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A Descriptive 5-Year Analysis of the Demographics and Therapies for Patients With Immune Thrombotic Thrombocytopenic Purpura in the USA: A Multicenter Study of 390 Disease Episodes From 2017 to 2021

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ABSTRACT

Immune thrombotic thrombocytopenic purpura (iTTP) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular occlusion secondary to acquired ADAMTS13 deficiency. Contemporary data regarding iTTP treatment practices in the US, including the use of caplacizumab, are lacking. We aimed to characterize the demographics and therapies, including medications and apheresis practices, in patients with iTTP in the US. We retrospectively analyzed iTTP cases at 15 sites in the US that provide comprehensive care for patients with iTTP. The time-period assessed was from January 1, 2017 to

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December 31, 2021. Our primary objective was to analyze data by iTTP episode, inclusive of initial episodes and relapses. A total of 390 iTTP episodes were reported for 280 unique individuals (187 females, 93 males). Thirty-day mortality was 3.7% (14/374), and 6-month mortality was 7.4% (27/367). TPE details were reported for 343 episodes, among which 261 underwent at least one procedure (median 6, IQR 3–11). Among the 261 episodes with at least one therapeutic plasma exchange (TPE) performed, 82.0% (214/261) used only plasma. Caplacizumab was used either alone or in combination with other agents in 43 (11.0%) episodes. Management strategies for iTTP remain varied across centers in the US, with a variety of combinations for TPE replacement fluids and therapeutic agents, as well as limited use of caplacizumab. Further research and standardization of treatment regimens may further reduce mortality in this condition.

1 | Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare hematologic disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular occlusion [1–4]. The etiology of TTP is a deficiency in a disintegrin-like metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), a zinc-containing metalloprotease enzyme responsible for cleaving von Willebrand factor (VWF) [5]. This deficiency in ADAMTS13 is most commonly acquired due to autoantibodies that inhibit its function or clear it from circulation (i.e., immune TTP, iTTP) [5–7], while a minority of cases are due to homozygous or compound heterozygous mutations in the *ADAMTS13* gene that result in markedly reduced protein production and/or function (i.e., congenital TTP, cTTP) [8, 9]. Without ADAMTS13, ultra-large VWF multimers accumulate and bind platelet glycoproteins with high affinity, specifically via the A1 domain, forming microthrombi in small vessels and capillaries with subsequent end-organ damage [5, 10, 11].

Without prompt therapy, the fatality rate in patients with iTTP exceeds 90% [12]. However, the use of therapeutic plasma exchange (TPE) and immunosuppressive therapies (e.g., corticosteroids, rituximab) has substantially decreased the mortality rate, though it remains high (i.e., up to, and potentially exceeding 10%, depending on the study) [5, 13, 14]. Further, the disorder is associated with significant morbidity and relapses [12]. Given these considerations, research into new therapies is ongoing. Rituximab, a humanized anti-CD20 monoclonal antibody, has demonstrated the ability to decrease the time to remission in patients with acute iTTP episodes and reduce the risk of relapse in patients who are in remission [15, 16]. While rituximab does not carry U.S. Food & Drug Administration (FDA) approval for use in iTTP, it has been used off-label with increasing frequency since 2002 [15]. In addition to rituximab, caplacizumab has recently been incorporated into treatment regimens. Caplacizumab is a novel agent that was approved in Europe in September 2018 and by the U.S. Food & Drug Administration (FDA) in February 2019 [17–19]. Caplacizumab is a nanobody (i.e., a small, single-domain antibody fragment) that targets the von Willebrand factor (VWF) A1 domain [18], which inhibits the interaction between VWF and platelets by preventing the binding of the VWF to the platelet glycoprotein Ib-IX-V receptor. With the implementation of these therapeutics, the management of iTTP is shifting to attempt to achieve optimal outcomes in this population [20].

Given the rarity of iTTP, with an approximate annual prevalence of 10 cases per one million persons and an annual incidence of approximately 1 case per million [5, 21], advancing our understanding of the disease requires large registries. Country-wide registries have contributed significantly to these efforts [7, 22–27]; however, given potential differences in patient demographics and treatment patterns, international registries may not represent US-specific practices. Prior studies have highlighted heterogeneity in iTTP treatment practices in the US [28–30], including an analysis of electronic health records between October 2015 and December 2019, which attempted to report the national epidemiology and treatment patterns [28]. However, that study included patients if they had either one or more documented ADAMTS13 test results less than 10% or one or more documented iTTP episodes using International Classification of Diseases (ICD) diagnosis of TMA. Thus, it was limited by the challenges associated with medical coding. Further, most of the study period preceded the introduction of caplacizumab. Therefore, we aimed to assess epidemiological details, patient demographics, treatment patterns, and outcomes using laboratory- and clinically proven cases of iTTP in the US, inclusive of the time period of caplacizumab approval.

