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# Postoperative Acute Kidney Injury Associated with Anesthesia Induction in Extremely Hypertensive Patients Undergoing Elective Non-Cardiac Surgery

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## ABSTRACT

**Introduction:** Some patients exhibit extreme hypertension before anesthetic induction. Although it is important to avoid hypotension during anesthesia to prevent major postoperative complications, it remains unknown how anesthetic hypotension should be managed in patients with hypertension. Therefore, we investigated the incidence of postoperative complications and their associations with low blood pressure during surgery in patients with a systolic blood pressure >200 mmHg before anesthetic induction.

**Methods:** We assessed the incidence of postoperative acute kidney injury (AKI), myocardial infarction (MI), and ischemic stroke. For postoperative AKI, we investigated the duration, between intubation and surgery initiation, for which the patients' mean arterial pressure (MAP) was below the threshold, and the duration from surgery initiation to the end of anesthesia. Based on these analyses, factors considered to be clinically associated with postoperative AKI were extracted and subjected to multivariate logistic regression analysis.

**Results:** In total, 274 patients were enrolled. Of these, 35 developed AKI and one experienced MI and ischemic stroke. The durations for which the MAP was <65, 70, and 75 mmHg between intubation and incision were significantly longer in the AKI group than in the non-AKI group ( $P < 0.01$ ). Multivariate regression analysis revealed a statistically significant association between the duration of having a MAP <75 mmHg and postoperative AKI (adjusted odds ratio = 1.04, confidence interval=1.02-1.07,  $P < 0.001$ ).

**Conclusions:** In patients with extreme hypertension before anesthetic induction undergoing elective non-cardiac surgery, a MAP <75 mmHg between intubation and incision may be an independent risk factor for postoperative AKI.

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**KEYWORDS: preinduction hypertension, anesthesia, surgery, postoperative complications, acute kidney injury**

## Introduction

It is generally known that chronic, severe hypertension before surgery is a risk factor for postoperative complications. According to the American College of Cardiology/American Heart Association guidelines,<sup>1)</sup> uncontrolled hypertension (systolic blood pressure  $\geq 180$  mmHg or diastolic blood pressure  $\geq 110$  mmHg) before surgery may increase the risk of developing various postoperative complications, and these guidelines recommend that such patients should postpone surgery until the blood pressure can be controlled. Moreover, the likelihood of successful management of anesthesia may decrease in patients with uncontrolled, severe hypertension undergoing scheduled surgery. In our hospital, based on these guidelines,<sup>1)</sup> when an anesthesiologist, who conducts a preoperative examination at approximately 3 weeks before the surgery, decides that the patient's blood pressure is poorly controlled, the patient is recommended to consult with the primary physician to regulate their blood pressure preoperatively. Therefore, most preoperative patients with hypertension have their blood pressure under control; however, even after these interventions, a certain number of patients still exhibit severe hypertension before the induction of anesthesia, which in some cases is related to the stress caused by the anxiety of undergoing surgery.

Although there are no specific guidelines regarding whether surgery should be postponed or not in patients with severe hypertension prior to anesthetic induction, some reports indicate that such hypertension is a risk factor for developing postoperative complications.<sup>2,3)</sup> In our hospital, we have defined patients with a systolic blood pressure  $>200$  mmHg before the induction of anesthesia as having uncontrolled and severe hypertension, and we have recommended that they postpone surgery. However, in some cases, the operation cannot be postponed because of deteriorating medical conditions and decisions must be made regarding the management of anesthesia.

In recent years, many studies have stated the importance of avoiding hypotension during anesthesia to reduce the risk of major postoperative complications, such as postoperative acute kidney injury (AKI), myocardial infarction (MI), and cerebral infarction.<sup>4-9)</sup> Therefore, it is ex-

pected that avoiding hypotension during surgery in patients with severe hypertension before anesthetic induction would also be important; however, it is unknown how low blood pressure should be managed in such patients to reduce postoperative complications.

