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RESEARCH ARTICLE

The seasonal distribution of immune thrombotic thrombocytopenic purpura is influenced by geography: Epidemiologic findings from a multi-center analysis of 719 disease episodes

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Abstract

Prior studies have suggested that immune thrombotic thrombocytopenic purpura (iTTP) may display seasonal variation; however, methodologic limitations and sample sizes have diminished the ability to perform a rigorous assessment. This 5-year

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retrospective study assessed the epidemiology of iTTP and determined whether it displays a seasonal pattern. Patients with both initial and relapsed iTTP (defined as a disintegrin and metalloprotease with thrombospondin type motifs 13 activity <10%) from 24 tertiary centers in Australia, Canada, France, Greece, Italy, Spain, and the US were included. Seasons were defined as: Northern Hemisphere—winter (December–February); spring (March–May); summer (June–August); autumn (September–November) and Southern Hemisphere—winter (June–August); spring (September–November); summer (December–February); autumn (March–May). Additional outcomes included the mean temperature in months with and without an iTTP episode at each site. A total of 583 patients experienced 719 iTTP episodes. The observed proportion of iTTP episodes during the winter was significantly greater than expected if equally distributed across seasons (28.5%, 205/719, 25.3%–31.9%; $p = .03$). Distance from the equator and mean temperature deviation both positively correlated with the proportion of iTTP episodes during winter. Acute iTTP episodes were associated with the winter season and colder temperatures, with a second peak during summer. Occurrence during winter was most pronounced at sites further from the equator and/or with greater annual temperature deviations. Understanding the etiologies underlying seasonal patterns of disease may assist in discovery and development of future preventative therapies and inform models for resource utilization.

1 | INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare hematologic disorder characterized by a thrombotic microangiopathy (TMA) and a severe deficiency of a disintegrin and metalloprotease with thrombospondin type motifs 13 (ADAMTS13). Most cases of TTP are due to an autoantibody against ADAMTS13 (i.e., immune TTP, iTTP), though 2%–10% of cases occur because of homozygous or compound heterozygous mutations in the *ADAMTS13* gene resulting in the absence of the protein.[1–3] ADAMTS13 is an enzyme that cleaves ultra-large von Willebrand factor (ULVWF) multimers involved in platelet adhesion and aggregation at sites of endothelial injury into smaller components.[4] In the absence of sufficient ADAMTS13 activity, these ultra-large von Willebrand factor multimers accumulate, resulting in microvascular thrombosis, regional ischemia, and end-organ damage. As iTTP is associated with significant morbidity and mortality, rapid diagnosis is essential for appropriate and timely management.[5,6] However, diagnostic challenges persist given the variably progressive nature of the condition and the multitude of signs and symptoms. Availability of ADAMTS13 activity testing to confirm the clinical suspicion of iTTP is also variable. If iTTP is clinically suspected, there should be a low threshold to initiate treatment.[7–9]

While iTTP is often idiopathic, various inciting events (e.g., infections and pregnancy) have been reported.[10] Seasonal variation in iTTP incidence has also been suggested, with prior groups hypothesizing that seasonal infectious disease patterns may influence iTTP epidemiology.[11–13] Ten previous studies have attempted to ascertain whether iTTP displays seasonality, though there is significant methodologic heterogeneity among these studies, and the findings have been inconclusive.[11–20] For example, among the 10 studies, three did not assess ADAMTS13 activity levels,[11,14,16] and a fourth used an ADAMTS13 activity threshold of <5% (vs. <10%) for their inclusion criteria.[17] Among the six studies that did use an ADAMTS13 activity level <10% to define their population, one only assessed initial iTTP presentations.[15] Only one of the five remaining studies found a significant seasonal association, with more cases in the winter.[18] Among the other four, no significant association was observed, though one demonstrated a trend for more cases in the summer,[12] one showed a trend for more cases in autumn,[19] and one found that cases tended to occur later in the year (i.e., in autumn/winter).[20] Two United States (US)-based studies that utilized International Classification of Diseases, ninth edition codes obtained from the National Inpatient Sample database were also unable to demonstrate statistically significant seasonal differences.[14,16] However, one did observe that after stratifying cases based on geographic regions, a significant monthly variation was noted in the Midwestern region, with peak incidence in July, which was significantly higher than the lowest incidence noted in November.[16]

Ultimately, the limitations of these 10 prior studies, including their small sample sizes, differences in how they defined iTTP and their inclusion criteria, restriction to single institutions with limited climate variability, and/or potential biases due to the shortcomings of medical coding, have resulted in inconclusive findings regarding any potential seasonal association with iTTP. Therefore, we investigated the seasonal epidemiology of iTTP among a large international cohort of laboratory-confirmed cases from multiple geographic regions with differing climates.

