Can J Anesth/J Can Anesth (2024) 71:343–352
https://doi.org/10.1007/s12630-023-02653-6

REPORTS OF ORIGINAL INVESTIGATIONS

Association between postinduction hypotension and postoperative mortality: a single-centre retrospective cohort study

Association entre hypotension post-induction et mortalité postopératoire : une étude de cohorte rétrospective monocentrique

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Received: 14 April 2023 / Revised: 12 August 2023 / Accepted: 16 August 2023 / Published online: 21 November 2023

Abstract

Purpose *We aimed to elucidate whether postinduction hypotension (PIH), defined as hypotension between anesthesia induction and skin incision, and intraoperative hypotension (IOH) are associated with postoperative mortality.*

Methods *We conducted a retrospective cohort study of adult patients with an ASA Physical Status I–IV who underwent noncardiac and nonobstetric surgery under general anesthesia between 2015 and 2021 at Nagoya City University Hospital. The primary and secondary outcomes were 30-day and 90-day postoperative mortality, respectively. We calculated four hypotensive indices (with time proportion of the area under the threshold being the primary exposure variable) to evaluate the association between hypotension (defined as a mean blood pressure < 65 mm Hg) and mortality using multivariable logistic regression models. We used propensity score matching and RUSBoost (random under-sampling and boosting), a machine-learning model for imbalanced data, for sensitivity analyses.*

Results *Postinduction hypotension and IOH were observed in 82% and 84% of patients, respectively. The 30-day and 90-day postoperative mortality rates were 0.4% (52/14,210) and 1.0% (138/13,334), respectively. Postinduction hypotension was not associated with 30-day mortality (adjusted odds ratio [aOR], 1.03; 95% confidence interval [CI], 0.93 to 1.13; P = 0.60) and 90-day mortality (aOR, 1.01; 95% CI, 0.94 to 1.07; P = 0.82). Conversely, IOH was associated with 30-day mortality (aOR, 1.19; 95% CI, 1.12 to 1.27; P < 0.001) and 90-day mortality (aOR, 1.12; 95% CI, 1.06 to 1.19; P < 0.001). Sensitivity analyses supported the association of IOH but not PIH with postoperative mortality.*

Conclusion *Despite limitations, including power and residual confounding, postoperative mortality was associated with IOH but not with PIH.*

Résumé

Objectif *Nous avons cherché à déterminer si l'hypotension post-induction (HPI), définie comme une hypotension entre l'induction de l'anesthésie et l'incision cutanée, et l'hypotension peropératoire (HPO) étaient associées à la mortalité postopératoire.*

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-023-02653-6.

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Méthode *Nous avons mené une étude de cohorte rétrospective de patient·es adultes ayant un statut physique I-IV selon l'ASA et ayant bénéficié d'une chirurgie non cardiaque et non obstétricale sous anesthésie générale entre 2015 et 2021 à l'Hôpital universitaire de la ville de Nagoya. Les critères d'évaluation principal et secondaire étaient la mortalité postopératoire à 30 et 90 jours, respectivement. Nous avons calculé quatre indices d'hypotension (la proportion temporelle de la zone sous le seuil étant la principale variable d'exposition) pour évaluer l'association entre l'hypotension (définie comme une tension artérielle moyenne < 65 mm Hg) et la mortalité à l'aide de modèles de régression logistique multivariée. Nous avons utilisé l'appariement par score de propension et le RUSBoost (sous-échantillonnage et boosting aléatoire), un modèle d'apprentissage automatique pour les données déséquilibrées, pour les analyses de sensibilité.*

Résultats *Une HPI et une HPO ont été observées chez 82 % et 84 % des patient·es, respectivement. Les taux de mortalité postopératoire à 30 et 90 jours étaient respectivement de 0,4 % (52/14 210) et de 1,0 % (138/13 334). L'hypotension post-induction n'était pas associée à la mortalité à 30 jours (rapport de cotes ajusté [RCa], 1,03; intervalle de confiance [IC] à 95 %, 0,93 à 1,13; P = 0,60) et à la mortalité à 90 jours (RCa, 1,01; IC 95 %, 0,94 à 1,07; P = 0,82). À l'inverse, l'HPO était associée à une mortalité à 30 jours (RCa, 1,19; IC 95 %, 1,12 à 1,27; P < 0,001) et à la mortalité à 90 jours (RCa, 1,12; IC 95 %, 1,06 à 1,19; P < 0,001). Les analyses de sensibilité ont confirmé l'association de l'HPO, mais pas de l'HPI, avec la mortalité postopératoire.*