Therefore, we investigated the incidence of postoperative AKI, MI, and cerebral infarction, and the associations between these complications and low blood pressure during surgery in patients with severe hypertension (systolic blood pressure  $>200$  mmHg) before applying anesthesia for elective, non-cardiac surgeries.

## Methods

### Study design

This was a retrospective cohort study using data collected from the Toho University Medical Center Omori Hospital's electronic medical records. The study protocol adhered to the ethical guidelines for epidemiological studies and the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Toho University Medical Center Omori Hospital (approval number: M 19135). Written informed consent was not required for this study owing to its retrospective design.

### Study population

The study population consisted of patients aged  $>20$  years who underwent non-cardiac surgery between January 2014 and December 2018 and who had a preinduction systolic blood pressure  $\geq 200$  mmHg, measured using a noninvasive blood pressure monitoring device (YP-713T; Nihon Kohden Corporation, Tokyo, Japan) with the patient in the supine position after entering the operating room. For inclusion, all patients should have been scheduled, electively, for overnight admission to the postoperative unit; in addition, they should have undergone a preoperative creatinine concentration assessment within 30 days prior to surgery and at least one creatinine measurement performed within 48 h postoperatively. Patients with preoperative stage V chronic kidney disease who were undergoing hemodialysis were excluded.

### Preoperative blood pressure management

The Japanese Society of Anesthesiologists (JSA)-qualified anesthesiologist in charge of each operation decided on each patient's medication regimen prior to sur-

gery, and antihypertensive medications were continued until the morning of the operation. Standard noninvasive monitoring was applied to all patients who underwent general anesthesia. In cases where the systolic blood pressure exceeded 200 mmHg at the first measurement, the attending anesthesiologist was consulted. Wax et al.<sup>2)</sup> reported that when the systolic blood pressure increased before the induction of anesthesia, the incidence of postoperative myocardial damage also increased. Interestingly, when the systolic blood pressure exceeds 200 mmHg, the incidence of myocardial damage rises sharply. The merits and risks of postponing surgery for these patients were discussed by the attending anesthesiologist and the surgeons. The final decision whether to proceed or not was based on mutual agreement.

#### **Anesthetic management**

When a participant underwent general anesthesia and surgery as planned, the choice of the anesthetic management procedure performed was at the discretion of the attending anesthesiologists. When an arterial catheter was used, the blood pressure was measured at the radial artery with a 22-gauge catheter with a transducer (Edwards Lifesciences, Tokyo, Japan) adjusted to the height of the right atrium by the anesthesiologist in charge of each surgery; for all cases, measurements were recorded directly in an electronic anesthetic chart (Cap-2000; Nihon Koden Corporation) over 1-2 min. When noninvasive blood pressure monitoring (Nihon Kohden Corporation) was used, the blood pressure was measured at the upper arm and recorded in an electronic anesthetic chart over 2-5 min. When the blood pressure was not recorded, the last artifact-free blood pressure measurement was carried forward.

#### **Outcome measures**

We investigated the number of patients who developed postoperative AKI, MI, and ischemic stroke. Patients were determined to have AKI when they had a 1.5-fold or 0.3 mg/dL increase in their serum creatinine concentration compared to preoperative measurements within 2 days postoperatively. We referred to the KDIGO criteria<sup>10)</sup> to determine the definition of postoperative AKI; however, the evaluation period was set to 48 h after the surgery because many previous reports<sup>4,11,12)</sup> have defined postoperative AKI based on the serum creatinine levels within 2 days postoperatively. Patients were determined to have MI or ischemic stroke when their electronic medical records indicated that they received definitive diagnoses

during hospitalization by a cardiologist and a neurologist.