2 | Methods

We retrospectively analyzed iTTP cases at 15 sites in the US that provide comprehensive care for patients with iTTP. These data represent a subset analysis of a larger, international cohort, which was previously published [31]. The time period assessed was from January 1, 2017, to December 31, 2021. We defined iTTP as a thrombotic microangiopathy (TMA) associated with an ADAMTS13 activity level $< 10\%$ with or without the presence of an inhibitor [32]. If ADAMTS13 antibodies were not detected, ADAMTS13 activity must have recovered during follow-up (without the use of prophylactic/maintenance plasma transfusion) to exclude cTTP. Patients with hemolytic uremic syndrome, drug-induced TMA, or TMA in the setting of sepsis, HIV, pregnancy, malignancy, or hematopoietic stem cell transplantation were excluded. We considered both initial and relapsed presentations of iTTP. Relapse was defined as one of the following occurring ≥ 30 days after the prior episode: (1) repeated detection of an ADAMTS13 inhibitor with an ADAMTS13 level $< 10\%$ or (2) a decrease in platelet count below the lower limit of the normal reference range at each respective site. Our primary objective was to analyze data by iTTP episode; therefore, a single patient may be represented more than once in the analysis.

For each iTTP episode, we collected the following data, where available: episode type (initial vs. relapse); patient sex, age, race, and ABO blood type; the number of TPE procedures performed; the type(s) of TPE replacement fluid and type(s) of plasma used; the immunomodulatory agent(s) used (e.g., rituximab, corticosteroids); whether caplacizumab was used; the presence/absence of immunization within 30 days prior to the diagnosis of an iTTP episode; COVID-19 diagnosis within 30 days prior to the diagnosis of an iTTP episode; and mortality at 30 days and 6 months. The geographic location of each iTTP episode was categorized into one of the four US Census Bureau geographic regions (Northeast, Midwest, South, West) [33].

All participating sites' institutional review boards approved this study for their respective patients. The institutional review board at the University of Texas Southwestern Medical Center approved the collection, management, and hosting of study data using Research Electronic Data Capture as part of a larger study cohort [31]. Statistical analysis was performed using Prism version 10.3.0 (GraphPad Software, La Jolla, CA, USA). Means and standard deviations were reported for normally distributed data, and medians and interquartile range (IQR) were reported for non-normally distributed data. Differences in means were assessed with two-sided *t*-tests. Chi-square tests were used to compare observed versus expected proportions.

3 | Results

3.1 | All iTTP Episodes

A total of 390 iTTP episodes were reported for 280 unique individuals (187 females, 93 males) at 15 sites in the US (Table 1, Figure 1). Among these 390 episodes, 141 (36.2%) were initial episodes, 195 (50.0%) were relapses, and 54 (13.8%) were unknown or not reported. Among the 390 episodes, females comprised 251 (64.4%) cases while males accounted for 139 (35.6%). Age was reported for 386 episodes (median 47 years, IQR 36–61 years). Race was reported for 383 (98.2%) iTTP episodes; most occurred in Black individuals (61.0%, 238/390).

TPE details were reported for 343 episodes; of these, 261 episodes received at least one procedure (median 6, IQR 3–11). Among the 261 episodes with at least one TPE performed, all used plasma either alone or in combination with another replacement fluid. The majority of iTTP episodes only utilized plasma ($n = 214$, 82.0%) for TPE, while 35 (13.4%) episodes used a combination of plasma and 5% albumin, 7 (2.7%) used plasma and normal saline, and 5 (1.9%) plasma, albumin, and normal saline (Table 2). Regarding the type of plasma, 227 (87.0%) episodes used only fresh frozen plasma/plasma frozen within 24 h after phlebotomy (FFP/PF24); 24 (9.2%) used only solvent/detergent-treated pooled plasma (i.e., Octaplas; Octapharma, NJ); four (1.5%) used a combination of FFP/PF24 and Octaplas; four (1.5%) used cryoprecipitate-reduced plasma (i.e., cryoprecipitate-poor plasma, CPP) only; one (0.4%) used a combination of FFP/PF24 and CPP; and one (0.4%) episode did not report the type of plasma used.

TABLE 1 | Demographics of 390 iTTP episodes.

