Observational Study

Medicine

OPEN

Acute kidney injury associated with thrombotic microangiopathy

Characterization, prevalence, and prognosis

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Abstract

Acute kidney injury (AKI) is an important feature of thrombotic microangiopathy (TMA). This present study aimed to describe and analyze the characterization, prevalence, and prognosis in TMA patients with AKI. This study was an observational, retrospective patient cohort study in which patients were classified as AKI and non-AKI groups. An analysis of the relationship between the risk factors and AKI and in-hospital mortality was conducted using logistic regression. Kaplan–Meier curves were adopted to obtain the link between AKI and in-hospital mortality. There were 27 and 51 patients in the AKI and non-AKI groups, respectively, and the morbidity and mortality of AKI were 34.62% and 40.74%, respectively. AKI was associated with an older age ($P = .033$) and higher infection rates ($P < .001$). In comparison with the non-AKI group, the AKI group had tremendously intrarenal manifestations: hematuria ($P < .001$), proteinuria ($P < .001$). The AKI group received all continuous renal replacement therapy treatment ($P < .001$), but fewer glucocorticoids were used ($P = .045$). In-hospital mortality ($P = .045$) were higher in the AKI group. The risk factors for AKI ($P = .037$) were age. In addition, higher total bilirubin ($P = .011$) and age ($P = .022$) were significantly correlated with increasing risk of in-hospital mortality. Survival analysis by Kaplan–Meier revealed a significantly poor prognosis predicted by the AKI group ($P = .045$). Acute kidney injury could be commonly seen in TMA pneumonia and was related to a higher mortality rate.

Abbreviations: AKI = acute kidney injury, CKD = chronic kidney disease, CRRT = continuous require renal replacement therapy, eGFR = estimated glomerular filtration rate, HUS = hemolytic uremic syndrome, MAHA = microangiopathic hemolytic anemia, TBIL = total bilirubin, TMA = thrombotic microangiopathy, TMA-AKI = TMA-associated AKI.

Keywords: acute kidney injury, in-hospital mortality, thrombotic microangiopathy

1. Introduction

Thrombotic microangiopathy (TMA) is conventionally classified as thrombotic thrombocytopenic purpura based on severe ADAMTS13 deficiency, hemolytic uremic syndrome (HUS), secondary HUS (sHUS), and atypical HUS (aHUS). As a general rule, HUS is induced by Shiga toxin-producing *Escherichia coli*. Meanwhile, sHUS is rising from a variety of causes, including connective tissue diseases, medications, malignancies, infections, organ transplantations, and COVID-19, as well as aHUS is mediated by complement dysregulation is becoming more prevalent.[1] It is a rare life-threatening condition with the widespread formation of microthrombi and endothelial damage, resulting in thrombocytopenia, microangiopathic hemolytic anaemia (MAHA), and organ dysfunction.[2] Most patients present with extrarenal manifestations, such as central nervous system impairment, gastrointestinal symptoms, cardiac abnormalities, and liver dysfunction.[3]

Many of the TMA syndromes, but not all, result in a serious degree of acute kidney injury (AKI),[4] and several reports indicate that some groups of TMA patients develop glomerular and vascular changes more frequently.[5] It has been found that patients with TMA-associated AKI (TMA-AKI) are more likely to develop chronic kidney disease (CKD) and end-stage renal disease. Creatinine levels may rise with no symptoms or continuous require renal replacement therapy (CRRT) depending on the severity of AKI.[6]

We, therefore, undertook a retrospective observational study of TMA-AKI to (a) better understand the prevalence and clinical characterization; (b) evaluate the potential risk factors associated with the occurrence of AKI, CKD and death; and (c) evaluate the significance of AKI in predicting prognosis.

2. Materials and methods

2.1. Study population and study design

We performed a retrospective, single-center analysis over 5 years between January 2017 and December 2021 among patients

This study was supported by Peking University People's Hospital Scientific Research Development Funds (RDJP2023-29) and National Natural Science Foundation of China (No. 82241052).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Dong G, Gao P, Shi F-E, Yu J, Zhu J. Acute kidney injury associated with thrombotic microangiopathy: Characterization, prevalence, and prognosis. Medicine 2024;103:35(e39431).