#### **Data collection**

The patients' preoperative demographic data were obtained from electronic medical records, including age, sex, body mass index, American Society of Anesthesiologists physical status, preoperative comorbidities (e.g., hypertension, diabetes, liver disease, angina, coagulopathy, pulmonary circulation disorder), preoperative hemoglobin concentration, chronic kidney disease severity calculated from the estimated glomerular filtration rate (eGFR),<sup>13)</sup> and preoperative medication use (i.e., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium blockers, beta-blockers, and diuretics). Patient comorbidities were identified in electronic medical records based on the issue lists written by the JSA-qualified anesthesiologist who was in charge of the preoperative outpatient clinic. Intraoperative data, except for blood pressure measurements, were obtained from electronic anesthetic charts, which included the amount of fluids received, transfusion of erythrocytes, volume of blood loss, and duration of surgery.

#### **Statistical analyses**

The data were analyzed using EZR ("Easy R") version 1.42 software (Jichi Medical University Saitama Medical Center, Saitama, Japan). The continuous and categorical variables are presented as medians with the 25th and 75th percentiles, and as numbers and percentages, respectively. For comparisons of the continuous variables, the nonparametric Mann-Whitney U test was used. Fisher's exact test or chi-squared test was used for categorical values.

We investigated the associations between several blood pressure-related factors and postoperative AKI; we primarily investigated the duration for which patients experienced MAPs of <65, 70, 75, 80, and 85 mmHg in the period between tracheal intubation and surgery initiation. We also investigated the durations for which patients experienced MAPs of <65, 70, and 75 mmHg in the period between the initiation of surgery and the end of anesthesia. These MAPs were selected based on thresholds shown to be associated with an increased risk of harm in previous studies.<sup>6,14)</sup> In addition, we stratified the period under anesthesia induction from tracheal intubation to surgery initiation, and from surgery initiation to the end of anesthesia, similar to that reported by Maheshwari et al.,<sup>14)</sup> as the factors that influence blood pressure are different in each period. Especially, the blood pressure in the former period is affected only by anesthesia, but that in the latter period is

Table 1 Modified perioperative risk score for postoperative acute kidney injury

Risk factor	Points in model
Obesity [BMI (kg/m <sup>2</sup> )>30.0]	1
Liver disease	1
Coagulopathy	1
Hypertension	1
Diabetes	1
Weight loss	1
Pulmonary circulation disorders	1
Anemia (hemoglobin concentration range, g/dL) (female, <12.0; male, <13.0)	2
CKD severity (eGFR range, mL/min/1.73 m <sup>2</sup> )	
Stage 2 (60–89)	2
Stage 3a (45–59)	3
Stage 3b (30–44)	3
Stage 4 (15–29)	4
Surgical body region	
Elevated risk (all regions except ENT, upper extremity, spine)	3
ASA class	
ASA class 3	3
ASA class 4	4
ASA class 5	5
Anesthesia duration >1 h <sup>a</sup>	h/4
General anesthesia	1

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ENT, ear, nose, throat; ASA, American Society of Anesthesiologists physical status

<sup>a</sup> One point for every 4 h

affected by the effects of anesthesia and those of surgery (i.e., bleeding, surgical invasion, and inflammation).

To adjust for the effects of factors other than blood pressure, we applied a perioperative risk scoring model with minor modifications<sup>5)</sup> (Table 1). As the effects of the MAP were assessed independently in this study, items other than blood pressure were used to calculate the risk score. Second, based on these analyses, the factors considered to be clinically associated with postoperative AKI were extracted and subjected to multivariate logistic regression analysis. The intraoperative fluid volume was reported to be associated with postoperative AKI in some previous reports;<sup>15, 16)</sup> as this was not included in Michael's risk score calculation, we included it as a covariate, as well as the modified risk score, in the multivariate logistic regression analysis. In our study, as the number of explanatory variables that could be used for multivariate analysis was limited, clinically significant variables were selected in advance and used as explanatory variables. The results of the logistic regression analysis are described as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). A P-

value <0.05 was considered statistically significant.

## Results

From January 2014 to December 2018, 308 patients were screened for eligibility, and 274 patients were ultimately enrolled (Fig. 1). During the perioperative phase, 35 (12.8%) patients developed AKI and one (0.36%) patient experienced an MI and ischemic stroke. As few patients developed MI and ischemic stroke, we analyzed only the association between MAP and postoperative AKI to examine the relationships between these postsurgical complications and MAP during anesthesia.

