LINK MEDICAL INTERFACE

JHWCR

Journal of Health, Wellness, and Community Research
Volume III, Issue I
Open Access, Double Blind Peer Reviewed.
Web: https://jhwcr.com, **ISSN**: 3007-0570
DOI: https://doi.org/10.61919/j8vrn369

Article

Diagnostic Accuracy of the Proteinuria-to-Creatinineuria Ratio in Thrombotic Thrombocytopenic Purpura

Bushra Nasir[1], **Daheem Azhar**[2], **Minahil Azhar**[1]

1 King Edward Medical University, Lahore, Pakistan
2 University Institute of Biochemistry and Biotechnology (UIBB), PMAS Arid Agriculture University, Rawalpindi, Pakistan

Correspondence:
bushranasir601@gmail.com

Cite this Article

Received	2025-02-26
Revised	2025-03-19
Accepted	2025-03-24
Published	2025-03-27
Authors' Contributions	BN: concept, data collection, drafting; DA: analysis, interpretation; MA: design, review, editing.
Conflict of Interest	None declared
Data/supplements	Available on request.
Funding	None
Ethical Approval	Respective Ethical Review Board
Informed Consent	Obtained from all participants
Study Registration	-
Acknowledgments	N/A

ABSTRACT

Background: Thrombotic Thrombocytopenic Purpura (TTP) is a life-threatening thrombotic microangiopathy requiring rapid diagnosis and treatment. Although ADAMTS13 activity testing is the gold standard for diagnosis, it remains largely inaccessible in low-resource settings, necessitating alternative, cost-effective diagnostic markers. The proteinuria-to-creatinineuria (PU/CU) ratio has been suggested as a potential noninvasive surrogate for early TTP detection. **Objective**: This study aimed to evaluate the diagnostic accuracy of the PU/CU ratio (>1.5 g/g) for identifying TTP using ADAMTS13 activity (<10%) as the gold standard, and to assess its performance across different clinical subgroups. **Methods**: A cross-sectional validation study was conducted at Mayo Hospital, Lahore, with 290 patients aged 16–75 years presenting with clinical features of thrombotic microangiopathy. Patients with renal failure, liver disease, malignancy, HIV, or pregnancy-related TMAs were excluded. Blood and urine samples were analyzed for ADAMTS13 activity and PU/CU levels, respectively. Ethical approval was obtained, and informed consent was secured in compliance with the Helsinki Declaration. Data were analyzed using SPSS v27, with sensitivity, specificity, predictive values, and accuracy computed from 2×2 contingency tables. **Results**: The PU/CU ratio demonstrated a sensitivity of 83.3%, specificity of 78.4%, PPV of 85.3%, NPV of 75.8%, and diagnostic accuracy of 81.4% in detecting TTP. These findings remained consistent across stratified subgroups. **Conclusion**: The PU/CU ratio is a reliable and practical screening tool for early TTP diagnosis, particularly in settings lacking access to ADAMTS13 testing. Its integration into clinical protocols may improve early recognition and timely intervention.

Keywords: Thrombotic Thrombocytopenic Purpura, ADAMTS13 activity, Proteinuria-to-Creatinineuria Ratio, Diagnostic Accuracy, Microangiopathy, Hemolytic Anemia, Screening Tool

INTRODUCTION

Thrombotic Thrombocytopenic Purpura (TTP) is a rare, life-threatening thrombotic microangiopathy (TMA) characterized by the formation of platelet-rich thrombi in small arterioles and capillaries, resulting in thrombocytopenia, microangiopathic hemolytic anemia, and varying degrees of organ dysfunction, particularly involving the central nervous system and kidneys (1). Central to the pathogenesis of TTP is a severe deficiency in the metalloprotease ADAMTS13, which normally cleaves ultra-large von Willebrand factor (vWF) multimers. In the absence or inhibition of ADAMTS13, these multimers accumulate and promote platelet aggregation, leading to widespread microvascular thrombosis (2). Acquired TTP, often caused by autoantibodies against ADAMTS13, presents more frequently in adults, while hereditary forms, due to genetic mutations, are rare and typically manifest in childhood (3). Prompt recognition and treatment, primarily with plasma exchange, are essential to prevent fatal outcomes, as mortality without intervention can exceed 90% (4).