Received: 13 January 2024 / Received in final form: 2 May 2024 / Accepted: 2 August 2024

http://dx.doi.org/10.1097/MD.0000000000039431

admitted to the Emergency Department at Peking University People's Hospital. The local ethics committees approved the protocol (Number: 2019-PHB-157). The trial was undertaken under the Declaration of Helsinki. Informed consent was waived as the study was retrospectively designed. Reporting in this study followed the guidelines described in the STROBE statement on strengthening the reporting of observational studies in epidemiology.[7]

All patients diagnosed with TMA received ADAMTS13 activity assay and received adequate treatment respecting the guidelines.[2,8] Which did not meet the following criteria would be excluded: (a) age ≤ 16 years, (b) transferred to other medical facilities or drop out of treatment, (c) with CKD or even ESKD[9] and requiring CRRT previously, and (d) missing clinical information data. All patients were classified into either the AKI or non-AKI groups based on whether they met the definition of Kidney Disease: Improving Global Outcomes.[10] The patient screening process is shown in Figure 1.

2.2. Data collection and endpoints

We conducted a review of the electronic medical records, and the information included age, gender, co-morbidities listed in the medical records (covering autoimmune diseases, pregnancy, malignant hypertension, hematopoietic stem cell transplantation, or infection), treatments before admission (including cytarabine, cyclosporine, cyclophosphamide, mycophenolate mofetil or hydroxychloroquine), intervention during the hospital (including plasma exchange, plasma infusion, glucocorticoids, immunoglobulin, rituximab or other immunosuppressive therapies, etc) and length of stay were recorded. The primary analyzed endpoint was in-hospital mortality.

2.3. Kidney function and laboratory parameters in hematologic features

Laboratory parameters associated with hemolysis, including ADAMTS13 activity, ADAMTS13 antibody titer (if obtained), cell-free hemoglobin, lactate dehydrogenase, indirect bilirubin, schistocytes, platelet, red blood cells, reticulocyte, total bilirubin (TBIL), and haptoglobin were recorded during the first 24 hours of admission. Also, we analyzed the following laboratory data about kidney function at the time of baseline and maximum serum creatinine values. Based on the CKD-EPI equation, the estimated glomerular filtration rate (eGFR) was calculated.[11] Hematuria and proteinuria were also recorded. The complete blood count was measured using the Sysmex XN-9000 automatic hematology analyzer (Sysmex, Japan). The urinalysis were measured using the Urisys 2400 automatic urine analyzer (Roche, Switzerland). The biochemical indexes were measured using the Roche Cobas 8000 automatic biochemical analyzer (Roche, Switzerland). ADAMTS13 activity and inhibitor dosing came from esoteric testing platforms.

2.4. Statistical analysis

Statistical analyses were performed by SPSS 25.0 (SPSS Inc., Chicago, IL) and GraphPad Prism mapping software. Variable distributions were assessed with the Kolmogorov–Smirnov test. Mann–Whitney U test was used for intercomparison of continuous variables expressed as median (interquartile range [IQR]). Qualitative variables were presented as n (%) and compared against each other via the Fisher exact test or chi-square test. To determine the risk factors associated with AKI, CKD, and hospital mortality, logistic regression analysis was performed. Cumulative survival of TMA patients with/without concurrent AKI was analyzed using Kaplan–Meier survival curve. Statistical significance was attributed to $P < .05$.

3. Results

3.1. Demographic and clinical characteristics

Ninety-five patients in total with TMA were treated at our institution throughout the study period, 78 of whom were admitted to the final analysis (Fig. 1), 25 (32.05%) patients had thrombotic thrombocytopenic purpura, while 2 (2.56%) patients had

