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Role of aldosterone in various target organ damage in patients with hypertensive emergency: a cross-sectional study

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Abstract

Background Hypertensive emergency is a critical disease that causes multiple organ injuries. Although the renin-angiotensin-aldosterone system (RAS) is enormously activated in this disorder, whether the RAS contributes to the development of the organ damage has not been fully elucidated. This cross-sectional study was conducted to characterize the association between RAS and the organ damage in patients with hypertensive emergencies.

Methods We enrolled 63 patients who visited our medical center with acute severe hypertension and multiple organ damage between 2012 and 2020. Hypertensive target organ damage was evaluated on admission, including severe kidney impairment (eGFR less than 30 mL/min/1.73 m^2, SKI), severe retinopathy, concentric left ventricular hypertrophy (c-LVH), thrombotic microangiopathy (TMA), heart failure with reduced ejection fraction (HFrEF) and cerebrovascular disease. Then, whether each organ injury was associated with blood pressure or a plasma aldosterone concentration was analyzed.

Results Among 63 patients, 31, 37, 43 and 8 cases manifested SKI, severe retinopathy, c-LVH and ischemic stroke, respectively. All populations with the organ injuries except cerebral infarction had higher plasma aldosterone concentrations than the remaining subset but exhibited a variable difference in systolic or diastolic blood pressure. Twenty-two patients had a triad of SKI, severe retinopathy and c-LVH, among whom 5 patients manifested TMA. Furthermore, the number of the damaged organs was correlated with plasma aldosterone levels (Spearman's coefficient = 0.50), with a strong association observed between plasma aldosterone (≥ 250 pg/mL) and 3 or more complications (odds ratio = 9.16 [95%CI: 2.76–30.35]).

Conclusion In patients with hypertensive emergencies, a higher aldosterone level not only contributed to the development of the organ damage but also was associated with the number of damaged organs in each patient.

Keywords Aldosterone, Hypertensive emergency, Kidney, Thrombotic microangiopathy, Retinopathy, Cardiac hypertrophy, eGFR

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Introduction

Despite the progress in diagnostic medicine and therapeutic pharmacology, uncontrolled severe hypertension remains a matter of great concern in emergency medicine. A variety of organ damage ensues following the development of acute severe hypertension, including cerebral hemorrhage, heart failure, retinopathy and acute kidney impairment. Although the pathophysiology of the organ injuries in hypertensive emergencies is attributed in large part to absolute levels and the pace of the changes in blood pressure (BP) [1], other factors may also contribute to the development of the organ damage [2]. Because the renin-angiotensin-aldosterone system (RAS) is activated in these patients [3, 4], it is reasonably surmised that RAS shares the responsibility for the organ damage with acute severe hypertension [5–7]. Nevertheless, there have been few studies that attempt to evaluate comprehensively the role of RAS and BP in the pathophysiology of the acute organ damage in hypertensive emergencies [3].

There are reported various incidence rates of acute target organ injuries among patients with hypertensive emergencies [8]. In patients with malignant hypertension, a subset of hypertensive emergencies, high-grade hypertensive retinopathy is observed, and renal functional impairment is reported to be common, with 63% of the patients manifesting this feature at the time of the presentation [9]. Furthermore, acute vascular endothelial damage could elicit thrombotic microangiopathy (TMA), which is characterized by fragmented erythrocytes and hemolytic anemia and is reported to be present in 25–44% of the patients with malignant hypertension [7, 10]. Left ventricular hypertrophy (LVH) is also observed frequently, which occurs most often in combination with other complications [2, 4, 8]. Although these observations imply that the patients with hypertensive emergencies possess multiple target organ injuries, it remains unknown which factors (e.g., BP or aldosterone) are associated more closely with the occurrence of multiple organ injuries.

In the present study, we attempted to characterize the acute severe hypertension-induced injuries of various organs, including the kidney, heart, retina, and microvessels, in patients with hypertensive emergencies. Because RAS is recognized to be markedly activated in this disorder [3–7, 11], we evaluated whether the augmented aldosterone was associated with or additively contributed to the development of these complications in patients with acute severe hypertension.

Methods

The aim of this cross-sectional study is to characterize various target organ damage induced by acute severe hypertension in patients with hypertensive emergencies, with special reference to plasma aldosterone levels. The Review Board and Ethics Committee of Tokyo Bay Urayasu-Ichikawa Medical Center approved the protocol of this study and waived the requirement for obtaining informed consent because of the retrospective nature of this study (approval No. 726). The opt-out information was published in our hospital website. The study was conducted to conform to the principles of the Declaration of Helsinki and was registered at UMIN (ID#; UMIN R000062848). Information from medical records was anonymized prior to final analysis.

Study population and design

During the period between April 2012 and August 2020, eighty-six patients visited the emergency department of Tokyo Bay Urayasu-Ichikawa Medical Center, presenting with severe hypertension (systolicBP ≥ 180 mmHg and/or diastolic BP ≥ 120 mmHg) and the associated complications (Fig. 1). Among them, eighteen patients were transferred to other hospitals for further assessment and the treatment of severe hypertension. Of 68 patients admitted to our hospital, five patients died upon admission (i.e., before detailed evaluation); the causes of the death were brainstem hemorrhage ($n=4$) and aortic dissection ($n=1$). Ultimately, 63 patients were eligible for further evaluation.

