

Long-term Kidney Outcomes in Patients With Acquired Thrombotic Thrombocytopenic Purpura



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Introduction: Severe acute kidney injury (AKI) and chronic kidney disease (CKD) are considered to be uncommon in patients with acquired thrombotic thrombocytopenic purpura. However, a recent case series from a tertiary care hospital indicated that 54 (59%) of 92 patients with thrombotic thrombocytopenic purpura presented with AKI; 14 (15%) required dialysis; and 12 (22%) of the 54 patients had CKD at follow-up.

Methods: In this prospective analysis of 78 patients diagnosed with their first episode of thrombotic thrombocytopenic purpura and enrolled in the Oklahoma Thrombotic Thrombocytopenic Purpura Registry from 1995 to 2015, we assessed AKI at diagnosis using Kidney Disease: Improving Global Outcomes criteria, and CKD at follow-up as defined by estimated glomerular filtration rate <60 ml/min per 1.73 m² determined by the Chronic Kidney Disease-Epidemiology Collaboration equation.

Results: Forty-five (58%) patients had AKI; 8 (10%) had stage 3 AKI, and 3 (4%) required dialysis. AKI was not associated with the patients' demographic or presenting clinical features. Three of the 8 patients with stage 3 AKI died; among the 5 survivors, estimated glomerular filtration rate was 77 to 107 ml/min per 1.73 m² (median, 92) with median follow-up of 8.1 years. Among all 62 surviving patients who have had follow-up serum creatinine measurements, 4 (6%) had CKD with median follow-up of 6.4 years. AKI was not associated with the occurrence of CKD ($P = 0.74$). No patients have required continuing renal replacement therapy.

Discussion: In this population-based prospective cohort of consecutive patients with thrombotic thrombocytopenic purpura, without selection or referral bias, severe AKI and CKD are uncommon.

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KEYWORDS: acute kidney injury; chronic kidney disease; estimated glomerular filtration rate; KDIGO criteria; thrombotic thrombocytopenic purpura

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Acquired autoimmune thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) syndrome defined by severe ADAMTS13 deficiency.¹ Fifty-one years ago, in the era before effective treatment when 90% of patients with TTP died, kidney failure was commonly observed and was a principal diagnostic feature.² Twenty-six years ago, with the advent of effective treatment with plasma exchange (PEX), kidney failure was less common.³

After the advent of effective treatment, the frequency of diagnosis of TTP increased,⁴ and it became recognized as an acute episodic disorder with apparent complete remission but risk for relapse.⁵ Nineteen years ago, a severe deficiency of ADAMTS13 activity was identified as the defining feature of TTP, and the presence of autoantibody inhibitors of ADAMTS13 function became a key criterion for the diagnosis of acquired, autoimmune TTP.^{6,7} Measurement of ADAMTS13 activity now provides greater specificity for the diagnosis of TTP; appreciation of the autoimmune etiology of acquired TTP provides the basis for more effective treatment. With current diagnosis and treatment, the uncommon occurrence of severe acute

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kidney injury (AKI) distinguishes TTP from other primary TMA syndromes.¹

At the inception of the Oklahoma TTP Registry, we established criteria to describe patients' presenting features and clinical outcomes.⁸ At that time, before current criteria for identifying and staging AKI (Risk, Injury, Failure, Loss, and End-stage Kidney [RIFLE],⁹ Acute Kidney Injury Network,¹⁰ Kidney Disease: Improving Global Outcomes [KDIGO]¹¹) were published, we described kidney function in 3 categories based on serum creatinine concentrations and the use of renal replacement therapy (RRT): normal kidney function, mild renal insufficiency, and severe AKI. Using these criteria, described here as Oklahoma criteria, to analyze our cohort of 78 patients enrolled in the Registry at the time of their first episode of acquired TTP, 1995 to 2015, we recently reported that severe AKI occurred in only 4 (5%) patients; 3 required RRT.¹² The uncommon occurrence of severe AKI was consistent with our observations during long-term patient follow-up. With a median follow-up of 5.9 years, the estimated glomerular filtration rate (eGFR), determined by the Chronic Kidney Disease-Epidemiology Collaboration equation¹³ in 57 patients with acquired TTP, was not different from that of the age-, race-, and gender-matched United States population.¹⁴ However, the frequency of "high-normal" urinary albumin excretion, defined by an albumin/creatinine ratio (ACR) of 10 to 29 mg/g, was increased in these patients.¹⁵ Long-term outcomes associated with AKI in survivors of TTP have not been described. Whether AKI at the time of the acute episode contributes to the increased rates of subsequent mortality and hypertension, which we have previously reported,¹⁴ is unknown.

