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Real- World Use of Complement Inhibitor Therapy in Critically Ill Children With Thrombotic Microangiopathy: Results From the Spanish Multicenter Matucip Registry.

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Abstract

Background

Complement inhibitor therapy is the first-line therapy for suspected complement-mediated hemolytic uremic syndrome (CM-HUS), but is also used off-label in other thrombotic microangiopathy (TMA) subtypes. This study aimed to characterize complement inhibitor therapy use in pediatric patients with TMA admitted to the pediatric intensive care unit (PICU).

Methods

Retrospective observational study of patients older than 1 month admitted to the PICU with TMA who received complement inhibitor therapy between 2017 and 2025, using data from the MATUCIP registry (20 Spanish PICUs).

Results

A total of 40 children were analyzed. Half were diagnosed with CM-HUS, 40% with infection-associated TMA, and 10% with secondary TMA. Eculizumab was used in 82.5% of cases. The median time from diagnosis to treatment initiation was 3 days (IQR 1–5). Compared to CM-HUS, non-CM-HUS patients exhibited a higher rate of extrarenal manifestations (95% vs. 50%; p = 0.003), later treatment initiation (4.5 [IQR 3–6] vs. 2 [IQR 1–3] days; p = 0.003), longer PICU stays (21 [IQR 11.5–27.5] vs. 9 [IQR 3.7–14.2] days; p = 0.003), and a higher incidence of hypertension at discharge (95% vs. 58%, p = 0.019). Kidney replacement therapy was required in 72.5%, with continuous kidney replacement therapy as the predominant modality. Mortality was 5%.

Conclusions

Among children with TMA admitted to the PICU and treated with complement inhibitor therapy, half had suspected CM-HUS, while the remaining half received off-label therapy. Patients with suspected CM-HUS initiated treatment significantly earlier than patients with other TMA subtypes.

INTRODUCTION

Thrombotic microangiopathies (TMA) constitute a heterogeneous group of diseases characterized by vascular endothelial injury that leads to microangiopathic hemolytic anemia, thrombocytopenia, and ischemic damage in different organs[1, 2]. TMAs are classified into different subgroups based on the pathophysiological mechanism responsible for vascular injury: severe deficiency in ADAMTS13 activity in thrombotic thrombocytopenic purpura, dysregulation of the alternative complement pathway in complement-mediated hemolytic uremic syndrome (CM-HUS), and infectious processes such as

hemolytic uremic syndrome secondary to Shiga toxin-producing *Escherichia coli* infections (STEC-HUS), among others [2–4].

Humanized anti-C5 monoclonal antibodies (eculizumab and ravulizumab) are drugs that bind to complement protein C5, thereby blocking its cleavage into C5a and C5b and consequently preventing the formation of the membrane attack complex (C5b-9) [5]. These agents constitute the treatment of choice in patients with suspected CM-HUS, as they act directly on its underlying pathophysiological mechanism. In clinical practice, they are also used off-label in other forms of TMA with severe and/or refractory involvement, since it is assumed that complement activation, although not the initiating mechanism, frequently contributes to the progression and amplification of endothelial damage [6–9].

Published evidence on the use of these agents in the pediatric population has focused primarily on specific subgroups of TMA, particularly CM-HUS [10–13] and STEC-HUS [14–18]. Recently, Lax et al. reported a cohort of 24 pediatric patients with CM-HUS, STEC-HUS, or transplant-associated TMA (TA-TMA) treated with eculizumab [19]. However, the available evidence mainly evaluates medium- and long-term outcomes, primarily in terms of disease control. Data on the impact of these drugs during the acute phase of the disease, particularly in the acute intensive care setting, are limited in both adult and pediatric patients. Understanding patient characteristics and the effects of these agents during this critical phase is essential to optimize initial therapeutic decision-making, establish prognostic factors, and improve the acute management of these patients in pediatric intensive care units (PICU).

Therefore, the primary objective of this study is to characterize the use of complement inhibitor agents in children diagnosed with TMA while admitted to the PICU, including indications, timing, and treatment patterns. As a secondary objective, we aimed to describe and analyze the clinical course during PICU admission in this population.

METHODS

Ethical aspects

The study was reviewed and approved by the Research Ethics Committee (REC) of Galicia (code 2018/228).

