Original Article

Clinical Profile and Outcomes of Thrombotic Microangiopathy: A Kidney Biopsy Registry Cohort

Abstract

Background: Thrombotic microangiopathy (TMA) is caused by injury to microvasculature that leads to thrombus formation and multisystem dysfunction. TMA can cause irreversible kidney failure and graft failure in kidney transplant patients. The data on etiology, clinical and histopathological characteristics, treatment patterns, and renal outcomes of patients with TMA from resource-limited health care setups is less. **Materials and Methods**: From a South Indian teritiary care center biopsy registry of 16,054 patients, 87 TMA cases diagnosed between January 2011 and April 2022 were included, and follow-up data were collected from electronic medical records until June 2023. **Results:** The mean age of the cohort was 31.7± 9.9 years. The biopsy incidence of TMA was 0.5% during the study period. The most common TMA etiology was autoimmune disease (25.2%), followed by atypical HUS (18.4%) and pregnancy-associated and malignant hypertension (14.9%) each. The most common renal biopsy finding was mesangiolysis (74.7%), followed by capillary wall thrombi and fragmented RBCS. On a median 6-month follow-up (1,36), 24 (27.6%) patients showed renal recovery, and 40 (46%) remained dialysis-dependent. Multivariate analysis showed that dialysis dependence at presentation adversely affected renal recovery. **Conclusion:** TMA, although rare, carries a high risk of renal failure and death. With early diagnosis and treatment, satisfactory renal outcomes can be achieved even in resource-limited health care settings.

Keywords: *Biopsy, Microangiopathy, Plasma exchange, Thrombosis, Transplantation*

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Introduction

Thrombotic microangiopathy (TMA) is pathologically characterized by microvascular occlusion and clinically by thrombocytopenia and microangiopathic hemolytic anemia (MAHA).[1] Its incidence is six in a million.[2] The old classification of TMA into hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) has changed following an improved understanding of the complement's role in the TMA pathogenesis and the availability of genetic analysis.[3] TMA etiology ranges from medication to genetic abnormalities. The propensity of the glomerular endothelium for microvascular injury makes the kidney prone to TMA. This condition's impact is compounded by the fact that TMA affects younger people, including pregnant and postpartum females, often resulting in end stage kidney disease (ESKD). TMA is also an important cause of post-transplant graft dysfunction and failure. Some cases, like those caused by drugs can easily be treated by discontinuing the causative drug. Hence, the early diagnosis and treatment of this life and organ threatening disease is important. If recognized properly and treated timely, renal damage due to TMA can be minimized even in resource-limited health care settings. Data from developing countries on TMA etiology, demography, clinical presentation, histopathological features, and treatment outcomes are limited. We examined the important aspects of this often-misdiagnosed condition in adult patients, which will provide data specific to the resource-limited developing countries.

Materials and Methods

The study was approved by the institutional review and ethics committee (IRB No.15029 dated 06/01/2023). This observational retrospective study used the renal biopsy registry at the Christian Medical College Vellore in south India. In total, 16,054 adult kidney biopsies were performed between

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January 2011 and April 2022, of which 87 were diagnosed with TMA. Only renal biopsy (native and graft) proven cases in adult patients were included. Those patients with only hematological manifestations and no renal biopsy were excluded. TMA cases in children (<18 years) also were not included, as most of them are Shiga toxin-associated HUS and are not commonly biopsied. Snake bites, in tropical countries and TTP are relatively common causes of TMA. But these two entities were excluded as these cases are rarely biopsied**.**

Data on demographic profile, clinical features, histopathological variables, treatment details, and outcomes were retrieved from electronic patient records. The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR).[4] Since it is a retrospective study, waiver of consent has been taken from Institutional Ethics Committee.

All biopsy specimens were processed for light microscopy and immunofluorescence. Chronic TMA was defined by double contours of glomerular capillary walls, fibrous intimal thickening with onion skin-like lamination in the arteries, and hyalinosis in arterioles[5] [Figure 1a]. Acute TMA was defined by the presence of thrombi, endothelial swelling or denudation, intramural fibrin, or intimal swelling in the arteriole [Figure 1b]. Thrombi, endothelial swelling, denudation, or mesangiolysis in the glomeruli were also classified as acute TMA [Figure 1c].