The KDIGO criteria for AKI diagnosis and staging, established in 2012,¹¹ have provided increased sensitivity for identifying less severe AKI, a condition with prognostic importance.^{16,17} In 2015, Zafrani *et al.* used the KDIGO criteria to evaluate kidney function in 92 patients with TTP (ADAMTS13 activity <10%) admitted to the medical intensive care unit of a tertiary hospital (Saint-Louis University Hospital) in Paris, France, from 2001 through 2013. They reported that 54 (59%) of the 92 patients presented with AKI; 25 (27%) patients had stage 3 AKI, and 14 (15%) required RRT.¹⁸ The 54 patients who had AKI survived. When they were tested 6 months after recovery from TTP, 12 (22%) had eGFR < 60 ml/min per 1.73 m²; 3 required continuing RRT.

To understand the apparent discrepancy between our experience and the experience reported by Zafrani *et al.*,¹⁸ we analyzed kidney function of the 78 patients in the Oklahoma Registry with their first episode of acquired TTP, from 1995 through 2015, using the

KDIGO criteria. First, we analyzed kidney function at presentation, comparing the results with our previous analysis in which the Oklahoma criteria were used. Next, we compared kidney function at presentation with the long-term outcomes of kidney function, hypertension, and death. Then we compared the initial kidney function and the long-term outcomes of patients in the Oklahoma Registry with the experience of Zafrani *et al.*¹⁸

METHODS

Patient Identification and Enrollment

The Registry, established January 1, 1989, is a population-based inception cohort of consecutive patients with clinically suspected TTP (or other thrombotic microangiopathies¹) identified by a request to the Oklahoma Blood Institute for PEX treatment.⁸ Among adults, TTP is typically the initial diagnosis for a patient who is acutely ill with microangiopathic hemolytic anemia and thrombocytopenia, and PEX is urgently requested because it has been the essential treatment for TTP for the past 26 years.³ All patients in 58 of Oklahoma's 77 counties, a geographic region with a population of 2.4 million, in whom the diagnosis of TTP was suspected and for whom a decision to initiate PEX treatment was made, have been enrolled in the Registry. Enrollment is without selection or referral bias because the Oklahoma Blood Institute is the sole provider of transfusion services and procedures, including PEX, for all hospitals in these counties. One of the authors (JNG) began seeing Registry patients at the time of their enrollment in 1995 to prospectively collect data on diagnosis and management; he has seen 385 of the 434 patients (89%) during their initial hospitalizations (1995–2015). The Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and participating hospitals.

ADAMTS13 Activity and Functional Inhibitor Measurements

ADAMTS13 activity has been measured in serum samples routinely collected immediately before the first PEX treatment, beginning November 13, 1995.¹⁹ Measurements were performed in all samples by means of both a fluorogenic assay with fluorescence resonance energy transfer substrate-von Willebrand factor 73 (FRETs-VWF73) substrate and a quantitative immunoblotting assay in the hematology laboratories of the University of Bern in Bern, Switzerland. Patients were initially diagnosed with TTP if they had ADAMTS13 activity < 10% as determined by either method. Patients with TTP were diagnosed as having an acquired

etiology if they had functional ADAMTS13 inhibitor activity, if their ADAMTS13 activity increased during remission, or if a functional inhibitor was documented at the time of relapse. The diagnosis of TTP was supported if patients with ADAMTS13 activity < 10% did not have an alternative diagnosis for their clinical features during the initial hospitalization.¹² In this report, TTP indicates acquired autoimmune TTP. Patients with hereditary TTP, which is much less common and has a different clinical course, are not included.

