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Original Research Article

Caplacizumab as an Empirical Therapy in Immune Thrombotic Thrombocytopenic Purpura: A Single Center's Proactive Strategy to Reduce Morbidity and Mortality

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Abstract

Background: Immune thrombotic thrombocytopenic purpura (iTTP) is a critical thrombotic microangiopathy in which early treatment is essential to reduce mortality and long-term complications. **Objectives:** To describe the local experience, at the National Center for Cancer Care and Research in Qatar, with the safety and practicality of initiating caplacizumab empirically in patients with a high clinical likelihood of iTTP before confirmation of ADAMTS-13 deficiency. **Methods:** Medical records of adults treated with caplacizumab for suspected iTTP between March 2021 and January 2025 were reviewed. The primary outcomes were the incidence and severity of adverse events and time to platelet recovery. **Results:** Twelve patients received caplacizumab; eight were treated empirically and four after diagnostic confirmation. The median age was 38.5 years (range 23–77), and 58.3% were female. The median PLASMIC score was 6.5 (range 5–7). ADAMTS-13 testing confirmed iTTP in 11 patients (median activity 5%, range 3–6), with a median turnaround time of 10 days (range 7–26). Platelet recovery occurred a median of 4.5 days (range 2–6) following caplacizumab initiation. All 11 patients with iTTP achieved a clinical response and were alive at last follow-up (median, 330 days). One experienced a relapse. Two grade 3 bleeding events were reported, with no fatal or intracranial hemorrhages. **Conclusion:** Early empiric use of caplacizumab in patients with a strong clinical suspicion of iTTP was safe and associated with favorable outcomes. This approach may be especially relevant in centers without rapid access to ADAMTS-13 testing, although larger studies are required to validate these findings.

Plain Language Summary

What is the context?

- iTTP is a rare but life-threatening blood disorder that causes small blood clots to form in blood vessels throughout the body.
- Treatment delays increase the risk of blood clots damaging the brain, kidneys, and other organs.
- Diagnosis of iTTP depends on a specialized laboratory test called ADAMTS13 activity testing.
- In many centers, ADAMTS13 testing is not rapidly available, and results may take several days or weeks.

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• Caplacizumab is a targeted treatment that blocks abnormal clot formation and has been shown to improve outcomes in patients with iTTP.
• Although disease-related consequences may occur despite therapy, delays in treatment may increase morbidity and mortality. Therefore, caplacizumab may be initiated before ADAMTS13 results are available in patients with a strong clinical suspicion of iTTP.

What is new?

• This retrospective study evaluated the experience of a single center in Qatar using caplacizumab empirically in patients with suspected iTTP between 2021 and 2025.
• Twelve patients received caplacizumab before or shortly after confirmation of the diagnosis.
• Most patients had a high PLASMIC score, indicating a strong likelihood of iTTP.
• ADAMTS13 test results required a median of 10 days to become available.
• Eleven of the twelve patients were ultimately confirmed to have iTTP.
• Patients treated empirically achieved rapid platelet recovery, with normalization occurring within a median of 4.5 days.
• All confirmed patients survived and achieved clinical remission during follow-up.
• No treatment-related mortality or severe long-term complications were observed.
• Bleeding events were infrequent and manageable.

What is the impact?

• This study provides real-world evidence supporting the safety and feasibility of starting caplacizumab early in patients with a high clinical suspicion of iTTP.
• Early empirical treatment may help reduce delays in care while awaiting ADAMTS13 results.
• Prompt initiation of caplacizumab may improve recovery and reduce the risk of severe complications and death.
• The findings are particularly relevant for centers with limited access to rapid ADAMTS13 testing.

