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Distinguishing and overlapping laboratory results of thrombotic microangiopathies in HIV infection: Can scoring systems assist?

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Abstract

Background: Patients with Human Immunodeficiency Virus (HIV) infection are at risk of thrombotic microangiopathies (TMAs) notably thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC). Overlap between laboratory results exists resulting in diagnostic ambiguity.

Methods: Routine laboratory results of 71 patients with HIV-associated TTP (HIV-TTP) and 81 with DIC with concomitant HIV infection (HIV-DIC) admitted between 2015 and 2021 to academic hospitals in Johannesburg, South Africa were retrospectively reviewed. Both the PLASMIC and the International Society of Thrombosis and Haemostasis (ISTH) DIC scores were calculated.

Results: Patients with HIV-TTP had significantly ($P < .001$) increased schistocytes and features of hemolysis including elevated lactate dehydrogenase (LDH)/upper-limit-of-normal ratio (median of 9 (interquartile range [IQR] 5-12) vs 3 (IQR 2-5)) but unexpectedly lower fibrinogen (median 2.8 (IQR 2.2-3.4) vs 4 g/L (IQR 2.5-9.2)) and higher D-dimer (median 4.8 (IQR 2.4-8.1) vs 3.6 g/L (IQR 1.7-6.2)) levels vs the HIV-DIC cohort. Patients with HIV-DIC were more immunocompromised with frequent secondary infections, higher platelet and hemoglobin levels, more deranged coagulation parameters and less hemolysis. Overlap in scoring systems was however observed.

Conclusion: The laboratory parameter overlap between HIV-DIC and HIV-TTP might reflect a shared pathogenesis including endothelial dysfunction and inflammation and further research is required. Fibrinogen in DIC may be elevated as an acute phase reactant and D-dimers may reflect the extensive hemostatic activation in HIV-TTP. Inclusion of additional parameters in TMA scoring systems such the LDH/upper-limit-of-normal ratio, schistocytes count

and wider access to ADAMTS-13 testing may enhance diagnostic accuracy and ensure appropriate utilization of plasma.

KEYWORDS

diagnostic scoring systems, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), treatment decisions

1 | INTRODUCTION

Thrombotic microangiopathy (TMA) is a clinical syndrome characterized by hemolytic anemia, thrombocytopenia and microvascular thrombosis resulting in life-threatening multi-organ failure.[1,2] TMAs are heterogeneous and include congenital and acquired thrombotic thrombocytopenic purpura (TTP) and TTP-like syndromes, hemolytic uremic syndrome (HUS) and the atypical form of this disease, aHUS.[1-3] Disseminated intravascular coagulation (DIC) can also be classified as a TMA.[4] TMAs can be the manifestation of common disease processes such as hypertension and malignancy as well as develop in relation to drug exposure.[1,4] Although the distinction between different TMA syndromes is often difficult, authors have advised against grouping of these disorders under a single pathological entity underlining the need for further studies in order to improve patient outcomes.[3]

There are more than 7.7 million people in South Africa infected with human immunodeficiency virus (HIV).[5] Antiretroviral therapy (ART) is often initiated late in these patients who consequently present with advanced HIV infection and high rates of non-communicable disease, like malignancy and cardiovascular disease, and opportunistic infections as well as associated complications such as TMAs.[5-8] HIV-infected patients with laboratory features of a TMA pose a diagnostic dilemma since infection with HIV predisposes to a number of these disease processes particularly secondary TTP (HIV-TTP) and DIC with background HIV infection (HIV-DIC).[9-14] Distinguishing these conditions is important since treatment differs. DIC is managed by treatment of the underlying pathogenic cause and HIV-TTP with therapeutic plasma exchange (TPE) or plasma infusion.[1,12,13,15,16] Treatment of patients with HIV-TTP is the most frequent request for TPE in South Africa.[17] Plasma infusion alone is also of therapeutic value in patients with HIV-TTP[16] but administration of insufficient amounts of plasma due to the risk of fluid overload and limited availability of plasma frequently results in poor responses and a need to convert to TPE.[16] Adverse events related to apheresis therapy and exposure to plasma still occur despite technological and procedural developments which have made operational systems safer.[18] For these reasons and to ensure best patient outcomes, correct distinction between secondary TTP and DIC is paramount.