Study design and study population

A retrospective descriptive observational study was conducted using data from the MATUCIP registry, a multicenter database involving 20 PICUs in Spain. Data collection comprised a retrospective phase from January 2017 to June 2018, followed by a prospective phase from July 2018 to December 2025. All pediatric patients older than 1 month of age with a diagnosis of TMA who received treatment with complement-inhibiting agents during their PICU admission were included and their data were pseudonymized according to REC indications.

Definitions and Measurements

- Demographic and clinical variables: age (months), sex, weight (kilograms), reason for admission, initial clinical manifestations (gastrointestinal, respiratory, neurological, or others), and relevant personal and family history. Chronic pharmacological treatment as well as recent exposure to drugs or vaccines were also recorded.
- TMA diagnosis. Blood analytical parameters at the time of suspected TMA were collected. Suspected TMA diagnosis was established in the presence of microangiopathic hemolytic anemia (hemoglobin < 10 g/dL together with > 1% schistocytes in peripheral blood and/or elevated LDH and/or decreased haptoglobin), thrombocytopenia (platelet count < 150,000/μL or > 25% decrease from baseline value), and acute kidney injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria[20]. Additionally, cases with clinical suspicion of TMA that did not meet the complete triad were also collected. Patients were classified into different TMA subtypes, as shown in Figure 1.
- Management and treatment. Administration of maintenance fluid therapy, intravenous fluid bolus, intravenous albumin, antibiotic therapy, antihypertensive drugs, need for kidney replacement therapy, plasmapheresis, or transfusion of red blood cells, platelets, and/or fresh frozen plasma were recorded. In cases where intravenous fluids or transfusions were administered, the volume in mL/kg was quantified. For all pharmacological treatments, the name of the drug name was recorded. Regarding complement inhibitor drugs, the number of doses, start date, and time in days from suspected TMA diagnosis to administration of the first dose were recorded. Early treatment initiation was defined as administration of the first dose within the first 48 hours after suspected diagnosis.
- Clinical evolution. Neurological, cardiac, and gastrointestinal involvement during admission were recorded. Blood laboratory tests were collected on days 1, 2, 3, 4, 5, 6, and 7 after TMA diagnosis, as well as at PICU discharge. Likewise, sequelae present at PICU discharge (kidney injury, hypertension, neurological, cardiac, or gastrointestinal involvement), mortality, and PICU length of stay (days) were documented.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 24.0 (SPSS Inc., Chicago, IL, USA) and JASP version 0.96.0 (JASP Team, University of Amsterdam, The Netherlands). Figures were created using JASP version 0.96.0 and Microsoft PowerPoint version 16.16.27 (Microsoft Corporation, Redmond, WA, USA). Categorical variables were reported as frequencies and percentages, while continuous variables were presented as medians with interquartile ranges (IQR). Univariate analyses were performed using the χ^2 test or Fisher's exact test for categorical variables, and the Mann-Whitney U test or Kruskal-Wallis test for continuous variables, as appropriate. Statistical significance was set at $p < 0.05$. Given the descriptive nature of the study and the limited sample size, between-group comparisons were considered exploratory. No formal primary outcome was defined for hypothesis testing.

RESULTS

Study population

Between 2017 and 2025, 160 patients were enrolled in the MATUCIP registry. Of these, 40 patients (25%) received treatment with complement inhibitors and constituted the study sample for the present analysis. Half of those patients (20/40) were diagnosed with CM-HUS, 40% (16/40) with infection-associated TMA — the majority in the context of STEC-HUS (13/16) — and the remaining 10% with secondary TMA, occurring in the setting of systemic lupus erythematosus, hematopoietic stem cell transplantation, and ciclosporin use in a patient with inflammatory bowel disease.

Baseline demographic, clinical, and laboratory characteristics

Of the 40 patients treated with complement inhibitors, 47% (19/40) were male, with a median age of 4.2 years (IQR 1.8–8.8) and a median weight of 17 kg (IQR 12–29). Relevant medical history was present in 22.5% of patients (9/40), with four cases involving significant underlying conditions: two patients with prior hematopoietic stem cell transplantation, one with inflammatory bowel disease, and one with suspected autoimmune hepatitis. At the time of diagnosis, hemolytic anemia was present in 72% of cases (29/40), and schistocytes were identified on peripheral blood smear in 87% (35/40). The classical clinical triad of anemia, thrombocytopenia, and acute kidney injury was present in 52% of cases (21/40). Baseline clinical and demographic characteristics, along with laboratory values at admission, are summarized in Table 1 for the overall cohort and stratified by TMA subtype.