At the time of admission, BP and laboratory data, including serum creatinine, hemoglobin A1c, hematocrit, urine protein/creatinine ratio, plasma renin activity, and aldosterone, were evaluated. One BP measurement taken in the supine position was recorded at the time of the emergency visit and was repeated for evaluation of serial changes in BP. Plasma aldosterone was measured using the radioimmunoassay method. Blood samples for renin and aldosterone were taken after 30 min of rest in a supine position.

Hypertensive emergency-associated organ damage

The hypertensive emergency-associated organ damage was evaluated on admission. They included cardiac complications (heart failure with ejection fraction (EF) less than 40% [HFrEF], LVH, myocardial infarction), impaired renal function (estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 or requirement for dialysis therapy), high-grade hypertensive retinopathy, cerebral complications (infarction, hemorrhage, encephalopathy) and TMA. EF was assessed with cardiac ultrasound and hypertensive retinopathy was evaluated with Scheie's classification, with grade 3 or 4 as high-grade retinopathy. Concentric LVH was defined according to the standard criteria [12]. TMA was determined based on the standard criteria (i.e., microangiopathic hemolytic anemia and thrombocytopenia [less than $15\times10^4/mm^3$]).

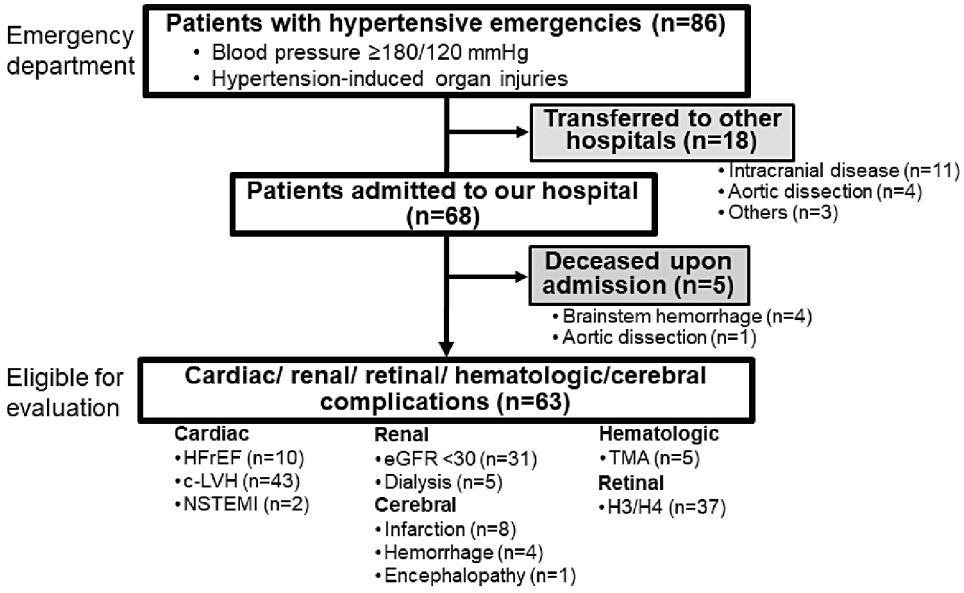

Fig. 1 Flow diagram illustrating the enrollment of patients with hypertensive emergencies. HFrEF; heat failure with reduced ejection fraction, c-LVH; concentric left ventricular hypertrophy, NSTEMI; non-ST elevation myocardial infarction, TMA; thrombotic microangiopathy

eGFR was assessed using the formula adapted to the Japanese population [13].

$eGFR = 194 \times age^{-0.287} \times serum\ creatinine^{-1.094}$ (×0.739, if female).

New onset cerebral infarction, cerebral hemorrhage and hypertensive encephalopathy were determined based on the neurological physical examination and brain CT/MRI imaging.

Statistical analysis

The results are expressed as the median [lower quartile-upper quartile: IQR]. The comparison between two groups was made with the Mann-Whitney U test, and the data among 3 or more groups were compared with the Kruskal-Wallis test, followed by the Steel-Dwass post-hoc test. The chi-square or Fisher's exact test was used to compare categorical variables, including the number of patients. Odds ratios (ORs) for each target organ damage were calculated in association with systolic BP, diastolic BP or plasma aldosterone. The relationship between the number of organ damage and various parameters, including plasma aldosterone concentration, systolic BP and diastolic BP, was analyzed using the Spearman's rank correlation test. Furthermore, the cut-off values of these parameters for 3 or more versus 2 or less organ injuries were determined, using the receiver operating characteristic (ROC) analysis. Then, logistic regression analysis was applied with inclusion of these parameters as independent variables and the adjusted OR for 3 or more complications was calculated. Statistical analyses were performed using the John Macintosh Project (JMP) statistical software (version 16, SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p<0.05$.

