annual prevalence was 21.44 patients per million people. The iTTP directly caused the deaths of 15 patients (7.4%), 6 of whom passed away before obtaining any iTTP-specific care. 51 (26.4%) of the 193 treated episodes (or 31.1%) required at least one exacerbation, while 31 (16.1%) were resistant to plasma exchange and corticosteroids. The rest of results are detailed in (Table 1).

Discussion

Incidence of iTTP events was 1.81 per million in the US. The high levels of aggravation, relapse, death, and TE occasions showed the importance of early diagnosis, timely therapy, even more potent medications to improve clinical results in individuals with iTTP, despite the fact that very severe incidents were treated having TPE and immunosuppression. Additionally, individuals with iTTP had more comorbidities than iTTP-free control cohort, which indicated a heavy burden of illness. According to statistics from 2010, 40% of patients may experience a recurrence within 7.5 years of their original iTTP event. Patients suffering one or more iTTP episodes have a persistent unmet need for prevention of recurrence. The literature reports that 8%–20% for individuals receiving TPE combined with immunosuppression is similar with the observed death incidence 14% of patients who have experienced one or more iTTP episodes. More recently, patients getting the most recent typical of care recommendations combining caplacizumab, TPE, and immunosuppression have been shown to have survival rates of above 95% [14, 21-23]. Corticosteroids are now a common kind of therapy because it is now known that acquired TTP is an autoimmune condition. Rituximab has been used to offer further immunosuppression since 2002. In 2003, physicians started using rituximab to treat TTP exacerbations and the first few cases of relapse [26]. Since physicians started using rituximab for these purposes, the frequency of recurrence has dropped, despite the fact that the rates of severe neurologic abnormalities, exacerbations, and mortality have remained constant. Some researchers have suggested using rituximab as a standard first-line therapy together with PEX and corticosteroids [15, 24-27]. The three forms of TMAs—The HUS, TTP, and caused by the Shiga toxin from E. coli—represent around 10% of TMAs in adulthood. Importantly, the choice of patients has a significant impact on the assessment of the proportional roles of main and also second. According to a recent study based on thrombocytopenia patients' plasma samples were forwarded to an establishment of national reference, the ADMTS13 test, for the vast majority of TMA patients TTP (38%) and E. coli Shiga toxin (11.5%), as well as aHUS -induced HUS (3.5%) [16, 22]. A study found that older patients who had iTTP had a higher death rate than younger patients, indicating that iTTP might place a heavier and worsening illness age-related load on patients who may also have other unrelated underlying comorbid disorders. An Italian registry research found that older patients with iTTP had a higher rate due to multimorbidity and polypharmacy than age-matched people without iTTP. Additionally, in line due to our cluster analysis, a French research reported that elderly patients had higher rates compared to younger patients where they exhibited increased short- and long-term death rates. They were more likely to be using antihypertensive medication and presented with more comorbidities. These results demonstrate the necessity for further vigilance while treating older people [14, 28, 29]. In Bayer et al. [16] study, most of the patients had secondary TMAs when they first showed up. The most common cause of TMA was pregnancy-related, and the majority of these individuals experienced HELLP. In another research, lower numbers were reported, but the researchers did not take into account cohorts of patients that received care over time. Infections, particularly those brought on by a variety of bacteria, viruses, and parasites, were the other major contributor of secondary TMA. Adenocarcinoma was the most common cancer among patients with malignancy-associated TMA. Leukaemia, like lymphomas, this agrees with additional evidence. Another often occurring cause of TMA was cancer. Mucin is produced by
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adenocarcinoma cells, and mucin may have an impact on vWF synthesis. It's also feasible that metastatic microemboli have a harmful effect on the microvessels [16, 30, 25].

Conclusion
Older patients had longer iTTP episodes and died at higher rates than younger patients. People that have iTTP carry a considerable risk of morbidity and mortality while receiving TPE and immunosuppressants, highlighting the need for more potent treatments. Secondary and primary thrombotic microangiopathies were more prevalent than thrombotic microangiopathies in general. Depending on the origin of thrombotic microangiopathies, there are different risks associated with dialysis, neurologic and cardiac issues, and mortality. Mortality rates are low for patients who received hospital care with low rate of complications.

Conflict of Interest
None

Funding
None

References