Keywords
Thrombotic thrombocytopenic purpura, Caplacizumab, Empirical therapy, ADAMTS13, PLASMIC score

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Introduction

Immune thrombotic thrombocytopenic purpura (iTTP) is a is a rare and life-threatening thrombotic microangiopathy in which prompt treatment can significantly reduce morbidity and mortality.[1] Since nearly four decades, therapeutic plasma exchange (TPE) represents the standard of care for iTTP, enabling survival in over 80% of patients when initiated before the onset of irreversible organ damage.[2] This fulminant thrombotic microangiopathy is driven by the severe deficiency of the von Willebrand factor (vWF) cleaving protease called a disintegrin-like and metalloproteinase with thrombospondin type-1 motif, member 13 (ADAMTS13). This leads to unchecked vWF-mediated platelet adhesion, widespread microvascular thrombosis and consumptive thrombocytopenia, microangiopathic hemolytic anemia, and ischemic organ injury.[3] The identification of ADAMTS13 as the key enzyme in the pathophysiology of iTTP clarified the remarkable effectiveness of TPE, which restores the deficient enzyme, and subsequently paved the way for the development of recombinant ADAMTS13.[4]

Consequently, prompt disruption of vWF–platelet binding has emerged as a key therapeutic objective to limit early microvascular thrombosis while immunosuppressive therapy facilitates recovery of ADAMTS13 activity.[5] Caplacizumab is a bivalent anti-vWF nanobody that targets the A1 domain of vWF, thereby preventing the interaction between activated platelets and ultra-large vWF multimers released from the endothelium.[6] By blocking the pathological platelet–vWF interactions that result from impaired vWF cleavage in the setting of ADAMTS13 deficiency, caplacizumab effectively suppresses ongoing thrombus formation.[6] Clinical benefit was demonstrated in the phase II TITAN and phase III HERCULES trials, in which caplacizumab added to plasma exchange and immunosuppression accelerated platelet count recovery, decreased disease refractoriness and exacerbations, and significantly improved a composite endpoint of iTTP-related mortality, recurrence, and thromboembolic complications.[7,8] In 2019, the US Food and Drug Administration (FDA) approved caplacizumab for the treatment of adult patients with iTTP in combination with TPE and other immunosuppressive therapies based on the promising results of these trials.

Although caplacizumab may be initiated prior to ADAMTS13 result confirmation, based on the eligibility criteria in TITAN and HERCULES trials, the initiation of caplacizumab following the confirmation of ADAMTS13 is the widely adapted approach by most centers and international guidelines.[7-13] However, such delays in diagnosis can adversely affect

outcomes and increase mortality.[11] While international guidelines recommend confirming iTTP via ADAMTS13 testing before treatment initiation,[12,13] the timely access to this test remains limited in many centers, with results often delayed by several days or even weeks. This can jeopardize the critical window for initiating potentially lifesaving therapy.[13]

Due to the limited timely access to ADAMTS13, and since the introduction of caplacizumab at our hematology center in 2021, it became routine practice to urgently treat patients presenting with high clinical suspicion of iTTP with empiric caplacizumab until ADAMTS13 result is available. Patients with high clinical suspicion for iTTP include those with high risk for thrombotic microangiopathy, characterized by microangiopathic hemolytic anemia and a high PLASMIC score (≥5). This empirical approach was adopted due to the ADAMTS13 test being sent to an accredited external laboratory overseas, with an expected turnaround time of 5 to 14 days. If iTTP is subsequently confirmed, treatment is continued as per routine treatment protocol. In this study, we aimed to assess the safety and feasibility of initiating empirical caplacizumab treatment in patients with a strong clinical suspicion of iTTP, prior to confirmation of ADAMTS13 activity.

Methods

The medical records for all adult patients (≥18 years of age) treated with caplacizumab for iTTP at the National Center for Cancer Care and Research in Qatar between March 2021 and January 2025 were retrospectively reviewed. Patients with a clinical diagnosis of iTTP who were not treated with caplacizumab were excluded, as were patients whose ADAMTS-13 activity subsequently confirmed an alternative diagnosis (detailed below).

Diagnosis of iTTP was based on clinical presentation (microangiopathic hemolytic anemia and thrombocytopenia with or without organ ischemia) combined with a PLASMIC score, a validated 7-point clinical prediction tool incorporating platelet count, evidence of hemolysis, absence of active cancer, absence of prior solid-organ or stem-cell transplantation, mean corpuscular volume, international normalized ratio, and creatinine. It is used to estimate pretest probability of severe ADAMTS-13 deficiency prior to assay confirmation with a higher score predicting a higher risk probability. The score is usually interpreted into three categories: low risk (score 0 to 4 of 7), intermediate (score 5 of 7), and high (score 6 to 7 of 7).[14]

Given the delay in obtaining ADAMTS-13 results locally, treatment was initiated empirically (pre-emptively) in patients with intermediate-to-high PLASMIC scores pending confirmatory testing, per institutional protocol; treatment intent (definitive, i.e., initiated after ADAMTS-13 confirmation, versus pre-emptive, i.e., initiated empirically before results were available) was recorded for each patient. Patients initiated pre-emptive therapy whose subsequent ADAMTS-13 activity returned above the diagnostic threshold (≥10%) were considered to have an alternative diagnosis, had caplacizumab discontinued, and were excluded from efficacy analyses while being retained for safety reporting.

