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Factors Predicting Renal Outcomes in Hypertensive Emergencies With Severe Renal Impairment: A Single-Center Retrospective Study

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ABSTRACT

Background and Aims: Hypertensive emergencies, characterized by elevated blood pressure (BP) and multiple organ damage, have poor prognosis. Patients occasionally show gradual improvement in renal function with appropriate antihypertensive treatment despite renal impairment. However, reports analyzing factors predicting prognosis in patients with hypertensive emergencies and severe renal impairment are limited. This retrospective study aimed to investigate clinical features and predictors of renal outcomes in such patients.

Methods: Patients admitted to our hospital diagnosed with hypertensive emergency with severe renal impairment (serum creatinine [Cr] level > 2.5 mg/dL) between 2007 and 2021, were enrolled and divided into two groups: those who received renal replacement therapy (RRT) after 3 years (RRT group) and those who did not (non-RRT group); clinical characteristics and laboratory data were compared.

Results: Fifteen patients were enrolled, with a median age and serum Cr level of 48 years and 5.97 mg/dL, respectively. No significant between-group difference was observed in serum Cr levels or kidney size. However, the non-RRT group exhibited significantly higher levels of serum lactate dehydrogenase (LDH) levels and significantly lower platelet counts (PLT), suggesting development of micro-angiopathic hemolysis due to severe endothelial damage. Furthermore, the non-RRT group exhibited lower serum potassium levels than the RRT group, accompanied by high plasma renin activity and serum aldosterone levels, suggesting activation of the renin-angiotensin system (RAS). In the non-RRT group, serum Cr, LDH, potassium levels, and PLT improved significantly after treatment.

Conclusions: Serum LDH, potassium levels, and PLT are useful predictors of renal prognosis in hypertensive emergencies with extremely poor renal function. In some cases, severe renal damage can be ameliorated by appropriate antihypertensive therapy. A positive response to treatment often signifies a favorable prognosis. Furthermore, early initiation of RAS inhibitors may be beneficial for lowering BP and providing renal protection.

1 | Introduction

Hypertension is a major risk factor for stroke, heart disease, cardiovascular disease, and chronic renal failure. An analysis of the global population aged 30–79 years showed that the number of patients with hypertension has doubled from 65 to 128 million over the past 30 years. While the overall prevalence rate remained relatively stable, and the percentage of patients treated and under control with antihypertensive medication increased, the number doubled—attributed to aging and population growth. Consequently,

the count of patients with poorly controlled blood pressure (BP) now surpasses the corresponding figure from three decades ago [1]. In Japan, as of 2017, the estimated population with hypertension was 43 million, of which 31 million had poorly controlled hypertension (BP ≥ 140/90 mmHg) [2].

A hypertensive emergency is a serious condition characterized by a marked increase in BP (generally 180/120 mmHg or higher) and rapid damage to major organs including kidneys [3]. Prompt diagnosis and appropriate antihypertensive treatment are essential to improve the prognosis of these patients. If left untreated, patients exhibit rapid deterioration of systemic symptoms, including kidney failure, heart failure, and hypertensive encephalopathy. The main histological features of the affected organs include fibrinoid necrosis of the arterioles accompanied by hyperplastic arteriolosclerosis. These changes result in vascular luminal narrowing and severe ischemic dysfunction, often leading to microangiopathic hemolysis. In addition, this condition triggers the activation of the renin-angiotensin system (RAS), leading to vasoconstriction and further progression of hypertension [4, 5]. The frequency of hypertensive emergencies has decreased due to the widespread use of antihypertensive treatments and recent improvements in social environment, and there has been a marked reduction in mortality rate. However, renal dysfunction at disease onset remains a predictor of the risk of death or dialysis [6–8]. Furthermore, when compared to patients with non-accelerated hypertension, those with accelerated hypertension not only display a clearly higher total mortality rate but also a higher likelihood of requiring renal replacement therapy (RRT), indicating a poorer renal prognosis. A previous study on the long-term (approximately 10 to 20 years) prognosis in patients with severe renal dysfunction (the mean serum creatinine [Cre] level: 2.49 mg/dL) reported that the initial presentation of renal function and urinary protein levels reflected poor renal outcomes [9]. Additionally, that study revealed that even among patients with worsening renal function, renal function remained relatively stable for 2 years after starting treatment, but then rapidly deteriorated after 3 years. In daily clinical practice, we also occasionally encounter cases in which renal function gradually improves with appropriate antihypertensive treatment, and the patient continues to have a good course of renal function for several years thereafter. However, no previous study has provided a detailed assessment of the prognostic factors affecting the reversibility of subsequent renal impairment in patients with hypertensive emergencies who present with severe renal impairment at the time of initial presentation.

In this study, we examined the factors that determine the reversibility of long-term renal dysfunction in hypertensive emergencies with severe renal impairment, with a target period of 3 years after the start of treatment.

2 | Methods

2.1 | Study Design

This single-center retrospective study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology [10] and conducted from January 1, 2007 to April 30, 2021, at Nippon Medical School in Japan.

2.2 | Participants

In the initial stage, we selected 94 patients admitted to our hospital with a diagnosis of "hypertensive emergency" or "malignant hypertension" from the medical records over a period of 14 years and 4 months (Figure 1).