The etiology of TMA was divided into several categories: pregnancy-associated (with normal ADAMTS 13, normal complement levels, and persistent renal dysfunction for > 6 weeks after delivery, thus requiring a renal biopsy), kidney transplant-related, post bone marrow transplant, lupus nephritis (LN), primary antiphospholipid antibody syndrome (APLA), scleroderma, malignant hypertension-related (presenting with diastolic BP >120 mmHg and hypertensive retinopathy features) and atypical HUS (with ADAMTS 13 activity >10%, no preceding diarrhea, features of MAHA, and no other etiologies or confirmation via genetic analysis).[6] All renal-transplant cases were classified into transplant-related TMA.

Follow-up data were collected for each review visit until June 2023. Renal recovery was defined as eGFR >90 mL/min/1.73m² or return to pre-morbid eGFR. Renal non-recovery was defined as failure to return to prebiopsy or eGFR < 15 mL/min/1.73m² or kidney replacement therapy (KRT) initiation. For transplant outcomes, graft recovery was the return of eGFR to premorbid levels. Persistent graft dysfunction was defined as failure to return to premorbid eGFR level, and graft loss was defined as eGFR worsening to <15 mL/min/1.73 m^2 for > 3 months OR initiation of dialysis. For pregnancy outcomes, low birth weight was defined as < 2500 g irrespective of gestational age (WHO). Hematological recovery was defined as platelet >150000/mm^3 and no lab parameters suggestive of active hemolysis, like schistocytes, hemoglobin drop, reticulocytosis, or LDH level > 500 U/L.

Statistical analysis

All clinical, laboratory, and histological data were entered in the Epidata version 4.6.0.6, and analysis was done using SPSS software version 25. Baseline characteristics were reported as mean ± standard deviation for normally distributed quantitative variables and median (IQR) for skewed variables. Categorical data were expressed as number (%). Differences among normally distributed variable groups were analyzed by the student t test. Differences among groups of nonparametric variables were analyzed by the Mann–Whitney U or Kruskal–Wallis tests. Categoric variables were compared using Pearson's chi-squared or Fisher's exact tests. Univariate and multivariate analyses for renal non recovery predictors were done using the Cox proportional hazard regression method.

Results

A total of 87 patients (0.5% of all biopsies) were included. Eleven (12.6%) were graft biopsies and 76 were native

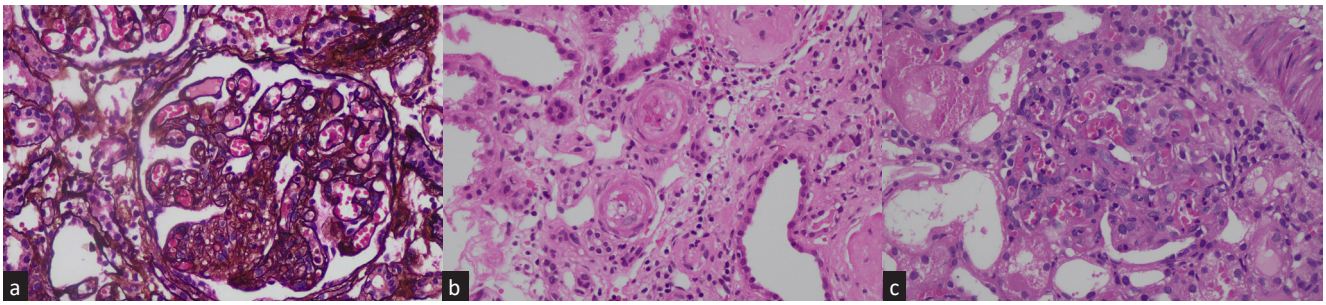

Figure 1: (a) Chronic changes of TMA: Glomerulus shows global capillary wall reduplication along with concomitant endothelial swelling of capillary tuft obliteration, Jones Methenamine silver stain, X400. (b) Acute TMA changes in arteriole with fibrinoid necrosis, endothelial swelling, karyorrhectic nuclear debris, and luminal obliteration, H&E stain, X400. (c) Acute changes of TMA: Glomerulus shows segments of mesangiolysis, endothelial swelling, congestion and karyorrhectic nuclear debris. Adjacent tubules show acute injury with epithelial loss of brush border, epithelial simplification and cytoplasmic protein resorption droplets, H&E stain, X400. TMA: Thrombotic microangiopathy