Acute Kidney Injury

AKI was defined and staged by both KDIGO¹¹ and Oklahoma⁸ criteria (Table S1). For comparison of AKI defined by Oklahoma criteria with AKI defined by KDIGO criteria, we designated our previous terms of “normal kidney function” as Oklahoma stage 0 AKI, “mild renal insufficiency” as Oklahoma stage 1 AKI, and “severe AKI” as Oklahoma stage 3 AKI. For the KDIGO assessment, we defined baseline serum creatinine concentration (SCr) as the SCr on the day of the TTP diagnosis, defined as the day of the first PEX treatment, for subjects with SCr < 1.5 mg/dl.²⁰ To avoid the assignment of inappropriately low KDIGO stages of AKI for subjects with higher SCr values on the day of diagnosis, we calculated a baseline SCr for patients whose presenting SCr was ≥ 1.5 mg/dl to produce an eGFR of 75 ml/min per 1.73 m², using the Chronic Kidney Disease-Epidemiology Collaboration equation.^{9,13,21}

Follow-up Patient Evaluations

Patients who survived their initial episode of TTP have been invited to annual evaluations beginning in 2004. Follow-up eGFR was calculated from the most recent SCr. At the 2011 annual evaluation, the urine ACR was measured in an untimed urine sample from the 36 patients who participated in that annual evaluation. Because ACR was not available for all subjects, chronic kidney disease (CKD) was diagnosed by eGFR and defined as eGFR < 60 ml/min per 1.73 m².²² Increased albuminuria was defined as ACR ≥ 30 mg/g. ACR ≥ 10 mg/g was also evaluated, because ACR of 10 to 29 mg/g is associated with increased mortality,²³ and we have previously shown high rates of ACR (≥ 10 mg/g) among survivors of TTP.¹⁵ Hypertension and diabetes were documented by requirement for prescribed daily medication.¹⁴

Statistical Analysis

Descriptive statistics were calculated using medians and proportions. Comparisons were made using the Wilcoxon Mann-Whitney test with normal approximation

(continuous variables) or the chi-square test (or the Fisher exact test) (categorical variables). Comparisons of the patients' demographic and clinical features with the 4 categories of AKI determined by KDIGO criteria were performed by using the Fisher exact and Kruskal-Wallis tests. An alpha of 0.05 was used. The weighted kappa statistic was used to compare the results of AKI determinations made by using the KDIGO and Oklahoma criteria.²⁴ Values of 0.40 or higher indicate moderate agreement; values of 0.8 or higher indicate excellent agreement. All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

From November 13, 1995, when systematic collection of serum samples began, through 2015, 83 patients had ADAMTS13 activity < 10% and were initially diagnosed with their first episode of acquired TTP. In 5 of these 83 patients, an alternative etiology was established at the time of the initial hospitalization.¹² Therefore 78 patients comprise the cohort of consecutive patients who have been diagnosed with a first episode of acquired TTP.

Presenting Demographic and Clinical Features

Table 1 describes the presenting features of these 78 patients. The demographic and clinical features have been previously reported.^{12,14,25} The frequencies of hypertension and diabetes at presentation are not different from those in the age-, race-, and gender-matched population.¹⁴ Thirty-three (42%) patients had no AKI; 25 (32%) had KDIGO stage 1 AKI, 12 (16%) had KDIGO stage 2 AKI, and 8 (10%) had KDIGO stage 3 AKI. Three patients (4%) received RRT. There was no apparent association of the patients' demographic or clinical features with the 4 KDIGO AKI categories (Table 2). When Oklahoma criteria were used, 37 patients (48%) had no AKI, 37 patients (48%) had Oklahoma stage 1 AKI, and 4 patients (5%) had Oklahoma stage 3 AKI. All 4 patients with Oklahoma stage 3 AKI also had KDIGO stage 3 AKI. Table S2 provides a comparison of the AKI categories determined by the KDIGO and Oklahoma criteria. The weighted kappa statistic was 0.61 (95% confidence interval, 0.44–0.77), indicating moderate agreement between the 2 criteria.

Clinical Course and Outcomes of the Initial TTP Episode

Ten patients (13%) died during their initial acute episode of TTP.¹⁹ There was a significant association between the AKI stage and the frequency of death (Table 3, $P = 0.020$), with greater frequency among

Table 1. Presenting demographic, clinical, and laboratory features of 78 consecutive patients with their first episode of acquired thrombotic thrombocytopenic purpura, 1995–2015