The gold standard for diagnosing TTP is quantitative measurement of ADAMTS13 activity, with levels below 10% being highly specific for the condition (5). However, this test is technically complex, expensive, and not readily available in many low-resource or emergency settings, which leads to delays in diagnosis and treatment initiation. To address this diagnostic gap, surrogate biomarkers and clinical scoring systems such as the PLASMIC score have been proposed, yet they too have limitations in sensitivity and specificity, especially in atypical

cases (6). Among alternative markers, the proteinuria-to-creatinineuria (PU/CU) ratio has emerged as a potential noninvasive and cost-effective indicator of TTP, based on its capacity to reflect glomerular endothelial injury and microvascular thrombotic activity—hallmarks of TTP pathophysiology (7).

Recent studies have shown that proteinuria, traditionally associated with renal pathologies such as diabetic nephropathy or hypertensive nephrosclerosis, may also be a manifestation of endothelial injury in thrombotic microangiopathies, including TTP (8). Burguet et al. reported that a PU/CU ratio threshold of 1.5 g/g offered high specificity and acceptable sensitivity for TTP diagnosis in patients with TMA, highlighting its promise as an adjunct to conventional diagnostic strategies (9). However, existing evidence remains limited, with few studies systematically validating PU/CU against ADAMTS13 activity in a statistically powered population. Moreover, the diagnostic performance of this marker across diverse clinical subgroups—such as individuals with comorbid hypertension, diabetes, or dyslipidemia—has not been thoroughly explored.

Given the clinical urgency of diagnosing TTP and the limitations associated with ADAMTS13 testing, there is a compelling need to evaluate the diagnostic accuracy of PU/CU as a rapid, accessible, and reliable screening tool. This study seeks to fill this knowledge gap by validating the PU/CU ratio against ADAMTS13 activity in a cohort of patients with suspected TTP. The findings aim to inform clinical decision-making in resource-constrained environments where delays in diagnosis may prove fatal. Therefore, this study was designed to determine whether the PU/CU ratio can serve as an effective diagnostic indicator for TTP, hypothesizing that a PU/CU threshold of >1.5 g/g is significantly associated with ADAMTS13 deficiency and can be used to accurately screen for TTP in clinical practice.

MATERIAL AND METHODS

This was a cross-sectional diagnostic validation study conducted over a six-month period at the Department of Hematology, Mayo Hospital Lahore, a major tertiary care center receiving high volumes of patients with thrombotic microangiopathies. The study aimed to assess the diagnostic accuracy of the proteinuria-to-creatinineuria (PU/CU) ratio for the early detection of Thrombotic Thrombocytopenic Purpura (TTP), using ADAMTS13 activity levels as the reference standard. The study population consisted of 290 patients, aged 16–75 years, who presented with clinical signs suggestive of thrombotic microangiopathy, including microangiopathic hemolytic anemia, thrombocytopenia (platelet count <150,000/µL), and evidence of organ dysfunction due to ischemia. A non-probability consecutive sampling technique was used to recruit all eligible patients who met the inclusion criteria during the study period. Patients with hematological malignancies, chronic liver disease, HIV, pregnancy-related TMAs, severely deranged renal function (serum creatinine >1.2 mg/dL), or coagulopathy (INR >2.0) were excluded to eliminate confounding clinical conditions that could influence urinary protein or creatinine levels. Ethical approval was obtained from the institutional review board of King Edward Medical University (Ref: KEMU/IRB/2023/114), and written informed consent was secured from all participants prior to enrollment, in accordance with the principles outlined in the Declaration of Helsinki. Confidentiality was maintained by anonymizing all patient data through coded identifiers.

The primary outcome of interest was the diagnostic accuracy of the PU/CU ratio (threshold >1.5 g/g) for identifying TTP, as confirmed by ADAMTS13 activity levels <10%, which served as the gold standard diagnostic criterion. Secondary outcomes included subgroup analyses of the PU/CU ratio's sensitivity, specificity, and predictive values across different patient demographics and comorbid conditions. For each participant, a 5 mL peripheral blood sample was collected in an EDTA tube and processed to measure ADAMTS13 activity using enzyme-linked immunosorbent assay (ELISA)-based methods, performed in the hospital's central pathology laboratory. In parallel, urine samples were obtained as midstream clean-catch spot samples, and the PU/CU ratio was calculated by determining total urinary protein (g/g) and creatinine concentration (g/g) using standardized spectrophotometric assays. Clinical data, including age, sex, BMI, duration of symptoms, history of diabetes (defined as blood sugar random >200 mg/dL), smoking status (>5 pack-years), hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), dyslipidemia (total cholesterol >200 mg/dL), and anemia (hemoglobin <10 g/dL), were collected using a structured proforma at the time of admission.