The perioperative characteristics of the patients, modified risk scores, and surgical characteristics are shown in Table 2. Patients with AKI were more likely to be older, male, and have diabetes mellitus and lower eGFRs, preoperatively. The modified risk score was higher in patients with AKI than in those without. Table 3 shows the durations where the MAPs were <65, 70, 75, 80, and 85 mmHg during the period between intubation and incision, and the corresponding durations where the MAPs were <65, 70,

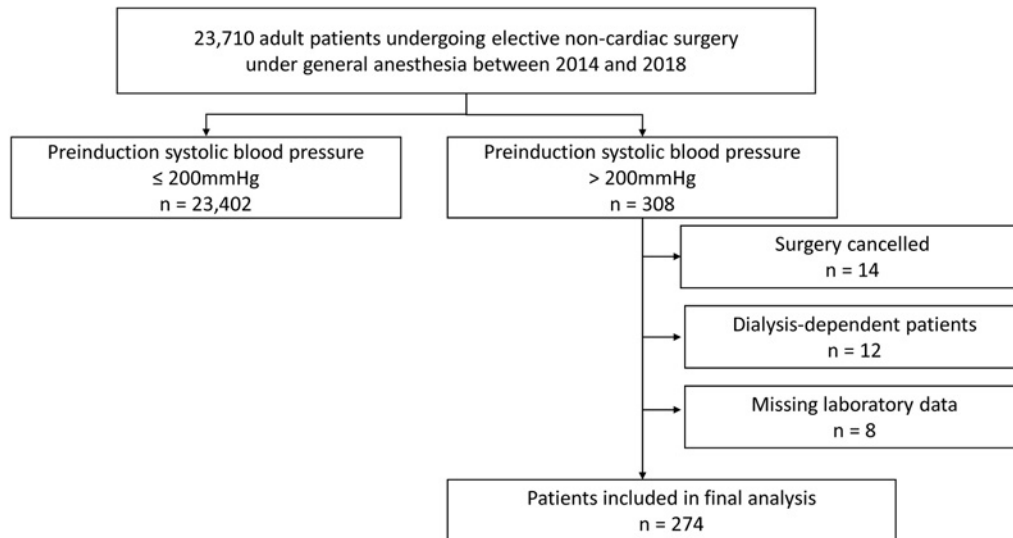


Fig. 1 Flowchart showing the selection of 274 patients for analysis of the association between preinduction extreme hypertension and postoperative outcomes.

and 75 mmHg in the period between incision and the end of anesthesia, in patients with and without postoperative AKI. The durations where the MAPs were <65, 70, and 75 mmHg during the period between intubation and incision were significantly longer in the AKI group than in the non-AKI group ( $P < 0.01$ ). Multivariate regression analysis revealed a statistically significant association between the duration, in which the MAP was <75 mmHg, and the incidence of postoperative AKI (aOR = 1.04, CI = 1.02-1.07,  $P < 0.001$ ) (Table 4). During the period from the start of surgery to the end of anesthesia, there was no significant association between the MAP and increased risk of AKI; therefore, multivariate analysis was not performed.

## Discussion

We investigated the incidence of postoperative cerebral infarction, MI, and AKI in patients who had extreme hypertension, defined as a systolic blood pressure >200 mmHg, before the induction of general anesthesia for elective non-cardiac surgery. Postoperative MI and cerebral infarction occurred in only one case (0.36%), whereas postoperative AKI occurred in 35 cases (12.8%). We found that the duration for which patients experienced a MAP <75 mmHg during the period from intubation to the start of surgery was an independent risk factor for postoperative AKI development, after adjusting for the respective preoperative risk factors.

