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Glomerular Hematuria as a Predictor of Renal Prognosis in Malignant Hypertension Patients with Thrombotic Microangiopathy: A Propensity Score-Matched Analysis of a Biopsy-Based Cohort Study

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Keywords
Malignant hypertension · Glomerular hematuria · Thrombotic microangiopathy · Renal replacement therapy · Renal biopsy

Abstract
Introduction: Malignant hypertension (mHTN) is a hypertensive emergency. Thrombotic microangiopathy (TMA) is a widespread complication of mHTN. Few studies have evaluated whether glomerular hematuria provides prognostic information for renal dysfunction in patients with mHTN-associated TMA. ***Methods:*** This observational cohort study included 292 patients with mHTN-associated TMA based on renal biopsy. Propensity-score matching (PSM) analysis was conducted to adjust for clinical characteristics in a comparison between with and without glomerular hematuria. Cox regression was employed to identify risk factors for renal prognosis. ***Results:*** A total of 70 patients with glomerular hematuria were compared to 222 patients with non-glomerular hematuria. After PSM, 67 pairs of patients with mHTN-associated TMA were matched. Patients with glomerular hematuria exhibited lower serum albumin levels, higher 24-h proteinuria, and a higher prevalence of glomerular sclerosis than those with non-glomerular hematuria. Glomerular hematuria was independently associated with deteriorated renal function compared with non-glomerular hematuria (HR: 0.51; 95% CI: 0.29–0.89, $p = 0.019$). This association remained significant after PSM (HR: 0.51; 95% CI: 0.28–0.91, $p = 0.022$). Additionally, glomerular hematuria was independently associated with renal replacement therapy (RRT) (HR: 3.14; 95% CI: 2.06–5.66, $p < 0.001$). This difference remained significant after PSM comparison (HR: 2.41; 95% CI: 1.34–4.33, $p = 0.003$). Furthermore, despite intensive blood pressure control, patients with glomerular

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hematuria experienced a higher incidence of RRT and a poorer recovery in renal function, specifically a 25% reduction of creatinine levels, compared to patients with non-glomerular hematuria. ***Conclusion:*** Glomerular hematuria is significantly associated with an increased risk of adverse renal outcomes in patients with mHTN-associated TMA.

Introduction

Hypertension is a common chronic disease worldwide [1]. It is a leading risk factor for stroke, cardiovascular diseases, and chronic kidney disease and is responsible for over 10 million deaths globally each year. Malignant hypertension (mHTN), recognized as a severe form of hypertension emergency, characterized by acute ischemic organ damage coupled with severe blood pressure elevations [2, 3]. Thrombotic microangiopathy (TMA) and resultant microvascular complications are prevalent in mHTN, which can lead to renal dysfunction [4–6]. Nevertheless, the investigation of risk factors for renal prognosis in mHTN patients with TMA has rarely been investigated in detail.

Glomerular hematuria is a frequent manifestation of various renal diseases and is also a significant predictor of adverse outcomes in kidney diseases [7–10]. A retrospective study indicated that persistent hematuria in patients with IgAN was associated with a higher likelihood of developing end-stage renal disease than minimal or negative hematuria [9]. Moreover, glomerular hematuria is a notable and independent risk factor for the development of non-diabetic kidney disease [10]. Previous studies have highlighted that the presence of hematuria in TMA patients induced by mHTN [11]. However, there is a paucity of literature on the renal prognosis of glomerular hematuria in patients with mHTN, particularly in those exhibiting pathological changes in TMA.

The objective of this study aimed to investigate the clinicopathological characteristics and renal prognosis in mHTN patients with TMA. The study underscored the prognostic value of glomerular hematuria in renal outcomes and offered guidance for clinical practice on blood pressure management strategies for mHTN patients.

Materials and Methods

Study Population and Cohort

This prospective study analyzed patients who underwent clinical renal biopsy at the First Affiliated Hospital of Sun Yat-sen University between 2008 and 2023, and received a pathological diagnosis of mHTN with TMA upon admission. Patients with other kidney diseases or follow-up periods of less than 3 months were excluded from the study. In accordance with the widely accepted clinical definition of glomerular hematuria [12], the patients were classified into two groups: the non-glomerular hematuria group (n = 222) and the glomerular hematuria group (n = 70). To mitigate the influence of selection bias on the findings, we used propensity-score matching (PSM) to adjust for the baseline differences between the non-glomerular hematuria group and the glomerular hematuria group [13]. This study adhered to the ethical standards set forth in the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Approval No. [2022]710). Prior to their participation in the study, all patients provided written informed consent.

Definitions

The clinical diagnosis of mHTN is characterized by a rapid increase in arterial blood pressure, with diastolic blood pressure exceeding 130 mm Hg, accompanied by hypertensive retinal changes such as retinal cotton exudation, and hemorrhage, with or without optic papillary edema [14]. The diagnosis of mHTN with TMA was confirmed based on renal pathological features, including diverse pathological changes such as capillary loop wrinkling, capsule thickening, significant renal artery intimal thickening, vessel wall "onion-peel" thickening, fibrinoid necrosis, intravascular thrombosis, ischemic glomerular alterations, and tubular necrosis [4, 6, 15]. Although there is no widely accepted definition of what constitutes glomerular hematuria, the presence of ≥40% dysmorphic red blood cells (RBCs) or ≥5% acanthocytes in two of three urine samples was considered indicative of glomerular origin [12, 16]. By referring to the foreign and domestic clinical guidelines [17–19], our study adopted systolic blood pressure ≤130 mm Hg as the criterion for intensive blood pressure control.

Clinical Characteristics, Laboratory Data, and Renal Histopathology

The medical records were used to obtain clinical characteristics and laboratory data, including age, sex, body mass index, smoking and drinking status, and blood pressure at admission and discharge. Furthermore, the use of medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or angiotensin receptor-neprilysin inhibitor (ARNI),

specifically sacubitril/valsartan, α-blockers, β-blockers, calcium channel blockers, statins, sulodexide, beraprost sodium, and febuxostat was also considered.