2 | METHODS

We performed a retrospective analysis of iTTP cases from 24 sites that provide comprehensive care for patients with iTTP in Australia, Canada, France, Greece, Italy, Spain, and the US over a 5-year period (January 1, 2017–December 31, 2021) (Figure S1). For the purposes of this study, iTTP was defined as a TMA associated with an ADAMTS13 activity level <10% with or without the presence of an inhibitor based on the American Society for Apheresis guidelines.[21] In patients without detectable ADAMTS13 antibodies, at least partial recovery of ADAMTS13 activity during follow-up (without the use of prophylactic/maintenance plasma transfusion) was required to exclude congenital TTP. Patients with hemolytic-uremic syndrome, drug-induced TMA, or TMAs arising 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) re-emergence of an ADAMTS13 inhibitor with an ADAMTS13 level <10% or (2) a decrease in platelet count below the lower limit of normal. We analyzed data by iTTP episode; thus, a single patient could have more than one episode.

Variables for each iTTP episode included the mean monthly temperature and latitude for the reporting site; the month and year of the ADAMTS13 result; episode type (initial vs. relapse); patient sex, age, race, and ABO blood type; the number of therapeutic plasma exchanges (TPEs); and 30–day mortality. The mean monthly temperature in degrees Celsius for each month at each participating site was obtained from the National Oceanic and Atmospheric Administration (https://www.ncei.noaa.gov/cdo-web/confirmation) or The Weather Channel via WeatherUnderground (https://www.wunderground.com/history). The latitude for each reporting site was obtained from Google Maps (Google, Mountain View, CA, USA).

iTTP episodes were stratified by month and by season. Seasons were defined as follows: Northern Hemisphere—winter (December–February); spring (March–May); summer (June–August); autumn (September–November) and Southern Hemisphere—winter (June–August); spring (September–November); summer (December–February); autumn (March–May).

We compared the mean monthly temperature for each iTTP episode to the mean temperature of months without an iTTP episode at each site. We also assessed the temperature variation over the study period for each site. This was performed to evaluate the seasonality of iTTP episodes among sites with less temperature variation (generally correlating with more consistent UV exposure) compared to more extreme temperature variation (i.e., colder winters and/or warmer summers). The cumulative temperature range for each site is displayed in Table S1.

As the study timeframe included the beginning of the COVID-19 pandemic, we compared the monthly frequency of iTTP episodes in the 38 months prior to the pandemic (January 2017–February 2020) with the frequency in the 22 months (March 2020–December 2021) following its onset.

The institutional review boards at all participating sites 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. Statistical analysis was performed using SPSS version 29.0.2.0. 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. Pearson correlation was performed to assess the association between latitude and seasonal iTTP incidence. Multinomial logistic regression was performed to evaluate if patient characteristics (age, sex, race, episode type, and ABO type) and/or site characteristics (latitude and temperature variation) were associated with the proportion of iTTP cases in autumn, spring, or summer compared to winter. A *p*-value <.05 was considered significant.

3 | RESULTS

A total of 583 patients experienced 719 iTTP episodes (Table 1). Approximately 64.7% (465/719) of iTTP episodes occurred in females, while 35.3% (254/719) occurred in males. Race data were available for 78.3% (563/719) of episodes: 54.2% (305/563) White, 42.8% (241/563) Black, and 1.8% (10/563) Asian. ABO blood type was reported for 79.1% (569/719) of episodes: 40.4% (230/569) type O, 35.0% (199/569) type A, 19.0% (108/569) type B, and 5.6% (32/569) type AB. Thirty-day mortality (3.2%, 20/617) was reported for 85.8% (617/719) of episodes.

The observed proportion of iTTP episodes during the winter was significantly greater than would be expected if episodes were distributed equally among all seasons (28.5%, 205/719, 95% CI: 25.3%–31.9%; $p = .03$). When the proportion of iTTP episodes between two seasons was assessed, significantly more episodes occurred in winter compared to spring (28.5%, 205/719, 95% CI: 25.3%–31.9% vs. 22.8%, 164/719, 95% CI: 19.9%–26.0%; $p = .01$) and in winter compared to autumn (28.5%, 205/719, 95% CI: 25.3%–31.9% vs. 23.1%, 166/719, 95% CI: 20.2%–26.3%; $p = .02$) (Figure 1A,B). More cases also occurred in winter compared to summer, but this difference was not statistically significant (28.5%, 205/719, 95% CI: 25.3%–31.9% vs. 25.6%, 184/719, 95% CI: 22.5%–28.9%; $p = .21$). No difference was seen in the proportion of cases in the summer compared to spring (25.6%, 184/719, 95% CI: 22.5%–28.9% vs. 22.8%, 164/719, 95% CI: 19.9%–26.0%; $p = .22$) or autumn (25.6%, 184/719, 95% CI: 22.5%–28.9% vs. 23.1%, 166/719, 95% CI: 20.2%–26.3%; $p = .27$). Similar findings were observed when stratified by sex, with the greatest proportion of iTTP episodes occurring in the winter for both females (28.0%, 130/465) and males (29.5%, 75/254).

