RESEARCH ARTICLE

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All-Cause and Exacerbation-Related Readmissions in Thrombotic Microangiopathy Requiring Plasmapheresis: A Population-Based Cohort Study

Plazmaferez Gerektiren Trombotik Mikroanjiyopatide Tüm Nedenlere Bağlı ve Alevlenmeye İlişkin Yeniden Yatışlar: Nüfus Tabanlı Bir Kohort Çalışması

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Abstract

Objective: Thrombotic microangiopathy (TMA) is a serious condition characterized by microangiopathic hemolytic anemia and thrombocytopenia, with high exacerbation rates. This study examined all-cause and exacerbation-related readmission risks among patients hospitalized with TMA requiring plasmapheresis.

Materials and Methods: Secondary analysis of the 2020 Nationwide Readmission Database was conducted, including discharge data from non-federal hospitals in 31 U.S. states. Patients aged 18 years or older admitted non-electively with a primary or secondary diagnosis of TMA requiring plasmapheresis were included. Exacerbation-related readmission was defined as subsequent admission requiring plasmapheresis within 7 or 30 days after the original discharge. Multivariable logistic regression and Cox proportional hazards models were used to assess readmission risks, adjusting for demographics, comorbidities, and predisposing factors.

Results: Among an estimated 1393 patients, 791 (56.8%) had predisposing conditions. All-cause readmissions were more frequent in patients with predisposing conditions (26.2% vs. 21.9%), while exacerbation-related readmissions were more common in TMA-only patients (9.0% vs. 3.4% at 7 days; 13.7% vs. 6.4% at 30 days). Most exacerbations occurred within 14 days after discharge. No patients treated with caplacizumab experienced exacerbation. TMA-only patients had a 2.1-times higher risk of 30-day exacerbation-related readmissions (adjusted hazard ratio: 2.10, p=0.04). Rural residence and patient-directed discharge were potential risk factors for exacerbation-related readmissions.

Öz

Amaç: Trombotik mikroanjiyopati (TMA), mikroanjiyopatik hemolitik anemi ve trombositopeni ile karakterize edilen ciddi bir durumdur ve yüksek alevlenme oranları gösterir. Bu çalışma, plazma değişimi gerektiren TMA tanısı ile hastaneye yatan hastalarda tüm nedenlere bağlı ve alevlenme ile ilişkili yeniden yatış risklerini incelemiştir.

Gereç ve Yöntemler: 2020 Ulusal Yeniden Yatış Veritabanı'nın ikincil analizine dayanarak, ABD'nin 31 eyaletindeki federal olmayan hastanelerden taburcu verileri kullanılmıştır. On sekiz yaş ve üzeri, plazma değişimi gerektiren birincil veya ikincil TMA tanısı ile elektif olmayan şekilde hastaneye yatan hastalar dahil edilmiştir. Alevlenme ile ilişkili yeniden yatış, orijinal taburculuktan sonra 7 veya 30 gün içinde plazma değişimi gerektiren subsequent yatış olarak tanımlanmıştır. Yeniden yatış risklerini değerlendirmek için demografik veriler, komorbiditeler ve predispozan faktörler için ayarlama yapılan çok değişkenli lojistik regresyon ve Cox orantılı tehlike modelleri kullanılmıştır.

Bulgular: Tahminen 1393 hastadan 791'inin (%56,8) predispozan durumları vardı. Tüm nedenlere bağlı yeniden yatışlar, predispozan durumu olan hastalarda daha sık görüldü (%26,2 vs. %21,9), alevlenme ile ilişkili yeniden yatışlar ise sadece TMA hastalarında daha yaygındı (7 günde %9,0 vs. %3,4; 30 günde %13,7 vs. %6,4). Çoğu alevlenme, taburculuktan sonraki 14 gün içinde meydana geldi. Kaplazizumab ile tedavi edilen hiçbir hastada alevlenme görülmedi. Sadece TMA hastaları, 30 günlük alevlenme ile ilişkili yeniden yatışlarda 2,1 kat daha yüksek riske sahipti (ayarlanmış tehlike oranı: 2,10, p=0,04). Kırsal yerleşim ve hasta yönlendirmeli taburculuk, alevlenme ile ilişkili yeniden yatışlar için potansiyel risk faktörleri olarak belirlendi.