Conclusion *Malgré les limitations, y compris la puissance et persistance de facteurs confondants, la mortalité postopératoire était associée à l'hypotension peropératoire mais pas à l'hypotension post-induction seule.*

Keywords intraoperative hypotension · noncardiac surgery · postinduction hypotension · postoperative mortality

Intraoperative hypotension (IOH), conventionally defined as mean arterial pressure (MAP) < 60–70 mm Hg or systolic blood pressure (SBP) < 100 mm Hg, is associated with postoperative acute kidney injury (AKI), myocardial injury, and mortality.[1–9] In two randomized controlled trials, interventions to prevent IOH did not reduce postoperative organ injuries and mortality.[10,11]

Compared with IOH, postinduction hypotension (PIH) is defined as hypotension occurring between anesthesia induction and skin incision.[5] Postinduction hypotension has greatly interested anesthesiologists because it is unaffected by surgery and must be controlled by themselves. Several investigators have attempted to predict PIH using statistical and machine-learning models.[12–15] Unlike IOH, the effect of PIH on postoperative patient outcomes has not been thoroughly examined. To our knowledge, only one study reported that PIH and IOH had a positive correlation with postoperative AKI.[5] Thus, whether PIH affects the hardest endpoint, i.e., postoperative mortality, is unclear.

We hypothesized that PIH, as well as IOH, would be associated with postoperative mortality. Thus, we aimed to elucidate the relationship between PIH and postoperative mortality in a retrospective seven-year cohort of a university hospital in Japan. We sought to reduce confounding of PIH on postoperative mortality using propensity score matching (PSM) models. Furthermore, we aimed to use the random under-sampling and boosting (RUSBoost) model, a decision tree type of machine-learning model designed for classifying imbalanced data, to explore the effects of PIH and IOH on mortality.[16]

Methods

This single-centre retrospective cohort study was approved by the Nagoya City University Graduate School of Medical Sciences and the Nagoya City University Hospital Institutional Review Board (60-21-0155, 15 March 2022). The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17] A data analysis and statistical plan was written after the data were accessed.

Participants

We included adult patients (aged ≥ 18 yr) with an American Society of Anesthesiologists Physical Status (ASA-PS) I–IV who underwent noncardiac and nonobstetric surgery with duration of ≥ 60 min under general anesthesia in Nagoya City University Hospital between January 2015 and December 2021. Additional inclusion criteria were patients without mechanical circulatory support before and during the surgery, patients who experienced 5–120 min of anesthesia induction time, defined as the duration between induction and skin incision,[5] and patients who underwent tracheal intubation or supraglottic airway device insertion at least once. After the automated extraction of eligible patients using the anesthesia information management system (AIMS), patients with incorrect data (ASA-PS classification or surgical type) or missing characteristic

data were excluded by reviewing the electronic medical records (EMR) according to the following rules. First, patients who underwent surgery for intracranial hemorrhage with mass effect or aortic rupture were reclassified as ASA-PS V and excluded from the study.[18] Second, patients who actually underwent cardiac or obstetric surgery were excluded. Finally, patients with missing data (characteristic data, blood pressure [BP] values, or postoperative outcomes) were excluded. If more than one surgical record met the inclusion criteria for the same patient, the most recent one was analyzed.