Complement inhibitor therapy

Of the 40 patients treated with complement inhibitors, 82.5% (33/40) received eculizumab, 15% (6/40) received ravulizumab, and one patient (2.5%) was initiated on eculizumab and subsequently switched to ravulizumab. The median time from diagnosis to treatment initiation was 3 days (IQR 1–5). Figure 2 shows the time from diagnosis to complement inhibitor administration according to TMA subtype.

Early treatment administration (within the first 48 hours of diagnosis) was carried out in 40% of cases (16/40). When analyzing by subgroups, CM-HUS patients received early treatment in 60% of cases (12/20), whereas in secondary TMA this percentage was 25% (1/4) and in infection-associated TMA patients 19% (3/16). No serious adverse effects related to complement inhibitor therapy were reported in any patient.

Clinical course during PICU stay

Regarding therapeutic management, 72.5% of patients (29/40) required kidney replacement therapy at some point during PICU admission. Some patients required more than one modality; continuous kidney replacement therapy (CKRT) was the most frequently used, accounting for 79% of cases (23/29), followed by intermittent hemodialysis in 21% (6/29) and peritoneal dialysis in 3.4% (1/29). Figure 3 illustrates the evolution of the main laboratory parameters and urine output throughout the admission.

The median length of stay in the PICU was 14 days (IQR 8–22.5). At discharge, hypertension and kidney injury were the most frequent sequelae, occurring in 74.3% of patients (29/39), while neurological sequelae were recorded in 10% of cases (4/40). Two patients (5%) progressed to brain death and died prior to PICU discharge. Table 2 summarizes the clinical course during admission and supportive therapies, both for the overall cohort and stratified by TMA subgroup.

Comparative analysis between patients with CM-HUS and patients receiving off-label complement inhibitor therapy.

When comparing patients with CM-HUS against those with other TMA subtypes, hereafter referred to as non-CM-HUS, both groups were comparable in terms of demographic variables and laboratory parameters at admission. Extra-renal manifestations were more frequent in the non-CM-HUS group compared to CM-HUS (19/20 [95%] vs. 10/20 [50%], $p = 0.003$), driven particularly by a higher rate of encephalopathy (9/20 [45%] vs. 2/20 [10%], $p = 0.031$) and respiratory involvement (8/20 [40%] vs. 1/20 [5%], $p = 0.02$). Patients with CM-HUS received complement inhibitor therapy significantly earlier than those with other TMA subtypes (2 [IQR 1–3] vs. 4.5 [IQR 3–6] days, $p = 0.003$) and required a shorter duration of CKRT (5 [IQR 1.5–8.2] vs. 14 [IQR 8–18.5] days, $p = 0.002$). At PICU discharge, the non-CM-HUS group exhibited a significantly higher prevalence of hypertension (18/19 [95%] vs. 11/19 [58%], $p = 0.019$). The median PICU length of stay was significantly longer in the non-CM-HUS group (21 [IQR 11.5–27.5] vs. 9 [IQR 3.7–14.25] days, $p = 0.003$). Detailed clinical characteristics, management, and clinical course for both groups are summarized in Table 3.

DISCUSSION

To our knowledge, this is the first multicenter study to specifically evaluate the use of complement inhibitors in pediatric patients with TMA admitted to the PICU, as well as their short-term clinical course. Eculizumab was the most commonly used agent, administered in 82.5% of cases. Among all the patients, 50% had a suspected diagnosis of CM-HUS, while the remaining 50% received these agents in other TMA subtypes on an off-label basis. Notably, initiation of complement inhibitor therapy occurred significantly earlier in patients with CM-HUS compared to those with other TMA subtypes.

Off-label use of complement inhibitor therapy

Off-label use of complement inhibitor therapy was highly prevalent in our cohort, accounting for half of the treated patients. This frequent use beyond approved indications likely reflects the severity and complexity of clinical presentation at the time of treatment initiation, as well as the challenges in establishing a definitive etiological diagnosis in the acute phase of TMA. A substantial proportion of patients exhibited significant organ involvement, including neurological complications—such as seizures (40%) and encephalopathy (45%)—and respiratory failure requiring invasive mechanical ventilation (30%). In this context, and given the potential role of complement dysregulation across different TMA subtypes, clinicians may have opted for early complement blockade as a therapeutic strategy in the absence of equally effective alternatives. These findings are consistent with previous reports describing increasing

off-label use of complement inhibitors in severe or unclear cases of TMA, particularly in critically ill patients, where early treatment is often prioritized despite limited high-quality evidence.