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Abstract

Conclusions: These findings highlight the need for improved post-discharge care and treatment strategies to prevent readmissions. Further studies should explore interventions to reduce exacerbation-related readmissions, particularly in high-risk populations.

Keywords: Database, Microangiopathy, Nationwide, Readmission, Thrombotic

Öz

Sonuç: Bu bulgular, taburculuk sonrası bakımın ve tedavi stratejilerinin iyileştirilmesi gerektiğini vurgulamaktadır. Daha fazla çalışma, özellikle yüksek riskli popülasyonlarda alevlenme ile ilişkili yeniden yatışları azaltmaya yönelik müdahaleleri incelemelidir.

Anahtar Sözcükler: Veritabanı, Mikroanjiyopati, Ulusal, Yeniden yatış, Trombotik

Introduction

Thrombotic microangiopathy (TMA) is a rare but life-threatening syndrome characterized by microangiopathic hemolytic anemia and thrombocytopenia, resulting from heterogeneous underlying disease processes [1]. TMA encompasses primary forms, such as immune-mediated thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (HUS), and secondary forms associated with identifiable triggers. TTP arises from severe ADAMTS-13 deficiency, usually caused by acquired autoantibodies, leading to aggregation of ultra-large von Willebrand factor (VWF) multimers and microthrombi formation [2]. Atypical HUS, or complement-mediated TMA, is driven by complement overactivation due to inherited defects or acquired autoantibodies against complement regulatory proteins [3]. In the United States, the unspecified TTP incidence is estimated at 8.9 cases per million person-years and the mortality rate can exceed 10% with standard treatment [4]. Furthermore, the mean cost of each hospitalization in the United States is estimated at greater than 200,000 USD, highlighting the critical need for effective management strategies [4].

Primary and secondary TMA are distinguished by the presence or absence of a precipitating cause. Secondary TMA is typically associated with malignancies, severe hypertension, autoimmune diseases, infections (e.g., Shiga-like toxins, HIV, and coronavirus disease-2019 [COVID-19]), pregnancy, or specific medications, whereas primary TMA arises without an identifiable trigger [1]. Severe ADAMTS-13 deficiency with activity of <10% is a critical diagnostic marker for immune-mediated TTP and hereditary TTP, enabling differentiation from other TMA forms. Patients with suspected TTP are typically started on empiric plasmapheresis and corticosteroids while awaiting evaluation of their ADAMTS-13 levels [2,5].

Data on TTP outcomes are largely derived from U.S. and international registries, such as the Oklahoma TTP-HUS Registry, which primarily include patients treated with plasmapheresis [6,7,8,9,10]. These registries predominantly report relapse rates, defined as recurrence at ≥30 days after treatment cessation, with first-year rates of 43% among idiopathic TTP cases involving severe ADAMTS-13 deficiency [8]. However, data on exacerbations, defined as disease recurrence within 30 days after cessation of treatments such as plasmapheresis or caplacizumab [11], are limited. Exacerbations represent a critical vulnerability period and present unique challenges for clinicians managing patients during transitions of care. Recent studies on caplacizumab have reported exacerbation rates between 20% and 44% following standard treatment [12,13,14].

Traditionally, the standard of care for immune-mediated TTP has entailed plasmapheresis, steroids, and rituximab [2,15]. Recent advances include caplacizumab, an anti-VWF nanobody, which has significantly reduced exacerbation, recurrence, and mortality rates in clinical trials [12,13,14]. However, most studies using national registries have been descriptive in nature; little is known about time-to-readmission or exacerbation rates, readmission risk factors, and the significance of triggering factors in TMA. Therefore, we sought to provide nationally representative estimates of hospitalizations for TMA requiring plasmapheresis in the United States using discharge data from the Nationwide Readmissions Database (NRD), a component of the Healthcare Cost and Utilization Project managed by the Agency for Healthcare Research and Quality [16].

The objectives of this study were to model the risks of exacerbation-related and all-cause readmissions within 7 and 30 days after discharge for patients with TMA requiring plasmapheresis, to examine differences in these risks between TMA cases with and without predisposing conditions and identify associated risk factors, and to describe the prevalence of caplacizumab use during index admissions. By pursuing these objectives, we aim to propose strategies for reducing readmissions and optimizing transitions of care for this high-risk population.