kidney biopsies. The mean ± (SD) age of patients was 31.7 ± (9.9) years. Females constituted 57.5% of the study population. At the time of clinical diagnosis, there were 16 pregnant or postpartum patients. Of these, three were diagnosed with primary APLA, classified as APLA-associated TMA. There were 19 post-transplant patients (21.8%), of which 11 were post-kidney transplant (KT), and 8 were post-bone marrow transplant patients (BMT). All 11 KT patients were on calcineurin Inhibitors (CNI) at the time of TMA diagnosis and were classified as transplant-associated TMA. There were 22 (25.2%) patients with underlying autoimmune disease; LN was the most common. Edema was the most common symptom in 52 (59.8%) patients, followed by oliguria in 48 (55.2%). The other baseline characteristics have been summarized in Table 1.

Autoimmune disease-associated TMA was the most common (25.2%). This included LN, scleroderma, and APLA-associated TMAs. It was followed by a-HUS (18.4%) and malignant hypertension (14.9%). One patient (heterozygous mutation for *CFH1*) with kidney failure due to a-HUS in the native kidneys developed graft failure 1-month post-transplant. The graft biopsy showed cortical necrosis features. Other causes have been described in Table 1.

The mean hemoglobin (SD) at presentation was 8.1 ± 1.9 g/dL, and the median platelet count (IQR) was 99,000 (58,000-1,73,000)/mm^3. Microscopic hematuria was present in 61 patients (70.1%). Median eGFR (IQR) at biopsy was 13.4 mL/min/1.73m^2 (7.2,41.5). At the time of kidney biopsy, 54 (62.1%) patients were dialysis dependent. Acute TMA changes were observed in 71 (81.6%) patients. Capillary thrombi were seen in 62 (71.3%) patients and arterial thrombi in 38 (43.7%). Crescents were observed in seven (8%) patients, of which four were fibro-cellular, two were cellular, and one was fibrous crescent. Arteriosclerosis of various degrees was seen in 71 (81.60%) biopsies [Table 2]. Renal-limited TMA was observed in 25 (28.7%) patients, and 62 (71.3%) had renal and hematological TMA manifestations [Table 3].

Sixteen (18.4%) patients received only supportive treatment, like initiation of anti-hypertensives to control BP and KRT. Plasma exchange (PLEX) and immunosuppressive medications were given to 57 (65.5%) and 58 (66.6%) patients, respectively [Table 3]. Infection risk increased in those receiving PLEX/immunosuppression. Of the 57 patients receiving PLEX, 27 had severe infections like catheter-related bloodstream infections (most common), urinary tract infections, renal abscesses, graft pyelonephritis, and pneumonia.

Table 1: Baseline characteristics

Baseline characteristics at biopsy	Entire cohort (n=87)
Age (years)	31.7 ± 9.99
Sex	
Female	50 (57.5%)
Comorbid illness	
Chronic kidney disease	11 (12.6%)
Diabetes mellitus	4 (4.6%)
Etiology	
a-HUS	16 (18.4%)
LN	15 (17.2%)
Malignant hypertension	13 (14.9%)
Pregnancy	13 (14.9%)
Post kidney transplant	11 (12.6%)
Post bone marrow transplant	8 (9.1%)
Primary APLA	5 (5.7%)
Scleroderma	2 (2.3%)
Drugs (Gemcitabine)	1 (1.1%)
Others*	3 (3.6%)
Transplant related TMA (n =19)	
Kidney	11 (57.9%)
Bone marrow	8 (42.1%)
Type of autoimmune diseases (n =22)	
SLE	15 (68.1%)
APLA	5 (22.7%)
Scleroderma	2 (9.0%)
Clinical features	
Edema	52 (59.8%)
Oliguria	48 (55.2%)
Fever	17 (19.5%)
Macroscopic hematuria	4 (4.6%)
Systolic BP (mmHg)	148.8 ± 28.6
Diastolic BP (mmHg)	92.8 ± 19.2

*ANCA associated, Membranous with crescents, Shiga toxin associated TMA. aHUS: Atypical hemolytic syndrome, APLA: Anti phospholipid antibody syndrome, SLE: Systemic lupus erythematosus. LN: Lupus nephritis, TMA: Thrombotic microangiopathy, BP: Blood pressure