The microvascular thrombosis in TTP and in DIC differs in both pathogenesis and in composition of the thrombi.[1,19] In acquired TTP, the cleavage of von Willebrand Factor (VWF) multimers released by the endothelium may be impaired by a reduction in activity of the VWF proteolytic enzyme, a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13 (ADAMTS-13), mediated by auto-antibodies.[1] Excessive release of high molecular weight VWF multimers from damaged endothelium resulting in a relative deficiency of ADAMTS-13 is another postulated pathogenic factor in secondary TTP termed TTP-like syndrome.[13,20] The resultant thrombi in TTP are therefore rich in VWF and platelets with abundant red blood cell (RBC) fragments (schistocytes) and severe thrombocytopenia.[1,9,12] The microvascular thromboses in DIC in contrast consist mainly of fibrin-platelet clots following the exposure of coagulation factors to tissue factor secondary to an initiating process such as sepsis or trauma.[10,21] Excessive bleeding occurs frequently in DIC secondary to the consumption of coagulation factors as well as platelets. Intravascular clot formation is further accelerated in DIC by the loss of natural anticoagulant and fibrinolytic activity.[15] Schistocytes are present in DIC but usually constitute <10% of the RBCs.[15] In both of these disease processes, endothelial damage and dysregulation of the coagulation cascade also contribute to disease pathogenesis.[22] In addition, HIV-infected patients often have background hematological abnormalities including cytopenias, underlying bone marrow dyshematopoiesis and baseline activation of the hemostatic system contributing to diagnostic uncertainty.[6,22-24]

The PLASMIC (platelet count, hemolysis, active cancer, MCV (mean red blood cell (RBC) volume), international normalized ratio (INR) and creatinine) score (Table 1) is based on clinical and routine laboratory parameters and predicts the likelihood of severe ADAMTS-13 deficiency in patients with a TMA since testing for this parameter is not widely available.[25] This score was designed to enable the distinction between TTP and other TMAs.[25] The International Society of Thrombosis and Haemostasis (ISTH) DIC score (Table 1), is a diagnostic tool to assist in the diagnosis of DIC in an

TABLE 1 The ISTH DIC score and the PLASMIC score for prediction of thrombotic microangiopathy associated with severe ADAMTS-13 deficiency[25,26]

ISTH diagnostic score for DIC		PLASMIC score	
Parameter	**Points**	**Parameter**	**Points**
Platelet count		Platelet count $<30 \times 10^9$/L	1 point
• $>100 \times 10^9$/L	• 0 points		
• $<100 \times 10^9$/L	• 1 point	Hemolysis[b]	1 point
• $<50 \times 10^9$/L	• 2 points		
Elevated fibrin markers (D-dimer)[a]		No active cancer	1 point
• No increase	• 0 points		
• Moderate increase	• 2 points	No solid-organ or stem-cell transplant	1 point
• Strong (marked) increase	• 3 points		
Prolonged prothrombin time (PT) vs control result		MCV <90 fL	1 point
• <3 seconds	• 0 points		
• >3 but <6 seconds	• 1 point	INR <1.5	1 point
• >6 seconds	• 2 points		
Fibrinogen level			
• >1 g/L	• 0 points	Creatinine <176.8 μmol/L	1 point
• <1 g/L	• 1 point		
Score: ≥5: compatible with overt DIC: repeat score daily <5: suggestive for non-overt DIC: repeat next 1 to 2 days		Likelihood score for severe ADAMTS-13 deficiency: • 0-4: low likelihood • 5: intermediate likelihood • 6 or 7: high likelihood	

Abbreviations: ADAMTS-13, a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13; INR, international normalized ratio; MCV, mean corpuscular volume.