Materials and Methods

Study Design, Setting, and Data Source

We conducted secondary data analysis of the 2020 NRD. This dataset includes deidentified, publicly available full discharge records from all non-federal hospitals in 31 participating U.S. states, representing 60.8% of all U.S. hospitalizations for the calendar year 2020 [16]. Sampling weights provided in the dataset were used to obtain national estimates. The University of Kentucky Institutional Review Board determined that this study met the federal criteria to qualify as an exempt study on 15/12/2023 (IRB #92969).

Participants

We included patients aged 18 years or older who were non-electively admitted with a primary or secondary diagnosis of TMA requiring plasmapheresis during the same hospitalization. TMA cases were captured using ICD-10-CM code M31.1 and plasmapheresis using ICD-10-PCS codes 6A550Z3 and 6A551Z3.

We focused on the index admission, which was defined as the first admission episode where both TMA and plasmapheresis were present. We excluded patients with elective admissions, admissions in December 2020 due to insufficient follow-up time, patients receiving plasmapheresis prior to the admission day, and cases involving primary diagnoses beyond the scope of this study, including acute chest syndrome with sickle cell crisis, Waldenstrom macroglobulinemia, Evans syndrome, hemophagocytic lymphohistiocytosis, cryoglobulinemia, and antiphospholipid syndrome. For readmission analyses, patients who died during the index hospitalization were excluded as they were not eligible for subsequent readmissions.

Measures

Primary Outcomes

Exacerbation-related readmissions were defined as hospital readmissions requiring plasmapheresis within 7 or 30 days after the initial discharge. These were analyzed as binary outcomes for 7-day readmissions and as both binary and time-to-event variables for 30-day readmissions. All-cause readmissions were defined as hospital readmissions for any reason within 7 or 30 days after the initial discharge, recorded similarly as binary and time-to-event outcomes.

Predisposing Conditions

TMA is a heterogeneous group of diseases with different pathophysiologies. Given that ICD-10 codes do not differentiate TMA subtypes and ADAMTS-13 activity data are unavailable in this database, we stratified TMA cases based on clinical characteristics to compare and contrast outcome differences. TMAs without predisposing factors served as a proxy for primary immune-mediated TTP, as these cases arise without an identifiable trigger. In contrast, TMAs with predisposing triggers and other special cases were considered to represent secondary TMA or other primary forms like complement-mediated TMA, whose clinical courses would be very different. This comparison, while imperfect, yielded valuable insight into how outcomes differed between these groups. Predisposing factors and special cases of TMA included the following: HUS (D59.3), pregnancy-related conditions (O00-O99 and Z3A.x), solid-organ or hematopoietic transplant (Z94.x and T86.x), autoimmune conditions (modifying the existing "autoimmune" variable in the Elixhauser index, excluding M31.1—TMA), malignancies (presence of metastatic cancer, leukemia, or lymphoma, using Elixhauser index variables), complicated hypertension (existing variable—cmr_htn_cx), sepsis (A40 and A41), and COVID-19 (U071), which also triggers TTP [17,18]. The relevant ICD-10 codes for specific predisposing conditions and covariates are provided in Supplementary Table 1.

Covariates

We considered several factors influencing readmissions, including age (≥65 years), sex, median household income (1st quartile), insurance type, discharge disposition, location of residence, and caplacizumab use (ICD-10-PCS: XW013W5). To account for the baseline complexity of patients at the time of discharge, we also included the Elixhauser comorbidity index, comprising 38 comorbid conditions, for predicting readmission risks. These variables were available in the 2020 NRD [19].

Statistical Analysis

Survey weights were applied throughout the analysis to produce nationally representative estimates. Descriptive statistics entailed design-based F-tests to account for the complex survey design.

For 30-day exacerbation-related and all-cause readmissions, we fitted multiple logistic regression and Cox proportional hazards models, adjusting for the complex survey design and demographic, clinical, and hospital-level characteristics. Caplacizumab was excluded from the exacerbation analysis as patients receiving caplacizumab did not experience exacerbations. For 7-day exacerbation-related and all-cause readmissions, multivariable logistic regression models were used with the same set of covariates. To ensure the robustness of the models, we evaluated the proportional hazards assumption using time-varying covariates, Schoenfeld residuals, and log-log survival curves, with Cox-Snell residual plots confirming a reasonable model fit. A conservative significance level of $p<0.05$ was used due to anticipated small sample sizes. Missing data accounted for 3.0% of the total (19 of 623 cases) and complete case analysis was used. All statistical analyses were conducted using Stata 17 (StataCorp, College Station, TX, USA).