Laboratory data at the time of biopsy were also obtained from the medical records, including platelet count, hemoglobin, serum albumin, lipid index, estimated glomerular filtration rate (eGFR), uric acid, C3, C4, and 24-h proteinuria level. If any results were missing from the medical records, we measured any missing laboratory data from the above list.

In addition to the aforementioned parameters, renal biopsy specimens were processed using light and electron microscopy. All biopsies were evaluated by senior pathologists. In instances where consensus could not be reached, further discussion was held until a resolution was achieved. The study collected data on various light microscopic parameters, including the number of glomeruli, global sclerosis, and segmental sclerosis. Tubulointerstitial parameters, such as tubular atrophy/interstitial fibrosis and tubular epithelial cell exfoliation, were also recorded. Additionally, vascular parameters, including fibrous necrosis, onion skin lesions, intravascular thrombosis, and intravascular RBC fragments, were documented. The electron microscopic evaluation entails the identification of deposits in the subepithelial, subendothelial, or mesangial areas, as well as assessing the degree of endothelial cell swelling. Patients less than 18 years old and those with an inadequate biopsy that does not offer a complete and conclusive diagnosis of the original disease were excluded.

Study Outcomes

The primary outcome of this study was renal function recovery, which was defined as a decrease of serum creatinine from baseline by >25%, a decrease in serum creatinine to normal, or renal survival free from hemodialysis or peritoneal dialysis for at least 1 month. The secondary outcome was renal replacement therapy (RRT), which was defined as the need for chronic dialysis or kidney transplantation at the end of follow-up. Patients were monitored by nephrologists and trained nurses through either in-person office visits or telephone interviews. The last follow-up date was June 30, 2023.

Statistical Analyses

The Shapiro-Wilk test for normality was initially conducted on all data. Continuous variables were presented as either the mean ± standard deviation or the median (interquartile range, 25th, 75th percentile) depending on their distribution. Continuous variables were compared using the Mann-Whitney U test for non-normally distributed variables and the Student's *t* test for normally distributed variables. Categorical variables were expressed as frequencies (percentages) and analyzed with the χ^2 test or Fisher's exact test. The time to reach study outcomes was estimated using the Kaplan-Meier model, with survival comparisons between the non-glomerular hematuria group and the glomerular hematuria group based on a log-rank test. The crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using univariate and multivariate Cox proportional hazards regression models. To adjust for the baseline differences and to minimize potential selection bias, we applied PSM between the non-glomerular hematuria group and the glomerular hematuria group. A 1:1 match was employed using the greedy-matching algorithm, with a 0.02 caliper [13, 20]. Survival analysis was used to assess the prognosis before and after PSM. All statistical analyses were conducted using SPSS (version 25.0; IBM, Armonk, NY, USA), with $p < 0.05$ indicating statistically significant.

Results

Baseline Demographics and Characteristics

In our cohort, 292 patients were available for evaluation and were pathologically diagnosed with mHTN-associated TMA. The baseline characteristics of the patients before and after PSM were shown in Table 1. A flowchart illustrating this process was presented in online supplementary Figure S1 (for all online suppl. material, see https://doi.org/10.1159/000541332). A total of 222 (76.0%) patients were initially classified into the non-glomerular hematuria group, while 70 (24.0%) patients were categorized into the glomerular hematuria group based on baseline characteristics. Compared to patients with non-glomerular hematuria, patients with glomerular hematuria were younger, more female, consumed fewer drinks, had lower levels of body mass index, hemoglobin, and serum albumin, and higher levels of total cholesterol and 24-h proteinuria. However, patients with non-glomerular hematuria were more likely to receive ACEI treatment, but no significant difference was observed in ARB or ARNI, calcium channel blocker, β-blocker, sulodexide, and statin treatment between the groups.

After PSM, 67 patients with glomerular hematuria were matched with 67 patients with non-glomerular hematuria (online suppl. Fig. S1). The baseline characteristics were reassessed after PSM and demonstrated that