[a]Moderate D-dimer increase: = 0.25-1 D-dimer units (mg/L)/ Strong (marked) D-dimer increase: ≥ 1 D-Dimer units (mg/L).[26]

[b]Reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin > 12.0 μmol/L.

appropriate clinical setting.[26] The utility of these scoring systems in HIV-infected patients with TMAs has not been comprehensively assessed and bedside treatment decisions are often inconsistent. It is further possible that the background hemostatic changes in HIV infected patients may alter TMA scoring system performance.[4,13,14,27] The objective of the current study was to identify distinguishing clinical and laboratory parameters to assist with the accurate diagnosis of HIV infected patients who present with a TMA suspected to be either HIV-TTP or HIV-DIC.

2 | METHODS

Approval for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Wits) (Certificate numbers: M160134 and M160839). Informed individual patient consent was waived for this retrospective record review in which all patient identifiers were removed. The authors independently and retrospectively applied both the PLASMIC and the ISTH DIC scores to the available results of consecutive HIV-infected patients who were diagnosed with either HIV-associated TTP (HIV-TTP) (n = 71) or overt, uncompensated DIC with background HIV infection (HIV-DIC) (n = 81) between 2015 and 2021 at the 3 academic hospitals affiliated to Wits. The diagnoses were made by treating physicians based on clinical and routine laboratory parameters. A diagnosis of HIV-TTP was made based on laboratory features of severe thrombocytopenia (Platelets $<30 \times 10^9$/L) and abundant schistocytes (constituting >10% of the RBCs on the peripheral film) in the absence of features suggestive of another TMA in most cases. ADAMTS-13 activity and autoantibody levels were not included in the initial diagnosis. Where possible, stored plasma was sent for batch ADAMTS-13 activity and autoantibody levels performed at the University of the Free State, Research Coagulation Laboratory. Diagnosis of DIC was made in patients in the

TABLE 2 Baseline median (IQR) results of 71 patients diagnosed with HIV-TTP (including 43 (61%) with confirmed reduced ADAMTS-13 levels) and 81 with HIV-DIC

Parameter (RI)	HIV-TTP cohort with confirmed low ADAMTS-13 level (n = 43)	Total HIV-TTP cohort (n = 71)	HIV-DIC cohort (n = 81)	*P* values[a] (HIV-TTP vs HIV-DIC)
Age in years	35 (29-40)	36 (33-44)	36 (31-43)	N/S
CD_4^+ T-cells (500-2010 cells/μL)	156 (92-220)	144 (94-191) (n = 64)	68 (22-184)	$P < .001$
HIV viral load (RNA copies/mL)	276 500 (52 925-894 384)	199 000 (21 275-597 626) (n = 62)	35 397 (524-512 200) (n = 70)	$P < .001$
Hemoglobin (12.1-17.5 g/dL)	6 (5.2-7.3)	6 (5.3-7.2)	7.5 (6.4-8.5)	$P < .001$
Red blood cell distribution width (RDW) (12.4-17.3%)	29 (24.3-31.9)	28 (23.2-33.1)	18 (16.3-21.2)	$P < .001$
Platelets (186-454 × 10^9/L)	7 (6-13)	9 (6-15)	40 (18-68)	$P < .001$
Lactate dehydrogenase (LDH) (100-190 U/L)	1645 (1185-2217)	1681 (1004-2340)	513 (350-1057) (n = 51)	$P < .001$
LDH/upper-limit-of-normal ratio	9 (6-11)	9 (5-12)	3 (2-5) (n = 51)	$P < .001$
C-reactive protein (CRP) (<10 mg/L)	22 (10-42)	19 (12-41) (n = 68)	149 (62-211)	$P < .001$
Prothrombin time (14 seconds)	15.1 (14.0-16.4)	15.1 (14.1-17.1) (n = 70)	20.5 (17.5-27.0)	$P < .001$
Fibrinogen (2-4 g/L)	3.0 (2.3-3.3)	2.8 (2.2-3.4) (n = 62)	4.0 (2.5-9.2)	$P < .001$
D-dimer levels (<0.25 mg/L)	5.0 (3.0-7.8)	4.8 (2.4-8.1) (n = 70)	3.6 (1.7-6.2)	$P < .044$
PLASMIC score	6 (6-6)	6 (6-6)	4 (3-5)	$P < .001$
ISTH DIC score	4 (4-5)	4 (4-5)	6 (5-6)	$P < .001$

Abbreviations: ADAMTS-13, a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13; HIV-TTP, HIV-associated thrombotic thrombocytopenic purpura; HIV-DIC, disseminated intravascular coagulation (DIC) with background HIV infection; IQR, interquartile range (25-75%); n, number of available results if not available in all patients; N/S, not significant; RI, normal reference interval.