Data collection was standardized using a pre-piloted case report form (Supplemental File 1) and included demographics; baseline comorbidities; clinical symptoms and signs at presentation; laboratory findings at baseline and at defined follow-up intervals (including hemoglobin, platelet count, schistocyte percentage, lactate dehydrogenase (LDH), haptoglobin, creatinine, total bilirubin, and ADAMTS-13 activity); PLASMIC score; turnaround time to ADAMTS-13 result (defined as the interval from sample collection to result availability); duration and intent of treatment; concomitant therapies (therapeutic plasma exchange, corticosteroids, rituximab) and their dosing/duration; caplacizumab dosing and duration; adverse events; and vital/remission status at last follow-up. The electronic data collection sheet was accessed only by the investigators and stored on password-protected institutional computer devices.

The primary outcome measures were safety, defined as the incidence and severity of adverse events (graded according to the Common Terminology Criteria for Adverse Events, where applicable) during and after caplacizumab treatment, and time to platelet count recovery, defined as the interval from caplacizumab initiation to the first platelet count $\geq 150 \times 10^9$/L. Secondary outcome measures included the number of therapeutic plasma exchange sessions required; iTTP-related morbidity, defined as new or progressive ischemic organ injury according to International Working Group criteria[15]; survival rate at last follow-up; relapse rate, defined as recurrence of thrombocytopenia and microangiopathic hemolysis requiring re-initiation of therapy after achievement of clinical remission; and incidence of major bleeding, defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria.[16] Clinical remission was defined as normalization of platelet count and LDH sustained without relapse through last follow-up.

Descriptive statistics were used to summarize findings; continuous variables are reported as means with standard deviations or medians with ranges depending on distribution, and categorical variables as frequencies and percentages. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Hamad Medical Corporation Medical Research Center (protocol number MRC-01-25-073); the requirement for informed consent was waived given the retrospective design.

Results

A total of 12 patients had clinical suspicion of iTTP and received caplacizumab during the study period. Caplacizumab was initiated empirically in patients with a high clinical probability of iTTP, based on a high PLASMIC score and the presence of thrombotic microangiopathy, without waiting for ADAMTS13 confirmation. TPE was initiated concurrently and provided by the mobile apheresis service of the Central Blood Bank at the referring hospital. The cohort had a median age of 38.5 years (range 23 – 77), with seven patients (n = 7/12; 58.3%) younger than 40 years. Seven patients (58.3%) were female, and none was pregnant at presentation. Only two patients had baseline comorbidities with one patient having asthma and systemic lupus erythematosus, and the other having coronary artery disease, hypertension, and diabetes mellitus. At presentation, neurological manifestations were reported in nine patients (n=9/12; 75%), and eight patients (66.7%) had dermatologic findings: seven had petechiae or purpura and one had ecchymosis; however, none had documented central nervous system (CNS) infarction or bleeding. Fatigue was a frequent symptom (n = 10/12; 83%), while fever was present in one-third of the patients (n = 4/12; 33%). Gastrointestinal symptoms were noted in three cases (n = 3/12; 25%), including abdominal pain, diarrhea, and vomiting. Laboratory evaluation showed a mean hemoglobin of 8.2 ± 2.1 g/dL and a mean platelet count of $16.6 \pm 11.7 \times 10^9$/L at diagnosis. Schistocytosis was observed in all patients with a median of 6.4% (range 1.9 % - 12%) in quantifiable samples. LDH levels were elevated at a median of 718 U/L (range 211 – 1,580) with low haptoglobin (<10 mg/dL) detected in 83% (n = 10/12) of cases. Serum creatinine was elevated in half of the patients (n= 6/12; 50%), while total bilirubin levels reached a median of 40.5 µmol/L (range 7 – 143). The median PLASMIC score was 6.5, ranging from 5 to 7. Table 1 summarizes the baseline characteristics of included patients.