When the mean monthly temperature for each iTTP episode was compared to the mean temperature of months without an iTTP episode at each site, we found that across all sites, months with an iTTP episode were statistically significantly colder than months without an iTTP episode (14.7°C, 95% CI: 13.3–14.6°C vs. 16.3°C, 95% CI: 14.8–15.9°C; $p < .001$).

TABLE 1 Characteristics of 719 immune thrombotic thrombocytopenic purpura episodes.

Variable	Median (IQR) or No. (%)
Age	49 years (37–61 years)
Sex	
Female	465 (64.7%)
Male	254 (35.3%)
Race	
White	305 (42.4%)
Black	241 (33.5%)
Asian	10 (1.4%)
AI/AN	5 (0.7%)
Pacific Islander	2 (0.3%)
Unknown/NR	156 (21.7%)
ABO type	
O	230 (32.0%)
A	199 (27.7%)
B	108 (15.0%)
AB	32 (4.5%)
Unknown/NR	150 (20.9%)
Episode type	
Initial	327 (45.5%)
Relapse	299 (41.6%)
Unknown/NR	93 (12.9%)
Location	
North America	509 (70.8%)
Europe	167 (23.2%)
Australia	43 (5.8%)

Abbreviations: AI/AN, American Indian/Alaskan Native; IQR, interquartile range; NR, not reported.

We assessed the latitude and the monthly temperature variation (i.e., the difference in the mean temperature of the warmest month and the mean temperature of the coldest month) among sites. Overall, a greater distance from the equator positively correlated with the proportion of iTTP episodes during the winter for a particular site, but this association was not statistically significant (slope = 0.18; 95% CI: −0.08 to 0.44; $y = 0.18x + 33.62$; $p = .16$; $r^2 = .089$) (Figure 2A).

Additionally, the greatest proportion of winter iTTP episodes tended to occur at sites with a greater temperature difference between the warmest month and the coldest month (i.e., temperature variation), though this was also not statistically significant (slope = 0.28; 95% CI: −0.05 to 0.60; $y = 0.28x + 15.77$; $p = .09$; $r^2 = .12$) (Figure 2B). We performed a subset analysis of the 15 sites with a mean temperature variation greater than the overall mean of 23.1°C as a proxy for sites with more seasonal variation in climate. Among these sites, 559 episodes of iTTP were reported: the largest proportion of cases occurred in winter (29.0%, 162/559), and the second largest proportion of cases occurred in summer (25.9%, 145/559) (Figure 1C). Winter accounted for a significantly greater proportion of cases compared to spring (56.5%, 162/287, 95% CI: 50.7%–62.1% vs. 43.6%, 125/287, 95% CI: 37.9%–49.4%; $p = .03$) and autumn (56.1%, 162/289, 95% CI: 50.3%–61.7% vs. 43.9%, 127/289, 95% CI: 38.4%–49.7%; $p = .045$). Among the nine sites with an annual temperature deviation <23.1°C, the proportion of cases was approximately equal across seasons (winter: 26.9%, 43/160; spring: 24.4%, 39/160; summer: 24.4%, 39/160; autumn: 24.4%, 39/160).

Of the episodes with available data on 30–day mortality, the highest mortality rate was observed in iTTP episodes that occurred during the summer (4.9%, 5/171), while the lowest mortality rate was among episodes that occurred during spring (1.4%, 2/146). However, there was no significant difference in 30-day mortality across all seasons ($\chi^2 = 3.20$, $p = .36$). Data regarding the number of TPEs performed per iTTP episode were available for 76.2% (548/719) of episodes. There was no significant difference in the median number of TPEs performed per iTTP episode among seasons: winter: 6 (IQR 4–11; 95% CI: 6–7); spring: 8 (IQR 5–14; 95% CI: 7–9); summer: 8 (IQR 5–14; 95% CI: 7–9); autumn: 8 (IQR 5–12.5; 95% CI: 7–9).

Among the 719 iTTP episodes, 328 were initial presentations, 301 were relapses, and 90 were unknown or not reported. 27.7% (91/328) of initial presentations occurred during the summer and 27.4% (90/328) occurred in the winter. Among relapses, 27.2% (82/301) occurred in the winter, followed by spring (25.2%, 76/301) and summer (24.6%, 74/301). More than one-third of all iTTP episodes in which the type of presentation (initial vs. relapse) was either not reported or unknown occurred in winter (36.7%, 33/90).

3.1 | Before and during the COVID-19 pandemic

Between January 2017 and February 2020, 473 episodes of iTTP (95% CI: 448–497 episodes) occurred (12.4 episodes/month), compared to 246 episodes (95% CI: 222–271 episodes) between March 2020 and December 2021 (11.2 episodes/month). This was not significantly different from the expected distribution of cases (455 episodes from January 2017 to February 2020 and 264 episodes from March 2020 to December 2021; $p = .16$). The number of iTTP episodes in the 12 months immediately preceding the COVID-19 pandemic was almost equivalent to the first year of the pandemic (151 episodes from March 2019 to February 2020 vs. 150 episodes from March 2020 to February 2021).