Results

Patient characteristics

Among the 63 patients enrolled in this study, approximately two-thirds of the patients were male and a half of the population had a smoking habit (Table 1). Although 79.4% of the patients were aware of having hypertension, only 22.0% of these subjects had been receiving antihypertensive treatment. Most of the patients were deemed to have essential hypertension but had no evidence of primary aldosteronism, renal vascular stenosis, or CKD, based on previous medical information and clinical examination [11]. Mild anemia and slightly elevated LDH were observed. Although the median value of the platelet count remained within the normal range, a quarter of the patients manifested the values less than $15\times10^4/mm^3$. eGFR was moderately to severely reduced; five patients commenced hemodialysis therapy upon admission (Fig. 1). Both plasma renin activity and aldosterone concentrations were elevated.

CT and MRI scans were performed only in cases with abnormal neurological findings, at the discretion of each clinician; CT examinations were performed in 25 out of 63 cases (39.7%) and MRI in 14 out of 63 cases (22.2%). Echocardiography was performed in 58 out of 62 patients (93.5%), regardless of the presence or absence of the symptoms. The number of days from admission

Table 1 Patients' characteristics

Number of patients (Total *n* = 63)			
Male/female, n (male%)	43/20 (68.3%)	Total protein (g/dL)	6.50 [6.05–7.20]
Age (y/o)	46.0 [41.0–54.0]	Hematocrit (%)	38.5 [30.8–44.5]
Systolic BP (mmHg)	221 [201–236]	Platelet count (x10^4/mm^3)	22.0 [15.2–25.0]
Diastolic BP (mmHg)	140 [127–155]	LDH (U/L)	330 [251–455]
Heart rate (beats/min)	105 [92–115]	Serum potassium (mEq/L)	3.70 [3.30–4.20]
Body mass index (kg/m^2)	28.2 [24.1–31.0]	LDL-cholesterol (mg/dL)	118 [101–147]
Diabetes, n (%)	9 (14.3%)	HDL-cholesterol (mg/dL)	43 [36–52]
Smoking, n (%)	34 (54.0%)	Hemoglobin A1c (%)	5.5 [5.0–6.0]
Aware of hypertension, n (%)	50 (79.4%)	eGFR (mL/min/1.73 m^2)	30.0 [11.7–51.3]
Treatment (-)	39 [78.0%]	Urine protein (g/gCr)	2.76 [0.62–4.53]
Treatment (+)	11 [22.0%]	PRA (ng/mL/hr)	12.5 [4.5–27.0]
Duration of hypertension (y)	4.0 [1.5–10.0]	Plasma aldosterone (pg/mL)	208 [133–371]
		BNP (pg/mL)	618 [289–1494]

BP; blood pressure, LDH; lactate dehydrogenase, PRA; plasma renin activity, BNP; brain natriuretic peptide

Results are median [IQR]