Presenting features	Patients
Demographics	
Age (yr, median, range)	41 (9–79)
Race (no., % black)	30 (38)
Gender (no., % female)	60 (77)
Body mass index (kg/m ² , median, range)	33 (15–65)
Medical history (no., %)	
Hypertension	21 (27)
Diabetes mellitus	12 (15)
Presenting clinical features (no., %)	
Severe neurologic abnormalities	41 (53)
Seizures	12 (15)
Coma	6 (8)
Stroke	9 (12)
Transient focal abnormalities	31 (41)
Laboratory data	
Hematocrit (%), median, range)	21 (13–33)
Platelets (/ μ l \times 10 ³ , median, range)	10 (2–101)
LDH (U/L, median, range)	1288 (274–3909)
Creatinine (mg/dl, median, range)	1.3 (0.7–6.8)
Acute kidney injury (KDIGO stage, No., %)	
0	33 (42)
1	25 (32)
2	12 (16)
3	8 (10)
Outcome	
Death (No., %)	10 (13)

KDIGO, Kidney Disease: Improving Global Outcomes; LDH, lactate dehydrogenase. Hypertension and diabetes mellitus were defined by the requirement for daily treatment. Severe neurologic abnormalities were defined as 1 or more of these 4 abnormalities.⁸ Because individual patients may have more than 1 severe neurologic abnormality, the sum of the frequency of the 4 individual abnormalities exceeds the overall frequency of severe neurologic abnormalities. Laboratory data are the most abnormal values on the day of presentation (the day of the first plasma exchange treatment) \pm 7 days, to avoid the influence of transfusions on the hematocrit and platelet counts, and to capture the maximum serum creatinine values.

patients with more severe AKI. The 8 patients with KDIGO stage 3 AKI are described in Table S3. Their median age was 55 years; 4 patients had preexisting hypertension; none had diabetes. Three patients (patients 3, 5, and 7) were hypotensive immediately preceding their diagnosis of TTP. Patient 6 had a stroke and became unresponsive and hypotensive during her first PEX treatment. Two of the 3 patients who required RRT died; the remaining patient (patient 6) did not require dialysis after hospital discharge.

Long-term Outcomes

Among the 68 patients who survived their initial episode of TTP, 2 have been lost to follow-up; 4 other patients have not had follow-up SCr measurements. Therefore data from 62 patients were available to describe long-term outcomes of kidney function. The relation of AKI to long-term outcomes of eGFR is presented in Table 4. Four of 62 patients (6%) had eGFR < 60 ml/min per 1.73 m². None of the 4 patients with eGFR < 60 ml/min per 1.73 m² had KDIGO stage 3

Table 2. Association of the presenting demographic and clinical features of 78 patients with their initial episode of acquired thrombotic thrombocytopenic purpura with their presenting kidney function

Patient features	KDIGO Stage				P value
	0	1	2	3	
Patients (no.)	33	25	12	8	
Age in years (median)	38	41	40.5	46.5	0.353
Race (black, %)	13 (39)	8 (32)	6 (50)	3 (38)	0.811
Gender (female, %)	25 (76)	18 (72)	11 (92)	6 (75)	0.630
Body mass index (median)	32.5	30.0	38.1	31.9	0.503
Hypertension (no., %)	6 (18)	7 (28)	4 (33)	4 (50)	0.286
Diabetes (no., %)	3 (9)	1 (4)	4 (33)	0	0.053
Severe neurologic abnormalities (no., %)	14 (42)	9 (36)	6 (50)	3 (38)	0.944
Hematocrit (%) (median)	21	21	21.5	21.5	0.572
Platelet count (μ l \times 10 ³) (median)	10	11	12	15	0.534
LDH (U/L) (median)	1302	1803	1578	2048	0.627

KDIGO, Kidney Disease: Improving Global Outcomes; LDH, lactate dehydrogenase. Hypertension and diabetes preceded the occurrence of thrombotic thrombocytopenic purpura, documented by requirement for daily treatment. Severe neurologic abnormalities were defined as coma, stroke, seizures, or transient focal signs. Data for hematocrit, platelet count, and LDH values were the most abnormal values on the day of diagnosis \pm 7 days. None of the demographic and clinical features were associated with KDIGO AKI stage. A test for trend of the data for hypertension was also not significant ($P = 0.059$).

AKI with their initial episode of TTP; 3 had KDIGO stage 0 or 1 AKI, and all 4 had Oklahoma stage 1 AKI. There was no association between the stages of AKI and the occurrence of CKD according to either the KDIGO or Oklahoma criteria. Among the 4 patients with eGFR < 60 ml/min per 1.73 m², 2 patients had preexisting hypertension, 1 had preexisting diabetes, and 1 had both preexisting hypertension and diabetes. The 5 patients with KDIGO stage 3 AKI who survived their initial episode were evaluated 2.9 to 16.8 years (median, 8.1 years) after their initial episode of TTP. Their eGFRs were 77 to 107 ml/min per 1.73 m² (median, 92 ml/min per 1.73 m²).