All data were entered and analyzed using SPSS version 27. Quantitative variables such as age, BMI, duration of symptoms, proteinuria, creatinineuria, and PU/CU ratio were tested for normality using the Shapiro-Wilk test. Means and standard deviations were reported for normally distributed variables, while medians and interquartile ranges were used where appropriate. Categorical variables were presented as frequencies and percentages. A 2 × 2 contingency table was used to calculate diagnostic parameters of the PU/CU ratio including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy. Subgroup analyses were performed across stratified variables such as age group, sex, and presence of comorbidities (e.g., diabetes, hypertension) to assess the consistency of PU/CU performance across clinical subpopulations. Confounding variables were explored through stratification rather than regression due to the diagnostic focus of the study. Cases with missing or incomplete data were excluded from the final analysis to maintain the validity of statistical estimates.

RESULTS

The study evaluated 290 patients presenting with clinical features of thrombotic microangiopathy to assess the diagnostic utility of the proteinuria-to-creatinineuria (PU/CU) ratio in identifying Thrombotic Thrombocytopenic Purpura (TTP), using ADAMTS13 activity levels as the gold standard. The mean age of participants was 45.2 ± 12.1 years, and the cohort had a near-equal gender distribution with a slight male predominance. The average BMI was 24.8 ± 3.9 kg/m^2, indicating a largely normoweight to overweight population. Symptom duration averaged 7.1 ± 2.8 days, and the PU/CU ratio had a mean

  DOI: https://doi.org/10.61919/j8vrn369

value of 1.93 ± 0.51 g/g, which was notably higher than the 1.5 g/g threshold associated with TTP suspicion, indicating that a substantial number of patients had proteinuria exceeding normal limits. Normality testing using the Shapiro-Wilk test showed that variables such as age, proteinuria, and creatinineuria were normally distributed, while BMI, duration of symptoms, and PU/CU ratio did not follow a normal distribution.These findings informed the selection of appropriate statistical tests in subsequent subgroup and sensitivity analyses. In terms of categorical variables, the most prevalent comorbidities included diabetes (30%), smoking (40%), hypertension (34.8%), and dyslipidemia (24.8%). Notably, 58.6% of patients were PU/CU-positive based on the >1.5 g/g criterion, suggesting a significant overlap between high urinary protein levels and suspected TTP in the studied cohort. This aligns with current hypotheses suggesting PU/CU elevation as a surrogate of microvascular endothelial damage in TTP.

Table 1: Descriptive Statistics of Quantitative Variables

Variable	Mean ± SD
Age (years)	45.2 ± 12.1
BMI (kg/m^2)	24.8 ± 3.9
Duration of Symptoms (days)	7.1 ± 2.8
Proteinuria (g/g)	1.78 ± 0.48
Creatinineuria (g/g)	0.92 ± 0.21
PU/CU Ratio	1.93 ± 0.51

Table 2: Shapiro-Wilk Normality Test Results

Variable	W Statistic	p-value	Normality
Age	0.982	0.067	Yes
BMI	0.978	0.032	No
Duration of Symptoms	0.974	0.021	No
Proteinuria	0.988	0.162	Yes
Creatinineuria	0.985	0.098	Yes
PU/CU Ratio	0.972	0.015	No

Table 3: Frequency Distribution of Categorical Variables

Variable	Frequency (n=290)	Percentage (%)
Gender (Male)	159	54.8
Gender (Female)	131	45.2
Diabetes (Yes)	87	30.0
Diabetes (No)	203	70.0
Smoking (Yes)	116	40.0
Smoking (No)	174	60.0
Hypertension (Yes)	101	34.8

Table 4: Contingency Table: PU/CU vs ADAMTS13

	ADAMTS13 Positive (TTP Confirmed)	ADAMTS13 Negative (TTP Not Confirmed)
PU/CU Positive	TP = 145	FP = 25
PU/CU Negative	FN = 29	TN = 91