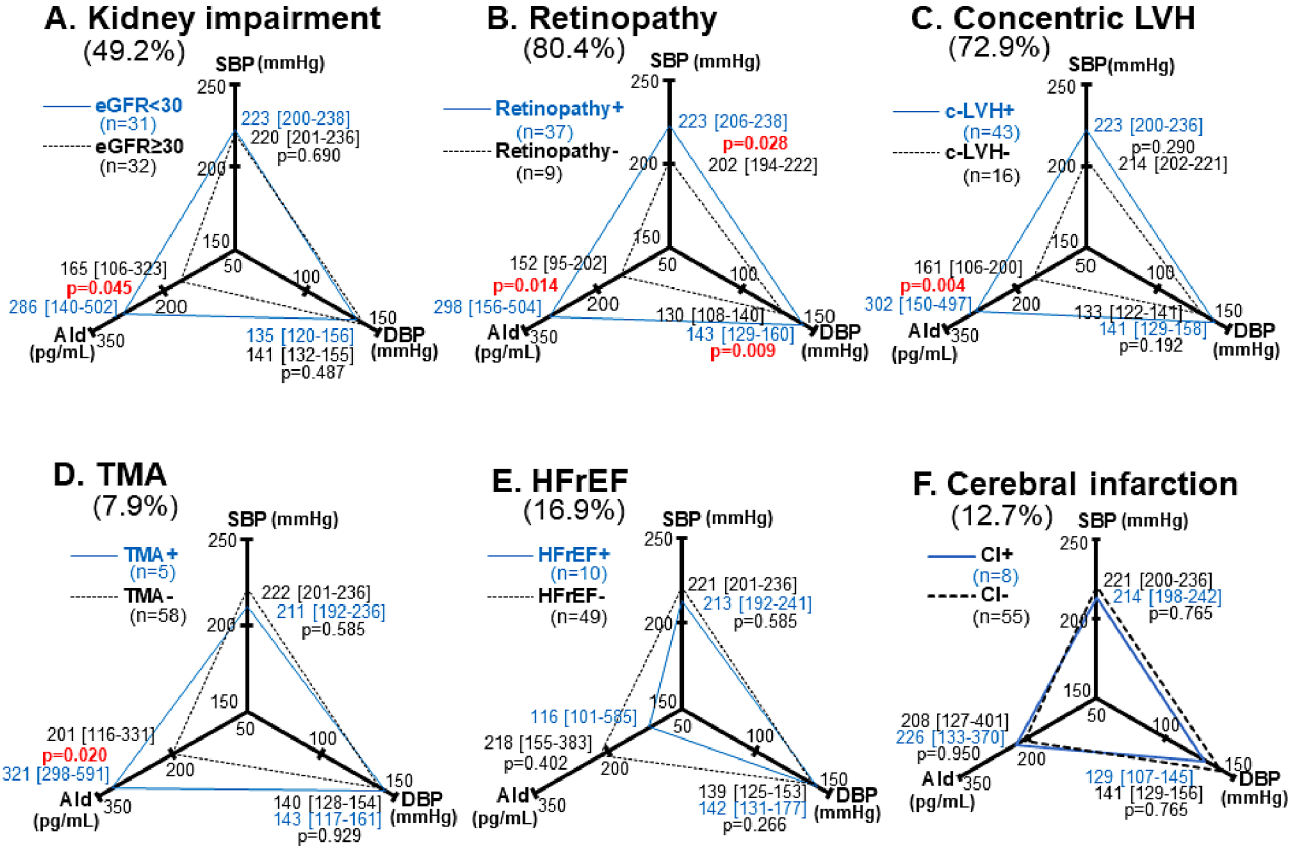

Fig. 2 Relationships among systolic blood pressure, diastolic blood pressure and aldosterone in patients with various organ damage. Ald; aldosterone, SBP; systolic blood pressure, DBP; diastolic blood pressure, c-LVH; concentric left ventricular hypertrophy, TMA; thrombotic microangiopathy, HFrEF; heart failure with reduced ejection fraction

to examination was 1.0 [IQR: 0.0–2.0] day for proteinuria measurement, 3.0 [IQR: 1.0–6.0] days for ophthalmic evaluation, and 6.0 [IQR: 2.5–12.5] days for MRI examination.

Target organ damage on admission

Thirty-one patients (i.e., 49.2%) had moderately to severely impaired renal function (i.e., eGFR < 30 mL/min/1.73 m^2 or need for dialysis therapy, Fig. 2A). In these patients, neither systolic nor diastolic BP differed from that in patients with eGFR ≥ 30 mL/min/1.73 m^2.

Plasma aldosterone was markedly higher in patients with eGFR < 30 mL/min/1.73 m^2.

Severe hypertensive retinopathy was observed in 37 patients (i.e., 80.4%, Fig. 2B). These patients manifested higher systolic ($p=0.028$) and diastolic BP ($p=0.009$) and elevated aldosterone concentrations ($p=0.014$). The patients with concentric LVH ($n=43$) had higher aldosterone ($p=0.004$) but no difference in systolic BP or diastolic BP was observed between the group with and without concentric LVH (Fig. 2C). Five patients (i.e., 7.9%) were diagnosed with TMA and had higher plasma aldosterone (321 [IQR: 298–591] vs. 201 [IQR: 116–331] pg/mL) and LDH (722 [IQR: 461–1552] vs. 325 [IQR: 243–447] U/L, $p=0.012$) whereas the BP was nearly the same as in patients without TMA (Fig. 2D).

Ten patients (i.e., 16.9%) manifested a feature of HFrEF (EF < 40%), but neither systolic BP, diastolic BP nor plasma aldosterone differed between the patients with HFrEF and those with EF ≥ 40% (Fig. 2E). Similarly, eight patients with cerebral infarction had nearly the same levels of aldosterone, systolic BP and diastolic BP as those with no apparent cerebral infarction (Fig. 2F) but higher LDL-cholesterol (149 [IQR: 126–172] vs. 113 [IQR: 101–136] mg/dL, $p=0.038$). Among the population who were eligible for detailed evaluation, there were a small number of the patients with cerebral hemorrhage ($n=4$); no difference in systolic BP, diastolic BP or aldosterone was found between the patients with and without cerebral hemorrhage (systolic BP; 219 vs. 221 mmHg, diastolic BP; 142 vs. 140 mmHg, aldosterone; 153 vs. 217 pg/mL, respectively). Thus, a total of 13 patients had clinically apparent cerebrovascular disease (cerebral infarction; $n=8$, cerebral hemorrhage; $n=4$, hypertensive encephalopathy; $n=1$). Finally, there were observed diverse incidence rates among these target organ complications ($p<0.001$).

The association between the target-organ damage and various parameters (systolic BP, diastolic BP, and aldosterone) was assessed, using the value approximate to the median for each parameter as a cut-off value. Thus, retinopathy and concentric LVH were closely associated with aldosterone (≥ 250 pg/mL) and had higher diastolic BP (≥ 140 mmHg) and systolic BP (≥ 220 mmHg), respectively (Supplementary Fig. 1). Reduced eGFR (< 30 mL/min/1.73 m^2) was marginally associated with aldosterone, but not with BP. Similarly, aldosterone ≥ 250 pg/mL was the only parameter that significantly affected the incidence of TMA. Neither HFrEF nor cerebral infarction had any association with BP or aldosterone.