In several patients, the blood pressure could rise before the induction of anesthesia, but few experience a systolic

blood pressure >200 mmHg. Although the mechanism is unknown, some reports indicate that preinduction hypertension is a risk factor for postoperative complications. Wax et al.<sup>2)</sup> reported that in patients with preinduction hypertension (systolic and diastolic blood pressures >180 and >90 mmHg, respectively) undergoing elective, non-cardiac surgery, increased preinduction systolic hypertension (per 10 mmHg) was an independent risk factor for postoperative cardiac injury and in-hospital mortality. This was especially true when the preinduction systolic blood pressure exceeded 200 mmHg, as the occurrence of postoperative cardiac injury and in-hospital mortality was more pronounced. Abdelmalak et al.<sup>3)</sup> reported that the composite incidence of postoperative complications, including renal, cardiovascular, and neurological complications, was 14.7% for patients with severe preinduction hypertension; they also showed that preinduction systolic hypertension (>160 mmHg) with a diastolic blood pressure >75 mmHg in patients who had a history of high Revised Cardiac Risk Index scores and underwent elective non-cardiac surgery was an independent risk factor for postoperative complications. Moreover, it has been reported that patients whose blood pressures fluctuate abnormally owing to external stimuli, such as those associated with stress, may experience baroreceptor reflex impairments due to arteriosclerosis.<sup>17-19)</sup> Therefore, patients exhibiting extreme hypertension under stress, which can occur before the induction of anesthesia, may also potentially have arteriosclerosis.

Table 2 Preoperative and intraoperative characteristics of patients with and without postoperative acute kidney injury

	Patients with AKI (n = 35)	Patients without AKI (n = 239)	P-value
Age (years)	75 (69–79.5)	71 (64–77)	0.031 *
Male sex, n (%)	24 (67)	105 (40)	0.003 *
Body mass index (kg/m <sup>2</sup> )	24.0 (21.3–26.9)	23.34 (21.4–26.2)	0.222
ASA, n (%)	6 (17)	33 (14)	0.240
I	2 (5.7)	13 (5.4)	1
II	27 (77.1)	193 (80.8)	0.650
III	6 (17.1)	33 (13.8)	0.611
Comorbidities, n (%)			
Chronic kidney disease	4 (11)	10 (3.8)	0.076
Ischemic heart disease	5 (14)	15 (5.8)	0.079
Diabetes mellitus	14 (39)	54 (21)	0.021 *
Hypertension	22 (61)	156 (60)	1
Liver disease	1 (2.8)	15 (6.3)	0.752
Coagulopathy	0 (0)	0 (0)	1
Pulmonary hypertension	0 (0)	0 (0)	1
Preoperative drug use, n (%)			
ACEI/ARB	13 (36)	68 (26)	0.232
Calcium channel blocker	15 (42)	88 (34)	0.350
β-blocker	5 (14)	19 (7.3)	0.192
Diuretic	4 (11)	11 (4.2)	0.101
Preoperative laboratory values			
Hemoglobin concentration (g/dL)	12.9 (11.4–14.2)	13.0 (11.8–14.0)	0.561
eGFR (mL/min/1.73 m <sup>2</sup> )	54.8 (44.7–67.5)	70.3 (58.0–78.9)	<0.001 *
Intraoperative characteristics			
Fluid volume administered (mL)	1,400 (875–2,100)	1,150 (760–1,800)	0.074
Erythrocyte transfusion volume (mL)	0 (0–0)	0 (0–0)	0.193
Blood loss volume (mL)	42 (0–150)	14 (0–120)	0.233
Duration of surgery (min)	175 (72.5–246)	125 (82–194)	0.122
Modified risk score	6 (5–7)	5 (4–6)	0.002 *

Values are presented as numbers (percentages) or medians (interquartile ranges). P-values for continuous data were calculated using the Mann-Whitney U test. P-values for discrete values were calculated using the chi-squared test.