3.2 | Multinomial logistic regression

The odds ratio for individuals of the Black race developing iTTP during the spring was 0.55 ([95% CI: 0.31–0.97]; $p = .04$) relative to developing iTTP during the winter. The odds ratios for individuals with type O blood and type A blood developing iTTP during the summer was 2.37 ([95% CI: 1.01–5.57]; $p = .049$) and 2.47 ([95% CI: 1.05–5.81]; $p = .04$) relative to developing iTTP during the winter, respectively (Table S2). All of the other variables were not significantly associated with the seasonality of iTTP.

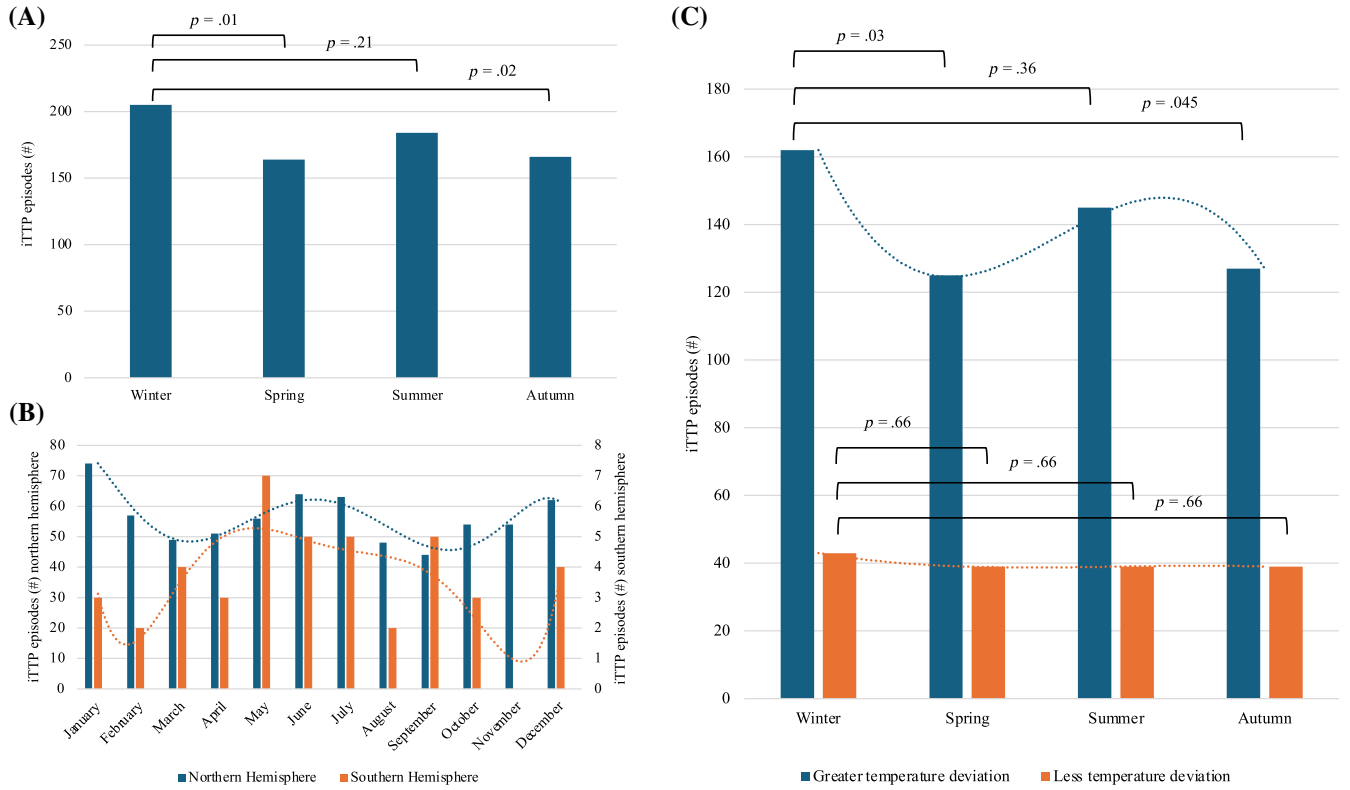


FIGURE 1 Total episodes of immune thrombotic thrombocytopenic purpura (iTTP) by (A) season, adjusted for Northern or Southern Hemisphere, and (B) month, as reported by 24 sites over a 5-year period. (C) Proportion of cases by season at sites with greater temperature deviation ($n = 15$) and sites with less temperature deviation ($n = 9$) compared to mean temperature deviation of all sites combined (23.1°C). [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This retrospective 5-year analysis found that among all sites, the greatest proportion of acute iTTP episodes occurred in winter, which was statistically significant when compared with spring and autumn. There was no statistically significant difference in the proportion of iTTP episodes between winter and summer. Additionally, among all sites, months during which an episode of iTTP occurred were significantly colder than months without an iTTP episode.