Table 1. Baseline characteristics of patients before and after PSM

Characteristic	Total ($n = 292$)	Entire cohort			Propensity score-matched cohort		
		non-glomerular hematuria ($n = 222$)	glomerular hematuria ($n = 70$)	p value	non-glomerular hematuria ($n = 67$)	glomerular hematuria ($n = 67$)	p value
Demographics							
Age, years	35 (30, 41)	36 (31, 42)	31 (27, 38)	<0.001	33 (28, 38)	31 (27, 38)	0.458
Sex, male, *n* (%)	260 (89.0)	204 (91.9)	56 (80.0)	0.005	56 (83.6)	55 (82.1)	0.819
BMI, kg/m^2	24 (22, 27)	24 (23, 27)	23 (21, 25)	<0.001	23 (21, 26)	23 (21, 25)	0.977
Smoking, *n* (%)	129 (44.2)	104 (46.8)	25 (35.7)	0.102	25 (37.3)	25 (37.3)	>0.999
Drinking, *n* (%)	84 (28.8)	72 (32.4)	12 (17.1)	0.014	13 (19.4)	12 (17.9)	0.825
SBP on admission, mm Hg	158 (138, 181)	160 (139, 181)	153 (138, 179)	0.617	151 (138, 171)	154 (138, 180)	0.367
DBP on admission, mm Hg	100 (87, 114)	100 (86, 114)	100 (87, 114)	0.663	94 (84, 107)	100 (88, 115)	0.067
MAP on admission, mm Hg	105 (117, 136)	117 (105, 136)	118 (105, 138)	0.916	113 (105, 126)	119 (105, 139)	0.115
Laboratory values							
Platelet count, 10^9/L	252 (201, 320)	254 (208, 316)	233 (193, 336)	0.311	245 (203, 307)	237 (194, 343)	0.871
Hemoglobin, g/L	107±23	109±23	99±22	0.001	101±24	99±22	0.496
Serum albumin, g/L	37±5	38±5	35±5	<0.001	37±4	34±5	0.001
Total cholesterol, mmol/L	4.7 (4.0, 5.7)	4.6 (4.0, 5.6)	5.1 (4.1, 6.1)	0.037	4.6 (3.9, 5.7)	5.1 (4.1, 6.1)	0.188
Triglycerides, mmol/L	1.8 (1.3, 2.4)	1.7 (1.3, 2.2)	2.0 (1.3, 2.5)	0.169	1.7 (1.3, 2.4)	2.0 (1.4, 2.5)	0.378
HDL-C, mmol/L	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	0.134	1.0 (0.8, 1.3)	1.0 (0.9, 1.2)	0.410
LDL-C, mmol/L	3.0 (2.4, 3.6)	2.9 (2.4, 3.6)	3.2 (2.2, 4.0)	0.240	2.8 (2.3, 3.5)	3.2 (2.3, 4.0)	0.237
eGFR, mL/min/1.73 m^2	10.32 (6.25, 19.75)	10.67 (6.69, 21.39)	9.09 (4.95, 16.11)	0.054	10.35 (5.99, 17.63)	8.76 (4.90, 15.54)	0.310
Uric acid, μmol/L	481±132	475±127	502±145	0.129	477±127	502±141	0.286
C3, g/L	0.98 (0.85, 1.15)	0.98 (0.85, 1.16)	0.97 (0.88, 1.11)	0.635	0.91 (0.78, 1.14)	0.97 (0.88, 1.14)	0.218
C4, g/L	0.28 (0.23, 0.36)	0.28 (0.23, 0.35)	0.31 (0.24, 0.38)	0.121	0.27 (0.23, 0.34)	0.32 (0.25, 0.39)	0.101
24-h proteinuria, g/day	1.41 (0.83, 2.56)	1.31 (0.77, 2.10)	2.23 (1.09, 3.74)	<0.001	1.20 (0.70, 1.94)	2.24 (1.13, 3.78)	<0.001
Medications, *n* (%)							
ACEI	61 (20.9)	54 (24.3)	7 (10.0)	0.010	17 (25.4)	6 (9.0)	0.012
ARB/ARNI	192 (65.8)	140 (63.1)	52 (74.3)	0.084	40 (59.7)	51 (76.1)	0.042
α-Blocker	181 (62.0)	143 (64.4)	38 (54.3)	0.128	39 (58.2)	37 (55.2)	0.727
β-Blocker	251 (86.0)	188 (84.7)	63 (90.0)	0.264	56 (83.6)	60 (89.6)	0.311
CCBs	282 (96.6)	214 (96.4)	68 (97.1)	1.000	64 (95.5)	66 (98.5)	0.310
Statin	133 (45.5)	102 (45.9)	31 (44.3)	0.808	31 (46.3)	30 (44.8)	0.862
Sulodexide	149 (51.0)	117 (52.7)	32 (45.7)	0.308	34 (50.7)	30 (44.8)	0.489
Beraprost sodium	75 (25.7)	59 (26.6)	16 (22.9)	0.535	16 (23.9)	16 (23.9)	>0.999
Febuxostat	58 (19.9)	44 (19.8)	14 (20.0)	0.974	12 (17.9)	14 (20.9)	0.662

Data are median (25th, 75th percentile), mean ± standard deviation, or number and percentage unless otherwise indicated. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; C3, complement 3; C4, complement 4; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker.

a satisfactory balance had been achieved between the two groups. Patients with glomerular hematuria had lower serum albumin levels (mean ± standard deviation 34 ± 5 vs. 37 ± 4 g/L, $p = 0.001$) and higher 24-h proteinuria (median [interquartile range] 2.24 [1.13, 3.78] vs. 1.20 [0.70, 1.94] g/day, $p < 0.001$) than patients with non-glomerular hematuria (Table 1). Regarding medical treatment, the patients with glomerular hematuria had a lower proportion of patients receiving ACEI treatment compared to those with non-glomerular hematuria (6 [9.0%] vs. 17 [25.4%], $p = 0.012$). Conversely, the patients with glomerular hematuria exhibited a higher percentage of ARB/ARNI treatment as expected (51 [76.1%] vs. 40 [59.7%], $p = 0.042$). There were no differences in the utilization of other medication between the two groups.

Renal Histopathological Characteristics

All patients with mHTN-associated TMA underwent percutaneous renal biopsy (Fig. 1). Light microscopic analysis revealed typical series of pathological changes in TMA, including diffuse winkling of the capillary loop and capsular thickening (Fig. 1a), typical intimal thickening and mucus degeneration of the renal artery (Fig. 1b), and vessel wall thickening with an "onion-peel" appearance (Fig. 1c). Electron micrograph showed endothelial cell swelling and marked subendothelial widening with flocculent material underneath (Fig. 1d).

Renal histopathological findings of patients are shown in Table 2. In comparison to patients with non-glomerular hematuria, patients with glomerular hematuria had a significantly higher prevalence of global sclerosis (12 [6, 17] vs. 7 [4, 11], $p < 0.001$) and tubular atrophy/interstitial fibrosis ($p < 0.001$). After PSM, patients with glomerular hematuria had a higher prevalence of global sclerosis (12 [6, 18] vs. 8 [4, 14], $p = 0.006$) and segmental sclerosis (1 [0, 2] vs. 0 [0, 1], $p = 0.019$). There were no differences in the number of cases with tubular atrophy/interstitial fibrosis, and other vascular lesions, including fibrous necrosis, onion skin lesions, intravascular thrombosis, and intravascular RBC fragments ($p > 0.05$).

Risk of Glomerular Hematuria on Primary Outcome of Renal Function Recovery

With a median follow-up period of 18.1 months (95% CI: 12.1–24.1), 133 (57.1%) of the primary outcomes occurred. The cumulative effect of patients with glomerular hematuria on the hazard of the first occurrence of renal function recovery was significantly lower compared to patients with non-glomerular hematuria (overall comparison, $p = 0.002$; propensity score-matched comparison, $p = 0.009$; Fig. 2). In the crude analysis, patients with glomerular hematuria were significantly associated with deteriorated renal function recovery than those with non-glomerular hematuria (HR: 0.28; 95% CI: 0.15–0.55; $p < 0.001$). This difference remained statistically significant after adjustment for both the overall comparison (HR: 0.51; 95% CI: 0.29–0.89; $p = 0.019$) and the propensity score-matched comparison (HR: 0.51; 95% CI: 0.28–0.91; $p = 0.022$) (Table 3).