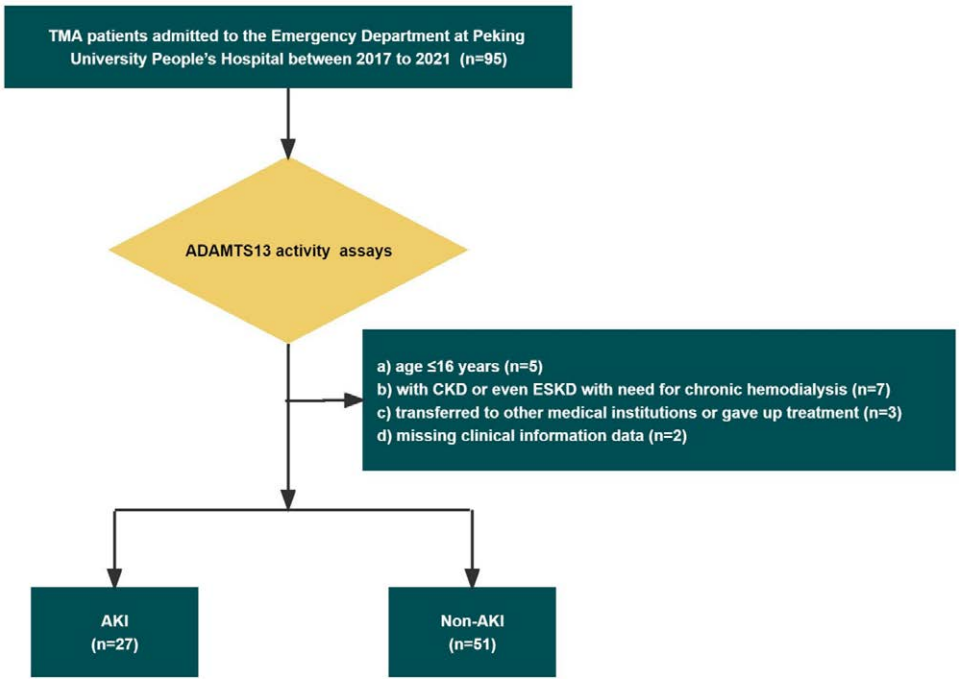

Figure 1. Study population.

HUS. There was an overrepresentation of females in the TMA group (n = 42, 53.85%), and the median age at diagnosis was 45 (IQR 30–62) years.

Patient demographics and clinical characteristics are exhibited in Table 1. The incidence of AKI was 34.62% (n = 27). AKI patients were slightly older than patients without AKI [48 (IQR: 40–73) vs 37 (IQR: 25–62) years, $P = .033$]. Significantly more TMA patients were diagnosed with secondary infection for the AKI group than for the non-AKI group (22.22% vs 0.00%, $P < .001$). Nevertheless, premorbid diseases, drug treatments before admission, baseline renal function and the etiologies were frequently observed among patients of both groups, without significant differences noted. No between-group differences in TMA phenotypes were observed. Overall, the central nervous system signs, MAHA, thrombocytopenia, fever, and abdominal pain affiliated with extrarenal manifestations were frequent in both groups without significant differences. The incidence of proteinuria (88.89% vs 27.45%, $P < .001$) and hematuria (74.07% vs 31.37%, $P < .001$) were significantly different between the 2 groups. The SCr_{max} and $eGFR_{max}$ were significantly higher in the AKI group (both $P < .001$).

3.2. Treatment and outcomes associated with TMA and AKI

As demonstrated in Table 2, patients with AKI received greater CRRT (51.85% vs 0.00%, $P < .001$). There were fewer glucocorticoids in AKI patients in comparison with non-AKI patients (59.26% vs 80.39%, $P < .001$), despite similar treatment with TMA preparations. Among patients with AKI, the proportion of non-survivors was higher than those without AKI (40.74% vs 19.61%, $P = .045$). In the AKI group, hospital stays were slightly longer than in the non-AKI group without statistical significance (22 [IQR 12, 53] vs 21 [IQR 11, 48], $P = .607$).

3.3. Hematological laboratory parameters analysis

The median levels of schistocytes (1.0% [IQR 0.1, 2.0] vs 1.0% [IQR 0.5, 2.0], $P = .473$), red blood cells ($2.72*10^9$/L [IQR 2.03, 3.15] vs $2.44*10^9$/L [IQR 1.95, 2.94], $P = .266$), platelet ($17*10^9$/L [IQR 7, 51] vs $17*10^9$/L [IQR 8, 39], $P = .686$), reticulocyte ($0.086*10^6$/μL [IQR 0.039, 0.147] vs $0.109*10^6$/μL [IQR 0.064, 0.211], $P = .174$), TBIL (66.6 μmol/L [IQR 16.9,

Table 1

Comparison of the clinical features of AKI and non-AKI patients.