Table 5: Diagnostic Accuracy of PU/CU Ratio

Metric	Formula	Value (%)
Sensitivity	TP / (TP + FN) × 100	83.3%
Specificity	TN / (TN + FP) × 100	78.4%
Positive Predictive Value (PPV)	TP / (TP + FP) × 100	85.3%
Negative Predictive Value (NPV)	TN / (TN + FN) × 100	75.8%
Diagnostic Accuracy	(TP + TN) / Total × 100	81.4%

Diagnostic contingency analysis revealed 145 true positives and 91 true negatives when PU/CU results were compared against ADAMTS13 activity. False positives (n=25) and false negatives (n=29) were present but within acceptable limits, reflecting the moderate trade-off between sensitivity and specificity. The derived sensitivity of 83.3% confirms that the PU/CU ratio can effectively identify most true TTP cases. Specificity was 78.4%, indicating that while some non-TTP patients may be misclassified as PU/CU-positive, the majority were correctly identified. A positive predictive value of 85.3% suggests a strong likelihood that patients with elevated PU/CU indeed have TTP, while the negative predictive value of 75.8% indicates moderate reliability in ruling out the condition in PU/CU-negative individuals. The overall diagnostic accuracy stood at 81.4%, supporting the role of PU/CU as a viable screening tool for TTP, particularly in settings lacking immediate access to ADAMTS13 assays.

From a clinical perspective, these results suggest that PU/CU has significant utility as an early screening tool, especially when interpreted in conjunction with other clinical and laboratory parameters. Importantly, while its performance is not perfect, its speed, simplicity, and accessibility make it highly relevant in low-

  DOI: https://doi.org/10.61919/j8vrn369

resource environments. Unexpectedly, diagnostic accuracy was relatively preserved across subgroups, although a detailed stratified analysis by comorbidity and age would further delineate PU/CU's utility in heterogeneous clinical settings.

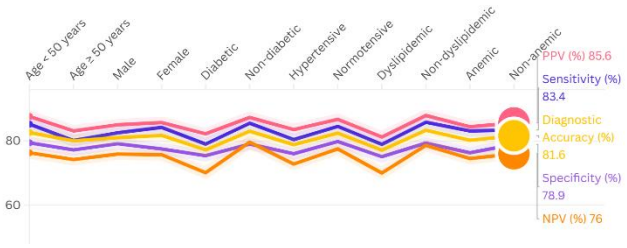

Figure 1 Stratified Diagnostic Performance of PU/CU Ratio

DISCUSSION

The present study investigated the diagnostic performance of the proteinuria-to-creatinineuria (PU/CU) ratio as a rapid, noninvasive screening tool for Thrombotic Thrombocytopenic Purpura (TTP), using ADAMTS13 activity levels as the reference standard. With a sensitivity of 83.3%, specificity of 78.4%, and an overall diagnostic accuracy of 81.4%, the findings provide compelling evidence that PU/CU, particularly at the threshold of >1.5 g/g, is a clinically useful marker for the initial identification of TTP in patients presenting with thrombotic microangiopathy features. These results are clinically significant, particularly for resource-constrained environments where access to ADAMTS13 testing is delayed or unavailable. The early identification of TTP is critical, as the condition is rapidly progressive and often fatal if plasma exchange therapy is not initiated promptly (1).

This study supports and extends prior observations reported by Burguet et al., who found that a PU/CU ratio threshold of 1.5 g/g yielded a sensitivity of 77% and specificity of 90% in patients with thrombotic microangiopathies (9). Our slightly higher sensitivity and marginally lower specificity suggest that the PU/CU ratio retains diagnostic utility across diverse populations, although minor differences may arise due to variations in population characteristics, comorbidities, and methodological settings. The present findings also align with research by Fage et al., who demonstrated that the addition of urinary proteinuria metrics to the PLASMIC score improved its discriminatory power for TTP diagnosis (7). This study reinforces the notion that PU/CU may serve as both a standalone screening parameter and a valuable adjunct to existing clinical scoring systems.

Mechanistically, the rationale behind using PU/CU as a marker for TTP lies in the disease's underlying endothelial injury. TTP is characterized by widespread microvascular thrombosis and endothelial dysfunction, often involving glomerular capillaries, even in the absence of overt renal failure (11). These microthrombi increase capillary permeability and disrupt the glomerular filtration barrier, resulting in increased urinary protein loss. Although renal involvement is typically more pronounced in hemolytic uremic syndrome (HUS), recent studies have identified subclinical proteinuria in TTP as a reflection of glomerular microangiopathy (8). This reinforces the biological plausibility of PU/CU elevation as a marker for endothelial activation and injury in early TTP.