Outcomes

At discharge, only 23 (26.4%) patients had both hematological and renal recovery. Six (6.9%) died during the hospital stay. On the median 6-month follow-up (1,36 months), nine (36%) patients with renal-limited TMA had renal recovery, and 15 (24.2%) with both renal and hematological involvement had renal recovery depicting an overall poor renal outcome [Supplemental Table 1]. There were 40 (46%) dialysis-dependent patients on the last follow-up. The median (IQR) eGFR at time of discharge was 17.2 (8.7, 49) mL/min/1.73m^2 [Table 3]. Patients receiving plasmapheresis showed statistically significant dialysis dependence over those who did not (OR, 3.6; 95% CI, 1.42-9.3). There was no significant renal outcome between those who had acute and chronic changes on biopsy (The unadjusted HR, 1.32; 95% CI, 0.69-2.51).

The fetal outcome was not favorable for pregnancies complicated by TMA. Only three (18.8%) out of 16 pregnancies complicated by TMA had full-term normal deliveries. Six (37.5%) resulted in stillbirths, and four (25.0%) infants had low birth weight.

The mortality rate was 10.3%, with six patients dying during the first hospital admission and three patients during follow-up.

Table 2: Laboratory and histopathological parameters

Laboratory parameter	Entire cohort (n=87)
Hemoglobin (g/dL)	8.1 ± 1.9
Platelet count (cells/mm^3)	99000 (58000,173000)
Albumin (g/dL)	3.18 ± 0.76
LDH at presentation (U/L)	911 (623.5, 1596.5)
Percentage of schistocyte	0.85 (0.1,2)
Reticulocyte count (%)	2.69 (1.75, 5.37)
Creatinine at presentation (mg/dL)	4.85 (2.1, 7.5)
eGFR at biopsy (mL/min/1.73m^2)	13.4 (7.2, 41.5)
Dialysis dependent at presentation	54 (62.1%)
24-hour urine protein at presentation (mg/24 hours)	1144 (343.2, 2607.2)
Microscopic hematuria	61 (70.1%)
PT INR within normal range	81 (93.1%)
Normal APTT (sec)	75 (86.2%)
C3 level (Available in 78 patients) (mg/dL)	
>100	36 (46.2%)
75-100	21 (26.9%)
50-75	7 (8.9%)
<50	14 (17.9%)
Number of glomeruli	13.69 ± 5.98
Mesangiolysis	65 (74.7%)
Capillary thrombi	62 (71.3%)
Fragmented RBCs	62 (71.3%)
GBM thickening	60 (69%)
Mesangial expansion	60 (69%)
Capillary wall wrinkling	57 (65.5%)
Tuft obliteration	51 (58.6%)
Endothelial swelling	55 (63.2%)
Fibrinoid necrosis	40 (46%)
GBM duplication	34 (39.1%)
Presence of crescents	7 (8%)
Fibro cellular	4
Cellular	2
Fibrous	1
Presence of acute tubular necrosis	72 (82.8%)
Severity of arteriosclerosis	
None	16 (18.4%)
Mild	52 (59.8%)
Moderate	15 (17.2%)
Severe	4 (4.6%)
Presence of arterial thrombosis	38 (43.7%)
Immunofluorescence	
Negative	53 (60.9%)
Full house	16 (18.4%)
IgG & C3	6 (6.8%)
IgM, IgG, IgA& C3	4 (4.6%)
C3 alone	3 (3.4%)
IgM alone	3 (3.4%)
IgM and C3	2 (2.3%)
Type of TMA on renal biopsy	
Acute	71 (81.6%)
Chronic	16 (18.4%)

APTT: Activated partial thromboplastin time, eGFR: estimated glomerular filtration rate, LDH: Lactate dehydrogenase, PT INR: Prothrombin time/International normalised ratio, GBM: Glomerular basement membrane, IQR: Interquartile range, LDH: Lactate dehydrogenase, RBC: Red blood cells, TMA: Thrombotic microangiopathy