Association between BP/aldosterone and the number of complications

The patients with hypertensive emergencies suffered multiple organ injuries (total number of complications = 2.0 [IQR: 1.0–3.0]) when admitted to our hospital. Twenty-seven patients (i.e., 42.9%) had 3 or more complications (Fig. 3A), among whom 22 cases had a triad of severe kidney impairment, severe retinopathy and concentric LVH (a∩b∩c, Fig. 3B). Of note, this population included all cases with TMA ($n=5$), who had a longer history of smoking habits but similar levels of BP and aldosterone, compared with the remaining population (Supplementary Table 1).

The relationship between systolic/diastolic BP and the total number of complications in each patient was depicted in Fig. 4A. There was no difference in systolic or

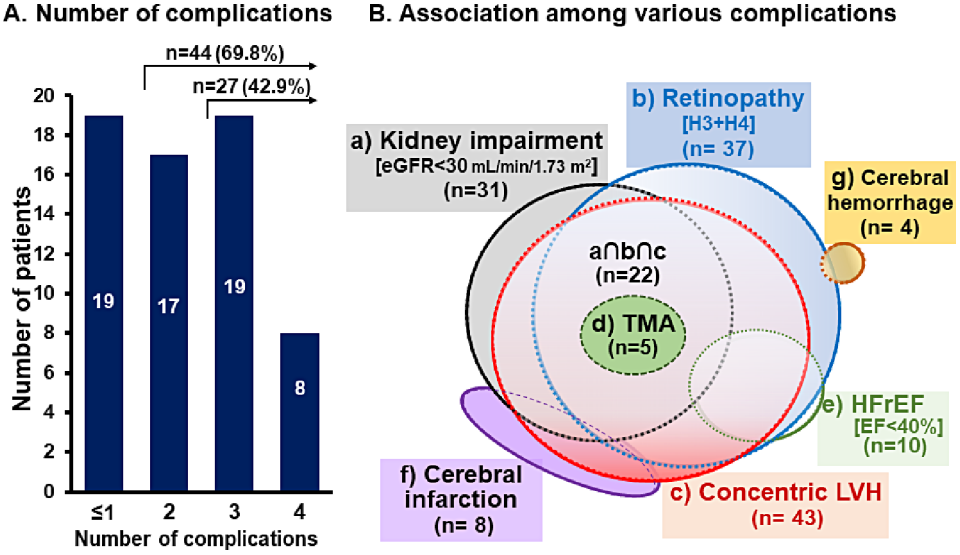

Fig. 3 Number of complications and the association among the complications. LVH; left ventricular hypertrophy, TMA; thrombotic microangiopathy, HFrEF; heart failure with reduced ejection fraction