The most frequent off-label indication was STEC-HUS. The role of complement inhibitors in this condition has been extensively studied, although current evidence does not support their systematic administration. Multiple case series[14, 21–23] and case reports[24–28] have described their use, but systematic reviews [15, 18] did not demonstrate consistent clinical benefit. The two available randomized controlled trials in pediatric patients have not fully clarified the role of complement inhibitor therapy in STEC-HUS. The ECULISHU trial (Garnier et al., 2023)[16] did not demonstrate benefit during the acute phase of the disease but reported a lower incidence of kidney sequelae at one year in patients treated with eculizumab, although patients with severe extrarenal involvement were excluded from this study. The ECUSTEC trial (Ives et al., 2024)[17], specifically designed to evaluate severe forms of STEC-HUS, did not demonstrate neurological benefit at 60 days. Evidence for complement inhibition therapy in Sp-HUS is even more limited, being restricted to small case series and case reports in patients with severe disease [29–33]. Another off-label indication with increasing use in practice is TA-TMA [34–36]. Jodele et al. [37]published the first prospective multi-institutional study in children and young adults with high-risk TA-TMA, demonstrating significantly superior survival at 6 months and at 1 year post-transplant compared with untreated historical controls. However, the safety profile of complement inhibitors in this setting remains controversial. Schoettler et al. (2025)[38], in a single-center retrospective case-control study, observed that pediatric patients with TA-TMA treated with eculizumab had a significant increase in bacterial and viral infections, as well as infection-related mortality.

Our findings reflect real-world clinical practice, where complement inhibitors are frequently used off-label in patients with severe TMA [39]. This observation aligns with Muff-Luett et al.[40], who reported that 44% of eculizumab treatments in a cohort of 152 pediatric patients were for non-approved indications. Similarly, studies examining off-label drug use in pediatrics have identified eculizumab as one of the most frequently prescribed medications outside approved indications [41, 42]. This practice pattern reflects the challenges of real-world clinical care of critically ill pediatric patients. When managing patients with severe, rapidly progressive TMA, clinicians are frequently confronted with diagnostic uncertainty and the urgency of the clinical situation, often having to initiate multiple empirical therapies simultaneously before a definitive etiologic diagnosis can be established. Moreover, etiologic diagnosis may be unclear in the early days of presentation, and even when a compatible etiology is identified (for example, through microbiological isolation of STEC), this does not exclude the possibility of underlying concomitant complement dysregulation [43]. As Kim et al. [44] noted, despite numerous case reports, case series, and descriptive studies of eculizumab use in off-label indications, there remains a striking paucity of well-designed clinical trials to rigorously evaluate its efficacy and safety. These challenges underscore the need for continued research into the potential role of complement inhibitors in different TMA subtypes, particularly those with severe organ involvement.

Differences between complement inhibitor therapy in CM-HUS and other TMA subtypes

In patients with suspected CM-HUS, the median time from clinical suspicion to treatment initiation was 2 days, consistent with previously reported intervals of 2–2.5 days [12, 13, 19]. This timing is similar to that reported in non-critically ill cohorts, suggesting that treatment is driven mainly by diagnostic suspicion rather than by disease severity, with prompt initiation once alternative etiologies are reasonably excluded in line with current guidelines. This highlights the importance of a rapid diagnostic evaluation, particularly since initial laboratory values and clinical presentation, with diarrhea as the predominant symptom, were similar across both groups. By contrast, initiation was significantly delayed in non-CM-HUS patients, likely reflecting off-label use as a rescue strategy in cases of clinical deterioration or lack of response to conventional therapy.

Limitations

Our study has several limitations. First, the absence of systematic follow-up data after PICU discharge limits the assessment of long-term outcomes, including chronic kidney disease, persistent neurological sequelae, and disease recurrence. It also restricts the evaluation of response to complement inhibitor therapy, given that complete response is generally defined in the literature as sustained hematological and kidney recovery persisting beyond four weeks. Second, the limited sample size reduces the statistical power of between-group comparisons and may limit the detection of clinically meaningful differences. This is further compounded by the etiological heterogeneity of the non-CM-HUS group, which additionally limits the interpretation of these comparisons. Finally, treatment indication was not standardized and was likely influenced by disease severity, clinical deterioration, and local practice patterns, introducing potential confounding by indication.