Variable	Median (IQR) or no. (%)
Patient age	47 years (36–61 years)
Patient sex	
Female	251 (64.4%)
Male	139 (35.6%)
Patient race	
Black	238 (61.0%)
White	117 (30.0%)
Other or mixed race	14 (3.6%)
Asian	7 (1.8%)
AI/AN	5 (1.3%)
Pacific Islander	2 (0.5%)
Unknown/NR	7 (1.8%)
Patient ABO type	
O	139 (35.6%)
A	101 (25.9%)
B	66 (16.9%)
AB	18 (4.6%)
Unknown/NR	66 (16.9%)
Episode type	
Initial	141 (36.2%)
Relapse	195 (50.0%)
Unknown/NR	54 (13.8%)
Episode location*	
Northeast	37 (9.5%)
South	192 (49.2%)
Midwest	121 (31.0%)
West	40 (10.3%)
Year of episode	
2017	74 (19.0%)
2018	82 (21.0%)
2019	70 (17.9%)
2020	98 (25.1%)
2021	66 (16.9%)

Abbreviations: AI/AN, American Indian/Alaskan Native; IQR, interquartile range; NR, not reported.
*Based on US Census Regions (https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf).

Of the 390 total iTTP episodes, 253 episodes specified the use of at least one therapeutic agent, 94 episodes did not clearly indicate whether any agents were used, and 43 episodes explicitly reported no therapeutic agent usage. Among the 253 episodes

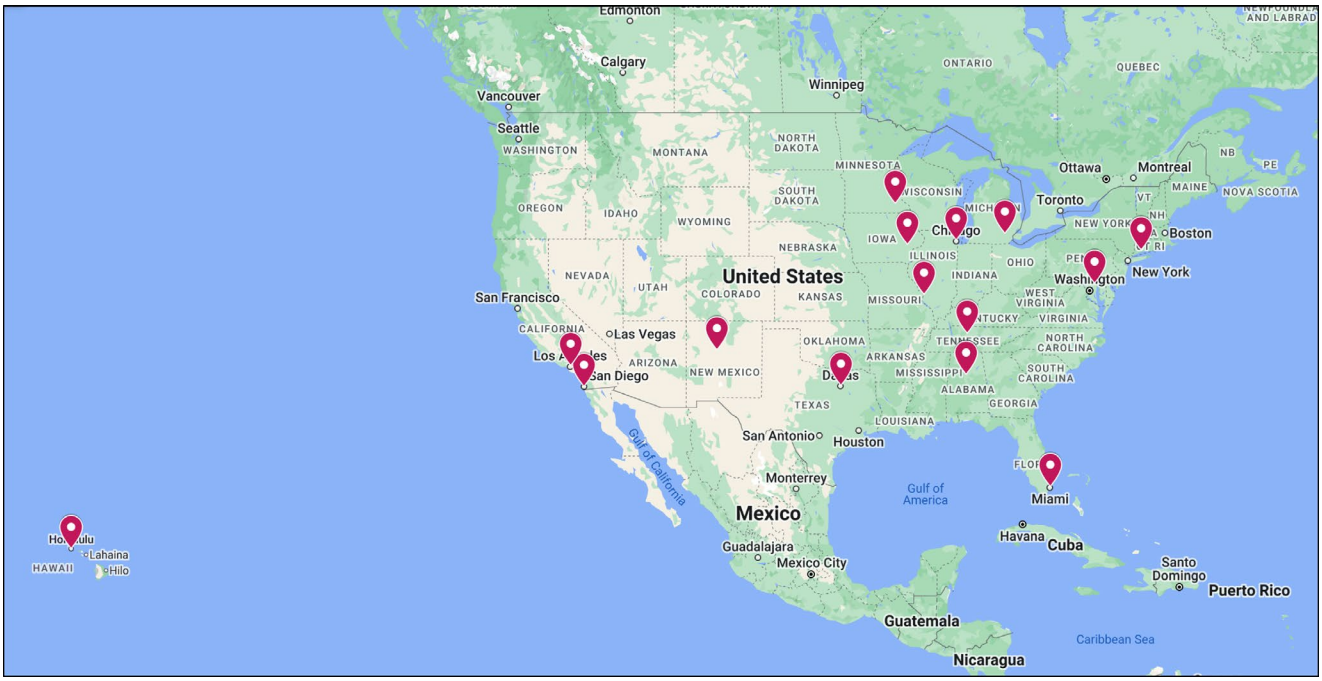

FIGURE 1 | Geographic distribution of study sites ($n = 15$).

TABLE 2 | Therapeutic plasma exchange details.