The diagnosis of hypertensive emergency was defined as a BP > 180/120 mmHg and the presence of target organ damage including brain, eyes, and kidneys on admission [3]. In the next step, we excluded the following conditions; aortic dissection, cerebral hemorrhage, acute pulmonary edema requiring artificial ventilation, and pre-eclampsia. We identified 15 patients with severe renal impairment (serum Cre > 2.5 mg/dL on admission) eligible for a 3-year follow-up by nephrologists. Subsequently, the patients were divided into two groups: those who received RRT (including hemodialysis, peritoneal dialysis, and renal transplantation) after 3 years (RRT group, $n = 6$) and those who did not receive RRT (non-RRT group, $n = 9$) within 3 years after the initial treatment.

The introduction of temporary RRT (such as continuous renal replacement therapy and extracorporeal ultrafiltration method) due to acute kidney injury and/or congestive heart failure was not included in the RRT group. The RRT group included only cases that required maintenance RRT).

2.3 | Data Collection

All patients were evaluated for medical history, medical checkups before admission, clinical characteristics, laboratory findings on admission, and course of treatment. The following parameters were included in the evaluation: age, sex, BP, height, body weight, and body mass index. Obesity was defined as a body mass index (BMI) ≥ 25 kg/m^2 in Japan [11]. A funduscopic examination was performed on admission, and the findings were classified using the Keith–Wagner and Scheie classifications to determine the presence of hypertensive retinopathy. Simple computed tomography (CT) of the abdomen was performed for all patients on admission. Long and short renal diameters were measured in all patients to evaluate renal morphology. All patients underwent renal vascular evaluation using renal artery ultrasound and/or abdominal magnetic resonance angiography. Magnetic resonance imaging of the head was performed for patients with neurological findings on admission. In addition, we recorded the type of antihypertensive drugs after admission within 1 month.

All patients underwent blood and urine tests upon admission. Blood tests included evaluation of blood urea nitrogen, serum Cre, potassium, lactate dehydrogenase (LDH), plasma aldosterone concentration, plasma renin activity, and platelet count (PLT). Urine tests included evaluation of urinary protein levels. We compared the data between RRT and non-RRT groups to determine if there were any differences in the listed parameters. Additionally, we examined whether these parameters improved after treatment. Since serum Cre levels in the non-RRT group often improved gradually over several months after treatment, we compared the data before and after treatment, examining values at admission and 1 year later. As for other parameters, which typically improve rapidly with treatment, we compared data from 1 month after treatment.

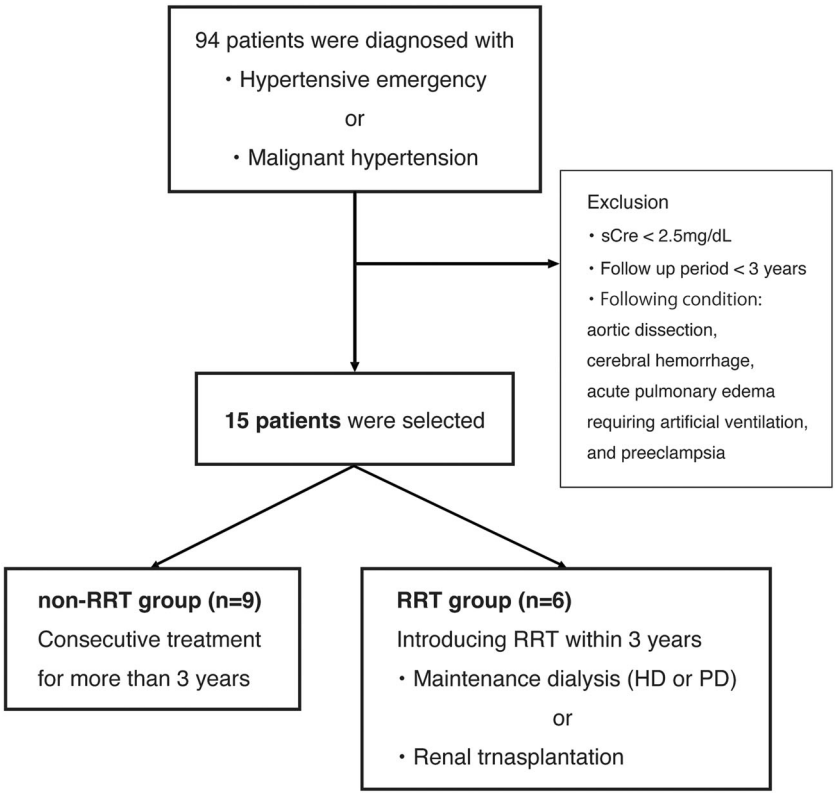

FIGURE 1 | Flowchart of study participants. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; sCre, serum creatinine.

2.4 | Statistical Analysis

Data are presented as median and interquartile range, or as mean and standard error, as appropriate. The nonparametric Mann-Whitney U test was used to evaluate the differences between the two groups. We then checked the q-value using the Benjamini-Hochberg false discovery rate (FDR) for multiple comparisons. The q-value was calculated using the following formula: $q = P^*N/i$ (where P is the p-value, N is the total number of hypotheses tested, and i is the rank of the p-value). The threshold for the q-value (considered statistically significant) was set at 0.1. To control for the influence of potential confounding factors, we conducted analysis of covariance (ANCOVA) to compare the two groups. The Wilcoxon signed-rank test was employed to analyze specific parameters that suggested differences, assessing within-group differences before and after treatment. Additionally, two-way analysis of variance (ANOVA) was conducted to examine whether there were differences in the change of each parameter between the two groups before and after treatment. Fisher's exact test was used to assess the differences in both sex and the use of RAS inhibitors between the two groups. Statistical analyses, excluding ANCOVA, were performed using Excel Statistics version 7.0 (ESUMI, Tokyo, Japan). ANCOVA was conducted using jamovi (version 2.6.2.0; The jamovi project, https://www.jamovi.org) with the GAMLj module for general linear models (version 3.0; https://gamlj.github.io/).