Table 3: Type of treatment and outcomes

Platelet transfusions	12 (13.8%)
PLEX required	57 (70.4%)
Dialysis requirement at biopsy	54 (62.1%)
Type of treatment received	
Supportive treatment and antihypertensives	16 (18.4%)
Plasma infusion	2 (2.3%)
Plasma infusion and PLEX	11 (12.6%)
Prednisolone alone	9 (10.3%)
Prednisolone and PLEX	24 (27.5%)
Rituximab alone	1 (1.1%)
Rituximab and PLEX	6 (6.9%)
Rituximab and Prednisolone	2 (2.3%)
Prednisolone, MMF, and PLEX	7 (8.0%)
Prednisolone, Cyclophosphamide, and PLEX	9 (10.3%)
Eculizumab	0
Renal function (eGFR) at different timelines (mL/min/1.73m^2)	
At Discharge (n=81)	17.2 (8.7, 49)
1 month (n=36)	37.6 (18.9,69.4)
3 months (n=28)	49.1 (34.2, 71.2)
6 months (n=31)	50.5 (33.5, 68)
1 year (n=27)	52.1 (31.7, 73.8)
Dialysis dependence at the last follow up	40 (46%)
Hemoglobin at different timelines (g%)	
Discharge (n=81)	8.9 ± 1.5
1 month (n=36)	9.8 ± 2.2
3 months (n=28)	10.6 ± 2.3
6 months (n=31)	11.3 ± 2.6
1 year (n=27)	11.7 ± 2.1
Last follow up outcome	
Renal limited TMA	25 (28.7%)
Renal recovery	9 (36%)
No renal recovery	15 (60%)
Death	1 (4%)
TMA with renal and hematological manifestations	62 (71.3%)
Hematological recovery alone	27 (43.5%)
Renal recovery alone	0
Both hematological or renal recovery	15 (24.2%)
No hematological or renal recovery	12 (19.4%)
Death	8 (12.9%)
If pregnant – outcome of pregnancy (n=16)	
Term delivery with normal birth weight	3 (18.8%)
Low birth weight	4 (25.0%)
Stillbirth	6 (37.5%)
Neonatal death	3 (18.8%)
If renal transplant – graft outcome (n=11)	
Graft recovery	6 (54.5%)
Graft loss	2 (18.2%)
Persisting graft dysfunction	1 (9.0%)
Death with functioning graft	2 (18.2%)

eGFR: estimated glomerular filtration rate, IQR: Interquartile range, MMF: Mycophenolate mofetil, PLEX: Plasma exchange, TMA: Thrombotic microangiopathy

Graft outcome

The median (IQR) kidney transplant vintage at TMA diagnosis was 38 days (5,95). All KT patients with TMA were on tacrolimus. One graft biopsy showed definitive CNI

toxicity features, whereas 5 showed antibody mediated rejection (ABMR) features. All transplant patients received PLEX. Two patients died due to treatment complications, one due to an intracranial bleed, and one due to disseminated intracranial coagulation (DIC). Details of post-renal transplant TMA have been given in Supplemental Table 2.

Eight post- BMT patients developed TMA during the study period. None of the patients were on drugs capable of causing TMA at the time of diagnosis. Four patients had a history of non-renal Graft Versus Host Disease and were on treatment for the same. Except for two patients with severe renal failure at TMA diagnosis, all others were treated with prednisolone +/ MMF or rituximab. Three patients received PLEX. On follow-up, two (25%) patients had normal renal function, while one (12.5%) had progressed to ESKD, and four (50%) had persistent renal dysfunction. One patient died during the hospital stay due to multiple infections following PLEX, prednisolone, and rituximab.

Univariate analysis found male gender, arterial thrombosis, and dialysis requirement at biopsy as factors significantly affecting renal recovery. Multivariate analysis found dialysis requirement at biopsy as the only statistically significant factor that adversely affected renal recovery [Supplemental Table 1].

Discussion

TMA is a spectrum of disorders characterized by microvasculature injury, causing endothelial damage and thrombi formation, resulting in organ injury. TTP was first described by Moschcowitz in 1924, in a teenage girl. HUS was described by Gasser in 1955.[7] We showed multiple TMA etiologies that cannot always be classified into TTP or HUS alone, as done previously. This study shows that TMA mainly affects the young (mean age was 31.7 years). There were >55% females, probably because of TMA's association with pregnancy and autoimmune diseases, which are common in young females. The study also highlights the severity of renal failure due to TMA, as the median GFR was <15 mL/min/1.73m^2, and > 60% of patients were on dialysis at the time of biopsy.