Variable	Median (IQR) or no. (%)
TPE procedures among iTTP episodes for which it was known if TPE was performed ($n = 333$ iTTP episodes)	6 (IQR 3–11)
Number of TPE procedures ($n = 390$ iTTP episodes)	
0	72 (18.5%)
> 0	261 (66.9%)
1–5	64 (24.5%)
6–10	111 (42.5%)
11–15	37 (14.2%)
16–20	23 (8.8%)
> 20	26 (9.9%)
Unknown/NR	57 (14.6%)
TPE composition ($n = 261$ iTTP episodes)	
Plasma only	214 (82.0%)
Plasma/albumin	35 (13.4%)
Plasma/normal saline	7 (2.7%)
Plasma/albumin/normal saline	5 (1.9%)
Type of plasma used ($n = 261$ iTTP episodes)	
FFP/PF24 only	227 (87.0%)
S/D plasma only	24 (9.2%)
FFP/PF24 and S/D plasma	4 (1.5%)
CPP only	4 (1.5%)
FFP/PF24 and CPP	1 (0.4%)
Unknown/NR	1 (0.4%)

Abbreviations: CPP, cryoprecipitate-poor plasma; FFP, fresh frozen plasma; IQR, interquartile range; iTTP, immune thrombotic thrombocytopenic purpura; NR, not reported; PF24, plasma frozen within 24 h after phlebotomy; S/D, solvent/detergent treated pooled human plasma (Octapharma, NJ, USA); TPE, therapeutic plasma exchange.

that documented at least one therapeutic agent, a total of eight unique agents were administered in 18 different combinations across 246 episodes (Figure 2). The remaining seven episodes documented the use of caplacizumab, but it was unclear whether additional agents were administered. The most frequently used treatment strategy was a combination of corticosteroids and rituximab ($n = 140$ episodes, 35.9%), while corticosteroids alone were used in 47 (12.1%) episodes.

Caplacizumab was used either alone or in combination with other agents in 43 (11.0%) episodes. Caplacizumab was used in at least one episode of iTTP at 73.3% (11/15) of sites, was not used at all at 20.0% (3/15) of sites, and 6.7% (1/15) of sites did not report whether it was used. A total of 225 episodes occurred following caplacizumab approval in the US; 191 of these reported if caplacizumab was used. Among these, 22.5% (43/191) of episodes used caplacizumab and 77.5% (148/191) did not use caplacizumab. Recipient race was available for 189 of the 191 episodes in which caplacizumab use was reported. Caplacizumab was given to a greater proportion of White individuals with iTTP compared to non-White individuals, although this difference was not statistically significant (26.5%, 13/49 vs. 21.4%, 30/140; $p = 0.55$). Temporal analysis of episodes in which it was known whether caplacizumab was used revealed that caplacizumab was given in 17.2% (10/58) of those that occurred during the first year of approval (February 2019–January 2020), 24.4% (21/86) during the second year (February 2020–January 2021), and 25.5% (12/47) in the most recent year (February 2021–December 2021). Caplacizumab was used alone without immunosuppressive agents or TPE in one relapsed episode.

Among all iTTP episodes, 30-day and 6-month mortality data were reported for 374 and 367 episodes, respectively. Overall, the 30-day mortality was 3.7% (14/374), and the 6-month mortality was 7.4% (27/367), though the specific cause of death was not reported. The results of 30-day and 6-month mortality data by sex, age, race, ABO type, geographic region, and year of iTTP episode are displayed in Table 3. 30-day and 6-month mortality data were available for 154 episodes and 149 episodes prior to caplacizumab approval, respectively: 30-day mortality was 3.2% (5/154) and 6-month mortality was 5.4% (8/149). Following caplacizumab approval, 30-day mortality data were available for 189 of the 191 episodes in which it was reported whether caplacizumab was administered. Among these, the 30-day mortality for episodes that received caplacizumab was 0.0% (0/43) compared with 6.2% (9/146) of episodes that did not receive caplacizumab. Six-month mortality data were available for 187 episodes in which it was reported whether caplacizumab was used following its approval: 0.0% (0/41) in episodes that used caplacizumab and 12.3% (18/146) in episodes that did not.

3.2 | Initial iTTP Episodes

A total of 141 initial episodes of iTTP were reported. The number of TPEs performed was reported for 133 episodes, with a median of 8 (6–14). The therapeutic agents utilized were reported for 87.9% (124/141) of initial iTTP episodes, and the majority used corticosteroids and rituximab (49.6%, 70/141), corticosteroids only (16.3%, 23/141), or caplacizumab, corticosteroids, and rituximab (12.1%, 17/141) (Figure 3).

Among the 141 initial iTTP episodes, 30-day mortality was reported for 138 episodes and 6-month mortality was reported for 135 episodes: 30-day mortality was 7.2% (10/138) and 6-month mortality was 8.9% (12/135).