2.5 | Ethics

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Review Committee of Nippon Medical School (approval number: B-2021-392). Informed consent was obtained in the form of an opt-out on the website (http://ctr-nms.com/disclosure/), and individuals who declined to participate were excluded.

3 | Results

3.1 | Clinical Characteristics of Hypertensive Emergencies With Severe Renal Impairment

Patient background and clinical characteristics are shown in Table 1. Patients were assigned individual numbers, with the cohort (15 patients) comprising nine individuals not on RRT after 3 years (numbers 1–9, non-RRT group) and six individuals receiving RRT (numbers 10–15, RRT group). All patients were first-time visitors to our hospital and were admitted as emergency or urgent cases. The median age of all patients was 48 (range: 41–54) years, and the majority were male. The male-to-female ratio in the two groups was 4:5 and 6:0, respectively, though there was no statistically significant difference between them. Nine out of the 15 patients did not undergo regular medical check-ups. Seven patients remained untreated despite being informed about their high BP, and one had a history of treatment discontinuation. Obesity (BMI > 25 kg/m^2) was present in 33% (5/15) of the patients. Systolic and diastolic BPs on admission were ≥ 180/120 mmHg, with median values of 217/133 mmHg. All patients had hypertensive retinopathy, except for two patients whose data could not be confirmed. Hypertensive encephalopathy was observed in two of the 15 patients. The median values of the long/short axes of the kidney diameters were 9.75 and 5 cm, respectively, with none of the cases showing obvious atrophy.

No evidence of renal artery stenosis was observed in any of the patients. None of the patients had been receiving regular outpatient treatment for hypertension at the time of hospitalization. Table 2 summarizes the antihypertensive drugs administered within 1 month after admission. Calcium channel blockers were used in all cases, and RAS inhibitors, such as angiotensin II receptor blockers (ARBs) and angiotensin II converting enzyme inhibitor (ACE-I), were given to 11 patients. Notably, RAS inhibitors were more frequently used in the non-RRT group, although no statistically significant difference was observed between the two groups. The laboratory findings on admission are shown in Table 3. The median serum Cre level was 5.97 mg/dL, which was very high. The median urine protein level was 3.85 g/g Cre in the nephrotic range, while the decrease in serum Alb level was not observed. Serum LDH levels were high and PLT were low on admission. Haptoglobin levels were measured in 4 out of 15 patients, and a decrease in haptoglobin was observed in three patients in the non-RRT group, indicating hemolysis. The other patients in the RRT group did not show a decrease. Furthermore, there was a low serum potassium level (3.2 mEq/L), accompanied by elevated plasma renin activity and aldosterone levels.

3.2 | Prognostic Factors in Long-Term Renal Outcome

We evaluated the renal prognosis at 3 years after the initial treatment by dividing patients into the non-RRT ($n = 9$) and RRT ($n = 6$) groups. We compared laboratory findings at admission using a nonparametric Mann–Whitney test and examined parameters on admission that may predict prognosis (Table 4). There was no clear difference in BMI between the two groups. Diastolic BP was significantly higher in the non-RRT group ($p = 0.033$), whereas systolic BP at admission was not significantly different between the two groups. The two groups showed no significant difference in kidney size (both long and short kidney diameters) at admission despite severe renal impairment. Furthermore, there were no significant differences in either the serum Cre levels or the urinary protein levels at admission between the two groups. However, the non-RRT group exhibited significantly higher LDH levels ($p = 0.007$), lower PLT ($p = 0.034$), and lower serum potassium levels ($p = 0.029$) compared to the RRT group. Notably, after applying FDR correction, serum LDH levels remained a significant marker (q-value $= 0.098 < 0.1$). Conversely, the plasma renin activity and aldosterone levels, which influence serum potassium levels, were not significantly different between the two groups.

To assess whether serum LDH levels are a useful marker while adjusting for confounding factors, we performed an ANCOVA with four covariates: serum Cre levels, age, sex, and the use of RAS inhibitors (Model 1; Table 5). Although serum LDH levels remained a significant marker (F (1, 9) $= 58.02$, $p < 0.001$), we could not demonstrate parallelism in the regression slopes. Given the small sample size and the anticipated strong impact of serum Cre levels on renal prognosis, we conducted a second ANCOVA focusing solely on serum Cre levels as the covariate (Model 2; Table 5). This analysis confirmed a significant difference in serum LDH levels between the two groups (F (1, 12) $= 14.38$, $p = 0.003$), with parallel regression slopes. Furthermore, considering both the potential role of sex as an interaction factor in ANCOVA and the higher incidence of malignant hypertension among males, we conducted an additional analysis focusing solely on male participants (n = 4 in the non-RRT group; n = 6 in the RRT group) (Model 3; Table 5). Despite the limited sample size, a significant difference in LDH levels between the two groups was observed (F (1, 7) $= 52.36$, $p < 0.001$).

3.3 | Changes in Each Parameter Before and After Treatment

The changes in each parameter before and after treatment in each group were assessed by the Wilcoxon signed-rank test (Table 6). Only the serum Cre level was evaluated 1 year after treatment due to its gradual improvement trend. Other data that suggested differences between two groups at admission, were assessed 1 month after treatment. Not surprisingly, the serum Cre level showed significant improvement 1 year after treatment in the non-RRT group. The serum LDH level significantly improved 1 month after treatment in both groups. However, the improvements in PLT and serum potassium levels were significant only in the non-RRT group, not in the RRT group.