These findings suggest that iTTP has a bimodal distribution, occurring most frequently in winter and during colder months, with a second peak in summer, particularly in regions with a greater variation in seasonal temperatures. These results are both more nuanced, and somewhat discrepant, from prior publications (Table 2), although the heterogeneity in the methods and design of earlier studies preclude direct comparison. For example, prior studies have utilized ADAMTS13 activity,[12,13,15,17–20] medical coding data,[14,16] and clinical features[11] to characterize patients with TTP. Among those that assessed patients using ADAMTS13 activity, only one reported a statistically significant seasonal association (winter) for patients with ADAMTS13 activity results below a specified threshold.[18] Notably, in our meta-analysis of the five prior studies that reported all iTTP episodes and defined iTTP using an ADAMTS13 activity level <10%,[12,13,18–20] among 297 iTTP episodes, the greatest proportion of cases occurred in autumn (27.3%, 81/297) and spring (26.6%, 79/297), while the fewest occurred in summer (22.2%, 66/297) and winter (23.9%, 71/297) (Table S3). These findings directly contrast with the results of our study.

The reasons for the discrepant findings across prior studies are likely multifactorial. In part, they may be ascribed to the small sample sizes of the majority of prior studies. For example, only one previous study with iTTP defined by ADAMTS13 activity levels included more than 100 cases, wherein Raval et al.[13] assessed 110 cases of iTTP. The relatively low number of cases in these earlier studies may have lacked sufficient power to detect a significant difference in seasonal presentation. Conversely, the discrepancy between the results of the meta-analysis of prior studies and the findings in our study are more difficult to discern, though potential differences in the patient populations and geography/location of sites may contribute. Additionally, the two largest studies used the US National Inpatient Sample database and relied solely on medical diagnosis coding with weighted estimates of expected cases.[14,16] There are inherent limitations to these approaches. First, the database analyses were confined to hospitalized patients and did not necessarily include all patients or all hospitals. Second, unique disease episodes versus exacerbations of the same episode (i.e., hospital re-admission prior to recovery) were not necessarily distinguished. Lastly, the analyses in some studies were not always specific for iTTP, as any patient with a documented TTP diagnosis code would be included (e.g., congenital TTP, drug-induced TMA, HIV- or transplant-associated TMA, etc.), as well as those with