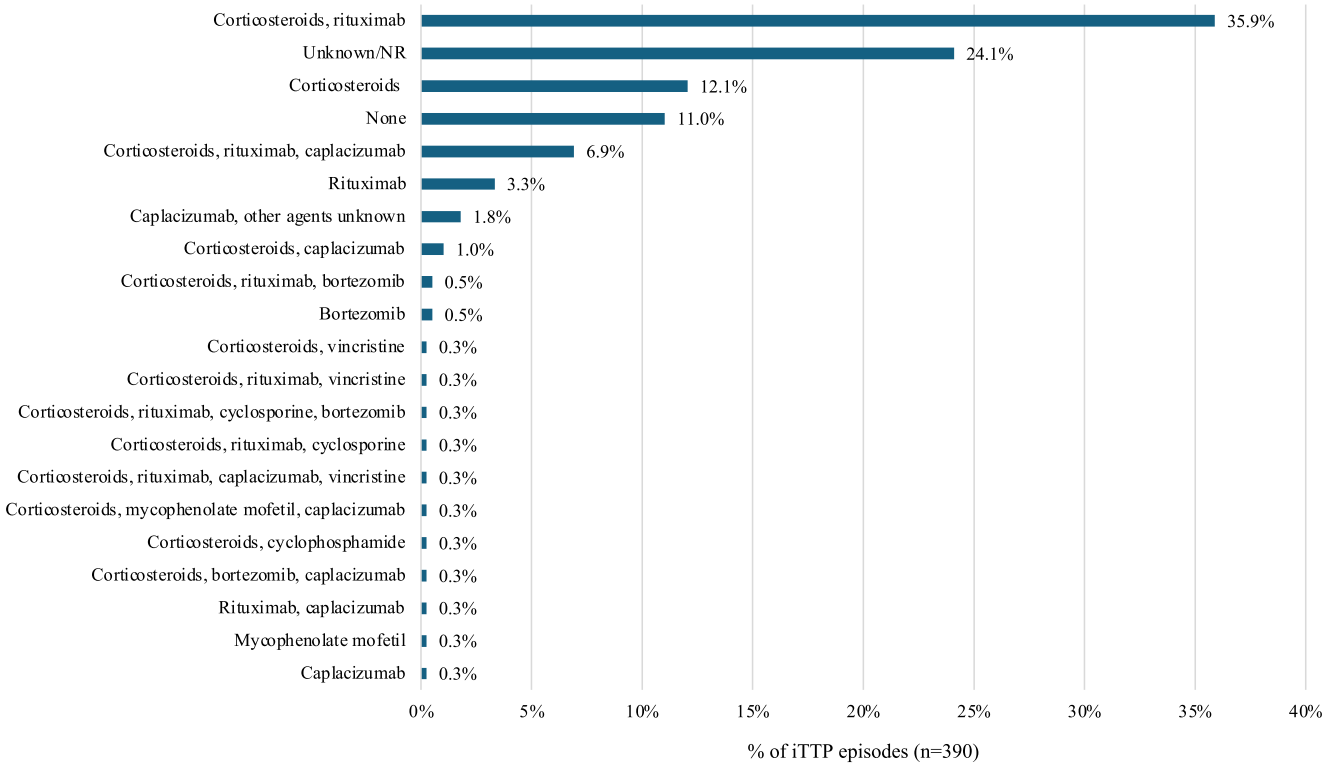

FIGURE 2 | Therapies employed in the 390 iTTP episodes not including therapeutic plasma exchange. NR, not reported.

TABLE 3 | 30-day and 6-month mortality by demographics among iTTP episodes.

Variable	30-day mortality	6-month mortality
Sex		
Male	9/133 (6.8%)	17/131 (13.0%)
Female	5/241 (2.1%)	10/236 (4.2%)
Age (median)	47 years (alive)	45.5 years (alive)
	56.5 years (deceased)	63 years (deceased)
Race		
Black	5/232 (2.2%)	15/226 (6.6%)
White	7/114 (6.1%)	8/113 (7.1%)
Non-White/non-Black	2/26 (7.7%)	3/26 (11.5%)
Patient ABO type		
O	6/136 (4.4%)	11/133 (8.3%)
A	5/94 (5.3%)	7/93 (7.5%)
B	3/65 (4.6%)	8/63 (12.7%)
AB	0/18 (0.0%)	0/17 (0.0%)
Region*		
Midwest	1/113 (0.9%)	5/113 (4.4%)
Northeast	1/37 (2.7%)	2/36 (5.6%)
South	5/185 (2.7%)	13/181 (7.2%)
West	7/39 (17.9%)	7/37 (18.9%)
Year		
2017	2/70 (2.9%)	4/68 (5.9%)
2018	3/77 (3.9%)	4/74 (5.4%)
2019	1/68 (1.5%)	3/68 (4.4%)
2020	6/97 (6.2%)	13/95 (13.7%)
2021	2/62 (3.2%)	3/62 (4.8%)

*By US Census Bureau geographic regions. Note that cases where the demographic variable was not reported or unknown, or where the outcome was unknown, were excluded from the analysis.