Subsequently, we explored significant differences in data changes before and after treatment between the two groups (Figure 2A–D). In the serum Cre level in each patient, all cases in the non-RRT group showed improvement in the data 1 year after treatment, compared to those in the RRT group (Figure 2A). Furthermore, we analyzed how serum LDH, PLT, and serum potassium levels changed before and after antihypertensive treatment (Figure 2B–D). Serum LDH levels, which were higher than the normal range at admission, decreased 1 month after treatment in both groups. Moreover, the non-RRT group showed significantly greater improvement than the RRT group (Figure 2B). The PLT significantly increased in the non-RRT group than in the RRT group (Figure 2C). The serum potassium levels were also dramatically improved after treatment in the non-RRT group than in the RRT group (Figure 2D).

3.4 | Presentation of a Representative Case in the Non-RRT Group

Based on our findings, we present the clinical course and histopathology of a representative case of reversible renal impairment (case no. 1 in Table 1 and Figures 3 and 4).

On admission, the patient had severe renal impairment (serum Cre, 7.07 mg/dL) with extremely high BP (230/140 mmHg). Blood analysis showed hemolytic anemia with thrombocytopenia (erythrocyte count, $362 \times 10^4/\mu L$; hemoglobin, 11.9 mg/dL; hematocrit, 33.5%; PLT, $11.6 \times 10^4/\mu L$; and haptoglobin, 3.0 mg/dL). ADAMTS13 activity (98%) was within the normal range, while the serum LDH level (941 IU/L) was markedly elevated, indicating microangiopathic hemolytic anemia (MAHA) attributed to severe endothelial injury. The serum potassium level was low (3.0 mEq/L), and the high plasma renin activity (> 20 ng/mL/h) and plasma aldosterone (302.9 pg/mL) levels suggested RAS activation. Rapid improvement in all data was observed with the initiation of antihypertensive treatment using calcium antagonists and

TABLE 1 | Clinical findings in each patient.

	No.	Age	Sex[a]	BMI	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)	Retinopathy KW/Scheie	Hypertensive encephalopathy	Kidney size (cm)		Observation period (months)
										long	short	
non-RRT group	1	32	M	22.3	230	140	170	KWIII/-	+	10	5.0	101
	2	56	F	19.9	206	130	155	-/H3S3	—	10.5	5.1	108
	3	54	F	20.0	208	120	149	-/H4S2	—	11.6	5.2	108
	4	47	M	36.0	262	182	209	-/H3S4	+	9.2	3.9	45
	5	54	M	19.9	270	167	201	KWII/-	—	9.8	2.8	40
	6	41	F	n/a	210	140	163	KII/-	+	9.8	5.4	*
	7	42	F	20.0	190	140	157	-/H3S1	—	7.8	5.9	50
	8	51	F	n/a	270	170	203	n/a	—	7.5	4.9	87
	9	51	M	n/a	205	132	156	n/a	—	9.3	5.5	93
RRT group	10	48	M	35.0	230	120	157	KWIV/-	—	8.7	4.2	28
	11	33	M	30.0	214	127	156	-/H2S2	—	10.4	5.5	19
	12	68	M	26.2	252	120	164	KWIII/H3S3	—	9.0	4.1	14
	13	45	M	19.9	217	139	165	KWIII/-	—	10.3	5.0	1.5
	14	31	M	25.3	193	124	147	KII/H3S2	—	10.0	5.5	1
	15	55	M	18.1	224	133	163	KII/H2S2	—	8.4	4.2	19
Median value		48		21.2	217	133	168			9.8	5.0	42.5

Note: * Case No. 6 in the non-RRT group passed away 73 months after the initial treatment.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; F, female; KW, Keith–Wagner; M, male; MBP, mean blood pressure; n/a, not assessed; RRT, renal replacement therapy; SBP, systolic blood pressure.

[a]For the statistical analysis, Fisher's exact test was used to assess differences in sex between the two groups, and no significant difference was found.

TABLE 2 | Type of antihypertensive drugs.

	No.	ARB/ACE-I[a]	CCB	other drugs
non-RRT group	1	+	+	—
	2	+	+	α1-blocker, methyldopa hydrate
	3	+	+	α1-blocker, methyldopa hydrate
	4	+	+	α1-blocker
	5	+	+	—
	6	+	+	β-blocker
	7	+	+	—
	8	—	+	—
	9	+	+	—
RRT group	10	+	+	—
	11	+	+	—
	12	—	+	β-blocker
	13	—	+	—
	14	—	+	—
	15	+	+	—

Abbreviations: ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; RRT, renal replacement therapy.
[a]For the statistical analysis, Fisher's exact test was used to assess differences in the use of RAS inhibitors (ARB/ACE-I) between the two groups, and no significant difference was found.

TABLE 3 | Laboratory data in each patient.