Results

Participant Characteristics

We identified an estimated 1393 hospitalized patients aged 18 years or older who underwent plasmapheresis with a primary or secondary diagnosis of TMA. See Table 1 for patient characteristics. Patients with predisposing conditions, constituting 56.8% of the cohort, had a higher mean Elixhauser index score. Among the patients without predisposing factors (i.e., the TMA-only group), younger patients aged 18-39 years were more prevalent. Socioeconomic factors were comparable between the two groups.

Table 1. Patient characteristics and outcomes of index admissions for thrombotic microangiopathies.

	TMA without predisposing conditions	TMA with predisposing conditions	All TMAs	p
Weighted count	n=602	n=791	n=1393	
Demographics				
Age group				<0.001
18-39 years	226 (37.5%)	215 (27.2%)	441 (31.6%)	
40-64 years	279 (46.3%)	340 (43.0%)	619 (44.4%)	
≥65 years	98 (16.2%)	235 (29.8%)	333 (24.0%)	
Female	432 (71.8%)	515 (65.0%)	947 (68.0%)	0.08
Insurance				<0.001
Medicare	129 (21.4%)	305 (38.7%)	434 (31.2%)	
Medicaid	173 (28.7%)	183 (23.1%)	356 (25.6%)	
Private	222 (36.9%)	258 (32.7%)	480 (34.5%)	
Other	78 (13.0%)	43 (5.5%)	121 (8.7%)	
Median household income per zip code				0.66
1st quartile	257 (33.3%)	212 (36.0%)	469 (34.5%)	
2nd quartile	195 (25.2%)	162 (27.6%)	357 (26.2%)	
3rd quartile	177 (22.8%)	119 (20.3%)	296 (21.7%)	
4th quartile	144 (18.7%)	95 (16.1%)	239 (17.6%)	
Patient location				0.80
Metropolitan area, ≥1 million people	340 (57.4%)	453 (57.7%)	793 (57.6%)	
Metropolitan area, 250,000-999,000 people	109 (18.4%)	150 (19.2%)	259 (18.8%)	
Metropolitan area, 50,000-249,000 people, or micropolitan	101 (16.9%)	140 (17.9%)	241 (17.5%)	
Not metropolitan or micropolitan	43 (7.3%)	41 (5.2%)	84 (6.1%)	
Predisposing conditions				
HTN, complicated	N/A	368 (46.5%)	368 (26.4%)	
Autoimmune conditions	N/A	186 (23.5%)	186 (13.3%)	
Transplant (solid-organ or hematopoietic)	N/A	84 (10.6%)	84 (6.0%)	
Pregnancy	N/A	45 (5.7%)	45 (3.2%)	
Malignancies	N/A	125 (15.8%)	125 (9.0%)	
COVID-19	N/A	56 (7.1%)	56 (4.0%)	
Sepsis*	N/A	219 (27.7%)	219 (15.7%)	
Special case of TMA (HUS)	N/A	177 (22.4%)	177 (12.7%)	
Other comorbid conditions				
Obesity	189 (31.4%)	156 (19.7%)	345 (24.8%)	0.001
Moderate to severe renal failure**	14 (2.3%)	303 (38.4%)	317 (22.8%)	<0.001
Mean Elixhauser index	3.85 (0.12)	5.71 (0.16)	4.91 (0.12)	<0.001
Outcomes of index admissions				
Caplacizumab use	13 (2.2%)	15 (1.8%)	28 (2.0%)	0.74
LOS	9 (IQR: 6, 14)	14 (IQR: 8, 22)	11 (IQR: 7, 19)	<0.001
Total charges, USD	232,607 (15,516)	383,969 (25,707)	318,384 (17,871)	<0.001
Discharge disposition				<0.001
Self-care or home health	525 (87.3%)	566 (71.5%)	1091 (78.2%)	<0.001
Transfer to short-term hospital	14 (2.3%)	20 (2.6%)	34 (24.7%)	
Rehab or nursing home	25 (4.1%)	71 (9.0%)	96 (6.9%)	
Patient-directed discharge	22 (3.6%)	18 (2.3%)	40 (2.9%)	
Deceased (in-hospital death)	16 (2.7%)	116 (14.6%)	132 (9.5%)	