Data sources

We collected patient data from the EMR, an AIMS (Fortec ORSYS, Koninklijke Philips N.V., Amsterdam, Netherlands), and a diagnosis procedure code (DPC) database of our hospital. All data were obtained between June and December 2022. The DPC database is used for the medical fee billing of inpatients in Japan and has been used in several epidemiological studies.[19–21] The DPC database includes administrative claims data and patient data, such as diagnoses and comorbidities at admissions identified by the International Classification of Diseases 10th Revision (ICD-10) codes, surgical procedures identified by the Japanese original codes (K codes), and malignancy.[20] A previous validation study of the DPC database reported that malignancy has 83.5% sensitivity and 97.7% specificity.[22]

Variables

Patient characteristics, including age, sex, height, weight, body mass index (BMI), and ASA-PS class, were collected from the AIMS. Outliers in the patient height and weight data with $>$ 3 standard deviations (SDs) were manually checked to determine if they were identical to the EMR data. If the outliers were erroneous and the correct values were obtained from the EMR, they were corrected. In addition, patients with a BMI of 30–40 kg m^{-2} and those with a BMI $\geq$ 40 kg m^{-2} were reclassified to be at least ASA-PS $\geq$ II and $\geq$ III, respectively.[18] Anesthetic and surgical data, such as duration, emergency surgery, anesthesia type (total intravenous or inhalational), neuraxial anesthesia (epidural or spinal), and peripheral nerve block, were extracted from the EMR and AIMS. Furthermore, the K codes were extracted from the DPC database, and each surgery was classified for three-level risk scores, i.e., low, intermediate, and high risk, defined by the European Society of Cardiology and the European Society of Anaesthesiology.[19,23]

The most recent blood testing data within 90 days preoperatively were extracted from the EMR. Preoperative medication types were also extracted from the EMR. To calculate the Charlson's comorbidity index, the ICD-10 codes for comorbidities and malignancies were extracted from the DPC database.[24]

Endpoints

The primary and secondary endpoints were the 30-day and 90-day mortality, respectively. These endpoints were extracted from the EMR. For patients discharged or transferred to another centre, the last outpatient visit data and mortality records written in the medical information forms from other centres were investigated.

Preprocessing of blood pressure data

Data preprocessing of BP is described in Electronic Supplementary Material (ESM) eAppendix. Hypotension was defined as a MAP below 65 mm Hg.[1,2,5–8] We used absolute values because there was no benefit to using relative rather than absolute thresholds for postoperative organ injuries in a large retrospective study.[8] Additionally, we used a threshold of 65 mm Hg based on a systemic review that showed an increased risk of organ injuries with MAP $<$ 65 mm Hg.[25] To quantitatively evaluate the degree of hypotension, the following four indices were calculated: duration, time proportion (hypotensive duration divided by the evaluated duration), area under the curve (AUC) of BP values $<$ 65 mm Hg, and the proportion of AUC (AUC divided by the evaluated duration [anesthesia induction time or surgical duration]). The proportion of AUC was defined as the most important exposure because it included the severity and duration of hypotension and was time-adjusted.

Statistical analysis

Data are reported as number (proportion) for categorical data and median [interquartile range] for continuous data. For comparisons of two groups, we used Fisher's exact test for binomial variables and the Mann–Whitney *U* test for continuous variables.

Multivariable logistic regression model

As a primary analysis, we used multivariable logistic regression models to reveal the relationship between hypotension and postoperative mortality. No sample size was calculated. The total number of patients in our cohort was expected to be approximately 16,000 cases. Based on recent reports, we assumed that the incidence rates of 30-day and 90-day mortality in our cohort would be 0.3%–0.5% and 0.8%–1.2%, respectively.[1,26–28] Considering a 10% dropout rate of patients because of missing variables,

30-day and 90-day mortality events were estimated as 40–70 and 100–180, respectively. Considering the model stability, four explanatory variables for 30-day mortality and eight for 90-day mortality classification were included in the logistic regression models.[29] From a clinical standpoint and previous literature, age, ASA-PS (dichotomized as ASA-PS $<$ III and $\geq$ III), emergency, and surgical risk (dichotomized as low risk and others) were initially selected as explanatory variables for the 30-day mortality classification models.[14,15] For the 90-day mortality models, age, sex, BMI, ASA-PS (four classes), emergency, surgical risk (three classes), anesthesia type, and neuraxial anesthesia were prespecified.