In addition, predictors for renal function recovery in patients with mHTN-associated TMA are shown in online supplementary Table S1. In the multivariable Cox regression model adjusting for confounders with a $p < 0.05$ in the univariate regression analysis, glomerular hematuria was significantly associated with poorer renal function recovery compared to patients with non-glomerular hematuria (adjusted HR: 0.51; 95% CI: 0.29–0.89; $p = 0.019$). Additionally, the results also indicated that a lower level of platelet count (adjusted HR: 1.003; 95% CI: 1.001–1.005; $p = 0.006$) and higher proportions of tubular atrophy/interstitial fibrosis in a renal biopsy specimen were significantly associated with a lower risk of the primary outcome of renal function recovery (adjusted HR: 0.59; 95% CI: 0.40–0.88; $p = 0.009$). A comparable pattern was observed in PSM cohort. After the multivariable Cox regression analysis, patients with glomerular hematuria (adjusted HR: 0.51; 95% CI: 0.28–0.91; $p = 0.022$) and a lower level of platelet count (adjusted HR: 1.004; 95% CI: 1.001–1.008; $p = 0.004$) were identified as risk factors for the renal function recovery in mHTN patients with TMA (Table 4).

Risk of Glomerular Hematuria on Second Outcome of Renal Replacement Therapy

During the follow-up from 2008 to 2023, with a median follow-up period of 48.8 months (95% CI: 35.5–62.2), 96 (42.7%) patients progressed to the second outcome. Patients with glomerular hematuria showed worse outcomes of RRT than those with non-glomerular hematuria (overall comparison, $p < 0.001$; propensity score-matched comparison, $p < 0.001$; Fig. 3). In the crude analysis, patients with glomerular hematuria exhibited a higher risk of RRT compared to patients with non-glomerular hematuria (HR: 3.83; 95% CI: 1.93–7.61; $p < 0.001$). This difference remained statistically significant after adjustment for both the overall comparison (HR: 3.41; 95% CI: 2.06–5.66; $p < 0.001$) and the propensity score-matched comparison (HR: 2.41; 95% CI: 1.34–4.33; $p = 0.003$) (Table 3).

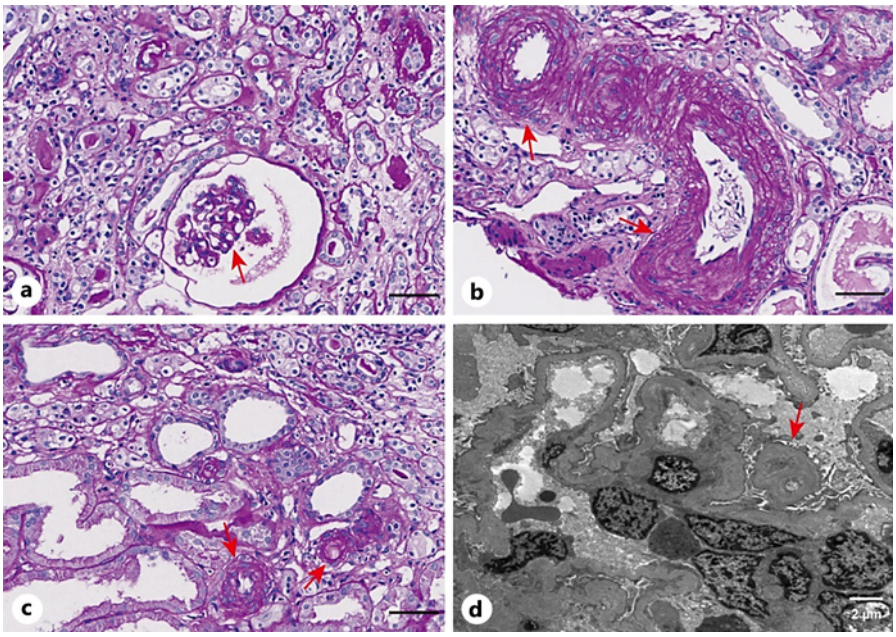

Fig. 1. Representative light, electron microscopic, and immunofluorescence findings in mHTN patients with TMA. **a** Periodic acid-Schiff (PAS) staining showing diffuse winkling of the capillary loop and capsular thickening. **b** PAS staining showing typical intimal thickening and mucus degeneration of renal artery. **c** Vessel wall thickening with an "onion-peel" appearance (red arrow). **a–c** Scale bar: 50 µm. **d** Electron micrograph showing endothelial cell swelling, capillary loop wrinkling, marked subendothelial widening and mesangial proliferation. Scale bar: 2 µm.

Table 2. Histopathological findings of patients before and after PSM

Renal pathology characteristics	Total (n = 292)	Entire cohort			Propensity score-matched cohort		
		non-glomerular hematuria (n = 222)	glomerular hematuria (n = 70)	p value	non-glomerular hematuria (n = 67)	glomerular hematuria (n = 67)	p value
Global lesions, n							
Glomeruli	23 (18, 32)	25 (18, 34)	21 (14, 26)	0.002	24 (17, 35)	21 (14, 27)	0.059
Global sclerosis	8 (4, 13)	7 (4, 11)	12 (6, 17)	<0.001	8 (4, 14)	12 (6, 18)	0.006
Segmental sclerosis	0.5 (0, 2)	0 (0, 1)	1 (0, 2)	0.075	0 (0, 1)	1 (0, 2)	0.019
Tubular atrophy/interstitial fibrosis, n (%)				<0.001			0.066
<25%	10 (3.4)	10 (4.5)	0 (0.0)		1 (1.5)	0 (0.0)	
25–50%	58 (19.9)	53 (23.9)	5 (7.1)		12 (17.9)	5 (7.5)	
50–75%	175 (59.9)	129 (58.1)	46 (65.7)		41 (61.2)	44 (65.7)	
>75%	49 (16.8)	30 (13.5)	19 (27.1)		13 (19.4)	18 (26.9)	
Vascular lesions, n (%)							
Fibrous necrosis	97 (33.2)	70 (31.5)	27 (38.6)	0.276	22 (32.8)	25 (37.3)	0.587
Onion skin lesions	175 (59.9)	138 (62.2)	37 (52.9)	0.166	47 (70.1)	36 (53.7)	0.051
Intravascular thrombosis	52 (17.8)	36 (16.2)	16 (22.9)	0.205	13 (19.4)	15 (22.4)	0.671
Intravascular RBC fragments	29 (9.9)	24 (10.8)	5 (7.1)	0.371	9 (13.4)	5 (7.5)	0.259

Data are median (25th, 75th percentile) or number and percentage unless otherwise indicated. RBC, red blood cell.