Of the 36 patients assessed for albuminuria, 3 (8%) had an ACR \geq 30 mg/g at follow-up, 1 had had no AKI, and 2 had had KDIGO stage 1 AKI with the initial TTP episode. An ACR \geq 10 mg/g was observed in 19 patients (53%); it was not associated with AKI at the time of the initial TTP episode (Table 3). Nine (56%) of 16 patients with no AKI (56%) had ACR \geq 10 mg/g compared with 10 of 20 patients with AKI (50%), KDIGO stages 1 to 3.

Among the 66 surviving patients with follow-up evaluations, 14 had hypertension preceding their initial episode of TTP. Among the 52 patients without preceding hypertension, 16 (31%) have developed hypertension. There was a significant association between the presence of AKI and the development of hypertension (Table 3, $P = 0.023$), with a suggestion of greater frequency among patients with more severe AKI.

Thirteen (20%) of the 66 surviving patients who had follow-up evaluations have died. There was a

Table 3. Relation of acute kidney injury stage at presentation to death with the initial thrombotic thrombocytopenic purpura episode and with the occurrence of albuminuria, hypertension, and death after recovery from thrombotic thrombocytopenic purpura

Patients	KDIGO AKI stage				Total patients	P value
	0	1	2	3		
Initial episode						
Death	1/33 (3%)	3/25 (12%)	3/12 (25%)	3/8 (38%)	10/78 (13%)	0.020
After recovery from the initial episode						
Albuminuria ^a	9/16 (56%)	8/16 (50%)	1/3 (33%)	1/1 (100%)	19/36 (53%)	0.051
Hypertension	7/25 (28%)	3/18 (17%)	3/6 (50%)	3/3 (100%)	16/52 (31%)	0.023
Death	4/30 (13%)	2/22 (9%)	5/9 (56%)	2/5 (40%)	13/66 (20%)	0.015

AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

Ten of 78 patients died with their initial episode of thrombotic thrombocytopenic purpura (TTP). There was a significant association between the acute kidney injury (AKI) stage and the frequency of death, with greater frequency among patients with more severe AKI. Urine albumin/creatinine ratio was measured in 36 patients at the 2011 annual follow-up evaluation, 1.1–15.7 years after their initial episode of TTP (median follow-up, 5.9 years).

^aAlbuminuria is defined as an albumin/creatinine ratio ≥ 10 mg/g. Only 3 patients had albuminuria (albumin/creatinine ratio ≥ 30 mg/g); 1 had no AKI at the time of the initial episode and 2 had stage 1 AKI. There was no appearance of greater frequency of albuminuria among patients with more severe AKI. Two of the 68 survivors were lost to follow-up. Among the 66 surviving patients with follow-up evaluations, 14 had hypertension preceding their initial episode of TTP. Therefore 52 surviving patients were analyzed for the subsequent development of hypertension. Sixteen (31%) of these 52 patients have developed hypertension 0.2–13 years (median, 5.5 years) after recovery from their initial episode of TTP. The frequencies of new-onset hypertension were significantly different in relation to AKI, with a suggestion of greater frequency among patients with more severe AKI. The 13 deaths among the 66 surviving patients who have been followed up regularly occurred 3 months to 11 years after recovery from the initial TTP episode (median, 7 years). The frequencies of death were significantly different in relation to AKI, with a suggestion of greater frequency among patients with more severe AKI.

significant association between the presence of AKI and death during the follow-up period (Table 3, $P = 0.015$), with a suggestion of greater frequency among patients with more severe AKI. The 13 deaths occurred 3 months to 11 years after recovery from the initial TTP episode (median, 7 years). Among the 5 patients with KDIGO stage 3 AKI who survived their initial episode, 2 have died. Patient 7 died 3 years after his initial TTP episode from recurrent myocardial infarction; patient 2 died 9 years after her initial TTP episode from metastatic ovarian carcinoma.