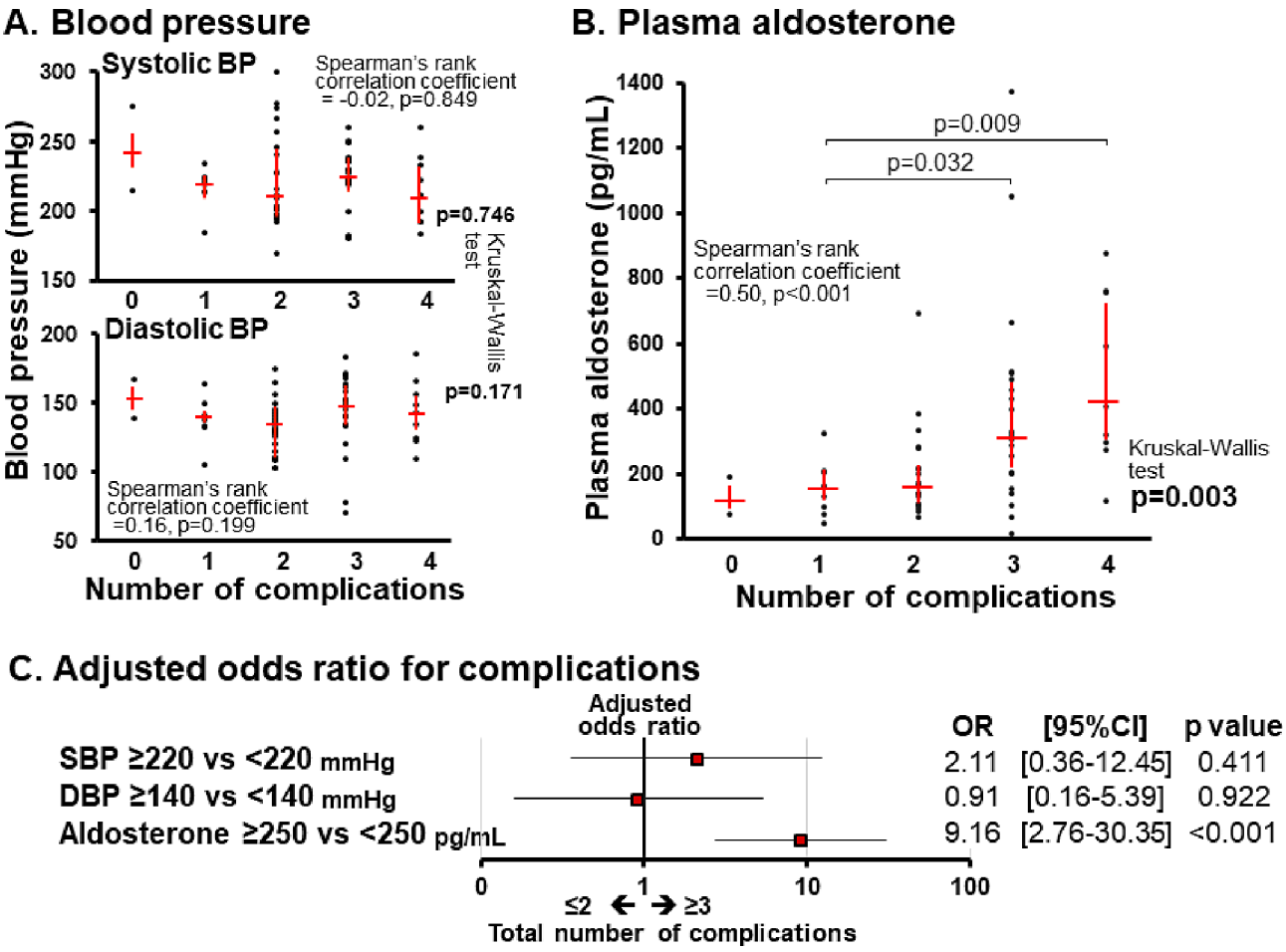

Fig. 4 Association between the number of complications and plasma aldosterone/blood pressure in patients with hypertensive emergency. BP; blood pressure, SBP; systolic BP, DBP; diastolic BP

diastolic BP among the groups with a single or multiple complications ($p=0.746$ and $p=0.171$, for systolic and diastolic BP, respectively). In contrast, plasma aldosterone was higher in patients who had 3 or 4 complications than in those with a single complication (Fig. 4B); a positive correlation was found between these two parameters (Rs=0.50).

ROC analysis showed that the cut-off values for aldosterone, systolic BP and diastolic BP in association with 3 or more versus 1 or 2 complications were 257 pg/mL, 219 mmHg and 143 mmHg, respectively (Supplementary Fig. 2). The presence of 3 or more complications was strongly associated with plasma aldosterone concentrations (≥250 pg/mL), but not with systolic (≥220 mmHg) or diastolic BP (≥140 mmHg, Fig. 4C).

The incidence of each organ damage was estimated based on the number of the complications. Thus, the incidence of impaired kidney function (eGFR<30 mL/min/1.73 m^2) was increased in parallel with the number of complications (Fig. 5). Both severe retinopathy and concentric LVH developed in 43% and 67–75% of the patients with 1 or 2 complications, respectively, and the incidence of these organ injuries rose in patients with 3 or more complications in whom aldosterone concentrations, but not systolic or diastolic BP, were markedly elevated. Cerebral infarction, cerebral hemorrhage and HFrEF occurred solely or in combination with other organ injuries but the incidence rates of these complications remained low even in the subgroup with 3 or more complications. TMA was found exclusively in patients with four complications.

Discussion

Hypertensive emergencies represent a form of acute severe hypertension with multiple organ damage and should bring about poor prognosis unless appropriately treated. Cardiac, renal and retinal disease are the commonly observed complications and traditionally, an acute and marked elevation in BP is recognized to be responsible for the development of these organ injuries. There is proposed, however, an additional thesis that enhanced RAS activity may play a substantial role in the

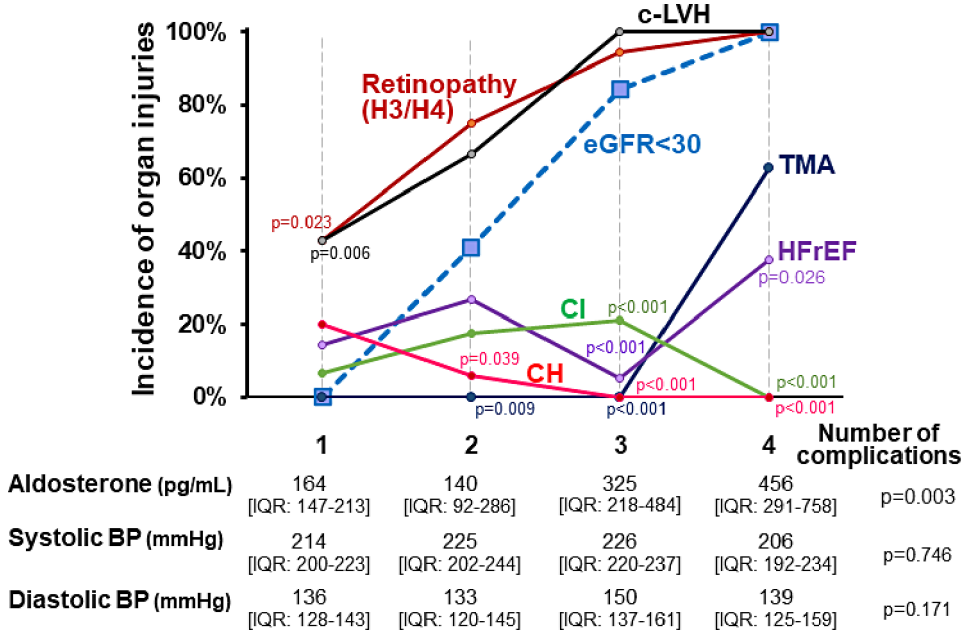

Fig. 5 Association between the incidence of organ injuries and the number of complications. The incidences of concentric left ventricular hypertrophy (c-LVH), severe retinopathy (H3/H4) and renal impairment (eGFR < 30) were increased with the number of complications. The patients with HFrEF, cerebral hemorrhage (CH) and cerebral infarction (CI) had relatively low incidence rates even among the subgroups with larger numbers (i.e., 3 and 4) of complications and higher aldosterone concentrations. The patients with thrombotic microangiopathy (TMA) were found exclusively in the subgroup with 4 complications. P values denote significant differences vs. eGFR at the respective number of complications