	No.	sCre (mg/dL)	UP (g/gCr)	sAlb (g/dL)	sLDH (U/L)	PLT ($\times 10^4/\mu L$)	sK (mEq/L)	PRA (ng/ml/hr)	PAC (pg/ml)
non-RRT group	1	7.07	10.7	3.1	948	11.6	3	> 20	302.9
	2	5.97	0.17	4.1	789	7.6	2.9	> 20	526
	3	3.54	2.61	3.5	594	13.9	3.2	4.1	228.2
	4	4.27	0.23	3.9	983	6.5	2.7	28	850.2
	5	4.9	n/a	3.9	1178	18.5	3.3	9	468.4
	6	6.73	4.2	4.2	554	6.5	2.5	n/a	409.9
	7	9.05	9.2	3.3	588	18.2	4.2	8.4	405.9
	8	5.7	0.64	3.8	587	9.9	3.2	40	118
	9	5.46	5	4.5	1079	8	2.4	> 20	468
RRT group	10	8.22	3.9	3.6	319	15.7	2.5	34	554.6
	11	8.7	2.9	4.3	222	24.1	5	13	337.9
	12	7.22	7.3	4.0	268	9.7	5.4	1.3	153.7
	13	9.49	0.4	3.0	678	24.5	4	25	728
	14	5.79	5.25	2.3	313	15	4.6	1.5	174.1
	15	2.95	3.8	3.4	230	23	5.5	1.5	184.5
Median		5.97	3.85	3.9	588	13.9	3.2	9	405.9

Abbreviations: n/a, not assessed; PAC, plasma aldosterone concentration; PLT, platelet count; PRA, plasma renin activity; RRT, renal replacement therapy; sCre, serum creatinine; UP, urine protein; sAlb, serum albumin; sLDH, serum lactate dehydrogenase; sK, serum potassium.

ARBs (Figure 3). A renal biopsy was performed 29 days after admission. Light microscopy revealed thickening of the vascular intima with onion-skin lesions, which resulted in marked narrowing and occlusion of the arterial lumen. The glomerular capillaries collapsed; however, there was no evidence of thrombus formation (Figure 4). A pathological diagnosis of malignant nephrosclerosis was made.

4 | Discussion

Hypertensive emergencies are an important cause of end-stage renal failure in both developed and developing countries, with prevalence showing no marked decrease despite advancements in treatment and social living conditions [12]. Regardless of the patients' social backgrounds, the mortality rate and the rate of

TABLE 4 | Comparison of clinical parameters between the both groups.

	non-RRT group Median (25%–75%)	RRT group Median (25%–75%)	*p*-value	*q*-value
BMI	20 (19.9–25.7)	25.8 (19.5–31.3)	0.62	0.87
SBP (mmHg)	230 (206–270)	221 (209–234)	0.59	0.92
DBP (mmHg)	140 (131–169)	120 (123–135)	0.033	0.15
MBP (mmHg)	163 (149–209)	160 (147–165)	0.44	0.88
Kidney size: major (cm)	9.8 (8.5–10.2)	9.5 (8.6–10.3)	0.95	1.023
Kidney size: short (cm)	5.1 (4.4–5.5)	4.6 (4.2–5.5)	0.67	0.85
sCre (mg/dL)	5.7 (4.6–6.9)	7.7 (5.1–8.9)	0.19	0.53
U-P (g/g Cr)	3.4 (0.3–8.2)	3.85 (2.3–5.8)	0.85	0.85
sAlb (g/dL)	3.9 (3.5–4.2)	3.5 (3.8–4.1)	0.34	0.79
sLDH (IU/L)	789 (588–1031)	290.5 (228–409)	0.007	0.098
PLT ($\times 10^4/\mu L$)	9.9 (7.1–16.1)	19.35 (13.7–24.2)	0.034	0.12
sK (mEq/L)	3.1 (2.7–3.3)	4.8 (3.6–5.4)	0.029	0.20
PRA (ng/mL/h)	9.0 (6.3–34.0)	7.3 (1.5–27.3)	0.79	0.92
PAC (pg/mL)	409.9 (265.5–497.0)	261.2 (169.0–598.0)	0.55	0.96

Note: For statistical analysis, the Mann–Whitney U test was used, and a *p*-value less than 0.05 was considered statistically significant. Next, the Benjamini-Hochberg false discovery rate was employed as a correction for multiple comparisons, and *q*-value less than 0.1 was considered statistically significant.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; MBP, mean blood pressure; PLT, platelet count; RRT, renal replacement therapy; PRA, plasma renin activity; PAC, plasma aldosterone concentration; SBP, systolic blood pressure; sCre, serum creatinine; U-P, urinary protein; sAlb, serum albumin; sLDH, serum lactate dehydrogenase; sK, serum potassium.

TABLE 5 | Adjusted comparison of serum LDH levels between the both group.

	non-RRT group Adjusted mean (SE) (n)	RRT group Adjusted mean (SE) (n)	*f*-value	*p*-value	η^2
Model 1	875.5 (± 58.6) (9)	88.9 (± 76.4) (6)	58.02	< 0.001	0.76
Model 2	812.2 (± 77.0) (9)	336.7 (± 95.3) (6)	14.38	0.003	0.52
Model 3	1074.6 (± 78.1) (4)	319.9 (± 62.6) (6)	52.36	< 0.001	0.83

Note: Analysis of covariance (ANCOVA) was used to control for confounding factors in the statistical analysis, and a *p*-value less than 0.05 was considered statistically significant. Three models were tested: First, an ANCOVA was performed with four covariates: serum creatinine (Cre) levels, age, sex, and the use of RAS inhibitors, although parallelism in the regression slopes could not be demonstrated (Model 1). In the second analysis, serum Cre levels were the sole covariate (Model 2). Lastly, a third ANCOVA was conducted focusing on male participants, with serum Cre levels as the covariate (n = 4 in the non-RRT group; n = 6 in the RRT group) (Model 3).
Abbreviations: LDH, lactate dehydrogenase; n, sample size; RRT, renal replacement therapy; SE, standard error.