Risk factors for RRT in patients with mHTN-associated TMA are shown in online supplementary Table S2. In the multivariable Cox regression analysis, patients with glomerular hematuria were more likely to require RRT than patients with non-glomerular hematuria (adjusted HR: 3.41; 95% CI: 2.06–5.66; p < 0.001). Furthermore, lower levels of platelet count (adjusted HR: 0.997; 95% CI: 0.995–1.000; p = 0.048), lower levels of eGFR (adjusted HR: 0.90; 95% CI: 0.87–0.94; p < 0.001), and higher prevalence of global

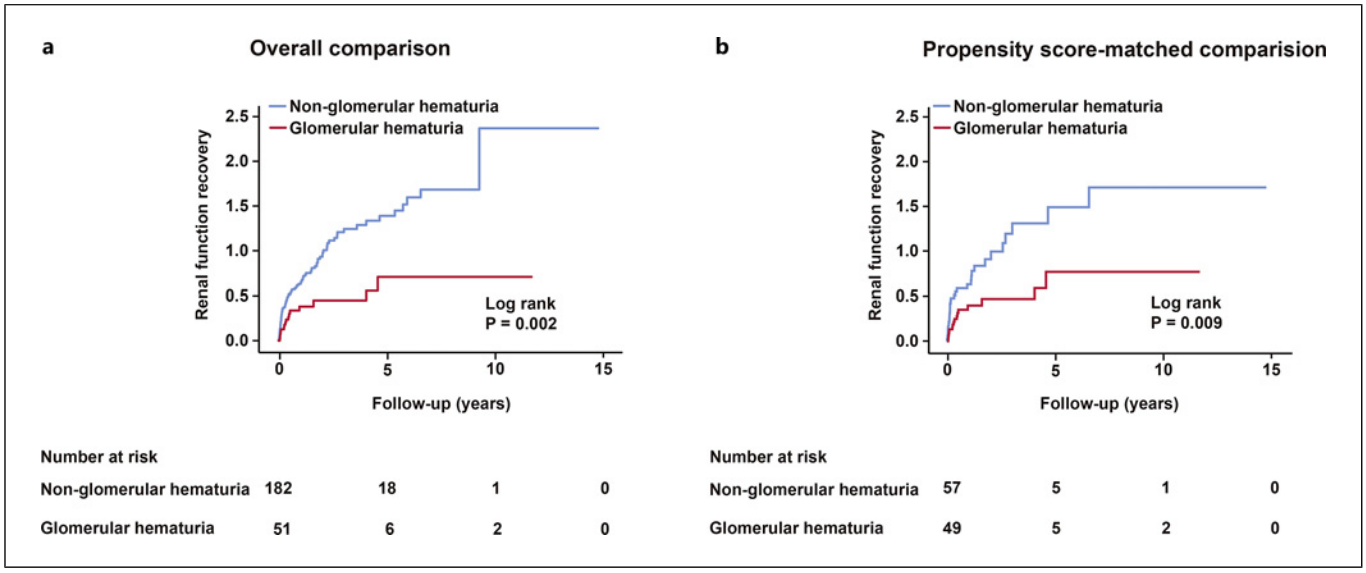

Fig. 2. Cumulative risk of primary outcome of renal function recovery in patients with or without glomerular hematuria in overall comparison (**a**) and propensity score-matched comparison (**b**). The primary outcome of this study was renal function recovery, which was defined as a 25% decrease in serum creatinine or a decrease in serum creatinine to normal, or renal survival free from replacement therapy for at least 1 month.

Table 3. Association between glomerular hematuria and study outcome within the crude analysis, multivariable analysis, and propensity score analysis

Variable	HR (95% CI) for study outcome	*p* value
The primary outcome of recovery of renal function		
Events/patients at risk, *n* (%)	133/233 (57.1)	<0.001
Non-glomerular hematuria	116/182 (63.7)	
Glomerular hematuria	17/51 (33.3)	
Crude analysis[a]	0.28 (0.15–0.55)	<0.001
Multivariable analysis[b]	0.51 (0.29–0.89)	0.019
PSM[c]	0.51 (0.28–0.91)	0.022
The second outcome of RRT		
Events/patients at risk, *n* (%)	96/225 (42.7)	<0.001
Non-glomerular hematuria	64/178 (36.0)	
Glomerular hematuria	32/47 (68.1)	
Crude analysis[a]	3.83 (1.93–7.61)	<0.001
Multivariable analysis[b]	3.41 (2.06–5.66)	<0.001
PSM[c]	2.41 (1.34–4.33)	0.003

The primary outcome was defined as a 25% decrease in creatinine, or a decrease in creatinine to normal, or renal survival free from replacements therapy for 1 month. The second outcome was defined as starting RRT. [a]The HRs from the bivariable model in all patients from the unmatched study. [b]The HRs from the multivariable stratified Cox proportional hazards regression model, with additional covariate adjustment. [c]The HR from propensity score-matched sample, constructed using 1:1 nearest neighbor matching with a 0.02 caliper.

sclerosis in a renal biopsy specimen (adjusted HR: 1.07; 95% CI: 1.04–1.09; $p < 0.001$) were associated with increasing odds of RRT. Moreover, ARB/ARNI treatment was related to a reduced likelihood of requiring RRT (adjusted HR: 0.46; 95% CI: 0.29–0.74; $p = 0.001$). The multivariable Cox regression analysis in PSM

Table 4. Univariable and multivariable Cox regression analysis for the primary outcome of renal function recovery in the PSM cohort