	AKI (n = 27)	Non-AKI (n = 51)	Overall population (n = 78)	*P*-value
Demographics				
Female, n (%)	14 (51.85%)	28 (54.90%)	42 (53.85%)	.797
Age, years, median (IQR)	48 (40, 73)	37 (25, 62)	45 (30, 62)	**.033***
Premorbid diseases, *n* (%)				
Diabetes mellitus	3 (11.11%)	3 (5.88%)	6 (7.69%)	.706[C]
Hypertension	7 (25.93%)	5 (9.80%)	12 (15.38%)	.060
Coronary artery disease	5 (18.52%)	2 (3.92%)	7 (8.97%)	.084[C]
Drugs before admission, *n* (%)				
Cytarabine	1 (3.70%)	11 (21.57%)	12 (15.38%)	.080[C]
Cyclosporine	3 (11.11%)	14 (27.45%)	17 (21.79%)	.169[C]
Cyclophosphamide	4 (14.81%)	10 (19.61%)	14 (17.95%)	.830[C]
Mycophenolate mofetil	2 (7.41%)	10 (19.61%)	12 (15.38%)	.275[C]
Hydroxychloroquine	0 (0%)	5 (9.80%)	5 (6.41%)	.157[F]
Baseline renal function				
SCr, μmol/L, median (IQR)	54.00 (46.10, 61.00)	55.40 (45.00, 65.00)	55.47 (48.22, 64.25)	.820
eGFR, (mL/min per 1.73 m^2), median (IQR)	115 (91, 141)	107 (92, 128)	110 (91, 134)	.659
Intrarenal manifestations, *n* (%)				
Proteinuria	24 (88.89%)	14 (27.45%)	38 (48.72%)	<**.001***
Hematuria	20 (74.07%)	16 (31.37%)	36 (46.15%)	<**.001***
SCr_{max}, umol/L, median (IQR)	182.00 (114.00, 276.00)	65.00 (43.00, 78.00)	78.50 (54.50, 128.25)	<**.001***
$eGFR_{max}$, (mL/min per 1.73 m^2), median (IQR)	10.09 (91.00, 39.10)	92.73 (67.09, 113.79)	70.08 (35.20, 105.40)	<**.001***
Extrarenal manifestations, *n* (%)				
CNS signs	11 (40.74%)	26 (50.98%)	27 (34.62%)	.389
MAHA	16 (59.26%)	36 (70.59%)	52 (66.67%)	.313
Thrombocytopenia	26 (96.30%)	48 (94.12%)	74 (94.87%)	1.000[C]
Fever	14 (51.85%)	26 (50.98%)	40 (51.28%)	.942
Abdominal pain	2 (7.41%)	7 (13.73%)	9 (11.54%)	.647[C]
Myocardial injury	14 (51.85%)	16 (31.37%)	30 (38.46%)	.077
Phenotype of TMA, *n* (%)				
Thrombocytopenic purpura	9 (33.22%)	16 (31.37%)	25 (32.05%)	.860
STEC-HUS	2 (7.41%)	0 (0.00%)	2 (2.56%)	.117[F]
sHUS	16 (59.26%)	35 (68.63%)	51 (65.38%)	.408
Etiology of TMA, *n* (%)				
Autoimmune diseases	6 (22.22%)	20 (39.22%)	26 (33.33%)	.130
Pregnancy	2 (7.41%)	5 (9.80%)	7 (8.97%)	1.000[C]
Malignant hypertension	3 (11.11%)	4 (7.84%)	7 (8.97%)	.688[F]
Hematopoietic stem cell transplantation	7 (25.93%)	20 (39.22%)	27 (34.62%)	.241
Infection	6 (22.22%)	0 (0.00%)	6 (7.69%)	<**.001F***

Data are presented as the median (IQR) or n (%). *P* was the comparison between AKI and non-AKI.