TABLE 6 | Changes in blood test parameters before and after treatment in each group.

		Before Median percentile (25%–75%)	After Median percentile (25%–75%)	*p*-value
non-RRT group	sCre (mg/dL)	5.7 (4.585–6.9)	2.52 (2.09–3.45)	0.001
	sLDH (IU/L)	789 (587.5–1031)	178 (152.5–206.5)	< 0.001
	PLT ($\times 10^4/\mu L$)	9.9 (7.05–16.05)	22.7 (18.1–27.65)	0.002
	sK (mEq/L)	3.0 (2.6–3.25)	4.1 (3.8–4.25)	0.003
RRT group	sCre (mg/dL)	7.72 (5.08–8.90)	8.88 (6.2–10.76)	0.302
	sLDH (IU/L)	290.5 (228–408.75)	173 (144–241)	0.028
	PLT ($\times 10^4/\mu L$)	19.35 (13.68–24.2)	22 (13.75–22.75)	0.855
	sK (mEq/L)	4.8 (3.63–5.53)	4.2 (4.05–4.3)	0.313

Note: For statistical nnalysis, the Wilcoxon signed-rank test was used and a *p*-value less than 0.05 was considered statistically significant.
Abbreviations: PLT, platelet count; RRT, renal replacement therapy; sCre, serum creatinine; sLDH, serum lactate dehydrogenase; sK, serum potassium.

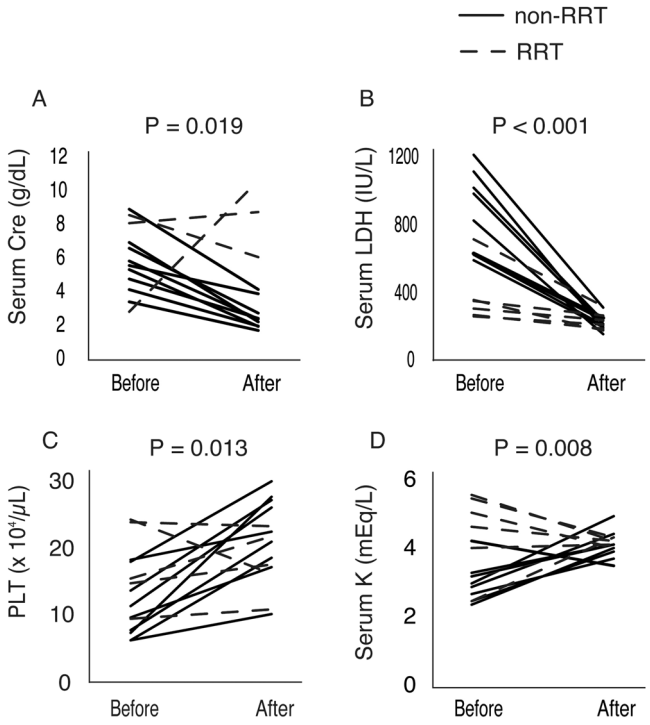

FIGURE 2 | Comparison of improvement in blood test parameters before and after treatment in both groups. (A) One year after treatment, serum creatinine levels in the non-RRT group showed a significant improvement compared to those in the RRT group. In the RRT group, three cases had undergone RRT within one year. Therefore, the remaining three cases are compared with nine cases in the non-RRT group. (B) Serum LDH levels in both groups decreased one month after treatment. Moreover, the decrease was more significant in the non-RRT group compared to that in the RRT group. (C) On admission, the PLT in the non-RRT group was lower and significantly improved one month after treatment compared to the RRT group. (D) Serum potassium levels were low in the non-RRT group before treatment and significantly improved one month after treatment compared to those in the RRT group. Abbreviations: LDH, lactate dehydrogenase; PLT, platelet count; RRT, renal replacement therapy. Statistical analysis, the two-way analysis of variance (ANOVA) was conducted for statistical analysis. A P-value less than 0.05 was considered statistically significant.

renal dysfunction associated with these emergencies remain significantly high [13]. Many patients do not undergo medical checkups or do not take antihypertensive medication appropriately. In this study, nine out of the 15 patients did not undergo medical checkups, and eight patients did not receive continuous treatment. The majority of cases had an onset age of 40–50 years, with extremely low renal function (median serum Cre level, 5.97 mg/dl). Recent reports demonstrated that renal dysfunction at presentation predicted worse renal outcomes in hypertensive emergencies [6–8]. However, there has been no examination of the renal prognosis in cases of hypertensive emergencies accompanied by extremely severe renal dysfunction as observed in our study. Our study showed no significant difference in renal function between the two groups at the time of admission; however, the non-RRT group showed a clear improvement in renal function after 1 year. Some studies have reported that renal cortex thickness and renal volume are predictors of renal prognosis [14, 15], with smaller values of these parameters associated with the presence of chronic renal impairment and worse renal prognosis. In this study, we evaluated the long/short axes of kidney size using simple abdominal CT scans and found no significant difference in kidney size between the two groups. Furthermore, all cases included patients who visited our hospital for the first time, many of whom had untreated hypertension, and their medical histories were unknown. This made it challenging to determine initially whether the clinical course of renal function was acute or chronic. While renal atrophy is not an absolute indicator of chronic renal dysfunction, we initially considered the patients to be in the acute phase of acute or chronic renal failure rather than chronic due to the lack of obvious atrophic kidneys on imaging findings. However, the retrospective analysis suggests that many patients in the RRT group likely had underlying chronic kidney disease progression.