Abbreviations: AKI, acute kidney injury; ASA, American Society of Anesthesiologists physical status; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; eGFR, estimated glomerular filtration rate

\*Statistically significant difference (P<0.05)

In our study, it was suggested that a MAP <75 mmHg during the period from intubation to the start of surgery may increase the risk of postoperative AKI in patients with preinduction hypertension. Many studies have stated that hypotension during anesthesia is associated with postoperative complications, and each report has identified a blood pressure threshold associated with postoperative complications. Especially, Sun et al.<sup>4)</sup> investigated the relationship between blood pressure during anesthesia and the incidence of postoperative AKI in patients undergoing elective, non-cardiac surgery and reported that a MAP

<60 mmHg for 11-20 min or a MAP <55 mmHg for >10 min was a significant risk factor. Walsh et al.<sup>18)</sup> investigated the relationship between the MAP during anesthesia and postoperative AKI in patients undergoing non-cardiac surgery with an eGFR >60 mL/min/1.73 m<sup>2</sup> and reported that a MAP <55 mmHg was a risk factor for postoperative AKI. Additionally, Salmasi et al.<sup>6)</sup> investigated the same relationship in patients with the same eGFR and reported that a MAP <65 mmHg was a risk factor for postoperative AKI. These reports demonstrated the importance of maintaining a MAP >55-65 mmHg dur-

Table 3 Mean arterial pressure during anesthesia in patients with and without postoperative acute kidney injury

	Patients with AKI	Patients without AKI	P-value
Duration of MAP below various thresholds before incision (min)			
<65 mmHg	7 (4–21)	2 (0–10)	<0.001 *
<70 mmHg	16 (7–30)	7 (0–15)	<0.001 *
<75 mmHg	27 (11–34)	12 (2–24)	<0.001 *
<80 mmHg	32 (15–38)	27 (19–44)	0.122
<85 mmHg	33 (24–40)	32 (25–46)	0.164
Duration of MAP below various thresholds after incision (min)			
<65 mmHg	20 (5–33.5)	11 (0–31.0)	0.320
<70 mmHg	51 (14–111)	43 (12–101)	0.623
<75 mmHg	90 (35–136)	73 (23–143)	0.643

Values are presented as the medians (interquartile ranges). P-values were calculated using the Mann–Whitney U test.

Abbreviations: AKI, acute kidney injury; MAP, mean arterial pressure

\*Statistically significant difference ( $P < 0.05$ )

Table 4 Multivariate analysis of risk factors for postoperative acute kidney injury during anesthesia

	Adjusted OR (95% CI)	P-value
Modified risk score	1.26 (1.05–1.50)	0.013
Intraoperative fluid volume	1.00 (1.00–1.00)	0.807
Duration for which MAP was <75 mmHg before incision	1.04 (1.02–1.07)	<0.001 *

Abbreviations: OR, odds ratio; CI, confidence interval; MAP, mean arterial pressure

\*Statistically significant difference ( $P < 0.05$ )

ing anesthesia.

Maheshwari et al.<sup>14)</sup> investigated the relationship between postoperative AKI and hypotension during the periods from the induction of anesthesia to surgery initiation, and from surgery initiation to the end of anesthesia in patients undergoing non-cardiac surgery. In that report, hypotension was defined as a MAP <65 mmHg. They reported that the group with postoperative AKI experienced a longer duration of hypotension during both the anesthesia periods compared to the group without postoperative AKI.

We investigated the relationship between these two periods and found that the durations when the MAP was <65, 70, and 75 mmHg were significantly longer in the AKI group than in the non-AKI group. In addition, regarding the duration of having a MAP <75 mmHg, we performed multivariate analysis using the modified risk score and intraoperative fluid volume as covariates. This analysis showed that the duration of having a MAP <75 mmHg during the period from intubation to surgery initiation was

an independent risk factor for postoperative AKI. This MAP was >65 mmHg that Maheshwari et al.<sup>14)</sup> defined as the level of hypotension associated with an increased risk of postoperative AKI.