A retrospective study from India found malignant hypertension followed by post-partum TMA to be the most common etiologies of TMA.[8] We found autoimmune disease-related TMA to be the most common (>1/4 of our cases). LN was the leading autoimmune disease-causing TMA. Some studies have found the TMA proportion in LN patients to be as high as 25%.[9]

Pregnancy accounts for 8-18% of TMA cases.[10] This study corroborates these findings, with ~15% of cases being associated with pregnancy. The increased TMA risk in pregnancy is due to increased procoagulant factors, decreasing fibrinolytic activity, loss of endothelial cell thrombomodulin, and decreasing ADAMTS13 activity.[11] Pre-eclampsia, DIC, and post-partum hemorrhage, can predispose females to TMA.[12] The pregnancy outcome in our cohort was not favorable; only three patients had normal-term delivery. The rest of the cases were complicated with stillbirth, neonatal death, or low birth weight infants.

The TMA incidence in renal transplant patients varies between 0.8-14%.[13] It can be *de novo* or recurrence of the native kidney disease. The TMA risk is highest in the first three months after transplant.[14.] A retrospective study from India showed acute rejection as the most common cause of post-renal transplant TMA, followed by CNIs.[15] TMA in the graft can be a manifestation of CNI toxicity or rejection, as shown in five patient biopsies. Overall post-kidney transplant prognosis was poor, with graft loss in up to 40% of the cases in the first 2 years, similar to our study.

Renal biopsy findings can be varied in TMA. Glomerular or arteriolar thrombi are pathognomonic.[16] Mesangiolysis, the presence of fragmented RBCs capillary thrombi, and endothelial swelling were the most common features in acute TMA. Glomerular basement membrane (GBM) thickening and duplication were observed in chronic cases. Arterial thrombosis was found to be higher than in similar studies, probably because of the higher number of the etiologies causing arterial injury like malignant hypertension, aHUS, scleroderma, and APLA-related TMA. Very importantly, ~20% of our cases had chronic biopsy changes although the symptom duration was short [Supplemental Table 3].

Treatment depends on the etiology. However, in a case with TMA diagnosis and no immediate evident cause, it is important to quickly initiate PLEX after taking samples for ADAMTS13, as TTP prognosis without PLEX is very poor.[17] In our cohort >70% of patients received PLEX. PLEX results in the administration of high doses of complement-regulating proteins, removal of dysfunctional endogenous soluble complement inhibitors and anti-FH antibodies.[18] Eculizumab the complement inhibitor were shown to improve the renal prognosis in patients with CM-TMA.[19]

The treatment in this study involved withholding the possible offending drug in case of drug-induced TMA, and control of hypertension in malignant hypertension-associated TMA, in addition to the other supportive treatment. Immunosuppression (IMS) was given based on the etiology, e.g., induction of remission in LN. In those with acute changes on biopsy and persistent renal dysfunction after PLEX, IMS with steroids or concomitantly with rituximab or cyclophosphamide were used. Those with chronic changes on biopsy and dialysis dependence after treatment with antihypertensives and PLEX were continued on non-immunosuppressive therapy, including dialysis. None of the patients received eculizumab due to non-

Table 4: Comparison of present study with similar studies

Study	Yu *et al.*[21]	Manickam *et al.*[8]	Bayer *et al.*[6]	Present study
Country/Region	China	India	France	India
Study duration (years)	2000-2012 (12)	2012-2017 (5.5)	2009-2016 (8)	2011 -2022 (11.5)
Study design	Retrospective	Retrospective	Retrospective	Retrospective
Total number of cases	109	40	564	87
Mean age of participants (years)	34.0 ± 11.1	31±12	37	31.7 ± 9.9
Follow up duration (months)	30.5 ± 36.5	8.8 ± 13		6 (1,36)
Most common etiology	Malignant hypertension (56%)	Malignant hypertension (39%)	Pregnancy (35%)	Autoimmune (25.2%)
Proportion of patients receiving PLEX	13.8%	45.5%	16%	65.5%
Most common IMS received by patients	Steroids		Steroids	Steroids
Persistent renal dysfunction or ESRD on last follow up	56%		20% (On dialysis)	72.4%
Mortality	7.3%		10%	10.3%
Statistically significant factors causing poor renal outcome	Male gender, Elevated serum creatinine Low Hb Presence of chronic renal TMA pathologic changes			Male gender, Arterial thrombosis Dialysis requirement at biopsy

ESRD: End stage renal disease, Hb: Hemoglobin, IMS: Immunosuppressant, PLEX: Plasma exchange, TMA: Thrombotic microangiopathy

availability. Renal outcomes in TMA remain poor despite advances in diagnosis and treatment. Patients are at high-risk of long-term complications like hypertension, stroke, pre-eclampsia, CKD, and cognitive impairment.[20] Although our study showed higher dialysis dependence in those who received PLEX, it may be due to the fact that those receiving plasmapheresis had more severe disease at presentation.