[a]$P \leq .05$ was deemed significant.

correct clinical context by applying the ISTH-DIC score. The available results for both cohorts, including full blood count (FBC) (performed on Sysmex XN analysers, Sysmex, Japan), peripheral smear findings, hemolytic and inflammatory markers (performed on Roche Cobas analysers, Roche, Switzerland) and coagulation assays (performed on a STAGO STA-R MAX analysers, Diagnostica Stago, France) from the accredited National Health Laboratory Service (NHLS) laboratory as part of routine patient management were collected. Summary statistics were computed for all parameters including a median and interquartile range (IQR). Results were compared using Graphpad Prism version 9 (Graphpad software, San Diego).

3 | RESULTS

The results of the 71 patients diagnosed with HIV-associated TTP (HIV-TTP) and 81 patients diagnosed with overt DIC with background of HIV infection (HIV-DIC) are included in Table 2. The patients with laboratory-confirmed DIC were less likely to have virological control and had significantly more pronounced immunodeficiency. The hemoglobin and platelet counts were also significantly higher and the prolongation of the PT was more pronounced in the DIC cohort. Although patients diagnosed with HIV-TTP showed less pronounced derangement of the coagulation system, that is,

less prolongation of the prothrombin time (PT), they presented with significantly higher D-dimer and significantly lower fibrinogen levels compared to the cohort with HIV-DIC. Underlying infection was identified in 68 (84%) of the DIC cohort. Identified pathogens included bacterial septicemia and *Mycobacterium tuberculosis*. In contrast, no secondary infection could be identified in 62 (88%) of the patients with HIV-TTP despite extensive investigations.

The diagnosis of HIV-TTP was made clinically in conjunction with routine results. In 43 of these patients (61%), ADAMTS-13 activity levels were measured retrospectively. A sub-analysis was performed comparing the results of routine parameters in patients with suspected TTP with and without confirmed ADAMTS-13 deficiency and those diagnosed with HIV-DIC. This sub-analysis confirmed that the differences persisted between HIV-DIC and HIV-TTP even when patients without confirmed ADAMTS-13 levels were excluded (P-value <.001). There was therefore no significant difference in the results of routine tests between the HIV-TTP groups with and without ADAMTS-13 results ($P > .9$). Clinically significant levels of autoantibodies to ADAMTS-13 were present in the 43 (61%) of the patients with HIV-TTP in whom ADAMTS-13 levels were measured. No ADAMTS-13 levels were measured in the patients who were diagnosed with HIV-DIC.

Although the PLASMIC score was high in 99% of the patients diagnosed with HIV-TTP (n = 71), 18 (31%) of these patients also had an ISTH DIC score of 5 or greater which is compatible with an underlying overt DIC. The PLASMIC score was also applied to the cohort of HIV infected patients diagnosed with an overt DIC as per the ISTH DIC score (n = 81) and 14 (17%) of these patients had a PLASMIC score of 5 (intermediate likelihood of severe ADAMTS-13 deficiency) and 19 (23%) had a PLASMIC score of 6 or higher (high likelihood of severe ADAMTS-13 deficiency). ADAMTS-13 levels were retrospectively available in 43 (61%) of the patients with HIV-TTP. All of these patients had levels below 15%, that is, severe ADAMTS-13 deficiency. Unfortunately, ADAMTS-13 levels were not available in the remaining 28 patients. Importantly, 69 (97%) of patients diagnosed with HIV-TTP responded to plasma therapy. Notable, exclusion of the patients without documented ADAMTS-13 levels from the final data analysis did not alter the statistical difference in parameter results between the HIV-DIC and the HIV-TTP cohorts.