AKI = acute kidney injury, CNS = central nervous system, eGFR = estimated glomerular filtration rate, MAHA = microangiopathic hemolytic anemia, SCr = serum creatinine, sHUS = secondary hemolytic uremic syndrome, STEC-HUS = hemolytic uremic syndrome caused by Shiga toxin-producing *Escherichia coli*, TMA = thrombotic microangiopathic anemia.

*$P < .05$ was considered statistically significant. C = continuity correction; F = Fisher Exact Test.

117.4] vs 32.3 μmol/L [IQR 22.0, 60.9], $P = .235$), indirect bilirubin (25.7 μmol/L [IQR 11.0, 43.5] vs 18.2 μmol/L [IQR 9.9, 42.7], $P = .729$), lactate dehydrogenase (564 U/mL [IQR 269, 1384] vs 624 U/mL [IQR 350, 1412], $P = .908$), haptoglobin (5.83 mg/dL [IQR 5.83, 51.03] vs 5.83 mg/dL [IQR 5.83, 26.88], $P = .971$), cell-free hemoglobin (78 mg/L [IQR 30, 133] vs 47 mg/L [IQR 23, 137], $P = .749$), and ADAMTS13 activity (26% [IQR 8, 45] vs 30% [IQR 5, 47], $P = .831$) were not significantly different between the 2 groups (Fig. 2).

3.4. Risk factors for AKI, CKD, and in-hospital mortality

As determined by univariate analysis across the patient group, AKI was associated with age (HR 1.026, 95% CI 1.002–1.052, $P = .037$). The significant predictors of in-hospital mortality were: TBIL (HR 1.013, 95% CI 1.003–1.023, $P = .011$) and age (HR 1.032, 95% CI 1.004–1.060; $P = .022$). None of the other components was significantly associated with AKI and in-hospital mortality. Further characteristics were shown in Table 3.

3.5. Outcome associated with AKI

Figure 3 illustrated that after the follow-up, in-hospital mortality occurred in 40.74% of the patients with AKI and 19.61% without AKI. Accordingly, increased all-cause mortality was observed in patients with AKI (log-rank test: $X^2 = 4.018$, $P = .045$).

4. Discussion

This study examined the occurrence and characteristics of TMA-AKI in patients treated in emergency rooms and their outcomes. AKI occurred in 34.62% of the TMA patients enrolled in the study. Patients with AKI were slightly older, with a more likely infection-induced cause, more prominent in the injuries bound up with the kidney. In the context of the same exposure to underlying diseases and the taken nephrotoxic medicine, the clinical manifestations and laboratory tests of MAHA were similar. Patients with AKI were less popular in any phenotype than those without AKI. The in-hospital mortality rate for patients with AKI was significantly higher than that for patients without AKI. The non-AKI patients were more likely to receive glucocorticoids. Older patients had more likelihood of having AKI and dying in the hospital. TBIL, a characteristic manifestation of hemolysis, would also significantly affect in-hospital mortality.

Although the incidence of AKI induced by TMA clinical phenotypes has been documented to be variable,[12–14] there are limited data on patients with TMA-AKI.[6] A retrospective observational study[15] demonstrated that 23% of patients had concurrent renal disease. Recent epidemiologic studies have only examined clinically diagnosed TMA cohorts, and as a result in terms of renal microangiopathy epidemiology, there is still a lack of a full understanding.[16] TMA-AKI is divided into systemic TMA and renal limited TMA; when systemic MAHA is indeterminate or absent, TMA-AKI is hard to be discovered without a kidney biopsy.[17]

Table 2

Therapy and outcome in AKI and non-AKI group.

	AKI (n = 27)	Non-AKI (n = 51)	Overall population (n = 78)	*P*-value
Therapy, n (%)				
Plasma exchange	12 (44.44%)	18 (35.29%)	30 (38.46%)	.429
Plasma infusion	17 (62.96%)	27 (52.94%)	44 (56.41%)	.396
Glucocorticoids	16 (59.26%)	41 (80.39%)	57 (73.08%)	**.045***
Immunoglobulin	14 (51.85%)	24 (47.06%)	38 (48.72%)	.687
Rituximab	4 (14.81%)	12 (23.53%)	16 (20.51%)	.540[C]
Other immunosuppressive therapies	4 (14.81%)	15 (29.41%)	19 (24.36%)	.249[C]
Continuous renal replacement therapy	14 (51.85%)	0 (0.00%)	14 (17.95%)	**<.001F***
Outcome				
In hospital mortality, n (%)	11 (40.74%)	10 (19.61%)	21 (26.92%)	**.045***
Length of stay (days)	22 (12, 53)	21 (11, 48)	22 (12, 49)	.607

Data are presented as the median (IQR) or n (%). *P* was the comparison between AKI and non-AKI.