Variables	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Glomerular hematuria, yes/no	0.31 (0.14–0.69)	0.004	0.51 (0.28–0.91)	0.022
Age (years)	1.05 (1.00–1.12)	0.069	–	–
Sex, male (vs. female)	0.87 (0.31–2.46)	0.791	–	–
BMI (kg/m^2)	0.95 (0.83–1.08)	0.395	–	–
SBP (mm Hg)	1.00 (0.99–1.01)	0.979	–	–
DBP (mm Hg)	1.00 (0.99–1.02)	0.644	–	–
MAP (mm Hg)	1.00 (0.99–1.02)	0.779	–	–
Platelet count, 10^9/L	1.006 (1.001–1.011)	0.019	1.004 (1.001–1.008)	0.004
Hemoglobin (g/L)	1.03 (1.01–1.05)	0.006	1.01 (1.00–1.02)	0.155
Serum albumin (g/L)	1.12 (1.03–1.22)	0.007	0.97 (0.92–1.03)	0.343
Total cholesterol (mmol/L)	0.95 (0.75–1.20)	0.657	–	–
Triglycerides (mmol/L)	0.79 (0.54–1.15)	0.220	–	–
HDL-C (mmol/L)	1.49 (0.69–3.23)	0.313	–	–
LDL-C (mmol/L)	0.93 (0.67–1.30)	0.685	–	–
Uric acid (μmol/L)	1.00 (1.00–1.00)	0.498	–	–
eGFR (mL/min/1.73 m^2)	1.02 (0.98–1.07)	0.288	–	–
C3 (g/L)	1.91 (0.37–9.80)	0.440	–	–
24-h proteinuria (g/day)	0.90 (0.73–1.13)	0.365	–	–
ACEI, yes/no	1.13 (0.43–2.93)	0.808	–	–
ARB/ARNI, yes/no	1.46 (0.68–3.15)	0.331	–	–
Statin, yes/no	1.35 (0.63–2.91)	0.437	–	–
Febuxostat, yes/no	1.24 (0.50–3.09)	0.643	–	–
Sulodexide, yes/no	2.32 (1.07–5.06)	0.034	1.56 (0.87–2.78)	0.136
Beraprost sodium, yes/no	2.02 (0.77–5.32)	0.155	–	–
Renal pathology characteristic (*n*)				
Global sclerosis	0.93 (0.89–0.98)	0.010	0.96 (0.92–1.01)	0.093
Segmental sclerosis	1.18 (0.88–1.58)	0.279	–	–
Tubular atrophy/interstitial fibrosis				
<50%	1 (ref)		–	–
>50%	0.49 (0.17–1.43)	0.191	–	–
Hyaline degeneration	1.60 (0.73–3.48)	0.238	–	–
Fibrous necrosis	1.21 (0.52–2.81)	0.666	–	–
Onion skin lesions	2.14 (0.94–4.84)	0.069	–	–

HR, hazard ratio; 95% CI, 95% confidence interval. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; C3, complement 3; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor.

cohort also indicated that glomerular hematuria (adjusted HR: 2.41; 95% CI: 1.34–4.33; $p = 0.003$), lower levels of eGFR (adjusted HR: 0.90; 95% CI: 0.86–0.95; $p < 0.001$), and higher prevalence of global sclerosis (adjusted HR: 1.06; 95% CI: 1.03–1.09; $p < 0.001$) were risk factors for the RRT in mHTN patients with TMA. No differences in medication usage were observed in PSM cohort (Table 5).

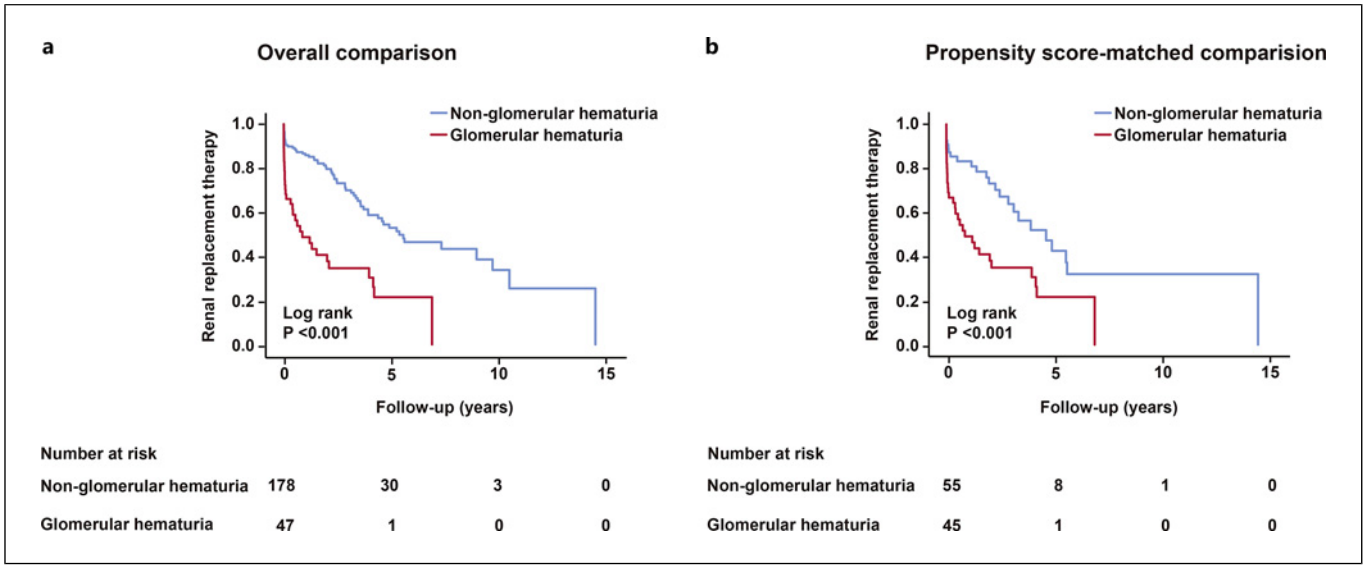

Fig. 3. Renal survival of RRT in patients with or without glomerular hematuria in overall comparison (**a**) and propensity score-matched comparison (**b**). The second outcome of this study was RRT.