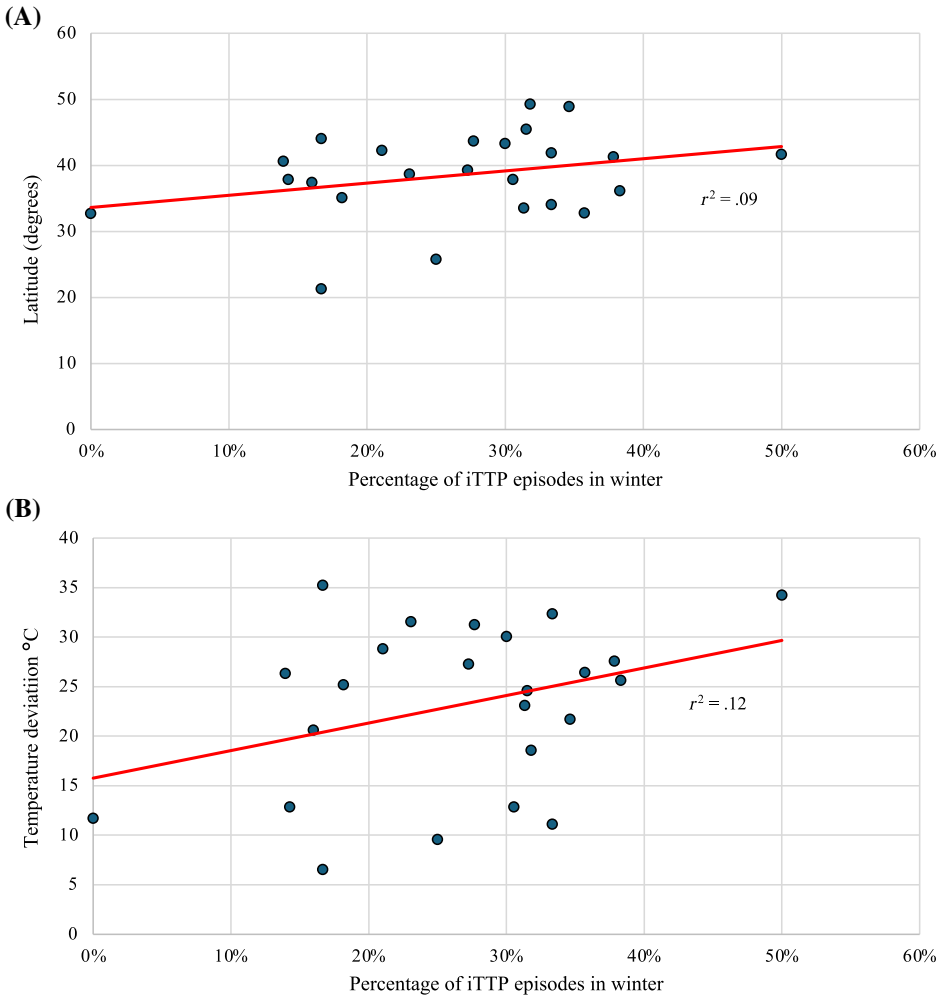


FIGURE 2 Correlation between the percentage of immune thrombotic thrombocytopenic purpura (iTTP) episodes in the winter and (A) latitude and (B) temperature deviation for each site. [Color figure can be viewed at wileyonlinelibrary.com]

an erroneous diagnosis related to miscoding, which can be common.[22] Our large patient cohort with documented severe ADAMTS13 deficiency in the absence of another secondary cause serves to minimize some of these potential confounding variables.

Infections have been implicated as an inciting event for iTTP,[23,24] potentially through molecular mimicry or other mechanisms, and may play a role in driving the rates of iTTP and other autoimmune diseases.[25] Considering that various infectious diseases (e.g., influenza virus, respiratory syncytial virus, parainfluenza virus, and enteroviruses) are influenced by seasonality, geography, and climate,[26–28] iTTP seasonality may also be influenced by local infectious disease epidemiology. For example, seasonal epidemics of influenza occur in winter months in more temperate areas, whereas onset is more variable and less seasonal in lower latitudes.[27] Conversely, RSV demonstrates distinct seasonality irrespective of latitude, beginning in late summer closer to the equator and in most temperate sites during winter months.[27] Parainfluenza tends to occur in spring and early summer months in both hemispheres.[27] The timing and intensity of enterovirus outbreaks correspond with latitude—cases are more regularly distributed year-round in the lower latitudes, whereas a pronounced peak occurs between July and September across much of the US.[28] As a rare disease, iTTP case numbers may be too small to allow for an observable seasonal pattern at single centers. However, we found that the proportion of iTTP cases during the winter positively correlated with greater distance from the equator and with larger temperature deviation during the year. Notably, sites with a greater temperature deviation had the largest proportion of iTTP cases during the winter, while those with less temperature deviation had an almost equal proportion of cases across all seasons. This finding suggests that iTTP may display more seasonality in areas with more distinct seasons and where infectious outbreaks display greater seasonal patterns. Conversely, iTTP may be less likely to demonstrate seasonality in areas where the climate is more consistent year-round.

We did not observe a difference in the proportion of iTTP episodes before and after the onset of the COVID-19 pandemic, contrasting with a significant decline in various respiratory pathogens during the first year due to social isolation and other public health measures.[29] It is possible that other infectious agents may have contributed to the development of iTTP. Further, SARS-CoV-2 may have replaced other seasonal infectious diseases as an inciting factor for a subset of iTTP cases.[30] Another possibility is that a portion of (primarily relapsed) iTTP episodes were potentially induced by COVID-19 vaccination.[31] The specific infectious agent and/or vaccination that preceded an iTTP event, if any, were not uniformly available in our sample; thus, the proportion of episodes that were associated with SARS-CoV-2 infection or vaccination is not known.

TABLE 2 Studies assessing the seasonal distribution of thrombotic thrombocytopenic purpura (TTP).