3.3 | Relapsed iTTP Episodes

A total of 195 relapsed episodes of iTTP were reported. The number of TPEs performed was available for 192 episodes, with a median of 6 (0–9). Various therapeutic agents were used, with a combination of corticosteroids and rituximab being the most common ($n = 70$ episodes) (Figure 4).

Among the 195 relapsed iTTP episodes, 30-day mortality was reported for 187 episodes and 6-month mortality was reported for 183 episodes: 30-day mortality was 1.6% (3/187) and 6-month mortality was 7.1% (13/183).

3.4 | Additional Data

The presence/absence of immunizations within 30 days prior to the diagnosis of an iTTP episode was available for 232 episodes—5.2% (12/232) were preceded by an immunization—including 6 (2.6%) episodes with a SARS-CoV-2 vaccine (mRNA vaccine, $n = 5$; adenovirus vector vaccine, $n = 1$). Four additional episodes occurred in individuals who were diagnosed with COVID-19 within 30 days of presentation.

4 | Discussion

This study found that management of iTTP episodes varies across centers in the US. The etiology of this variability is likely multifactorial and may include differences in disease severity (e.g., necessitating use of various immunosuppressive agents), practical aspects (e.g., use of solvent-detergent plasma to mitigate allergic transfusion reactions, blood shortages and supply-chain constraints limiting use of particular replacement fluids), and financial considerations [34–36]. However, it demonstrates that therapeutic strategies have not yet been standardized.