*: Sepsis may be POA or non-POA; **: renal failure may be POA or non-POA; TMA: thrombotic microangiopathy; HTN: hypertension; HUS: hemolytic uremic syndrome; LOS: length of stay; IQR: interquartile range; N/A: not applicable; POA: present on admission.

Among patients with predisposing conditions, the most common comorbidities included complicated hypertension, autoimmune conditions, malignancies, and sepsis. Transplantation, pregnancy, and COVID-19 were less common. HUS accounted for 22.4% of cases in this group.

Caplacizumab was rarely used during index admissions, being administered for an estimated 28 cases nationwide in 2020. Median length of stay was significantly shorter in the TMA-only group. The in-hospital mortality rate was markedly lower in the TMA-only group.

Unadjusted and Adjusted Outcomes

Table 2 presents the observed rates and odds ratios for 7-day and 30-day all-cause and exacerbation-related readmissions in logistic regression models. All-cause readmission rates at 7 days after discharge were similar between the two groups; however, a clinically significant 5% difference was observed at 30 days (21.9% vs. 26.2%). Exacerbation-related readmissions were significantly higher in the TMA-only group at both 7 days and 30 days. Most exacerbations occurred within the first 14 days: 61.9% within 7 days and 84.1% within 14 days. Logistic regression analysis showed that the odds of all-cause readmissions at both 7 and 30 days were similar between the two groups. In contrast, the TMA-only group had significantly higher odds of exacerbation-related readmissions at both 7 days and 30 days.

Time-to-Event Analysis

Table 3 shows each factor's hazard ratios for 30-day exacerbation-related and all-cause readmissions from the Cox proportional hazard models. The risk of 30-day exacerbation-related readmission was significantly higher in the TMA-only group, with an adjusted hazard ratio of 2.10 (p=0.04).

Patient-directed discharge was associated with a tendency toward an increased hazard ratio for exacerbation. Residence outside of metropolitan or micropolitan areas showed a similar trend. In contrast, medium-sized metropolitan residence, discharge to rehabilitation or nursing facilities, and patient-directed discharge were significantly associated with increased hazard ratios for 30-day all-cause readmissions.

Cumulative hazard plots for 30-day exacerbation-related readmissions (Figure 1) revealed that the TMA-only group exhibited a higher and steeper cumulative hazard curve. Both groups demonstrated the highest risk for exacerbations within the first week after discharge, followed by a gradual decline over the subsequent two weeks.

Discussion

This study provides a comprehensive analysis of exacerbation-related and all-cause readmissions among adult patients hospitalized with TMA requiring plasmapheresis, utilizing data from the 2020 NRD. By analyzing a nationally representative cohort, we quantified the risk of exacerbation-related readmissions, identifying critical risk periods and associated factors. Due to the lack of ADAMTS-13 activity data, our TMA-only group most likely represents a heterogenous mix of immune-mediated TTP and other TMA subtypes without a known trigger, which limits the specificity of our findings to true immune-mediated TTP. However, comparing our findings with those

Table 2. Odds ratios for all-cause and exacerbation-related readmissions with thrombotic microangiopathies.

	Counts (%)	Unadjusted OR [95% CI]	p	Adjusted OR [95% CI]	p
All-cause readmission in 7 days					
TMA without predisposing conditions	67 (12.4%)	1.07 [0.62, 1.83]	0.81	1.10 [0.59, 2.03]	0.77
TMA with predisposing conditions	72 (11.7%)				
All TMAs	139 (12.0%)				
All-cause readmission in 30 days					
TMA without predisposing conditions	117 (21.9%)	0.79 [0.53, 1.17]	0.23	1.01 [0.63, 1.60]	0.98
TMA with predisposing conditions	161 (26.2%)				
All TMAs	278 (24.2%)				
Exacerbation-related readmission in 7 days					
TMA without predisposing conditions	48 (9.0%)	2.82 [1.31, 6.06]	0.008	2.61 [1.05, 6.48]	0.04
TMA with predisposing conditions	21 (3.4%)				
All TMAs	69 (6.0%)				
Exacerbation-related readmission in 30 days					
TMA without predisposing conditions	73 (13.7%)	2.31 [1.26, 4.21]	0.007	2.21 [1.04, 4.67]	0.04
TMA with predisposing conditions	40 (6.4%)				
All TMAs	113 (9.8%)				