One patient was initially misdiagnosed, as The ADAMTS13 activity result was 48% and became available after three doses of caplacizumab. This patient was therefore excluded from the efficacy analysis, and caplacizumab was discontinued after three doses. The patient was 77 years old and was the only patient with an intermediate PLASMIC score of 5, while all other patients were younger than 60 years and had a high PLASMIC score of 6 or 7. Unfortunately, the patient died 90 days later due to sepsis and multi-organ failure, an outcome considered unrelated to caplacizumab treatment. For the remaining eleven confirmed cases, the median ADAMTS-13 activity at diagnosis was 5% (range 3 – 6), confirming severe deficiency. The median turnaround time for ADAMTS-13 results was 10 days (range 7 – 26). All patients received daily therapeutic plasma exchange (median 12 sessions, range 8–15), corticosteroids (median 40 days, range 25–45), rituximab (median 4 doses, range 3–8), and caplacizumab (median 28 doses, range 10–34). The median time from caplacizumab initiation to ADAMTS-13 result availability, among the empirically treated patients was 8 days (range 3 – 46). The median hospital stay was 21 days (range 10 – 143), and ICU stay lasted a median of 18 days (range 3 – 42). The median time from caplacizumab initiation until LDH normalization was 3 days (range 1 – 25; Figure 1).

At the last follow-up (median 330 days; range 43 to 1,460), all 11 patients with confirmed iTTP were alive, with 10 maintaining sustained remission and one experiencing a relapse. All patients exhibited a favorable clinical response, with normalization of hemolysis markers, liver function tests, and platelet counts. The median time to normalization of the platelet count was 4.5 days (range 2 – 6; Figure 1) following caplacizumab initiation. No long-term disease sequelae, morbidity, or treatment-related mortality were observed during follow-up.

Two grade 3 bleeding events occurred, though no serious adverse reactions attributable to caplacizumab were observed. The first grade 3 bleeding event was gastrointestinal and occurred in the misdiagnosed patient. The bleeding event did not require holding of caplacizumab or additional blood transfusion. Caplacizumab was discontinued after three doses when iTTP was excluded. The second grade 3 bleeding event was vaginal, requiring interruption in caplacizumab therapy, but no blood transfusion. This patient was concomitantly receiving apixaban, which was also held.

Discussion

Timely ADAMTS13 testing remains a significant challenge in managing iTTP, a life-threatening thrombotic microangiopathy. In decentralized health care settings, many hematology centers depend on referral-based testing, which can result in delays of several days to weeks. Although ADAMTS13 deficiency was not a required criterion for enrollment in the landmark clinical trials of caplacizumab, this single-center cohort describes empirical initiation of caplacizumab when ADAMTS13 results were delayed. Our findings suggest that early initiation of caplacizumab, guided by the PLASMIC score and clinical assessment, is both safe and feasible. All patients with confirmed iTTP achieved rapid platelet recovery and sustained remission with 100% survival. These outcomes are consistent with those reported in pivotal international trials.

The median time to platelet normalization in our cohort was 4 days, comparable to the 2.69 days reported in the HERCULES trial among patients treated with caplacizumab.[8] Our finding of complete hematologic response and absence of iTTP-related mortality is consistent with both the HERCULES and TITAN trials, which established caplacizumab as an effective adjunct to plasma exchange and immunosuppression, significantly reducing the composite endpoint of TTP-related

Table 1. Baseline Characteristics of All Patients Who Received Caplacizumab (N=12)