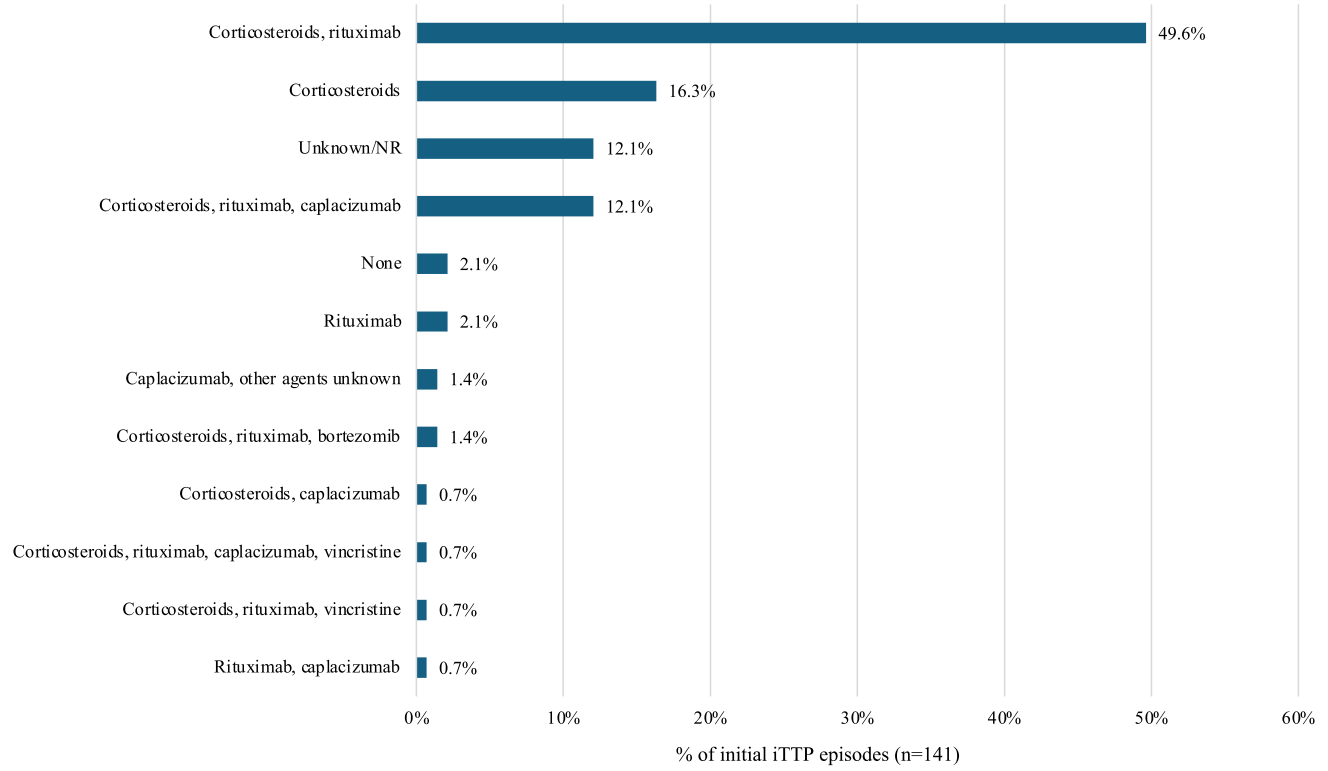

FIGURE 3 | Therapies employed in the 141 initial iTTP episodes not including therapeutic plasma exchange. NR, not reported.

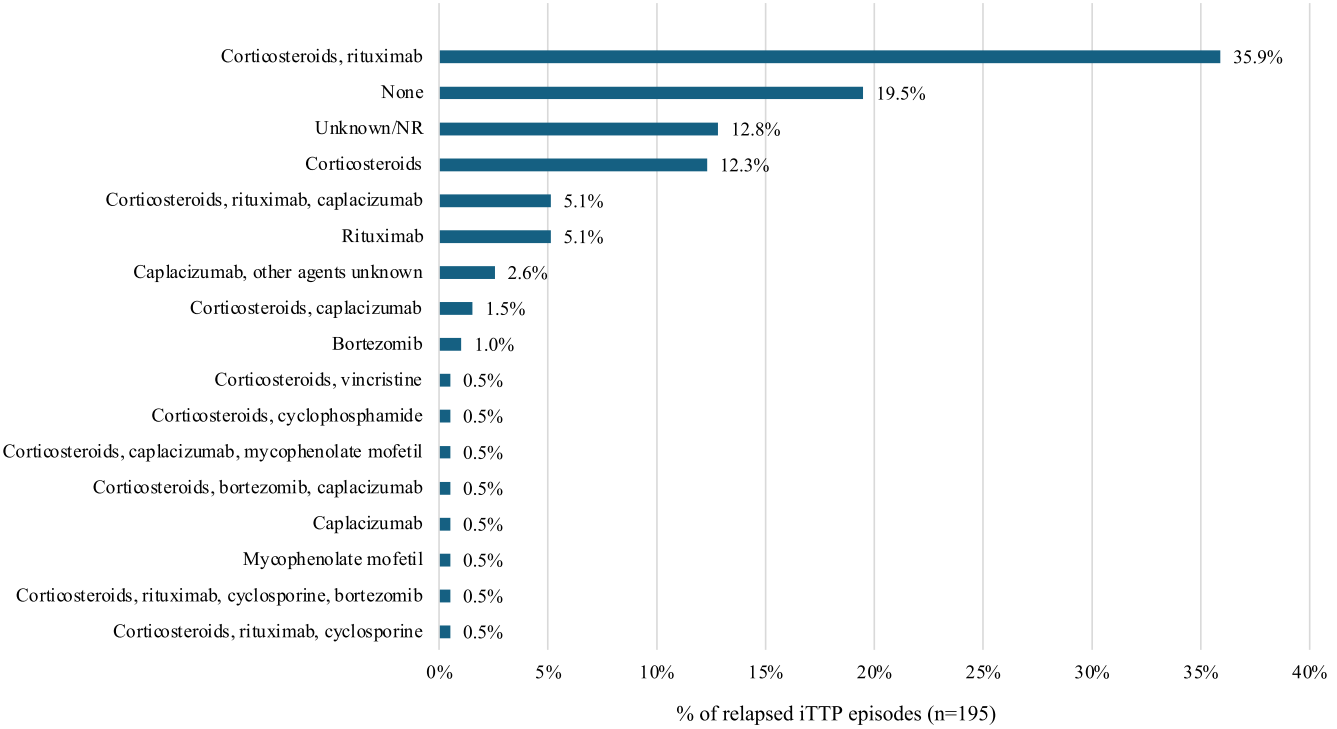

FIGURE 4 | Therapies employed in the 195 relapsed iTTP episodes not including therapeutic plasma exchange. NR, not reported.

Instead, institutions, and even individual providers at the same location, may differ in their treatment algorithms, including which combination of agents is used for initial episodes, if caplacizumab is used, and therapeutic apheresis variables such as replacement fluid.