The typical pathology of hypertensive emergency involves severe endothelial cell damage. The intraglomerular pressure in the kidneys is usually maintained by an autoregulatory system. However, when the systolic BP exceeds 200–230 mmHg a rapid increase in intraglomerular pressure occurs and causes severe endothelial injury [16]. Moreover, it leads to (1) fibrinoid necrosis, platelet thrombus, and intramural hemorrhage, and (2) proliferative endarteritis, causing narrowing of the lumina with hyperplastic arteriolosclerosis and severe tissue ischemia [17]. Van den Born et al. reported that MAHA, commonly known as thrombotic microangiopathy (TMA), in the setting of hypertensive emergencies with (1) low PLT ($< 150 \times 10^9$/L) and elevated serum LDH levels (> 220 U/L) or the presence of schistocytes and (2) normalization of these values with BP control [18]. According to their report, while patients with hypertensive emergencies accompanied by TMA exhibit more severe renal dysfunction on admission, MAHA is also the most significant indicator of renal improvement during follow-up [18]. However, these findings seem contradictory to other recent reports suggesting that renal dysfunction at presentation is a predictor of worse renal outcomes [6–8]. Interestingly, another report suggested that the presence of pathological renal TMA findings might serve as a protective factor against renal damage [19]. On the contrary, there is a report suggesting that the presence or absence of TMA does not affect long-term renal prognosis [20]. As of now, no definitive consensus has been reached based on the reports. In our cohort, patients in the non-RRT group exhibited more pronounced decreases in platelet counts and increases in serum LDH levels compared to the RRT group. The serum LDH level was suggested to be a useful marker for distinguishing between the two groups, even after FDR correction and adjusting for confounding factors. We speculate that the acute phase of TMA in our patients, particularly in the non-RRT group, may have been triggered by the rapid and severe rise in BP. Appropriate BP control resulted in a significant improvement in LDH and PLT levels. The lowering of BP might have contributed to the recovery from TMA, hemolysis, and renal dysfunction, leading to a favorable long-term renal prognosis. Marked activation of the RAS is evident in patients with hypertensive emergencies [21]. Activation of the RAS has also been studied in animal models of malignant hypertension [22]. While there was no significant difference in systolic blood pressure between the patients receiving low-dose angiotensin-converting enzyme (ACE) inhibitors and the

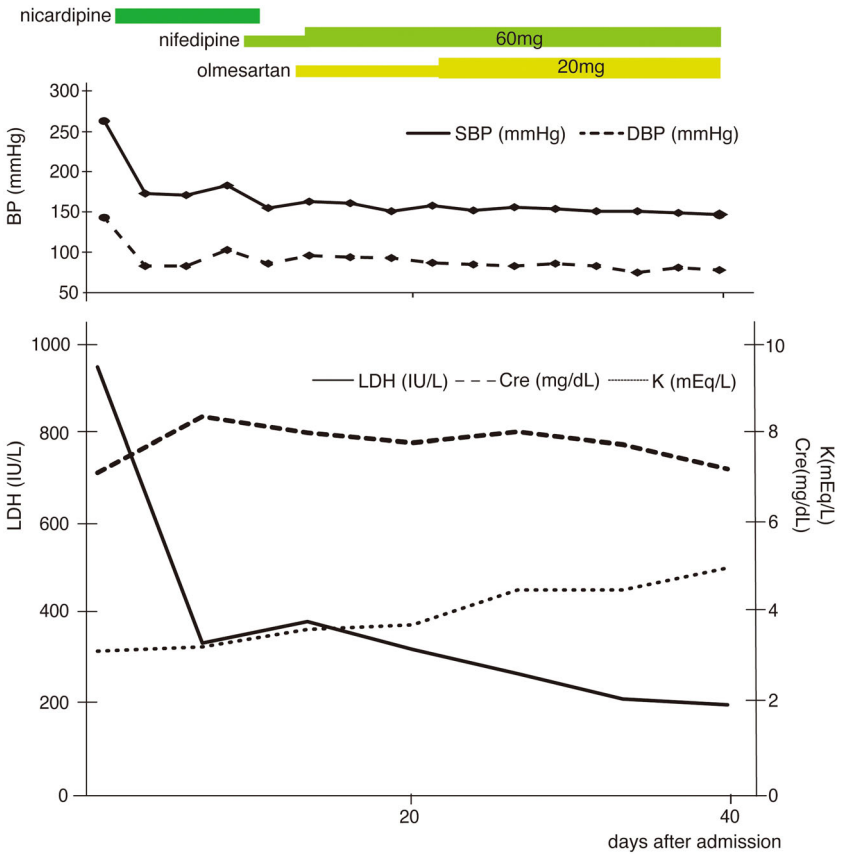

FIGURE 3 | Clinical course of a representative case (Case 1) in our study. Upon admission, the patient had severe renal impairment, with significantly high serum lactate dehydrogenase (LDH) and low platelet levels. The serum potassium level had clearly decreased. The levels of LDH and platelet count rapidly improved with the initiation of antihypertensive treatment with calcium channel blocker. The serum potassium levels also gradually improved after the initiation of an angiotensin II receptor blocker.