The ORs quantify the risk of readmission for TMA patients without predisposing conditions compared to those with them. TMA: Thrombotic microangiopathy; OR: odds ratio; CI: confidence interval.

Table 3. Risk factors (hazard ratios) for 30-day exacerbation-related and all-cause readmissions with thrombotic microangiopathies.

	30-day exacerbation			30-day readmission		
	aHR	95% CI	p	aHR	95% CI	p
TMA without predisposing conditions	**2.10**	**[1.02, 4.32]**	**0.04**	1.02	[0.689, 1.52]	0.90
Caplacizumab use*				0.30	[0.03, 2.69]	0.28
Age ≥65 years	0.60	[0.25, 1.45]	0.26	0.78	[0.44, 1.38]	0.39
Female	0.95	[0.50, 1.81]	0.87	1.04	[0.66, 1.63]	0.88
Elixhauser index	0.99	[0.84, 1.17]	0.89	**1.08**	**[0.99, 1.19]**	**0.09**
Payer						
Medicaid	0.71	[0.27, 1.92]	0.51	0.91	[0.48, 1.72]	0.77
Private	0.88	[0.38, 2.01]	0.75	1.06	[0.59, 1.90]	0.85
Other	0.68	[0.17, 2.76]	0.59	0.43	[0.14, 1.33]	0.14
Median household income in 1st quartile	0.69	[0.33, 1.41]	0.30	0.83	[0.54, 1.29]	0.41
Location						
Metropolitan area, 250,000 to 999,000	1.72	[0.85, 3.46]	0.13	**1.64**	**[1.07, 2.50]**	**0.02**
Micropolitan to metropolitan area, <250,000	0.95	[0.36, 2.48]	0.91	1.16	[0.68, 1.99]	0.59
Not metropolitan or micropolitan	**2.80**	**[0.86, 9.10]**	**0.09**	1.77	[0.73, 4.33]	0.21
Discharge disposition						
Rehab or NH	0.49	[0.09, 2.53]	0.39	1.96	[1.04, 3.68]	0.04
Transfer to short-term hospital	0.78	[0.08, 8.05]	0.84	0.84	[0.19, 3.78]	0.82
Patient-directed discharge	**2.24**	**[0.95, 10.99]**	**0.06**	**2.84**	**[1.10, 7.36]**	**0.03**

Variables with values of p<0.10 are presented in bold.
*Caplacizumab use was omitted from Cox proportional hazard regression analysis as no patient using it experienced readmission for exacerbation. In other words, caplacizumab eliminated the exacerbation risks. TMA: Thrombotic microangiopathy; aHR: adjusted hazard ratio; CI: confidence interval; NH: nursing home.

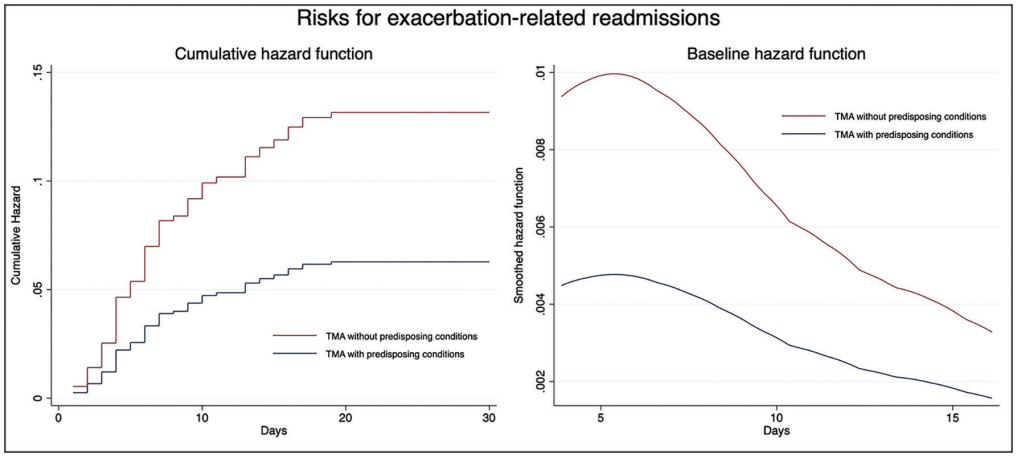

Figure 1. Risks for exacerbation-related readmissions.
TMA: Thrombotic microangiopathy.