At presentation, >60% of our patients were dialysis dependent, highlighting the condition's severity. On the last follow-up ~50% of our patients remained dialysis-dependent. Dialysis dependence at biopsy was significantly associated with poor renal outcomes. The TMA prognosis in renal transplants is poor and the recurrence rate is between 60-70%.[17] One patient had TMA recurrence within 3 months post-renal transplant. The study also showed hematological recovery of ~70% and renal recovery in < 30% of cases. The mortality rate was high (10%), comparable to a similar study by Yu *et al.*[21] [Table 4].

In conclusion, our study highlights the significant morbidity and mortality in TMA irrespective of etiology, especially in developing countries. The study also shows condition's predilection for the young population. TMA can complicate autoimmune diseases, which were the most common etiology, renal and BM transplants, and pregnancy. Thus, it is important to remember this differential diagnosis when these patients present with new onset or worsening renal or hematological parameters. Timely diagnosis and appropriate treatment increase the chance of renal and patient recovery. There is an urgent need for newer diagnostic modalities like complement studies and genetic analysis, as well as the availability of treatment options like complement inhibitors in developing countries. Our study is novel from a developing country with a large cohort who had biopsy-proven diagnoses.

This was a single-center study. Genetic analysis and complement factor analysis were done in only a few patients due to logistic reasons. Hence and some cases classified as transplant, pregnancy, or hypertension-related cases may have had underlying complement/genetic abnormalities. However, it reflects the real-life scenario of a clinical set-up in a developing world. CFIs like eculizumab were not given to any patient.

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Supplemental table 1: Univariate and Multivariate analysis of variables determining renal non recovery

Serial Number	Variable	Number of renal non-recovery Patients	Unadjusted Hazard ratio (95%CI)	Adjusted Hazard ratio (95%CI)	P- value
1.	Gender A. Male B. Female	 29 25	 **1.83 (1.07, 3.14)** -	 1.47(0.84, 2.57)	 0.18
2.	Aetiology A. Autoimmune disease B. Others	 12 42	 0.63 (0.33, 1.20)		
3.	Hb at presentation(gm/dl) A. >10 B. <10	 6 48	 - 1.50 (0.64, 3.52)		
4.	Platelet count at presentation (per mm3) A. >100000 B. <100000	 26 28	 - 1.15 (0.67, 1.99)		
5.	Dialysis requirement at presentation	41			**.007**

	A. Yes B. No	13	**3.38 (1.77, 6.46)**	**2.60(1.29, 5.25)**	
6.	Fibrinoid necrosis A. Yes B. No	 27 27	 1.13 (0.65, 1.91) -		
7.	Arterial thrombosis A. Yes B. No	 28 26	 **2.14 (1.23, 3.70)** **-**	 1.56(0.89, 2.85)	 0.12
8.	GBM duplication A. Yes B. No	 20 34	 0.93(0.53, 1.63) -		
9.	**Changes on biopsy** **A. Acute** **B. Chronic**	 **42** **12**	 **-** **1.32 (0.69, 2.51)**		
10.	**PLEX requirement** **A. Yes** **B. No**	 **35** **19**	 **1.40 (0.80, 2.46)** **-**		
11.	Treatment A. Without Immunosuppressant B. With Immunosuppressant	 16 38	 1.04 (0.58, 1.87) -		