Sensitivity analyses

We performed sensitivity analyses using the PSM and RUSBoost models for the robustness of the results. Patients whose DPC data were unavailable or whose induction time was $<$ ten minutes were excluded. Missing values of the blood tests were imputed by the mean values.

Propensity score matching model

We compared postoperative mortality rates between the two groups divided by the degree of PIH using PSM. For intuitive understanding and evidence of a significant increase in mortality in MAP $<$ 65 mm Hg for ten minutes,[25] patients were divided using the duration of hypotension, i.e., $<$ 10 or $\geq$ 10 min of PIH. The propensity scores were calculated using 11 patients' characteristics, 13 types of preoperative medication, 12 types of blood testing data, and Charlson's comorbidity index score for each 30-day and 90-day mortality model. These 37 variables were determined based on clinical knowledge and previous literature. Propensity score matching was conducted with a 1:1 ratio by nearest-neighbour matching using 0.2 of the caliper width for the SD difference in the propensity scores without replacement.

RUSBoost model

We created machine learning models to predict postoperative mortality in each of the four hypotensive indices, and we evaluated the effects of hypotension using feature importance. As postoperative mortality rates were expected between 0.3% and 1.2% in our cohort, we used the RUSBoost model to classify imbalanced data.[16] The RUSBoost algorithm consists of random undersampling and boosting algorithms. In these algorithms, the major class (survivor) is undersampled to a defined ratio to the minor class (deceased), and multiple models are trained sequentially to improve the classification performance.

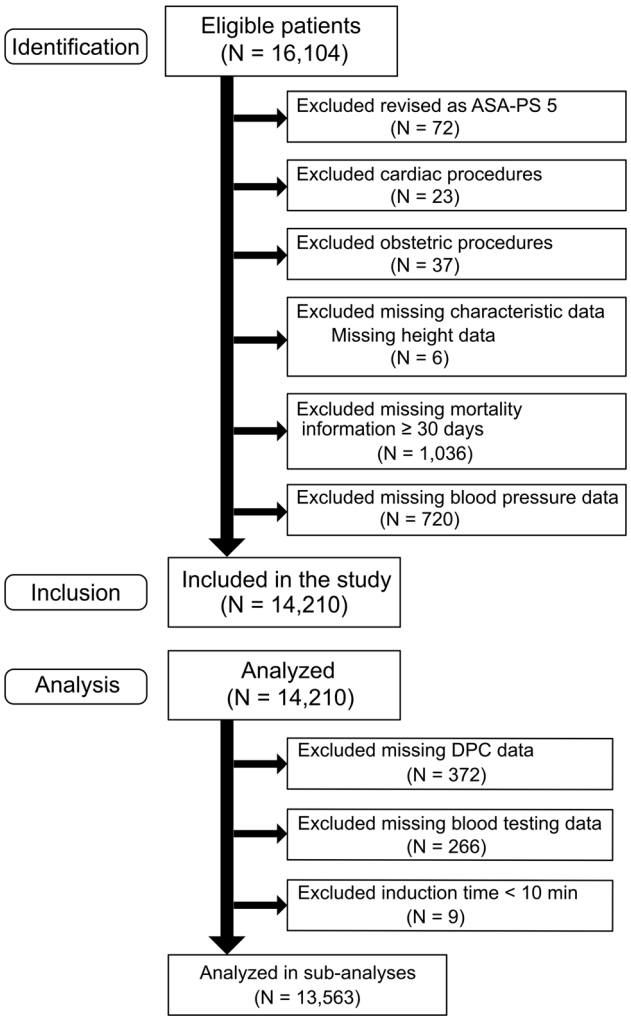

Fig. 1 Study flow chart
ASA-PS = American Society of Anesthesiologists Physical Status; DPC = diagnostic procedure codes

Feature importance measures how much a feature contributes to classifying a target and is used to interpret the relationship among variables.[30] To construct RUSBoost models, patients were divided into training and test cohorts with a 7:3 ratio. Hyperparameters such as the learning rate and max depth were determined by GridSearch with five-fold cross-validation. Feature importance values were calculated for the patients' characteristics and hypotensive indices of PIH and IOH. The performance of the created RUSBoost models for predicting postoperative mortality was assessed by the test data set using precision, recall, geometric mean (G-mean), and area under the precision–recall curve, considering the imbalanced nature of the outcome. The G-mean is the square root of the product of sensitivity (recall) and specificity. In total, 100 repeated trials were performed to precisely evaluate feature importance and model performance.