pathogenesis of the acute organ injuries in hypertensive emergencies [3, 4, 14]. We therefore attempted to characterize the clinical features underlying the acute hypertensive organ damage, based on the levels of BP and RAS, especially aldosterone.

Role of aldosterone in hypertensive emergency-associated organ damage

Evidence has been accumulated that RAS constitutes a pivotal aspect in the pathological process of malignant hypertension, a major subset of hypertensive emergencies. Thus, aldosterone, acting as a hormonal mediator, contributes to the development of retinopathy through vascular endothelial dysfunction and retinal inflammation [5, 15–18]. In the present study, we found that the patients with severe retinopathy had higher aldosterone levels along with systolic and diastolic BP (Fig. 2, Supplementary Fig. 1). Although acute severe hypertension-induced organ damage is recognized as the consequence of the organ ischemia and/or the hyperperfusion-induced capillary leakage attributed to disrupted blood flow autoregulation [19], elevated aldosterone levels may also act in concert with the hemodynamic factor to cause severe retinopathy [5]. Furthermore, aldosterone could promote hypertrophic changes in cardiomyocytes [20] and may contribute to the development of concentric LVH [6].

In addition to the classic action on renal electrolyte and body fluid balance, excess aldosterone may exert deleterious effects on various organs [5–7]. The present study revealed that higher plasma aldosterone was associated with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and the development of TMA (Fig. 2 and Supplementary Fig. 1). Because aldosterone causes endothelial dysfunction [15, 16], acute complications of TMA and renal impairment may be relevant to the previous reports showing aldosterone-mediated endothelial injury independent of renin or angiotensin [17, 18]. Elevated aldosterone may therefore facilitate multiple organ injuries under the milieu of acute severe hypertension.

Of note, the present study showed that both renal impairment and TMA were closely associated with elevated aldosterone, but neither systolic nor diastolic BP differed between the presence and the absence of these complications (Fig. 2A and D and Supplementary Fig. 1). Akimoto et al. [7] found higher aldosterone levels in patients with TMA than in those without TMA. An experimental study also revealed that aldosterone played a crucial role in the pathogenesis of TMA, independently of hypertension, in stroke-prone spontaneously hypertensive rats [20]. Interestingly, van den Born et al. [10] demonstrated a close relationship between TMA and renal dysfunction in patients with malignant hypertension. They also showed that RAS activation was associated with enhanced microangiopathic damage and renal dysfunction [3]. It is reasonably inferred therefore that aldosterone could participate in the development of microangiopathy and accelerate the progression of renal impairment.

We observed 10 cases with HFrEF (i.e., EF < 40%). Although chronic exposure to excess aldosterone was associated with collagen accumulation in the myocardium [21], we failed to show any significant difference in plasma aldosterone concentration between the subgroup with EF < 40% and that with EF ≥ 40% (Fig. 2E). Similarly, the patients with cerebral infarction also manifested no differences in these three parameters (Fig. 2F) but higher LDL-cholesterol levels. Other factors such as hypertension history, the presence of diabetes and the level of renal function may need to be taken into consideration.

Number of complications and BP/aldosterone

The present study demonstrated that the incidence of each complication varied depending on the target organs (i.e., 49.2%, 80.4%, 72.9%, 7.9%, 16.9%, 12.7%, and 6.3%, for kidney impairment, severe retinopathy, concentric LVH, TMA, HFrEF, cerebral infarction, and cerebral hemorrhage, respectively, $p < 0.001$, Fig. 2). Whereas we arbitrarily defined some of these complications, the differences in the incidence of the complications could be attributed to the diverse vulnerability of the organs to BP and aldosterone. Of note, the present study failed to include the 4 patients with brainstem hemorrhage because they died before detailed evaluation (Fig. 1). When these patients were incorporated in the overall incidence calculation, 25% of the 68 patients admitted to our hospital with hypertensive emergencies had cerebrovascular disease. Furthermore, this rate could have been higher if all patients had undergone detailed brain imaging.

In our study, 44 patients (i.e., 69.8%) had multiple organ injuries at the time of admission, and as many as 27 cases (i.e., 42.9%) possessed 3 or more complications (Fig. 3A). Among these, 22 cases manifested a triad of acute kidney impairment, severe retinopathy and concentric LVH (i.e., a∩b∩c, Fig. 3B) and had a higher aldosterone concentration (321 [IQR: 218–553] pg/mL, Supplementary Table 1). These observations lend support to the premise that aldosterone is involved in the pathophysiology of the multiple organ injuries in hypertensive emergencies. Indeed, a strong correlation was noted between the number of complications and plasma aldosterone levels (Rs = 0.50, $p < 0.001$, Fig. 4B). The fact that higher plasma aldosterone (≥ 250 pg/mL) is associated with 3 or more complications also indicates a close relationship between these two factors (Fig. 4C).