Authors	Years included in study	Study population	Number of unique patients with ADAMTS13 <10%	Number of TTP episodes	Geographic region	Findings
Karimi et al.[11]	1991–2004	Patients with a clinical diagnosis of TTP (megakaryocytic thrombocytopenia, Coombs-negative microangiopathic hemolysis with schistocytosis, neurological symptoms and/or signs of mild renal involvement and/or fever, in the absence of such other identifiable causes)	ADAMTS13 activity testing not performed	35	Shiraz, Iran	Most (85.7%) cases of TTP occurred between April and September
George and Vesely[15]	1996–2010	Patients with ADAMTS13 activity <10%	61	61 (only assessed initial presentations)	Oklahoma, US	Highest number of initial presentations occurred in the spring but there was no statistically significant difference in the incidence of initial presentations among seasons
Park et al.[12]	1999–2008	All clinically suspected TTP-HUS cases treated with TPE, with two groups: 1. Idiopathic TTP group—Patients that did not have malignant hypertension (>180/100), transplantation, malignancy, HIV, pregnancy, connective tissue disorders, drug-related (quinine, clopidogrel, ticlopidine), or congenital TTP or E. coli O157:H7 positive 2. Patients with clinically-suspected TTP with ADAMTS13 activity <10%	Not reported	97 cases of idiopathic TTP 31 cases of clinically-suspected TTP	North Carolina, US	Cases of idiopathic TTP occurred statistically more often in the summer (36.1%). When limited to cases with <10% ADAMTS13 activity, cases still occurred more often in the summer (35.5%), but this was not statistically significant
Hsu et al.[17]	2004–2010	Two groups of patients: 1. Cases of TTP with detectible ADAMTS13 and absence of inhibitor were defined as clinical TTP 2. Cases of TTP with ADAMTS13 activity <5% and/or presence of ADAMTS13 inhibitor were defined as iTTP	Not reported	87 cases of clinical TTP 40 cases of iTTP	Missouri, US	Increased incidence of iTTP, but not clinical TTP, in warmer months
Scott et al.[19]	2003–2012	Patients with ADAMTS13 activity <10% due to an inhibitor	66	84	Alabama, US	Highest number of TTP episodes occurred in autumn but no statistical difference between seasons
Raval et al.[13]	2005–2012	Patients with ADAMTS13 activity <10%. Patients with congenital TTP, disseminated intravascular coagulation, HELLP syndrome, hepatic failure, HIV infection, malignancy, malignant hypertension, organ transplantation, pregnancy, active rheumatologic/connective tissue disorders, sepsis, trauma, or drug-associated TTP were excluded	73	110	Pennsylvania, US	No statistically significant differences in time of presentation were identified between the four seasons or calendar months

(Continues)

TABLE 2 (Continued)

Authors	Years included in study	Study population	Number of unique patients with ADAMTS13 <10%	Number of TTP episodes	Geographic region	Findings
Hussein.[18]	2008–2019	Patients with a clinical diagnosis of idiopathic TTP associated with ADAMTS13 activity <10%	44	47	Cairo, Egypt	The highest number of cases occurred in winter. Significantly fewer episodes of TTP occurred in the summer compared to all other seasons
Simenson et al.[20]	2010–2018	Patients with ADAMTS13 activity <10%	Not reported	25	Louisiana, US	Trend for more confirmed episodes of TTP later in the year (autumn/winter), but this seasonal association was not statistically significant
Current study (Jacobs et al.)	2017–2021	Patients with ADAMTS13 activity <10%	583	719	Australia, Canada, France, Greece, Italy, Spain, US	Significantly more episodes of iTTP occurred in winter compared to the other three seasons combined, as well as compared to spring and autumn
Studies that did not assess ADAMTS13 activity						
Giri et al.[16]	2009–2011	Patients with an ICD-9 code for TTP in the National Inpatient Sample database who also had a code for therapeutic plasmapheresis during hospitalization	Not reported	Weighted estimate of 6360 TTP-related hospitalizations across the US	US	No seasonal variation among overall TTP related hospitalizations in the US. After stratifying the cases based on the regions, a significant monthly variation was noted in the Midwestern region, with peak incidence observed in July which was significantly higher than the lowest incidence noted in November
Carter et al.[14]	1999–2013	Patients with an ICD-9 code for TTP in the National Inpatient Sample database, weighted to approximate the full inpatient population of the US	Not reported	30 011 cases (weighted estimate)	US	No statistically significant seasonal variation in presentation of TTP

Abbreviations: ADAMTS13, a disintegrin and metalloprotease with thrombospondin type motifs 13; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelets; HUS, hemolytic uremic syndrome; ICD-9, international classification of diseases, ninth edition; iTTP, immune TTP; TPE, therapeutic plasma exchange; US, United States.

Seasonal variation has been observed in the initial manifestation and/or reactivation of other autoimmune conditions (e.g., multiple sclerosis, rheumatoid arthritis, and type I diabetes mellitus), with suboptimal vitamin D levels implicated as one potential cause.[25] Vitamin D levels generally correlate with UV light exposure, which is lowest in winter months and at higher latitudes. The lack of vitamin D is theorized to contribute to aberrations in immunomodulation and regulation of inflammation and alter the protective effects of the innate immune system.[32] We observed a positive correlation between higher latitudes and the proportion of iTTP cases in winter. Additionally, the proportion of iTTP episodes was equal across seasons at sites with less temperature variation (generally correlating with more consistent UV exposure), whereas iTTP demonstrated greater seasonality among sites with more extreme temperature variations (i.e., colder winters and/or warmer summers), further supporting this hypothesis. Thus, vitamin D levels in patients with iTTP may warrant future exploration.

The current study has limitations. Data were not available for selected outcomes and type of presentation (initial vs. relapse) for a subset of patients. Infection-related data were generally not available, and there was heterogeneity among those that provided these data (e.g., some centers provided all suspected and laboratory-confirmed infections, while others only provided laboratory-confirmed data). The rarity of iTTP and the relatively short analysis timeframe preclude our ability to assess seasonality at each individual site in our study. Furthermore, this large sample was mainly contributed by well-recognized iTTP treatment centers, which allowed for more precise inclusion criteria, but also produced lower than expected mortality rates, which may not reflect other centers. Finally, we were unable to obtain data from centers in Asia, Africa, and South America, and additional climatologic data (e.g., precipitation, relative humidity, cloud type, solar radiation, and atmospheric pressure) were unavailable. Nevertheless, the large sample size and the inclusion of patients from multiple centers in different geographic regions with varying climates provide the largest analysis to date regarding seasonality and its potential role in iTTP.