Comparison of Oklahoma Registry Patients with TTP to Patients with TTP Reported From Saint-Louis University Hospital, Paris, France

Table 5 compares the occurrence of AKI and requirement for RRT during the initial TTP episodes, death from the initial TTP episode, and the frequency of CKD after recovery between Oklahoma Registry patients with TTP and patients with TTP reported from Hôpital

Saint-Louis in Paris.¹⁸ The occurrence of AKI was different between the 2 groups, with a greater frequency of KDIGO stage 3 AKI among the Paris patients. Requirement for RRT during the initial TTP episode was greater among Paris patients than Oklahoma patients. CKD, defined by an eGFR < 60 ml/min per 1.73 m², was also greater among the Paris patients.

DISCUSSION

In the Oklahoma Registry's prospective cohort of 78 patients with acquired TTP enrolled across 20 years, severe kidney injury was uncommon. The frequency of severe, stage 3 AKI was 10% when the KDIGO criteria were used¹¹ and 5% when the Oklahoma criteria were used.⁸ Only 3 patients (4%) required RRT. The

Table 5. Kidney involvement in patients with acquired TTP: Comparison of Oklahoma Registry patients with patients reported from Saint-Louis University Hospital, Paris, France

Patients	Oklahoma Registry (78 patients)	Hôpital Saint-Louis, Paris (92 patients)	P value
Acute kidney injury			
KDIGO stage 0	33 (42%)	34 (37%)	0.041
KDIGO stage 1	25 (32%)	24 (26%)	
KDIGO stage 2	12 (15%)	9 (10%)	
KDIGO stage 3	8 (10%)	25 (27%)	
RRT	3 (4%)	14 (15%)	0.019
Death (initial TTP episode)	10 (13%)	4 (4%)	0.054
CKD (eGFR < 60 ml/min per 1.73 m ²)	4/62 (6%)	12/54 (26%)	0.017
Follow-up (yr, median)	6.4 (0.2–18.2)	0.5	NA
Long-term RRT	0	3/88 (3%)	0.251

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy; TTP, thrombotic thrombocytopenic purpura.

Ten of the 78 Oklahoma Registry patients died during their initial episode; 2 patients have been lost to follow-up, and 4 patients have not had follow-up serum creatinine concentration measurements. Therefore, Oklahoma long-term outcomes of CKD and RRT are from data on 62 patients. Hôpital Saint-Louis, Paris data are from their published report. Chronic kidney disease was determined at 6 months after recovery from the acute episode by estimated glomerular filtration rate < 60 ml/min per 1.73 m² in 54 of 88 surviving patients.¹⁸

Table 4. Relation of acute kidney injury stage at presentation with long-term outcome of estimated glomerular filtration rate in 62 Oklahoma patients who survived their initial episode of TTP and had follow-up serum creatinine measurements

AKI stage	Patients	eGFR				Follow-up duration
		≥ 90	60–89	45–59	30–44	
KDIGO 0	27	17	9	1	–	5.4
KDIGO 1	21	14	5	1	1	8.1
KDIGO 2	9	4	4	0	1	4.5
KDIGO 3	5	4	1	0	–	8.1
All patients	62	39	19	2	2	6.4

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

Among the 78 patients in the Oklahoma Thrombotic Thrombocytopenic Purpura Registry, 68 survived their initial episode; 2 patients have been lost to follow-up, and 4 patients have not had follow-up serum creatinine concentration measurements. There was no association between KDIGO AKI stage and eGFR ($P = 0.74$). Dash indicates that no subjects had eGFR within this range.

presence of AKI was not related to the presenting demographic or clinical features of our patients, including the presence of preexisting diabetes or hypertension. Among the 8 patients with KDIGO stage 3 AKI, critical complications were common. Three patients were hypotensive immediately preceding their diagnosis of TTP related to sepsis, cardiac arrest after cardiac surgery, and myocardial infarction. One other patient became hypotensive with a stroke during her first PEX treatment for TTP. Three of the 8 patients with KDIGO stage 3 AKI died. Two of the 3 patients who had required RRT died; the surviving patient did not require RRT after discharge from the hospital.

Differences between our experience and recently published data suggesting that severe AKI is prevalent in patients with TTP¹⁸ may be related to patient selection. The report from Paris described patients in an intensive care unit of a tertiary referral hospital in a large city.¹⁸ The Oklahoma Registry cohort includes all patients within a defined geographic region for whom PEX treatment is requested for a suspected diagnosis of TTP. Many of the Oklahoma Registry patients were not severely ill.¹² We believe that our cohort of patients is more representative of the complete clinical spectrum of TTP. However, we acknowledge that patients may not be included in the Registry if they had been critically ill and died before PEX was requested, or if they had only mild symptoms that were not recognized as TTP and responded to treatment with corticosteroids, without a request for PEX treatment.