Strengths and clinical implications

This study provides relevant data to characterize the use of complement inhibitor therapy in pediatric patients with TMA admitted to the PICU, a setting in which available evidence remains limited. Its multicenter design, with the participation of 20 PICUs, strengthens the validity of the results and reflects real-world clinical practice in a heterogeneous and representative setting. The high proportion of off-label use of these agents observed in our cohort highlights that, in daily clinical practice, complement inhibitors are frequently employed beyond their approved indications, underscoring the need for further research into their role in TMA subtypes other than CM-HUS.

CONCLUSION

In this national multicenter registry, among pediatric patients admitted to the PICU with suspected TMA who received complement inhibitor therapy, half were treated off-label, while the remaining half were treated for suspected CM-HUS. Patients with suspected CM-HUS initiated complement inhibitor therapy significantly earlier than those with other TMA subtypes.

Declarations

Funding: The study has not received private or public fundind.

Data availability: the datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: ARN has received funding from Alexion for academic activities. LBB has received honoraria from Alexion for educational activities and congress attendance support. The rest of the authors report no conflicts of interest.

Author contribution: All authors contributed to the study conception and design. Material preparation and data collection were performed by LBB, EGR, SBP, CEP and the MATUCIP registry group. Statistical analysis was performed by SBP and EGR. The first draft of the manuscript was written by EGR and reviewed by ARN, LBB, SBP and CEP. Critical review was performed by ARN. All authors read and approved the final manuscript.

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Tables

Table 1 to 3 are available in the Supplementary Files section.

Figures

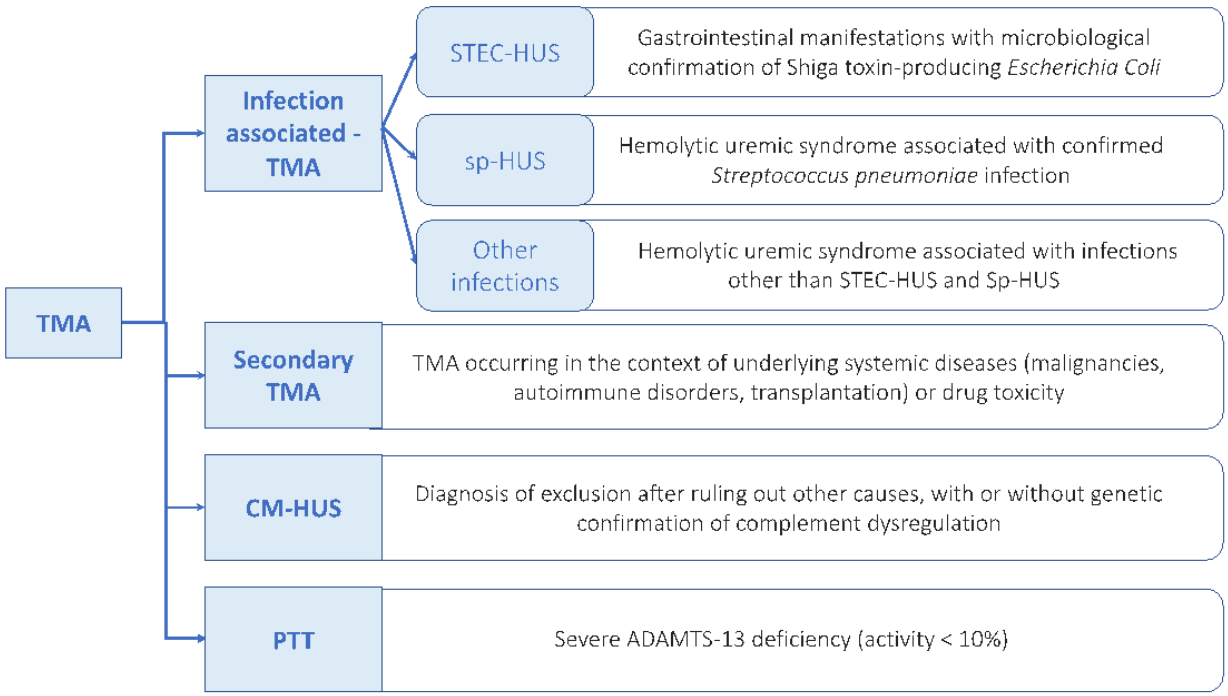


Figure 1

Diagnostic criteria and definitions of TMA subtypes. TMA: Thrombotic microangiopathy; STEC-HUS: hemolytic uremic syndrome secondary to Shiga toxin-producing *Escherichia coli* infections; sp-HUS: *Streptococcus pneumoniae*-associated hemolytic uremic syndrome; CM-HUS: complement-mediated hemolytic uremic syndrome ; TTP: thrombotic thrombocytopenic purpura