Demographics	
Age [years old; median (range)]	38.5 (23 – 77)
Female sex [n (%)]	7 (58.3)
No comorbidities present [n (%)]	10 (83.3)
No autoimmune disease present [n (%)]	11 (91.7)
Body Mass Index (BMI)	
Low [n (%)]	1 (8.3)
Normal [n (%)]	6 (50)
High [n (%)]	5 (41.7)
Laboratory parameters at presentation	
White Blood Cell Count [Males and Females 4 – 10 x10^9/L; median (range)]	7.08 (4 – 11)
Hemoglobin [Males 13 – 17 g/dL, Females 12 – 15 g/dL; median (range)]	8.35 (4 – 12)
Platelets [Males and Females 150 – 410 x10^9/L; median (range)]	12.5 (3 to 40)
Serum Creatinine	
Normal [n (%)]	6 (50)
Elevated [n (%)]	6 (50)
Alanine aminotransferase [Males 0 – 41 U/L, Females 0 – 33 U/L; median (range)]	30.5 (21 – 70)
Aspartate Aminotransferase [Males 0 – 40 U/L, Females 0 – 32 U/L; median (range)]	39 (18 – 80)
Total Bilirubin [Males and Females 0 – 21 µmol/L; median (range)]	40.5 (7 – 143)
Normal [n (%)]	3 (25)
Elevated [n (%)]	9 (75)
Elevated reticulocyte count [n (%)]	9 (75)
Low haptoglobin [n (%)]	10 (83.3)
LDH [Males 135 – 225 U/L, Females 135 – 214 U/L; median (range)]	718 (211 – 1,580)
Normal [n (%)]	1 (8.3)
Elevated [n (%)]	11 (91.7)
Clinical presentation	
PLASMIC score [median (range)]	6.5 (5 to 7)
Low (0 – 4; [n (%)])	0 (0)
Intermediate (5; [n (%)])	1 (8.3)
High (6 – 7; [n (%)])	11 (91.7)
French score [median (range)]	2 (0 to 2)
Low (0; [n (%)])	1 (8.3)
Intermediate (1; [n (%)])	1 (8.3)
High (2; [n (%)])	10 (83.3)
CNS symptoms [n (%)]; overlapping symptoms present	9 (75)
Confusion	4 (33.3)
Dizziness	2 (16.7)
Headache	2 (16.7)
One-sided weakness	2 (16.7)
Slurred speech	1 (8.3)
Seizure	1 (8.3)
Dermatologic symptoms present [n (%)]	8 (66.7)
Petechiae or purpura	7 (58.3)
Ecchymosis	1 (8.3)
Gastrointestinal symptoms present [n (%)]	3 (25)
Abdominal pain	1 (8.3)
Diarrhea	1 (8.3)
Epigastric pain and vomiting	1 (8.3)
Other symptoms [n (%)]	
Fatigue	10 (83.3)
Fever	4 (33.3)
Menorrhagia	1 (8.3)
Confirmed iTTP, n (%)	**11 (91.67)**
ADAMTS13 activity result [Median (range)]	5 (3 – 6)
Turnaround time to result [Days; Median (range)]	10 (7 – 26)

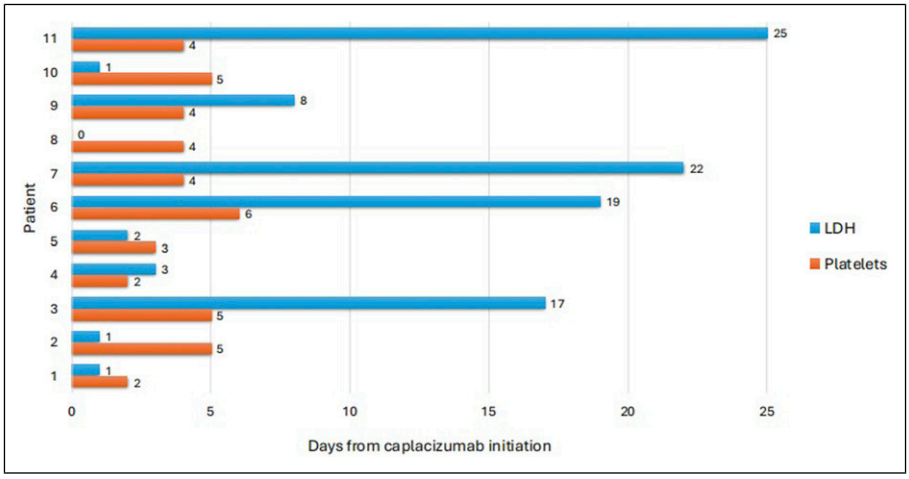


Figure 1. Time from caplacizumab initiation to platelet count recovery and lactate dehydrogenase (LDH) normalization in 11 patients with confirmed iTTP.

death, recurrence, or thromboembolic events.[7,8] Furthermore, the results align with real-world data from the Spanish and European multicenter cohorts who were guided by ADAMTS13 testing, confirming comparable efficacy and safety.[9,10]