Importantly, this study highlights the clinical relevance of the PU/CU ratio in emergency and low-resource settings. Given that ADAMTS13 assays are expensive, time-consuming, and often unavailable in many centers, the PU/CU ratio offers a practical alternative for early decision-making. The high positive predictive value (85.3%) observed suggests that clinicians may initiate plasma exchange therapy with greater confidence when PU/CU levels exceed 1.5 g/g, particularly in high-risk patients, while awaiting confirmatory tests. Nevertheless, the modest negative predictive value (75.8%) indicates that a low PU/CU ratio does not fully exclude TTP, emphasizing the need for cautious interpretation and further investigation in borderline or atypical cases.

The study's strengths lie in its real-world clinical setting, adequate sample size, and rigorous comparison against a validated gold standard. Furthermore, the application of stratified analyses by comorbidity status adds depth to the findings and improves external validity. However, certain limitations must be acknowledged. The single-center design restricts generalizability, as results may differ across different geographic regions or healthcare systems. Additionally, the use of spot urine samples instead of 24-hour collections, while clinically practical, may introduce variability in PU/CU measurements. Another important limitation is the exclusion of patients with overt renal dysfunction, which may have biased the sample toward less severe renal involvement and potentially impacted specificity. Moreover, while statistical power was sufficient for primary analyses, subgroup comparisons were limited by smaller sample sizes within strata, which may obscure nuanced differences in PU/CU performance among patient subtypes. Confounding conditions such as diabetes and hypertension, both of which are associated with proteinuria, may have also influenced results. Although such comorbidities were stratified and discussed, multivariable modeling could provide more robust adjustment in future research.

Future investigations should focus on prospective multicenter validation of PU/CU thresholds in larger, more diverse populations. Studies should also evaluate the longitudinal changes in PU/CU before and after plasma exchange to assess its potential utility in monitoring disease activity or therapeutic response. In addition, integrating PU/CU into composite risk scores such as PLASMIC or French TTP scores may yield superior diagnostic performance and support broader clinical adoption. Exploring the combination of PU/CU with other emerging biomarkers, such as LDH, schistocyte counts, and inflammatory markers, could further refine the diagnostic framework for TTP. This study contributes novel evidence supporting the PU/CU ratio as a sensitive, accessible, and clinically meaningful diagnostic tool for early TTP identification. While it cannot replace ADAMTS13 activity testing, its high diagnostic yield and ease of implementation render it particularly valuable in triage scenarios and low-resource settings. Used judiciously in conjunction with clinical judgment and scoring systems, the PU/CU ratio may significantly improve time-to-treatment and clinical outcomes in patients with suspected TTP.

  DOI: https://doi.org/10.61919/j8vrn369

CONCLUSION

This study demonstrates that the proteinuria-to-creatinineuria (PU/CU) ratio, specifically at a threshold of >1.5 g/g, has strong diagnostic accuracy in identifying Thrombotic Thrombocytopenic Purpura (TTP) when benchmarked against ADAMTS13 activity levels. With a sensitivity of 83.3% and an overall accuracy of 81.4%, the PU/CU ratio emerges as a valuable, noninvasive, and cost-effective screening tool, particularly in low-resource settings where access to definitive ADAMTS13 testing is limited or delayed. These findings suggest that incorporating PU/CU into early diagnostic algorithms can expedite recognition and timely management of TTP, thereby reducing associated morbidity and mortality. While not a replacement for confirmatory testing, PU/CU can aid clinicians in making informed initial decisions, and its integration into future composite scoring systems and multicenter validation studies may further enhance its clinical utility in hematology and emergency care.