AKI = acute kidney injury.

*$P < .05$ was considered statistically significant. C = continuity correction; F = Fisher Exact Test.

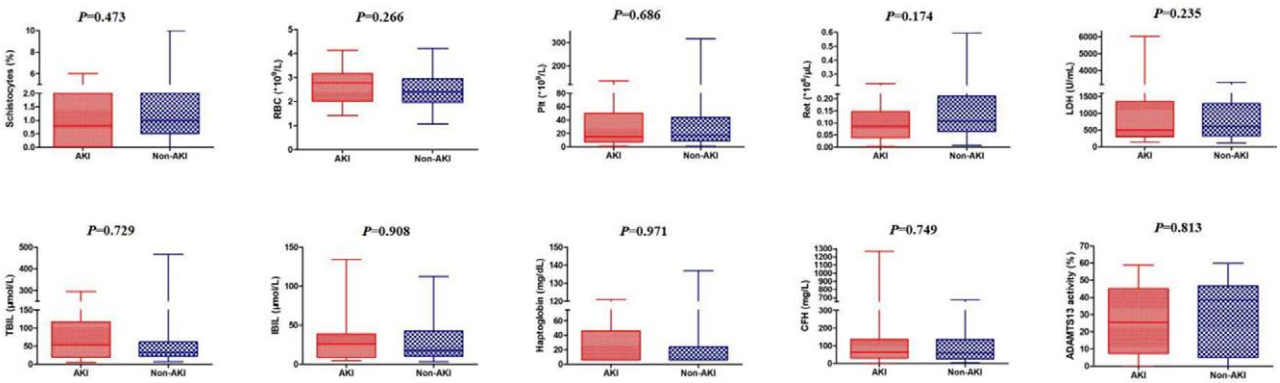

Figure 2. Laboratory findings about hemolysis for AKI and non-AKI. AKI = acute kidney injury.

Table 3

Logistic regression analysis of the risk factors for AKI, CKD, and in-hospital mortality.

	AKI		In hospital mortality	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Age	1.026 (1.002, 1.052)	**.037***	1.032 (1.004, 1.060)	**.022***
Gender	1.130 (0.444, 2.879)	.797	1.083 (0.398, 2.954)	.875
Schistocytes	0.774 (0.542, 1.104)	.157	1.285 (0.973, 1.697)	.077
RBC	1.506 (0.770, 2.947)	.232	0.627 (0.296, 1.327)	.222
Plt	0.996 (0.986, 1.006)	.411	0.977 (0.952, 1.003)	.084
Ret	0.006 (0.000, 2.419)	.094	0.456 (0.002, 87.699)	.770
TBIL	1.003 (0.997, 1.010)	.304	1.013 (1.003, 1.023)	**.011***
IBIL	1.007 (0.991, 1.023)	.392	1.016 (0.999, 1.033)	.061
LDH	1.000 (1.000, 1.001)	.353	1.000 (1.000, 1.001)	.099
Haptoglobin	1.001 (0.988, 1.015)	.868	0.996 (0.980, 1.011)	.596
CFH	1.001 (0.998, 1.003)	.612	1.002 (0.999, 1.005)	.118
ADAMTS13	0.994 (0.971, 1.018)	.626	0.978 (0.953, 1.003)	.086

AKI = acute kidney injury, CFH = cell-free hemoglobin, IBIL = indirect bilirubin, LDH = lactate dehydrogenase, Plt = platelet, RBC = red blood cell, Ret = reticulocyte, TBIL = total bilirubin.
*$P < .05$ was considered statistically significant.