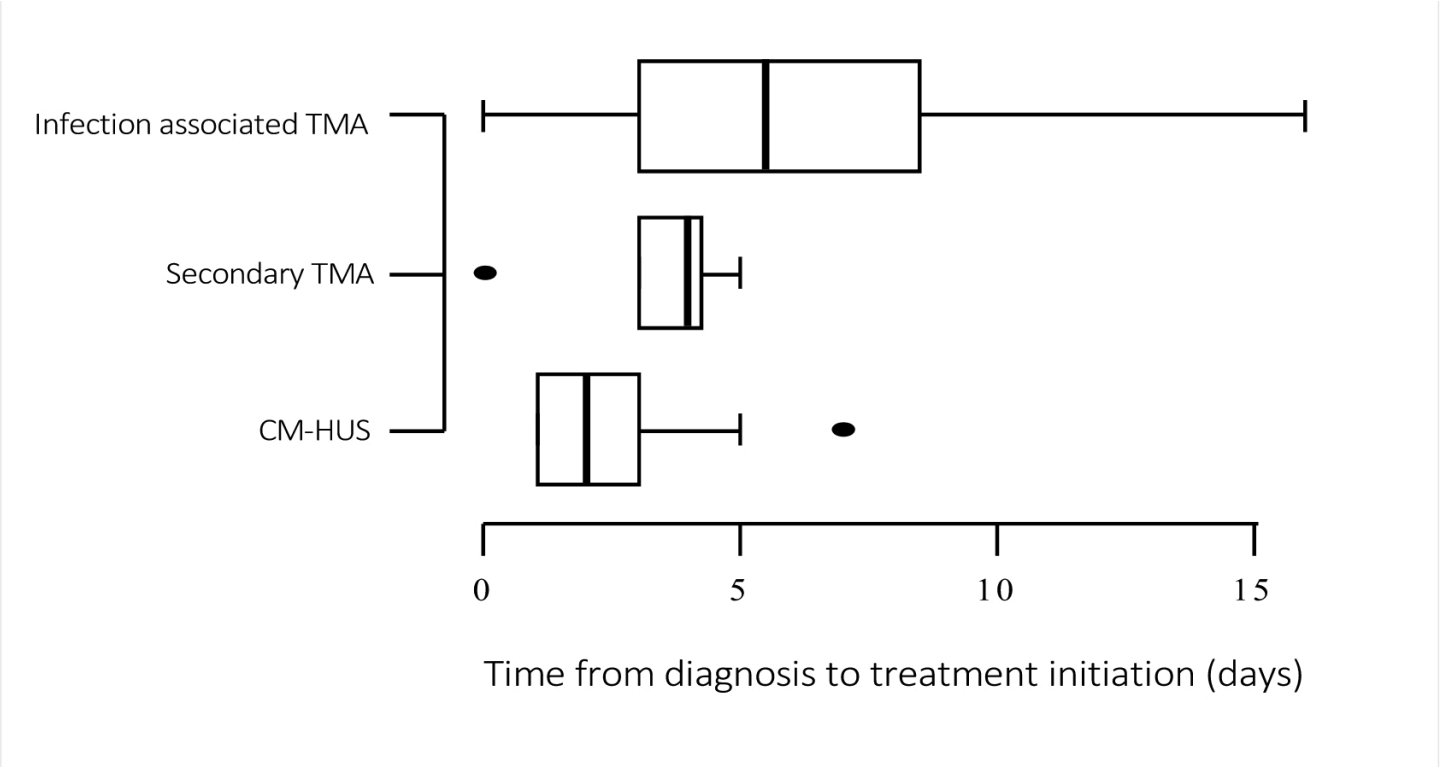


Figure 2

Time from diagnosis to complement inhibitor initiation according to TMA subtype. Data are presented as box plots with whiskers (median, IQR, and extreme values)