Intensive Blood Pressure Control Management

To assess the benefit of intensive blood pressure control, patients were divided into ≤130 mm Hg and >130 mm Hg groups based on discharge systolic blood pressure. The effect of glomerular hematuria on renal prognosis was evaluated. Table 6 shows that patients with glomerular hematuria had a higher incidence of receiving RRT compared to those without glomerular hematuria, regardless of the degree of blood pressure ($p < 0.05$). In addition, patients with non-glomerular hematuria were more conducive to the renal function recovery of a 25% reduction in creatinine levels, regardless of the degree of blood pressure ($p < 0.05$). Importantly, patients with non-glomerular hematuria were more likely to achieve the renal function recovery of a 50% reduction in creatinine levels ($p = 0.013$) despite the absence of intensive blood pressure control.

Discussion

This observational cohort study demonstrated that mHTN patients with glomerular hematuria had significantly lower serum albumin, higher 24-h proteinuria, and higher prevalence of global sclerosis and tubular atrophy/interstitial fibrosis in renal biopsy specimens compared to patients with non-glomerular hematuria. Additionally, patients with glomerular hematuria were more likely to exhibit a poorer recovery of renal function (overall comparison, HR: 0.51; 95% CI: 0.29–0.89; $p = 0.019$; propensity score-matched comparison, HR: 0.51; 95% CI: 0.28–0.91; $p = 0.022$) and progress to RRT outcomes (overall comparison, HR: 3.41; 95% CI: 2.06–5.66; $p < 0.001$; propensity score-matched comparison, HR: 2.41; 95% CI: 1.34–4.33; $p = 0.003$). In particular, multivariable regression analysis revealed that lower platelet count and higher proportions of tubular atrophy/interstitial fibrosis were negative predictors of renal function. Lower platelet count and eGFR level, and higher numbers of global sclerosis were associated with increasing odds of RRT. Finally, our study confirmed that glomerular hematuria may be a significant risk factor for a higher ratio of receiving RRT and poorer renal function recovery of a 25% reduction in creatinine levels, not affected by intensive blood pressure control.

The kidneys are frequently affected in patients with mHTN, who often present with elevated serum creatinine levels, proteinuria, hemolysis, low platelet counts, and renal failure, all of which are key markers of TMA [21]. The results of our cohort study were surprising in that a proportion of mHTN patients with TMA were accompanied by glomerular hematuria, and also found that patients with glomerular hematuria were more likely to have higher levels of 24-h proteinuria and global sclerosis numbers. This conclusion was consistent with several studies on kidney disease, and the mechanism of this association may be attributed to impaired filtration barrier function of the glomerulus, causing leakage of proteins and RBCs and further exacerbating glomerulosclerosis [22–25]. Although early reports have confirmed that glomerular

Table 5. Univariable and multivariable Cox regression analysis for the second outcome of starting RRT in the PSM cohort

Variables	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Glomerular hematuria, yes/no	2.95 (1.30–6.73)	0.010	2.41 (1.34–4.33)	0.003
Age (years)	0.98 (0.91–1.03)	0.264	–	–
Sex, male, yes/no	0.95 (0.34–2.64)	0.918	–	–
BMI (kg/m^2)	0.99 (0.86–1.13)	0.853	–	–
SBP (mm Hg)	1.00 (0.99–1.02)	0.856	–	–
DBP (mm Hg)	0.99 (0.97–1.01)	0.467	–	–
MAP (mm Hg)	1.00 (0.98–1.02)	0.701	–	–
Platelet count, 10^9/L	1.00 (0.99–1.00)	0.069	–	–
Hemoglobin (g/L)	0.98 (0.96–1.00)	0.012	0.99 (0.98–1.01)	0.392
eGFR (mL/min/1.73 m^2)	0.92 (0.87–0.97)	0.003	0.90 (0.86–0.95)	<0.001
ACEI, yes/no	0.41 (0.15–1.16)	0.093	–	–
ARB/ARNI, yes/no	0.81 (0.35–1.90)	0.628	–	–
Renal pathology characteristic (*n*)				
Global sclerosis	1.09 (1.03–1.16)	0.004	1.06 (1.03–1.09)	<0.001
Segmental sclerosis	1.05 (0.79–1.39)	0.736	–	–
Tubular atrophy/interstitial fibrosis				
<50%	1 (ref)		1 (ref)	
>50%	7.58 (2.02–28.47)	0.003	1.61 (0.49–5.36)	0.436
Fibrous necrosis	2.29 (0.96–5.43)	0.061	–	–
Onion skin lesions	0.77 (0.33–1.76)	0.530	–	–
Intravascular thrombosis	1.90 (0.70–5.21)	0.211	–	–

HR, hazard ratio; 95% CI, 95% confidence interval. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor.

Table 6. Renal survival in different groups according to intensive blood pressure control

Events	SBP ≤130 mm Hg			SBP >130 mm Hg		
	non-glomerular hematuria	glomerular hematuria	*p* value	non-glomerular hematuria	glomerular hematuria	*p* value
RRT	17 (27.9)	15 (60.0)	0.005	47 (39.8)	17 (77.3)	0.001
Recovery 1	44 (69.8)	11 (42.3)	0.015	72 (60.5)	6 (24.0)	0.001
Recovery 2	22 (34.9)	4 (15.4)	0.065	44 (37.9)	3 (12.0)	0.013
Recovery 3	4 (18.2)	3 (17.6)	>0.999	20 (30.3)	3 (13.6)	0.123

RRT, renal replacement therapy. Recovery 1: A 25% decrease in creatinine, or a decrease in creatinine to normal, or renal survival free from replacements therapy for 1 month. Recovery 2: A 50% decrease in creatinine, or a decrease in creatinine to normal, or renal survival free from replacements therapy for 1 month. Recovery 3: Free from dialysis for patient dependent on dialysis at baseline.

hematuria is a common indicator of various kidney diseases, the renal prognosis of mHTN patients with glomerular hematuria remains unclear [16].