PLEX – Plasma Exchange

Supplemental Table 2: Characteristics of TMA in Renal Transplant patients

Age at the time of Transplant	Transplant vintage at the time of developing TMA	Probable cause of TMA	Treatment received	CNI withdrawal duration (If yes)	Immediate graft Outcome (at 3 months –)	Long term graft – Last follow up Outcome(> 3 months)	Duration for haemat recovery
31	5 months	ABMR	Plasmapheresis	----------	Graft dysfunction (GFR 61 ml/ min / 1.73m2)	Persistent graft dysfunction(GFR 52 ml/ min / 1.73m2) at 4th months	No haemat involvement
38	2 weeks	CNI induced	Plasmapheresis and CNI withdrawal	2 weeks	Graft dysfunction (GFR 56 ml/ min / 1.73m2)	Persistent graft dysfunction(GFR 58 ml/ min / 1.73m2) at 2 years	10 days
22	1 day	CNI induced	Plasmapheresis and CNI withdrawal	----------	Death with functioning graft on 3rd POD – Due to severe intra-abdominal bleeding following plasmapheresis	---------	Not recovered
52	1 week	ABMR	Plasmapheresis	----------	Normal graft functions	Graft dysfunction(GFR 29.89 ml/ min / 1.73m2) at 2 years	7 days
31	3 weeks	CNI induced	Plasmapheresis and CNI withdrawal	Changed to Everolimus	Graft dysfunction (GFR 52.94 ml/ min / 1.73m2)	Dialysis dependent	No haemat involvement
20	4 months	CNI induced	Plasmapheresis and CNI withdrawal	----------	Graft failure and death following intracerebral bleed and pneumonia following plasmapheresis	----------	No haemat involvement

31	2 weeks	CNI induced	Plasmapheresis and CNI withdrawal	Changed to Everolimus	Graft dysfunction (GFR 52.57 ml/ min / 1.73m2	Persistent graft dysfunction(GFR 52.2ml/ min / 1.73m2) at 2 years	No haemat involement
32	2 weeks	CNI induced	Plasmapheresis and CNI withdrawal	Changed to Everolimus- Recurred TMA on everolimus	Normal graft function	Normal graft function at 5 years	10 days
26	First week after transplant	ABMR	Plasmapheresis and Rituximab	----------	Graft dysfunction (GFR 47.6 ml/ min / 1.73m2	Persistent graft dysfunction(GFR 52ml/ min / 1.73m2) at 8 years	3 weeks
31	First week after transplant	ABMR	Plasmapheresis and Rituximab	----------	Normal graft function	Graft dysfunction(GFR 51ml/ min / 1.73m2) at 8 years	3 weeks
34	4 months	ABMR	Plasmapheresis and Rituximab	Withheld and not restarted	Graft dysfunction (GFR 24.7 ml/ min / 1.73m2	Dialysis dependent at 5 months . Graft nephrectomy for renal abscess at 3 months	1 month

ABMR – Antibody Mediated Rejection CNI – Calcineurin Inhibitor

Supplemental Table 3: Pathological characteristics according to TMA subtypes

Pathologic finding	Pregnancy N=13	Post-transplant N=11	Autoimmune N=22	aHUS N=16	Others N=25
Low flow ischemic changes	9(69.2%)	7(63.6%)	12(54.5%)	12(75%)	16(64%)
Mesangial Expansion	8(61.5%)	6(54.5%)	19(86.4%)	10(62.5%)	17(68%)
Mesangial Hypercellularity	8(61.5%)	4(36.4%)	14(63.6%)	11(68.8%)	10(40%)
Endocapillary Hypercellularity	7(53.8%)	4(36.4%)	18(81.8%)	9(56.3%)	11(44%)
Fibrinoid necrosis	4(30.8%)	4(36.4%)	14(36.6%)	9(56.3%)	9(36%)
Prescence of crescents	0	0	4(18.2%)	1(6.3%)	2(8%)
Fragmented RBCs	10(76.9%)	6(54.5%)	17(77.3%)	10(62.5%)	19(76%)
GBM thickening	7(53.8%)	6(54.5%)	17(77.3%)	12(75%)	18(72%)
GBM duplication	5(38.5%)	3(27.3%)	11(50%)	6(37.5%)	9(36%)
Glomerular capillary thrombi	11(84.6%)	8(72.7%)	17(77.3%)	10(62.5%)	16(64%)
Tuft obliteration	5(38.5%)	3(27.3%)	16(72.7%)	12(75%)	15(60%)
Mesangiolysis	10(76.9%)	9(81.8%)	16(72.7%)	14(87.5%)	16(64%)
Acute tubular necrosis	10(76.9%)	9(81.8%)	20(90.9%)	16(100%)	17(68%)
Thickening of arterial wall	9(69.2%)	5(45.5%)	17(77.3%)	11(68.8%)	17(68%)
Arterial thrombi	6(46.2%)	3(27.3%)	8(36.4%)	9(56.3%)	12(48%)