The incidence of each organ injury may vary depending on the multiplicity of the complications in hypertensive emergencies. Thus, the incidence rates of severe kidney impairment, concentric LVH and retinopathy rose in parallel with the number of the complications (Fig. 5). Additionally, concentric LVH and retinopathy were found more frequently than other organ injuries among the patients with 1 or 2 complications in whom plasma aldosterone levels were not elevated. In contrast, TMA was observed exclusively in patients with 4 complications. Finally, no apparent association was seen between the number of complications and the incidence of cerebral infarction or hemorrhage. These findings thus suggest that the organ damage in hypertensive emergencies is mediated by at least two mechanisms, including a hemodynamic burden and a hormonal factor to which each organ has variable susceptibility. Alternatively, antecedent treatment of hypertension and pre-existing metabolic factors may modify the severity of organ damage at presentation [22] although our study shows a modest impact of smoking habit on concentric LVH (Supplementary Table 2).

Intriguingly, all cases with TMA were found among the subgroup with a triad of impaired renal function, severe retinopathy and concentric LVH (Fig. 3B) and hence had 4 complications. This subgroup could therefore be regarded as manifesting a severer form of hypertensive emergencies. Although aldosterone plays a pivotal role in the development of TMA (Fig. 2D and Supplementary Fig. 1) [7, 20], there was found no difference in its concentration between the subgroup with TMA and that without TMA when evaluated among the population with the triad (Supplementary Table 1). Since endothelial injury constitutes a major determinant of TMA, additional factors favoring endothelial damage may predispose this population to TMA under the high aldosterone milieu; smoking-related vascular injury could be a possible factor (Supplementary Table 1) [23, 24].

Limitation

The results from our cross-sectional study contain several caveats to be mentioned. This study was conducted in a single medical center located in the suburbs of Tokyo and the patients enrolled in this study might have some bias that affected patient profiles. Indeed, 79.4% of the patients were aware of hypertension but only 22.0% had been receiving medical management (Table 1) and many of the remaining subpopulation discontinued the treatment, i.e., non-adherence to antihypertensive medications [1]. Furthermore, quite a few patients did not consult a doctor with unclarified reasons. The rate of smoking habits (54.0%) was also higher than that in the general population in Japan (16.7%, https://www.health-net.or.jp/tobacco/statistics/kokumin_kenkou_eiyou_report.html) though smoking is associated with the development of malignant hypertension [25]. It requires more thorough evaluation to clarify whether the diverse patient profiles or event rates affected our observations.

Both absolute BP levels and the rate of the change in BP determine acute hypertension-induced organ damage [1]. In this study, however, many of the patients were

non-adherent to medications or saw a doctor at variable intervals, making it difficult to assess systematically the pace of changes in BP before admission. More sophisticatedly designed studies will clarify the role of the pace of rise in BP and/or aldosterone in the development of acute hypertension-induced organ damage.

Finally. the present study evaluated the role of aldosterone as a representative of RAS in hypertensive emergencies. Although angiotensin II constitutes one of the most potent factors determining the development or aggravation of malignant hypertension, its measurement is not readily available in clinical practice, compared with PRA or aldosterone. In this regard, we also measured PRA (Supplementary Table 3, Supplementary Fig. 3) and found that both aldosterone and PRA levels changed in a similar manner in hypertensive emergencies, thus confirming the credibility of aldosterone in the assessment of RAS activity.

Conclusion

Acute severe hypertension causes deranged organ circulation and imposes a tremendous pressure burden on various organs. Furthermore, enhanced RAS during the establishment of this disorder could accelerate the progression of organ damage and may multiply the number of complications in hypertensive emergencies. Whether the antecedent treatment or early blockade of RAS activity alleviates the organ damage and accelerates the recovery from organ injuries awaits further investigations.

Abbreviations

BP	Blood pressure
RAS	Renin-angiotensin-aldosterone system
TMA	Thrombotic angiopathy
LVH	Left ventricular hypertrophy
EF	Ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IQR	Interquartile range
OR	Odds ratio
ROC	Receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03769-7.

Supplementary Material 1

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Author contributions

AM and KE participated in study design, data collection, analysis, and manuscript drafting. YH and TH assisted the data collection and interpretation. SI, KT, KY, KK and MS contributed to data analysis. NI and SF contributed to critical revision of this study. KH and TS contributed to the study design, implementation, analysis, drafting, and modification of the manuscript. All authors have read and approved the final manuscript.

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None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The study was approved by the Institutional Review Board and Ethics Committee of Tokyo Bay Urayasu-Ichikawa Medical Center with waiver of the requirement for obtaining informed consent (approval No. 726) and was conducted in accordance with the Declaration of Helsinki. Information from medical records was anonymized prior to final analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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