This empirical strategy directly addresses the diagnostic and therapeutic gap emphasized by international guidelines. The 2020 ISTH guidelines recommend that treatment with TPE and corticosteroids for suspected iTTP should not be delayed while awaiting ADAMTS13 results. Moreover, recommended considering early administration of caplacizumab before receiving ADAMTS13 test results, provided that timely ADAMTS13 testing is available.[12] Similarly, the 2023 British Society for Hematology guideline endorses the early initiation of caplacizumab in high-probability cases based on clinical and laboratory features.[13] In our institution, the median turnaround time for ADAMTS13 testing was 10 days, underscoring the practical need for empiric treatment in resource-limited or centralized testing environments. The current findings therefore support the ISTH and BSH recommendations that early use of caplacizumab is clinically justified in high-probability cases (PLASMIC $\geq$ 6), reducing time-dependent morbidity and mortality.[12,13]

The bleeding rate observed in our study (two grade 3 events) was comparable to that reported in well controlled prospective clinical trials and real-world studies, where most bleeding episodes were mucocutaneous and managed with transient drug interruption.[7-10] No fatal, intracranial, or life-threatening hemorrhages occurred, confirming the acceptable safety profile of caplacizumab even when administered empirically. Importantly, all patients achieved sustained remission during follow-up, and only one experienced disease relapse, emphasizing the long-term efficacy of combining early vWF blockade with immunosuppressive therapy. Although local cost-effectiveness analysis is not yet feasible, the reduction in the number of plasma exchange sessions, disease-related complications, and hospitalization time that was demonstrated in the landmark trials for caplacizumab may justify the routine use of the medication despite the significant cost.

Our study also demonstrates the practical utility of the PLASMIC score as a rapid and reliable bedside tool to identify patients with TMA suitable for empirical therapy. This approach enables clinicians to make timely, evidence-based decisions in settings where ADAMTS13 testing is delayed, bridging a critical diagnostic gap. Similar pragmatic frameworks have been advocated internationally as part of precision-medicine strategies to optimize iTTP management.[4,12,13]

Despite the encouraging results, certain limitations must be acknowledged. The retrospective design, small sample size, and single-center scope may limit generalizability. Nonetheless, the uniform treatment protocol, completeness of follow-up, and reflection of real-world challenges enhance the validity and relevance of our observations. Furthermore, we recognize the limitations of PLASMIC scoring in some special populations, such as elderly patients, that were demonstrated by Singh et al (2026).[17] Indeed, the only patient whose ADAMTS13 result did not have confirm the iTTP diagnosis, was the only patient with age > 60 and had an intermediate PLASMIC score of 5, while the age of all the patients with confirmed diagnosis was <60 with a high PLASMIC score (6 (n=5) or 7 (n=6)). Hence, clinicians depending on clinical suspicion of TTP need to be aware of these limitations of the scoring systems. Larger multicenter prospective studies are warranted to further assess cost-effectiveness and long-term outcomes associated with empirical caplacizumab therapy. In addition, although the safety of empiric caplacizumab use in our population, it does not negate the importance of the timely availability of ADAMTS13, which is a prioritized logistic aim at our center.

Conclusion

Initiating caplacizumab empirically on the basis of clinical assessment and an established international risk score may be a safe and practical means of preventing treatment delays and improving clinical outcomes when rapid access to ADAMTS-13 testing is limited. Additional large-scale, prospective investigations are required to inform wider clinical adoption.

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Ethical Considerations

This research was conducted in accordance with the Institutional Review Board guidelines of the Medical Research Center at Hamad Medical Corporation (MRC-01-25-073).

Consent to Participate

Consent to participate was waived by local IRB as this is a retrospective study.

Author Contributions

Conceptualization: SE, HC, AH; Data Curation: AA, SM, HES: Formal Analysis: MB, KS; Funding Acquisition: SE, AA,HC; Investigation: SE, HES, HEO; Methodology: AA, MB, SE; Project Administration: SE, HC; Supervision: HC, SE; Validation: MB, AA; Visualization: HC, MB; Writing– Original Draft: SE, MB, HC; Writing – Review & Editing: SE, HC, MB, AA, AH, SM, KS, HES, HEO

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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