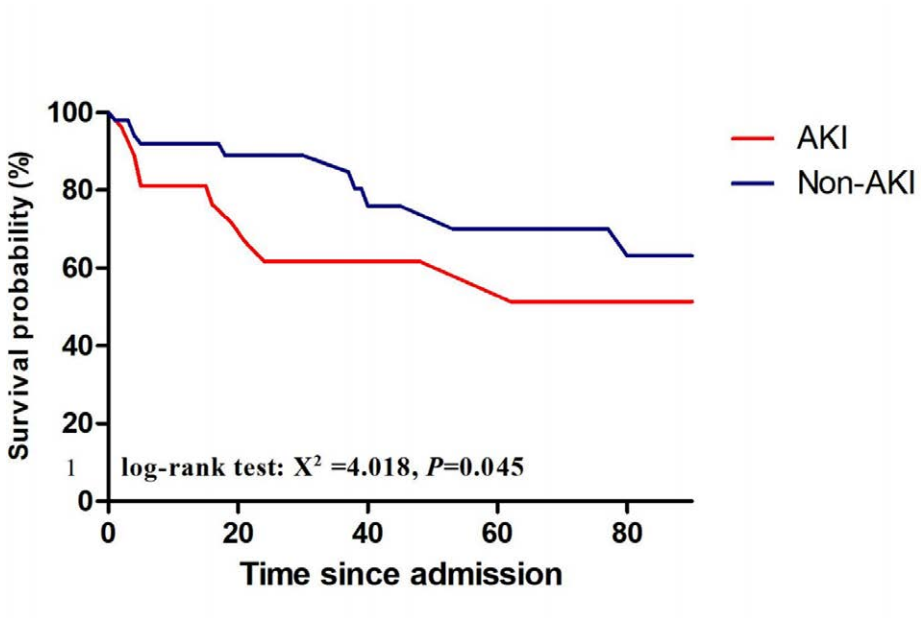

Figure 3. Kaplan–Meier curve on in-hospital mortality resulting from renal function status.

AKI is much more prevalent in critically ill patients, with considerable research focusing on the mechanisms of AKI.[18] TMA-specific mechanisms include the thrombi in the glomerular capillaries, arteries, and arterioles.[19] Meanwhile, non-thrombotic features include endothelial swelling and denudation, double contours of the glomerular basement membrane, mesangiolysis, and subendothelial accumulation of electron-lucent, flocculent material. It is possible to find intramural fibrin and myxoid intimal thickening in arteries and arterioles (onion-skinning).[20] TMAs secondary to infection were predominated in this study. In this part of the population, multiple AKI mechanisms caused by sepsis could not be excluded,[21,22] which was evoked by reduced secondary tubular epithelial cell death, global renal blood flow, or acute tubular necrosis, autonomic nervous system response, activation of the coagulation cascade and shedding of the glycocalyx, endothelial injury.

Some studies showed that schistocytes,[23] ADAMTS13,[24] eGFR,[25] haemoglobin,[4] etiology,[15,26] blood pressure,[27] and histologic location[5] were associated with in-hospital mortality in TMA-AKI patients. Poor outcomes are often related to the combination of fundamental illness, TMA and AKI, progressing to the point where CRRT is required, often leading to progressive CKD and end-stage renal disease, and even death.[6,20] In our study, nearly half of the TMA-AKI patients did not survive, which is poorer than the average survival for critically ill patients as a whole.[28] AKI is a common manifestation of TMAs, and the clinical consequences of HUS related AKI will be more serious than other subtypes of TMA.[29] At the same time, our study has neither phenotype predominance or etiology predominance.

Notably, our study has certain limitations. Small sample sizes of all groups compromised the power of our statistical analyses and failed to conduct in-depth research on Kidney Disease: Improving Global Outcomes-AKI staging. Estimation of AKI onset was independent of the details of biopsy pathology, complement, and genetic detection, therefore, it may not appear to be always comprehensive and thorough.

In conclusion, AKI is commonly found in TMA, and it is linked to inferior long-term clinical outcomes. The older the age, the higher the risk of developing AKI.

Acknowledgments

The authors would like to thank all patients and their families for contributing. They also thank the staff of the Emergency Department, including doctors, nurses, and assistants, for their contributions and support.

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