The most prominent laboratory features in the cohort of patients with HIV-TTP were marked peripheral schistocytosis (>10% of RBCs) which was present on admission in 65 of 71 patients (91.5%) and developed within 24-h in five additional patients. The LDH/upper-limit-of-normal ratio was also significantly elevated in the patients with HIV-TTP compared to the patients with a HIV-DIC. LDH levels were however only performed in 51 (71%) patients in the DIC cohort.

67 (94%) of the patients with HIV-TTP were treated with fresh frozen plasma (FFP) with 64 (90%) receiving TPE and 3 (4%) plasma infusion only for a median of 10 days (IQR 7-13). 69 (97%) of the patients who received plasma therapy responded and 2 (3%) deteriorated and demised in hospital despite plasma therapy, ART and additional supportive care

4 | DISCUSSION

The differentiation between TTP and DIC represents an important diagnostic decision since TTP is managed primarily with TPE in our treatment center and delays in initiation of therapy may adversely impact patient outcomes.[1,28] Although plasma infusions may be used in DIC to correct severe hemostatic abnormalities, primary management is treatment of the underlying pathogenic cause.[15]

HIV represents a significant risk factor for both secondary TTP and DIC.[10,12,22,29] The HIV viral load results were significantly higher in the HIV-TTP group compared with the HIV-DIC cohort but despite better HIV viral control in the HIV-DIC cohort, the CD_4 positive T-cell counts were lower ($P < .001$). This finding probably reflects acute concomitant infections in the HIV-DIC cohort.

Normal D-dimer levels were previously considered a feature of TTP and, that together with preserved time-to-clot formation assays, for example, PT as well as antithrombin (AT), were suggested to be useful in distinguishing between these conditions in HIV-uninfected patients.[30] In the current study, patients with HIV-TTP however presented with significantly elevated D-dimer levels suggesting widespread microthrombosis although mucocutaneous bleeding was probably also contributory.

In this study, we demonstrate that there is significant overlap between the laboratory parameters included in diagnostic scores in patients with HIV-TTP and those with HIV-DIC with 51 of the 152 patients having scores which were diagnostic for both conditions. Important differentiators in these patients included the abundance of schistocytes and the elevated LDH/upper-limit-of-normal ratios which appeared to show a higher specificity for TTP. The prothrombin time in patients with DIC was significantly more prolonged vs the HIV-TTP cohort. Importantly, D-dimers were a poor discriminator between the two populations with TTP patients showing higher D-dimer levels than patients with DIC. Elevated D-dimer

levels in patients with HIV-associated TTP have also been observed in other studies.[13,31] Median fibrinogen levels were within the normal reference range in both cohorts but were significantly higher in patients with HIV-DIC mirroring the CRP levels most likely reflecting increased production of fibrinogen as an acute phase reactant. CRP was a distinguishing parameter between the two cohorts with elevated levels in the HIV-DIC cohort probably related to underlying concomitant infections and this routine parameter therefore could have clinical utility in distinguishing between HIV-DIC and HIV-TTP. D-dimers and fibrinogen form important components of the ISTH DIC score and should be interpreted with caution in HIV infected patients with a TMA.[11,32] The authors caution against favoring a diagnosis of HIV-DIC instead of HIV-TTP based on elevated D-dimer levels when additional features are compatible with HIV-TTP.