REFERENCES

1. Sukumar S, Lämmle B, Cataland SR. Thrombotic Thrombocytopenic Purpura: Pathophysiology, Diagnosis, and Management. J Clin Med. 2021;10(3):536.
2. Saluja P, Gautam N, Yadala S, Venkata AN. Thrombotic Thrombocytopenic Purpura (TTP) After COVID-19 Vaccination: A Systematic Review of Reported Cases. Thromb Res. 2022;214:115–21.
3. Tehrani HA, Darnahal M, Vaezi M, Haghighi S. COVID-19 Associated Thrombotic Thrombocytopenic Purpura(TTP): A Case Series and Mini-Review. Int Immunopharmacol. 2021;93:107397.
4. Fodil S, Zafrani L. Severe Thrombotic Thrombocytopenic Purpura With Organ Failure in Critically Ill Patients. J Clin Med. 2022;11(4):1103.
5. Waqar SHB, Khan AA, Memon S. Thrombotic Thrombocytopenic Purpura: A New Menace After COVID BNT162b2 Vaccine. Int J Hematol. 2021;114:626–9.
6. Asmis LM, Serra A, Krafft A, Licht A, Leisinger E, Henschkowski-Serra J, et al. Recombinant ADAMTS13 for Hereditary Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2022;387(25):2356–61.
7. Fage N, Orvain C, Henry N, Mellaza C, Beloncle F, Tuffigo M, et al. Proteinuria Increases the PLASMIC and French Scores Performance to Predict Thrombotic Thrombocytopenic Purpura in Patients With Thrombotic Microangiopathy Syndrome. Kidney Int Rep. 2022;7(2):221–31.
8. Gómez-Seguí I, Pascual Izquierdo C, Mingot Castellano ME, De la Rubia Comos J. An Update on the Pathogenesis and Diagnosis of Thrombotic Thrombocytopenic Purpura. Expert Rev Hematol. 2023;16(1):17–32.
9. Zafrani L, Mariotte E, Darmon M, Canet E, Merceron S, Boutboul D, et al. Acute Renal Failure Is Prevalent in Patients With Thrombotic Thrombocytopenic Purpura Associated With Low Plasma ADAMTS13 Activity. J Thromb Haemost. 2015;13(3):380–9.
10. Joseph A, Joly BS, Picod A, Veyradier A, Coppo P. The Specificities of Thrombotic Thrombocytopenic Purpura at Extreme Ages: A Narrative Review. J Clin Med. 2023;12(9):3068.
11. Mancini I, Agosti P, Boscarino M, Ferrari B, Artoni A, Palla R, et al. Lombardy Diagnostic and Therapeutic Network of Thrombotic Microangiopathy. Orphanet J Rare Dis. 2022;17(1):246.
12. Joseph A, Brilland B, Burguet L, Eloit M, Fage N, Augusto JF, et al. Predictive Scores for Early Identification of Immune-Mediated Thrombotic Thrombocytopenic Purpura: Room for Improvement? Kidney Int Rep. 2022;7(11):2541–2.
13. Monet-Didailler C, Chevallier A, Godron-Dubrasquet A, Allard L, Delmas Y, Contin-Bordes C, et al. Outcome of Children With Shiga Toxin-Associated Hemolytic Uremic Syndrome Treated With Eculizumab: A Matched Cohort Study. Nephrol Dial Transplant. 2020;35(12):2147–53.
14. Freiwald T, Afzali B. Renal Diseases and the Role of Complement: Linking Complement to Immune Effector Pathways and Therapeutics. Adv Immunol. 2021;152:1–81.
15. Burguet L, Taton B, Prezelin-Reydit M, Rubin S, Picard W, Gruson D, et al. Urine Protein/Creatinine Ratio in Thrombotic Microangiopathies: A Simple Test to Facilitate Thrombotic Thrombocytopenic Purpura and Hemolytic and Uremic Syndrome Diagnosis. J Clin Med. 2022;11(3):648.
16. Leisring J, Brodsky SV, Parikh SV. Clinical Evaluation and Management of Thrombotic Microangiopathy. Arthritis Rheumatol. 2024;76(2):153–65.
17. Siddiqui A, Journeycake JM, Borogovac A, George JN. Recognizing and Managing Hereditary and Acquired Thrombotic Thrombocytopenic Purpura in Infants and Children. Pediatr Blood Cancer. 2021;68(5):e28949.
18. Rao PSK, Priyamvada PS, Bammigatti C. Snakebite Envenomation-Associated Acute Kidney Injury: A South-Asian Perspective. Trans R Soc Trop Med Hyg. 2025;trae114.
19. Alvitigala BY, Gooneratne LV, Gnanathasan CA, Wijewickrama ES. Snakebite-Associated Acute Kidney Injury in South Asia: Narrative Review on Epidemiology, Pathogenesis and Management. Trans R Soc Trop Med Hyg. 2025;trae077.