Our experience is similar to that described in the report of 772 patients with acquired TTP from the French National Registry for TMA.²⁶ In the French cohort, 309 patients (40%) were described as having “renal insufficiency,” and 77 (10%) were described as having “acute renal failure.” The criteria for these designations were not described, but the descriptive phrases and the frequency of patients with each stage are similar to the KDIGO stages 1 to 2 (48% of Oklahoma patients) and stage 3 (10% of Oklahoma patients), respectively. Also, only 12 of the French National Registry TTP patients (2%) required RRT, which is comparable to the 3% frequency of RRT among Oklahoma patients.

Our results substantiate that AKI is less common and less likely to be severe in TTP than in other primary TMA syndromes.¹ In 125 adults with complement-mediated TMA (also described as “atypical hemolytic uremic syndrome”), mean SCr at presentation was 7.2 mg/dl, and 81% required RRT.²⁷ In another study of 41 adults with complement-mediated TMA, mean SCr at presentation was 4.6 mg/dl, and 59% required RRT.²⁸ In 21 adults with Shiga toxin-mediated TMA reported from the Oklahoma Registry, mean SCr at

presentation was 4.9 mg/dl, and 43% required RRT.²⁹ In 19 patients with quinine-induced TMA, reported from the Oklahoma Registry, mean SCr at presentation was 7.6 mg/dl, and 89% required RRT.³⁰ TMA secondary to vascular endothelial growth factor inhibition is characterized by glomerular disease.³¹ Although these other etiologies of TMA are distinct from TTP because kidney involvement is the principal abnormality, our results also highlight that the diagnosis of TTP cannot be excluded solely by the presence of severe AKI, since 10% and 5% of patients had severe AKI as determined by KDIGO and Oklahoma criteria, respectively.

CKD was also uncommon among our patients with acquired TTP; only 4 of 62 surviving patients (6%) with follow-up evaluation of kidney function had $eGFR < 60$ ml/min per 1.73 m², and 3 of 36 tested patients (8%) had an $ACR \geq 30$ mg/g. The occurrence of CKD was not associated with the occurrence of AKI, as determined by either KDIGO or Oklahoma criteria. The occurrence of CKD in patients who have recovered from TTP may reflect the inherent risk for CKD associated with diabetes and hypertension, since the 4 patients with follow-up $eGFR < 60$ ml/min per 1.73 m² all had hypertension and/or diabetes preceding their initial episode of TTP. Although the frequency of CKD was low and the $eGFR$ of our patients with median follow-up of 5.3 years was not different from the age-, race-, gender-, and body mass index-matched United States population, the frequency of hypertension among our patients was greater than the age-, race-, gender-, and body mass index-matched United States population.¹⁴ The frequency of new-onset hypertension after recovery was greater among patients with more severe AKI during their initial episode of TTP. The occurrence of hypertension after recovery may also reflect kidney disease that is not apparent from $eGFR$. Our patients did have higher than expected rates of high-normal albuminuria,¹⁵ which is associated with greater risk for cardiovascular mortality.²³ Finally, the increased frequency of death after recovery from TTP, which we have previously reported,¹⁴ also appeared to be associated with increasing severity of AKI during the initial episode.

Our observations are limited by the small number of patients in our cohort, an expected limitation for an uncommon disorder. We used previously reported methods to estimate baseline SCr values, because baseline values were not often available in our previously healthy patients. Use of untimed urine specimens for ACR determination may have led to overestimation of albuminuria. Our study also has several strengths, including detailed analyses of prospectively collected individual patient data and comprehensive long-term

follow-up. These features allowed an accurate description of patients with AKI during their initial TTP episodes, as well as their long-term outcomes after recovery. Our use of KDIGO criteria, in addition to the Oklahoma criteria, which we developed at the beginning of the Oklahoma Registry specifically for analysis of our patients with TTP,⁸ allowed comparison of our previous experience with current observations of AKI incidence and severity in patients with TTP.