Previous studies have highlighted the detrimental effect of hematuria on kidney function, with a tendency to promote acute kidney injury and progression to chronic kidney disease [26, 27]. Persistent glomerular hematuria can cause renal inflammation and acute kidney injury, which in turn may result in oxidative stress and tubular cell injury, potentially exacerbating hypertension and kidney disease [27]. Moreover, in patients with diabetic nephropathy, hematuria is associated with more severe renal pathology and can serve as an independent predictor of renal outcomes [28]. Consistently, our cohort study provided reliable evidence that glomerular hematuria was identified as an independent risk factor for renal outcomes in mHTN, increasing the risk of renal function recovery by 0.5-fold and the risk of receiving RRT by 3.4-fold. Therefore, persistent glomerular hematuria could be considered as an important and readily identifiable predictor of adverse outcomes in patients with mHTN-associated TMA. Regular monitoring and comprehensive assessment of glomerular hematuria are essential for the early detection of potential kidney disease in mHTN. For patients with glomerular hematuria in mHTN, active therapeutic management is essential to preserve renal function, mitigate kidney progression, and minimize complications, with an emphasis on blood pressure control.

A retrospective study in China revealed a strong correlation between platelet levels and renal outcomes, with the platelet-albumin ratio identified as an adverse prognostic factor in patients with IgAN [29]. Interestingly, our results suggest that the reduction in platelet levels is a risk factor for renal function recovery and RRT in mHTN patients with TMA, which challenges the conclusions of previous studies. Nevertheless, the resolution of this discrepancy is still under investigation. Given that low platelet count is a common clinical manifestation of TMA, which may increase the risk of bleeding during renal biopsy and consequently affect the prognosis of kidney disease [30–32]. In summary, it is imperative to assess the platelet count in patients with mHTN to prevent the progression to deteriorated renal function recovery.

Pathological changes represent a common final pathway leading to end-stage renal disease [33–35]. A Chinese study based on 45 patients with renal biopsies suggested that consideration of the background pathological phenotype, including global sclerosis, crescents, and vascular endothelial cell damage, was crucial for improved outcomes in patients with IgAN-mHTN [36]. Kadiri et al. [37] showed that glomerulosclerosis may contribute to renal dysfunction in mHTN patients, and those with global glomerulosclerosis appeared to have the highest serum creatinine levels. A retrospective study from Northern India concluded that a tubular atrophy/interstitial fibrosis score of ≥25% may be associated with a poorer treatment response in IgA nephropathy patients with mHTN [38]. Similarly, we analyzed the pathological changes of glomeruli, tubules, and blood vessels in mHTN patients and found that both the number of global sclerosis and tubular atrophy/interstitial fibrosis >50% were independently predictive of the renal outcomes of renal function recovery or RRT in mHTN patients with TMA. Thence, the severity of renal pathology may be a risk characteristic for mHTN, with the potential to result in more severe renal outcomes, including progression to RRT.

Drugs for hypertension treatment may also affect the outcome of mHTN [39]. A European study revealed that immediate treatment with RAS blockers seemed to be safe and effective in treating patients with mHTN [2]. Consistently, our study showed that ARB/ARNI treatment exerts a protective effect on mHTN patients undergoing RRT. This provided evidence to support for the widespread use of ARB/ARNI in mHTN patients. Concurrently, blood pressure control is a critical component of disease management and has a substantial impact on the quality of life [40, 41]. However, no well-designed studies have examined the relationship between blood pressure targets and renal prognosis in patients with mHTN. A meta-analysis confirmed that intensive blood pressure achieved reductions for cardiovascular events and albuminuria, definitely the greatest benefit among patients with kidney disease [42]. In our study, we investigated whether glomerular hematuria was associated with renal prognosis in different blood pressure groups. Those who without glomerular hematuria showed a better renal function recovery, even in the absence of intensive blood pressure control. Although this conclusion appears to be contrary to previous study [42, 43], it serves to underscore the importance of glomerular hematuria in renal prognosis. Further studies are required to expand the sample size and perform a more detailed blood pressure classification in order to evaluate the optimal blood pressure range that benefits to patients with mHTN.

The strength of our study lies in its prospective design, using renal biopsy to confirm mHTN with TMA and PSM to mitigate imbalances in confounding variable between groups with and without glomerular hematuria. This approach allowed a detailed comparison of clinicopathological backgrounds and renal prognostic risks. However, it also has limitations: its single-center, predominantly Chinese patient cohort limits generalizability; unaddressed confounders and variables may influence outcomes; and it lacks follow-up on mHTN progression

or improvement. In addition, the current clinical diagnosis of glomerular hematuria is limited, as the morphology of RBC in urine depends not only on the origin of RBC but also on the storage time of the urine sample before testing, and the osmolarity of the urine, which may affect the diagnosis of patients with glomerular hematuria. Future efforts will focus on collecting follow-up data and expanding the sample size to deepen our understanding of the impact of mHTN.

In conclusion, this study contributes to the accumulating evidence supporting that glomerular hematuria is associated with deteriorated renal function, and the need for RRT compared to those with non-glomerular hematuria in patients with mHTN-associated TMA. Systematic monitoring of glomerular hematuria is essential for the early detection and management of potential renal disorders in individuals with mHTN.

Statement of Ethics

This study protocol was reviewed and approved by the First Affiliated Hospital of Sun Yat-sen University (Approval No. [2022]710). Prior to the participation in the study, all patients provided written informed consent. This study was performed fulfilling the principles of the Helsinki Declaration.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

All authors contributed to each of the following aspects of the study: Jianbo Li and Feng He designed the research study and revised the manuscript. Zhaocai Zhou, Wanxin Shi, and Shengyou Yu collected the data and wrote the paper. Jianwen Yu and Naya Huang were responsible for data acquisition. Zhong Zhong, Fengxian Huang, and Wei Chen were responsible for data analysis and statistical analysis. All authors reviewed and approved the final manuscript.

Data Availability Statement

The data underlying this article cannot be shared publicly to protect the study participants' privacy. The datasets generated and analyzed during the current study are available from the corresponding author upon request.

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