Almeida et al.<sup>20)</sup> investigated the changes in eGFR by intravenously injecting nitroprusside into patients with severe hypertension who had a diastolic blood pressure >120 mmHg to rapidly reduce their blood pressure to a normal range. In these patients, a decreased eGFR was observed even in the normal blood pressure range. They reported that in patients with severe hypertension, the vasodilatory capacity may be impaired owing to anatomical or functional defects in preglomerular blood vessels; therefore, the automatic regulation of blood flow to counteract a sudden drop in blood pressure may be impaired. The results of our study suggested that the vasodilatory ability to respond to a rapid decrease in blood pressure may be impaired in patients with severe hypertension pre-anesthetic induction. Therefore, a rapid decrease in the MAP after the induction of anesthesia may result in a de-



crease in the GFR even when the MAP is  $>65$  mmHg, which is the typical threshold associated with the risk of postoperative AKI. Conversely, there was no significant difference in durations between the AKI and non-AKI groups for all MAP thresholds for the period from the start of surgery to the end of anesthesia. Few reports have investigated the relationship between the MAP during this period and postoperative AKI incidence. Maheshwari et al.<sup>14)</sup> also reported that a MAP  $<65$  mmHg during the period from surgery initiation to the end of anesthesia was a risk factor for postoperative AKI; however, we do not know why we did not observe the same association during this period in our study.

We found that a MAP  $<75$  mmHg during the period from intubation to the start of surgery was an independent risk factor for postoperative AKI in patients with a systolic blood pressure  $>200$  mmHg before anesthesia. As the blood pressure during this period is affected strongly by anesthetic management, we recommend that anesthesiologists observe the blood pressure carefully and employ early interventions, such as the administration of vasopressors and infusion solutions, to optimize the circulating blood volume and counteract decreases in the MAP.

### Limitations

First, this was a single-center, retrospective study. Second, to investigate the incidence of postoperative AKI, we assessed only patients who underwent blood tests of serum creatinine concentrations at least once within 48 h from the end of surgery. Thus, we may have overlooked patients whose serum creatinine levels were elevated after this period. Third, as the incidence of MI and cerebral infarction in our study was too low to assess the associations with the MAP during anesthesia, we were unable to analyze these two complications owing to the low diagnostic sensitivity. Fourth, Wax et al.<sup>2)</sup> also reported that delaying surgery did not reduce the incidence of postoperative complications, and thus, our institutional policy of delaying surgery (preinduction systolic blood pressure  $>200$  mmHg) remains controversial. Fifth, there may have been factors that could have impacted the risk of postoperative AKI, apart from those analyzed as covariates in the multivariate analysis. To adjust for the effects of perioperative factors other than blood pressure, we employed the perioperative risk scoring model developed by Michael et al.,<sup>6)</sup> with some minor modifications. As that was a large-scale, multicenter study, we considered the scoring model to be a reliable method to adjust the effect of perioperative

risk factors other than blood pressure. Sixth, we observed that there was no association between intraoperative hypotension and the incidence of postoperative AKI. This may be because of the small number of cases, which may have reduced the statistical power compared with that reported in previous works.

### Conclusion

In patients with extreme hypertension with a systolic blood pressure  $>200$  mmHg before the induction of anesthesia for elective non-cardiac surgery, a MAP  $<75$  mmHg during the period from intubation to the start of surgery may be an independent risk factor for postoperative AKI. Larger-scale studies are needed to confirm the generalizability of these findings.

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**Author's contribution:** The primary author contributed to the study design development, data collection, data interpretation, and writing of the manuscript.

Dr. Satomoto contributed to the study design development and writing of the manuscript.

Mr. Hanai contributed to data interpretation.

Dr. Ochiai contributed to the study design development and writing of the manuscript.

Dr. Kotake contributed to data interpretation and writing of the manuscript.

**Ethics statement:** The studies involving human participants were reviewed and approved by the Ethics Committee of the Toho University Medical Center Omori Hospital (approval number: M19135).

**Conflicts of interest:** Dr. Ochiai received speaker's fees and consulting fees from Nihon Koden Corp.

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