In summary, severe AKI determined by both KDIGO and Oklahoma criteria is uncommon in patients with acquired TTP. Severe AKI may occur in patients with TTP when additional severe systemic complications occur, such as hypotension complicating myocardial infarction, stroke, and sepsis. CKD is also uncommon and may occur when other risk factors for kidney disease, such as hypertension and diabetes, are present. These observations support previous impressions that TTP is unique among TMA syndromes for the uncommon occurrence of severe kidney involvement. Even though severe AKI is uncommon, AKI at the time of an acute episode of acquired TTP may be a significant contributor to long-term risks for hypertension and premature death.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. Definitions, identification, staging, features and clinical course of acute kidney injury by Kidney Disease: Improving Global Outcomes (KDIGO) and Oklahoma criteria.

Table S2. Comparison of identification and staging of acute kidney injury by KDIGO and Oklahoma criteria.

Table S3. Presenting features and clinical course of 8 patients with Kidney Disease: Improving Global

Outcomes (KDIGO) stage 3 acute kidney injury at diagnosis.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

- George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371:654–666.
- Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine*. 1966;45:139–159.
- Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med*. 1991;325:393–397.
- Clark WF, Garg AX, Blake PG, et al. Effect of awareness of a randomized controlled trial on use of experimental therapy. *JAMA*. 2003;290:1351–1355.
- Shumak KH, Rock GA, Nair RC, et al. Late relapses in patients successfully treated for thrombotic thrombocytopenic purpura. *Ann Intern Med*. 1995;122:569–572.
- Furlan M, Robles R, Galbusera M, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med*. 1998;339:1578–1584.
- Tsai HM, Lian EC-Y. Antibodies to von-Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med*. 1998;339:1585–1594.
- Vesely SK, George JN, Lämmle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. 2003;101:60–68.
- Bellomo R, Ronco C, Kellum JA, et al. RIFLE: acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204.
- Mehta RL, Kellum JA, Shah SV, et al. AKIN: Acute Kidney Injury Newtork: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
- Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
- Page EE, Kremer Hovinga JA, et al. Thrombotic thrombocytopenic purpura: diagnosis, presenting features, management, long-term outcomes: 1995-2015. *Blood Advances*. 2017;1:590–600.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
- Deford CC, Reese JA, Schwartz LH, et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood*. 2013;122:2023–2029.
- Little DJ, Reese JA, Vesely SK, et al. Increased urinary albumin excretion following recovery from acquired thrombotic thrombocytopenic purpura. *Am J Kidney Dis*. 2014;64:317–318.

16. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol.* 2004;15:1597–1605.
17. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16:3365–3370.
18. Zafrani L, Mariotte E, Darmon M, et al. Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. *J Thromb Haemost.* 2015;13:380–389.
19. Kremer Hovinga JA, Vesely SK, Terrell DR, et al. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood.* 2010;115:1500–1511.
20. Fliser D, Laville M, Covic A, et al. European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant.* 2012;27:4263–4272.
21. Bagshaw SM, George CB, Dinu I, et al. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant.* 2008;23:1203–1210.
22. Stevens PE, Levin A, Members KDIGO CKD GWG. Evaluation and management of chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. *Ann Intern Med.* 2013;158:825–831.
23. Consortium CKDP. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375:2073–2081.
24. Stokes ME, Davis CS, Koch GG. *Categorical data analysis using SAS.* Vol. 3. Cary, NC: SAS Institute Inc; 2012.
25. Reese JA, Muthurajah DS, Kremer Hovinga JA, et al. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired ADAMTS13 deficiency: comparison of incidence, demographic and clinical features. *Pediatr Blood Cancer.* 2013;60:1676–1682.
26. Mariotte E, Azoulay E, Galicier L, et al. Epidemiology and pathophysiology of adult-onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. *Lancet Haematol.* 2016;3:e237–e245.
27. Fremeaux-Bacchi V, Fakhouri F, Garnier A, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol.* 2013;8:554–562.
28. Fakhouri F, Jourmant M, Campistol JM, et al. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. *Am J Kidney Dis.* 2016;68:84–93.
29. Karpac CA, Li X, Terrell DR, et al. Sporadic bloody diarrhoea-associated thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome: an adult and paediatric comparison. *Br J Haematol.* 2008;141:696–707.
30. Page EE, Little DJ, Vesely SK, et al. Quinine-induced thrombotic microangiopathy. *Am J Kidney Dis.* In Press.
31. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med.* 2008;358:1129–1136.