In summary, acute iTTP episodes were associated with the winter season and colder temperatures, with a second disease incidence peak in summer. This seasonal association was most pronounced at sites further from the equator and/or with greater annual temperature variation. While the reasons for seasonal variation remain unclear, possible contributors include infectious disease patterns and vitamin D levels related to UV light exposure. However, additional components, such as genetic factors and various environmental exposures, are likely involved. Ultimately, identifying the etiologies underlying seasonal patterns of disease may assist in discovery and development of future preventative therapies and inform models that could be used to enhance resource distribution and conservation, including blood products.

AUTHOR CONTRIBUTIONS

JWJ, BDA, and GSB designed the study and drafted the manuscript. CGS, GSB, AS, AWS, ESA, EG, BJG, KP, AM, FP, PA, IM, LDS, JSR, MEM-C, EPC, LD, MP, DMA, MBM, RH, TWS, GS, RCS, LRW, CY, MAD, YW, TJH, DMB, AB, AKD, DHR, QE, CAFV, JEJ, GK, EK, EK, IP-A, MSK, NK, CL, EM, FA, RA, ZM, AP, MGP, AJS, CAT, CW, EMW, SJ, APW, AAP, CBW, SGY, RB, PC, EMB, and BDA provided data and critically revised the manuscript. All authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

None of the authors have conflicts related to the content of this manuscript. Unrelated, the following authors disclose: EG has consulted for AstraZeneca, Novartis, Omeros, Sanofi, and Sobi Pharmaceuticals. MEM-C participates in advisory boards and speaker sessions for Takeda, Sanofi, Novartis, Novo Nordisk, Amgen, Sobi, Grifols. EM has consulted for AstraZeneca, Sanofi, and Sobi Pharmaceuticals. TWS has participated in an advisory board session for Alexion. AKD participated in advisory boards and speaker sessions for Sobi. PA received honoraria for participating as a speaker at educational meetings organized by Sanofi. EK has consulted for Sanofi, Novartis, Astra-Zeneca, GSK, Pfizer, Sobi. ZM has consulted for Sanofi. IM received honoraria for participating as a speaker at educational meetings organized by Werfen and Sanofi. CL has consulted for Novartis, Sanofi, and Sobi Pharmaceuticals. AS has received research grants through his Institution by Abbvie, Amgen, BMS, Gilead, Glaxo, Incyte/Genesis, Janssen, Pfizer, Roche, Sanofi, Servier, Sobi and Takeda and has consulted for Abbvie, Astra-Zeneca, BMS, Gilead, Glaxo, Janssen, Novartis, Sanofi, Servier, Sobi, and Takeda. EMB was supported in part by the National Heart Lung and Blood Institute (1K23HL15182). EMB reports personal fees and non-financial support from Grifols, Abbott, UptoDate, Tegus, and Health Advances outside of the submitted work. EMB is a co-investigator on a US government-funded clinical trial evaluating Mirasol Pathogen Reduction Technology. EMB is a member of the U.S. Food and Drug Administration (FDA) Blood Products Advisory Committee. Any views or opinions expressed in this manuscript are his and are based on his own scientific expertise and professional judgment; they do not necessarily represent the views of the Blood Products Advisory Committee or the formal position of the FDA and also do not bind or otherwise obligate or commit either the Advisory Committee or the FDA to the views expressed. MBM is a member of the U.S. Food and Drug Administration (FDA) Blood Products Advisory Committee. Any views or opinions expressed in this manuscript are hers and are based on her own scientific expertise and professional judgment; they do not necessarily represent the views of the Blood Products Advisory Committee or the formal position of the FDA and also do not bind or otherwise obligate or commit either the Advisory Committee or the FDA to the views expressed. AS has consulted for Abbvie, BMS, Gilead, Incyte/Genesis, Janssen, Novartis, Sanofi, and Sobi. EMW is supported by an Australian National Health and Medical Research Council Leadership Fellowship (1177784). EMW reports research funding to her institution from: Abbvie, Amgen, Antengene, AstraZeneca, Beigene, BMS, Celgene, CSL Behring, Gilead, Janssen, Novartis, Roche, Sanofi, Sobi, and Takeda. FP: Participation to advisory board: CSL Behring, Biomarin, Roche, Sobi, Sanofi; honoraria for educational meetings and symposia: Takeda, Spark. KP reports unpaid consultancy to Sanofi and Takeda; participation in industry-sponsored trials Roche, Sanofi.

DATA AVAILABILITY STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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