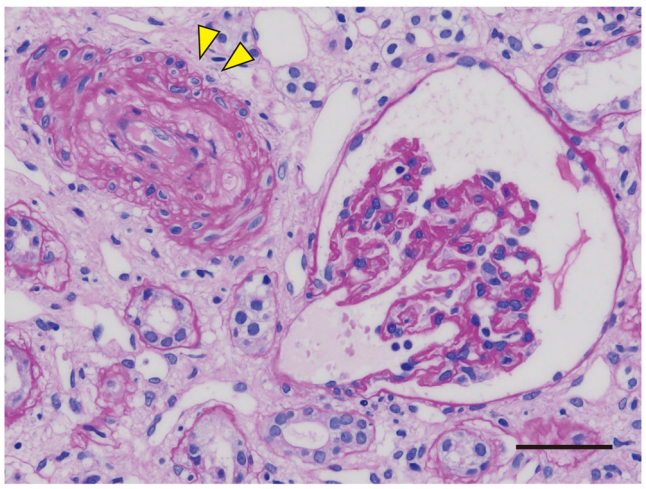

FIGURE 4 | Kidney biopsy findings. Arrowheads show marked thickening of the arteriolar intima with onion-skin lesions and narrowing of the arterial lumen. Collapsed glomeruli and tubular atrophy with interstitial edema and fibrosis were observed (PAS stain; scale bar, 50 μm).

control groups, the mortality rate was significantly lower in those receiving ACE inhibitors. This suggests a clear improvement in organ damage with ACE inhibitors despite the absence of blood pressure reduction [23]. The association between increased RAS activity and decreased potassium levels is established [24]. It has been suggested that ACE-inhibitor-induced potassium elevation may have a protective effect against endothelial cell damage. Conversely, some experimental studies have reported that a high-potassium diet or potassium supplementation reduces endothelial permeability in stroke-prone spontaneously hypertensive rats, inhibits macrophage adhesion and infiltration, and reduces endothelial cell damage [23, 24]. In a retrospective study on the relationship between the RAS and the severity of MAHA, it was reported that hypertensive emergencies with MAHA showed increased renin activity and elevated aldosterone levels, suggesting a correlation between increased RAS and MAHA [25, 26]. In our study, the non-RRT group exhibited significantly lower serum potassium levels at admission compared to the RRT group, and there was a clear improvement after treatment.

As demonstrated in the representative case, the patient showed rapid improvements with antihypertensive treatment, averting end-stage renal failure even 3 years later. Renal histopathology in this case revealed robust sub-acute lesions, suggesting potential reversibility of the disease. In our study, renal biopsy was performed in three cases, including this one, to further elucidate the underlying factors, but all revealed images consistent with malignant nephrosclerosis. Although no thrombus was detected in the renal biopsy tissue in this case, another patient in the non-RRT group displayed thrombus, indicating

pathological renal TMA findings. Consistent with previous reports, pathological TMA findings may serve as a predictor of favorable prognosis with appropriate treatment [20]. Thrombotic thrombocytopenic purpura with markedly decreased ADAMTS13 activity is a well-known cause of TMA. Recently, there have been several reports suggesting an association between decreased ADAMTS13 activity and malignant hypertension, suggesting the importance of measuring ADAMTS13 activity [27, 28]. In our representative case, ADAMTS13 activity was measured and did not show an obvious decline. It should be noted that ADAMTS13 activity could not be measured in all patients in the current study due to the rapid improvement in PLT after treatment; however, this may serve as a useful marker. The patient also showed hypokalemia (serum potassium, 3.0 mEq/L) upon admission. Following the initiation of RAS inhibitors, the potassium level improved, and the serum Cre level decreased gradually. While there was no significant difference in the use of RAS inhibitors between the two groups in our study, many patients in the non-RRT group also showed improvement in serum potassium levels after initiating antihypertensive therapy with calcium channel blockers and RAS inhibitors, which may have contributed to the suppression of the progression of organ damage. Thus, active use of RAS inhibitors may have substantial benefits and should be considered even in patients with severe renal impairment.

The primary limitation of this study lies in the notably small number of cases for analysis. Because this is a single-center study and the subset of cases with severe renal impairment (serum Cre > 2.5 mg/dL) and eligible for a 3-year follow-up was substantially reduced from initial selection. In this study, several clinical parameters were compared between the two groups. However, due to the small sample size, multivariate analysis could not be conducted to evaluate the association between these parameters.

Therefore, caution is advised when extrapolating these results to broader populations, and future research with larger cohorts is needed to validate and extend our observations.

5 | Conclusion

In hypertensive emergencies accompanied by severe renal impairment, extremely high BP and RAS activation disrupt autoregulation of intraglomerular pressure, causing endothelial cell damage, MAHA, and decreased serum potassium levels. These symptoms are more pronounced in patients experiencing acute symptoms. However, long-term improvements in renal prognosis can be achieved with appropriate BP-lowering treatment. It is suggested that serum levels of LDH, potassium, and PLT may serve as predictive factors for renal prognosis in hypertensive emergencies with severe renal impairment. Additionally, a positive response to treatment suggests a favorable prognosis.

Author Contributions

Rei Nakazato: conceptualization, data curation, formal analysis, investigation, writing–original draft. **Akiko Mii:** conceptualization, investigation, methodology, project administration, writing–original draft, writing–review and editing. **Natsumi Kamijo:** data curation. **Takashi Tani:** data curation. **Yusuke Arakawa:** data curation. **Toshiaki Otsuka:** formal analysis, methodology. **Yukinao Sakai:** supervision. **Tetsuya Kashiwagi:** supervision. **Masato Iwabu:** supervision.

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Disclosure

The lead author Akiko Mii affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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