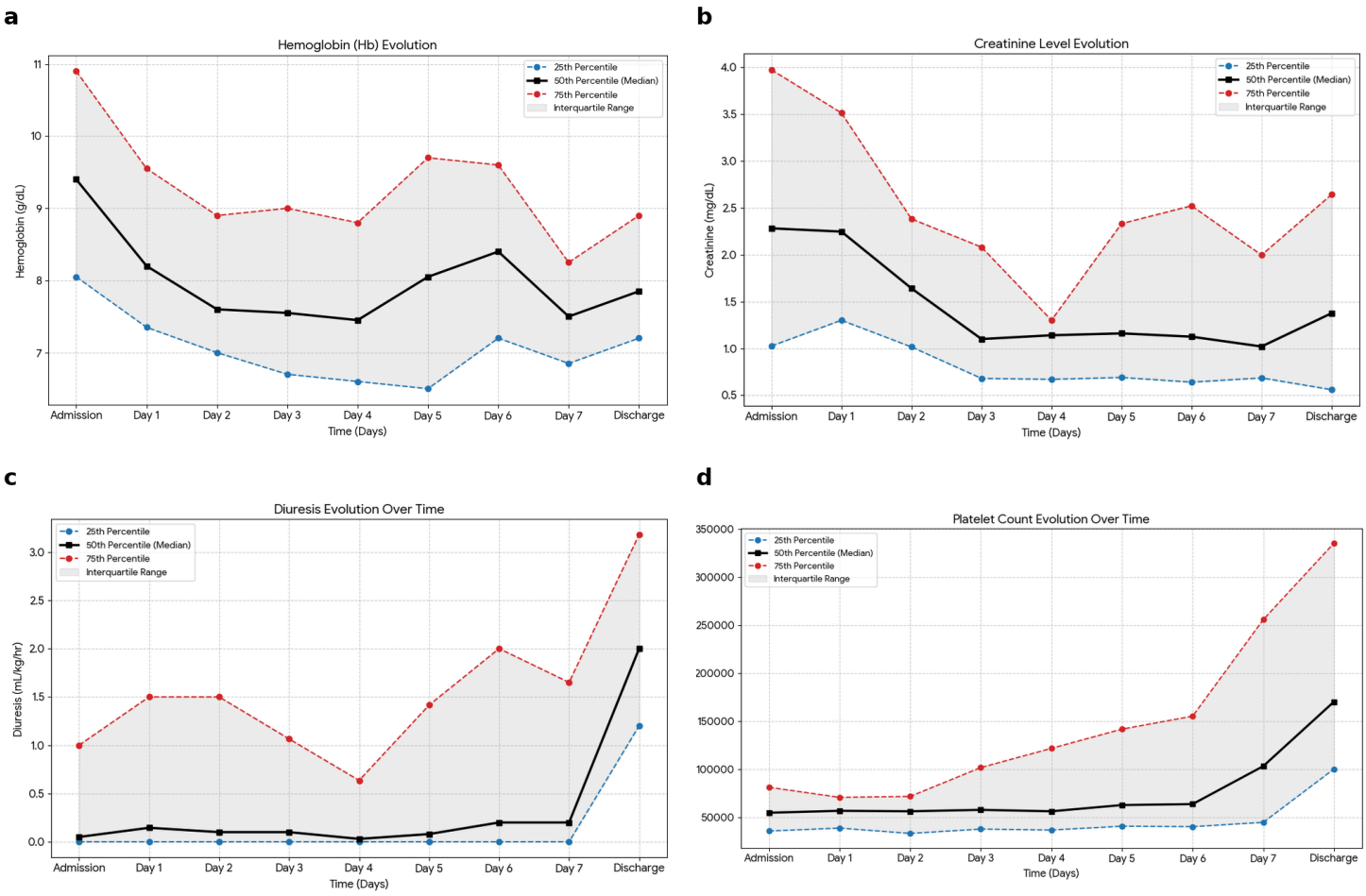


Figure 3

Evolution of hemoglobin, creatinine, urine output, and platelet count from pediatric intensive care unit admission to discharge in patients with thrombotic microangiopathy treated with complement inhibitors. Data are presented as median (black line) and interquartile range (shaded area, bounded by the 25th and 75th percentiles) for each time point. a Hemoglobin (g/dL). b Creatinine (mg/dL). c Urine output (mL/kg/h). d Platelet count (/mm³).

Supplementary Files

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- GraphicalAbstrac.June2026.pptx
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