of previous studies can shed light on a critical gap in current practice to reduce readmissions in this population nationally. Our findings show that the highest risk of exacerbation-related readmission is within the first week, with over 80% occurring within 14 days. These results are consistent with data from the Oklahoma TTP-HUS registry, which demonstrated early post-treatment relapse patterns in patients with idiopathic TTP [20]. In our cohort, the TMA-only group exhibited a higher exacerbation-related readmission rate (13.7% vs. 6.4%), while all-cause readmission rates were higher in the group with predisposing conditions (26.2% vs. 21.9%). This heterogenous TMA cohort had a 13.7% exacerbation-related admission rate, lower than previously reported rates of 20%-44% in immune-mediated TTP, while our all-cause readmission rates were consistent with the rate of 20.2% found in 211 hospitalized U.S. patients with severe ADAMTS-13 deficiency [21]. Readmissions remain a significant burden, evidenced by persistently high rates across different databases.

This study expands prior research by providing nationally representative data and explicitly quantifying exacerbation and readmission timing and risk factors. While randomized trials have shown that most early exacerbations occurred within 7 days after the cessation of plasmapheresis [12], prior studies did not systematically assess exacerbation timing relative to discharge [12,13,14,20]. U.S. and international registries also lack 30-day timelines of these events [6,7,8,9,10,22]. Our findings bridge this gap, demonstrating that early post-discharge exacerbations are a significant concern and underscoring the need for closer monitoring.

In our nationally representative cohort, nearly one-fourth of patients were readmitted for any reason within 30 days after discharge for TMA requiring plasmapheresis. Exacerbation-related readmission rates within 7 and 30 days were respectively estimated at 9% and 14% in the TMA-only group, a proxy for primary immune-mediated TTP. This group also exhibited more than twice the risk for exacerbation-related readmissions compared to those with predisposing conditions. This group should be considered high-risk. In practice, these patients are closely monitored with frequent laboratory evaluations for the first month after discharge [23]. Our findings suggest that they benefit from close follow-up, especially in the first two weeks. Early detection and outpatient treatment, such as treatment with rituximab or caplacizumab, could potentially reduce exacerbation-related readmissions. In contrast, patients with predisposing conditions warrant efforts to reduce complications given their higher comorbidity burdens (e.g., higher Elixhauser score and 5% higher all-cause readmission rates).

Our findings also suggest that rural residence and patient-directed discharge contribute to increased exacerbation risks. These associations highlight disparities in access to follow-up care and the necessity of targeted interventions and management strategies, including prioritizing outpatient follow-up and laboratory monitoring.

In our cohort, patients receiving caplacizumab did not experience exacerbation-related readmissions, although its use was infrequent (2.0% of cases). This low utilization likely reflects barriers such as cost, access, and limited experience as of 2020. While our finding aligns with clinical trial data [12,13,14], the small subgroup size prevents a robust analysis, highlighting the need for further real-world evidence from more recent datasets as the adoption of caplacizumab increases. Despite treatment advances, gaps remain in implementing effective treatment approaches and care transition [15,24,25].

This study also provides novel insight into the association between COVID-19 and TMA. In the 2020 NRD, COVID-19 was identified as a predisposing condition in 7.1% of patients with TMA with predisposing conditions or even more patients when excluding HUS, reflecting its role as a trigger for TMA [17,18]. This finding provides a foundation for future investigations into the interplay between viral infections and TMA.