These findings parallel a prior study that assessed treatment patterns and outcomes in patients with iTTP in the US from October 2015 to December 2019 [28]. That study relied in part on ICD data to identify patients and therefore is subject to the limitations and potential inaccuracies inherent to medical coding.

However, the authors discovered variabilities in treatment practices and significant mortality. We show that this variability in practice remains, and we extend these findings to highlight variability in apheresis practices more specifically.

One notable finding from our analysis that builds on this prior study was the infrequent incorporation of caplacizumab into therapeutic regimens, as it was used in less than a quarter of iTTP episodes that occurred following US FDA approval. However, we acknowledge that the International Society on Thrombosis and Hemostasis (ISTH) guidelines for the treatment of iTTP, which make a conditional recommendation for using caplacizumab over not using it, were published in 2020, toward the end of our study period [20]. Caplacizumab has been shown to reduce the time to platelet count normalization, plasma usage, hospitalization time, iTTP recurrence, and mortality [37–39]. Despite its limited use, we also found that both 30-day and 6-month mortality were lower among episodes in which caplacizumab was incorporated (i.e., zero deaths) compared to episodes in which it was not used.

In addition to the use of caplacizumab, we observed another discrepancy with recommended treatment algorithms. In 47 episodes, corticosteroids were used without concomitant rituximab, despite the ISTH guidelines suggesting the addition of rituximab to corticosteroids for both initial and relapsed episodes [20]. While this was a conditional recommendation, rituximab may reduce relapses and may be particularly beneficial in patients who have previously relapsed [16, 19, 20].

We also observed some notable epidemiological trends in our dataset. For example, Black individuals were overrepresented among iTTP episodes compared to their population composition in the US. This finding is similar to studies from various iTTP registries wherein individuals identifying as Black or Caribbean are overrepresented [7, 40–42]. However, both 30-day and 6-month mortality was lower among iTTP episodes that occurred in Black individuals compared to White individuals and non-Black/non-White individuals, a finding that has also been reported previously [43]. We also observed that following caplacizumab approval, a greater proportion of iTTP episodes in White patients included caplacizumab compared to the proportion of iTTP episodes that occurred in non-White patients, though this finding was not statistically significant, perhaps owing to the overall low use of caplacizumab. Nevertheless, this finding highlights the importance of ensuring that the availability of therapies is equitable irrespective of demographic factors.

It is important to note that this dataset, while one of the largest compilations of iTTP episodes and related treatment practices in the US, is derived from 15 centers that provide comprehensive care to patients with iTTP. The treatment practices at these centers may not necessarily reflect the diversity of practices at other centers in the US, particularly those in more rural regions and/or centers with limited access to therapies that might be financially prohibitive. This is especially true for caplacizumab, wherein the cost per dose is $7700 and $270 000 for an average therapy course [44]. In addition to financial considerations for medications, the availability of ADAMTS13 testing and apheresis and/or blood product availability may influence practices. Thus, standardization of treatment protocols across the US would require investment into ensuring that diagnostic testing, therapeutic agents, apheresis capabilities, and a sustainable blood supply are available. Given that the availability of these services, inclusive of staffing, physical space, and logistical support, are themselves variable across the country [45], this standardization represents a formidable challenge.

We recognize limitations to this study. We included iTTP episodes through December 31, 2021. As such, we cannot exclude the possibility that practices have subsequently become more standardized. Nevertheless, our study included data for 35 months following US FDA approval of caplacizumab, with only 25% of episodes in the most recent year reporting caplacizumab use. As such, additional studies to assess the uptake (and challenges hindering the uptake) of this agent, as well as other therapeutic considerations (e.g., tapering of TPE, rituximab prophylaxis to prevent clinical relapse) would be valuable. Further, we did not capture data regarding the use of recombinant ADAMTS13, which received FDA approval for patients with cTTP in 2023 and is not yet approved for patients with iTTP [46]. Additionally, while we did not intentionally exclude them, our data set did not include pediatric patients. Finally, not all data were available for a subset of patients in this study, reflecting one of the limitations and challenges with relying on longitudinal, multi-center studies.

In conclusion, this 5-year retrospective multi-center analysis demonstrates ongoing variability in treatment regimens for patients with iTTP. It illustrates that the incorporation of caplacizumab into therapeutic algorithms was slow, highlighting the need for additional studies to determine the causes and solutions given its evidence-based benefit. Further, we found that mortality remains significant, even for patients treated at advanced tertiary care centers in the US, underscoring the need for ongoing research into improved recognition and treatment of patients with iTTP.

Disclosure

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Ethics Statement

This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board and all of the participating sites' review boards.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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