The overlap in laboratory parameters between acquired TTP and DIC in HIV infected patients may reflect a shared pathogenesis. Contributory factors include chronic inflammation with baseline activation of the hemostatic and complement systems as a result of ongoing viral replication, microbial translocation across a disrupted gastrointestinal mucosal barrier and opportunistic infections.[23,33,34] Inflammation and complement activation causes endothelial damage which predispose to coagulopathies including TMAs.[6] The background derangements of the coagulation and hematopoietic systems in patients with underlying HIV infection should also be considered when making diagnostic and treatment decisions in patients with HIV-TMAs.[24,35] Scoring systems standardize diagnoses to ensure appropriate therapy and improve patient outcomes.[25,27] The PLASMIC score is based on clinical parameters and the results of routine tests to predict the likelihood of significant ADAMTS-13 deficiency which is indicative of the presence of TTP in a patient with laboratory features of a TMA.[25] Although the PLASMIC score predicted a high probability of severe ADAMTS-13 deficiency in 99% of the cohort diagnosed with HIV-TTP, it also predicted a similar risk in 23% of HIV-infected patients with an overt DIC based on the ISTH DIC score. The PLASMIC score may therefore not have sufficient specificity to delineate between HIV-TTP and HIV-DIC in all cases and inclusion of the LDH/upper-limit-of-normal ratio is likely to improve the specificity and accuracy. Zhao et al[36] also demonstrated that inclusion of the LDH/upper-limit of-normal ratio improved the accuracy of the PLASMIC score in identifying patients who suffered from TTP. Increased schistocyte count was also a distinguishing feature between the TTP and DIC cohort but this parameter is poorly standardized with considerable inter-observer variability since it often relies on the subjective methodology of light microscopy and manual counting of cells.[37,38] Wider access to ADAMTS-13 testing, possibly even on a Point-of-Care-Testing (POCT) platform, could also improve the accuracy of the diagnosis of the pathophysiological cause in patients presenting with a TMA.[39] Although all 43(61%) patients in the HIV-TTP cohort who were tested for ADAMTS-13 autoantibodies had clinically significant levels, the diagnostic utility of this parameter is uncertain as it probably forms part of the HIV polygammaglobulinemia in HIV infected individuals and is present even in the absence of TTP.[12]

The limitations of this study include the retrospective nature which resulted in some results being unavailable. No ADAMTS-13 levels were performed in the DIC-cohort of patients. The details of the treatment administered and the patient outcomes for the HIV-DIC cohort were also not available and based on the PLASMIC scores, some of these patients may have benefited from plasma treatment. Unfortunately, the details of the ART regimens and duration of treatment in the HIV-DIC cohort were not available. ART status could therefore not be evaluated as a distinguishing feature between the two TMAs. Further studies in this regard are required. The study data, however, reflect the diagnostic and treatment decisions made on admission in the patient cohorts. All requests for DIC screen analysis were available to the authors but patients with a diagnosis of HIV-TTP may have been treated by attending physicians without the knowledge of the authors and were therefore not included in the study. Irrespective of these limitations, we are of the opinion that the study results reflect the overlapping findings of these serious conditions in our population with HIV infection.

5 | CONCLUSION

HIV infection is prevalent in the African context[5] with secondary HIV-associated TTP and DIC in the background of HIV infection constituting the most prevalent TMAs in this group of patients.[2,22] The diagnostic distinction between these conditions can be ambiguous resulting in inappropriate treatment due to the background activation of the coagulation system and inflammation in HIV infected patients.[9,11,40] The addition of the LDH/upper-limit-of-normal ratio and objective, automated quantification of schistocytes will probably improve the accuracy of the PLASMIC score.[28,41] The LDH/upper-limit-of-normal ratio standardizes across different reagents and reference indices. The value of longitudinal, repeated application of scoring systems in patients with a TMA in our setting must also be evaluated. The cause and significance of the elevation of D-dimers in patients with HIV-associated TTP also requires further investigation.[13,31] Based on the results of the study, the authors

support the addition of the LDH/upper-limit-of-normal ratio to the PLASMIC score for improved diagnostic accuracy and to guide urgent, but appropriate, institution of therapeutic plasma exchange (TPE) as was proposed by Zhao et al.[36]

AUTHOR CONTRIBUTIONS

Susan Louw: study design, data collection and analysis, manuscript writing and critical review, and approval of submission. Barry Frank Jacobson: study design, critical review, and approval of submission. Elizabeth Sarah Mayne: study design, data collection and analysis, manuscript writing and critical review, and approval of submission.

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CONFLICT OF INTEREST

The authors declare no conflict of interest pertaining to the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

Approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Wits) (Certificate numbers: M160134 and M160839). Individual patient consent was waived for this retrospective record review.

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