Study Limitations

Our study has several limitations. First, the inability of ICD-10 codes to differentiate between TMA subtypes, coupled with the lack of ADAMTS-13 activity data, prevented precise case classification. Plasmapheresis is often used empirically for suspected primary immune-mediated TTP until diagnosis is confirmed. Claims-based identification of idiopathic TTP is difficult [26], and our use of the TMA-only group as a proxy for immune-mediated TTP and the lack of data on ADAMTS-13 levels limit the study's generalizability. Furthermore, administrative data lack clinical granularity, such as laboratory values or treatment details beyond ICD-10 codes, which hinders a deeper interpretation of our results. Despite these limitations, the large, nationally representative dataset utilized in this study provides valuable insights into the timing, risk factors, and outcomes associated with exacerbation-related and all-cause readmissions in patients with TMA requiring plasmapheresis.

Conclusion

Our findings highlight unmet needs in post-discharge management for patients with TMA requiring plasmapheresis. The TMA-only group has the highest risk for exacerbation-related readmissions, particularly within the first two weeks after discharge. Rural residence and patient-directed discharge further exacerbate these risks, reflecting disparities in follow-up care.

Future research should focus on validating these findings using national registries and more recent datasets and examining the impact of evolving therapies, including caplacizumab, on exacerbation and readmission outcomes. Additionally, studies exploring strategies to improve care transitions, such as outpatient infusions, telemedicine, and patient education initiatives, could provide actionable solutions to reduce readmission risks in this vulnerable population.

Ethics

Ethics Committee Approval: The University of Kentucky Institutional Review Board determined that this study met the federal criteria to qualify as an exempt study on 15/12/2023 (IRB #92969).

Informed Consent: The requirement for informed consent was waived because this study utilized a publicly available, de-identified database.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.R.T., T.Y., S.X.M., M.I., A.Q., H.K.; Concept: A.R.T., T.Y., S.X.M., A.Q., H.K.; Design: A.R.T., T.Y., S.X.M., M.I., A.Q., H.K.; Data Collection or Processing: H.K.; Analysis or Interpretation: A.R.T., T.Y., S.X.M., M.I., A.Q., H.K.; Literature Search: A.R.T., T.Y., A.Q., H.K.; Writing: A.Q., H.K.

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Supplementary Table 1. Definitions and ICD-10 codes for predisposing factors for thrombotic microangiopathies.

Variable name	ICD-10 codes	Note
Hemolytic uremic syndrome (HUS)	D59.3	HUS is caused by various mechanisms. Even though HUS should ideally be separated from atypical HUS, the ICD-10 code does not differentiate HUS from atypical HUS. Given the fact that the management is different from that of TTP, HUS cases were categorized as TMA with predisposing conditions in our analysis.
Pregnancy-related conditions	O00-O99 and Z3A.x	"x" indicates gestational weeks (e.g., Z3A.10 = 10 gestational weeks).
Solid-organ or hematopoietic transplants	Z94.x and T86.x	A transplant-associated TMA diagnosis code was added in 2022, which was not available in NRD 2020.
Autoimmune conditions	Modified "cmr_autoimmune"	Modification of an existing "autoimmune" variable from Elixhauser index variables in the dataset by removing M31.1 (TMA).
Malignancies	Combined "cmr_cancer_ lymph," "cmr_cancer_leuk," and "cmr_cancer_mets"	Combination of three existing Elixhauser variables: malignancy = 1 for the presence of metastatic cancer, leukemia, or lymphoma in the dataset.
Complicated hypertension	"cmr_htn_cx"	An existing variable (cmr_htn_cx) was used.
Sepsis	A40 and A41	The database does not distinguish between POA and hospital-acquired diagnoses (non-POA) except for the primary diagnosis.
COVID-19	U071	COVID-19 has been reported to trigger TTP.

HUS: Hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura; TMA: thrombotic microangiopathy; POA: present on admission.

Covariates for readmission analyses

- Discharge disposition was categorized as (1) home with or without home health, (2) rehab or nursing home, (3) short-term hospital transfer, or (4) against medical advice (patient-directed discharge).
- Location of residence was categorized as metropolitan areas with (1) ≥1 million, (2) 250,000 to 999,000, and (3) 50,000 to 249,000 people or (4) other rural areas.
- Elixhauser comorbidity index scores used all 38 comorbid conditions regardless of present-on-admission status. Since we were interested in assessing risk factors for readmissions, it was reasonable to include all patient conditions available at the time of discharge for Elixhauser index calculations.