Table 1 Baseline and perioperative characteristics of the groups with and without postinduction and intraoperative hypotension

	Postinduction hypotension			Intraoperative hypotension		
	Any *N* = 11,627	None *N* = 2,583	SMD	Any *N* = 11,975	None *N* = 2,235	SMD
Age (yr), median [IQR]	67 [53–75]	57 [44–70]	0.43	67 [52–75]	58 [45–70]	0.38
Female, *n*/total *N* (%)	6,316/11,627 (54%)	964/2,583 (37%)	0.35	6,308/11,975 (53%)	972/2,235 (44%)	0.19
Height (cm), median [IQR]	160 [153–166]	164 [157–170]	0.40	160 [153–166]	162 [156–169]	0.29
Weight (kg), median [IQR]	57 [50–66]	63 [54–71]	0.37	58 [50–66]	62 [53–70]	0.29
BMI ($kg \cdot m^{-2}$), median [IQR]	23 [20–25]	23 [21–26]	0.20	23 [20–25]	23 [21–26]	0.17
ASA-PS, *n*/total *N* (%)			0.18			0.21
I	1,948/11,627 (17%)	607/2,583 (24%)		2,033/11,975 (17%)	522/2,235 (23%)	
II	8,123/11,627 (70%)	1,706/2,583 (66%)		8,310/11,975 (69%)	1,519/2,235 (68%)	
III	1,434/11,627 (12%)	248/2,583 (10%)		1,502/11,975 (13%)	180/2,235 (8%)	
IV	122/11,627 (1%)	22/2,583 (0.9%)		130/11,975 (1%)	14/2,235 (0.6%)	
Emergency, *n*/total *N* (%)	840/11,627 (7%)	189/2,583 (7%)	0.004	876/11,975 (7%)	153/2,235 (7%)	0.02
TIVA, *n*/total *N* (%)	6,178/11,627 (53%)	1,241/2,583 (48%)	0.10	6,164/11,975 (52%)	1,255/2,235 (56%)	0.09
Neuraxial anesthesia, *n*/total *N* (%)	2,538/11,627 (22%)	292/2,583 (11%)	0.29	2,670/11,975 (22%)	160/2,235 (7%)	0.44
Epidural anesthesia, *n*/total *N* (%)	2,533/11,627 (22%)	289/2,583 (11%)	0.29	2,664/11,975 (22%)	158/2,235 (7%)	0.44
Spinal anesthesia, *n*/total *N* (%)	5/11,627 (0.04%)	3/2,583 (0.1%)	0.03	6/11,975 (0.05%)	2/2,235 (0.09%)	0.02
Peripheral nerve block, *n*/total *N* (%)	995/11,627 (9%)	196/2,583 (8%)	0.04	1,007/11,975 (8%)	184/2,235 (8%)	0.006
Surgical risk, *n*/total *N* (%)			0.13			0.30
Low	2,256/11,627 (19%)	556/2,583 (22%)		2,232/11,975 (19%)	580/2,235 (26%)	
Intermediate	8,482/11,627 (73%)	1,905/2,583 (74%)		8,784/11,975 (73%)	1,603/2,235 (72%)	
High	889/11,627 (8%)	122/2,583 (5%)		959/11,975 (8%)	52/2,235 (2%)	
Induction duration (min), median [IQR]	42 [33–52]	37 [30–46]	0.32	42 [33–52]	37 [30–46]	0.33
Anesthesia duration (min), median [IQR]	227 [159–327]	198 [143–268]	0.29	230 [162–330]	179 [134–246]	0.52
Surgery duration (min), median [IQR]	167 [106–259]	144 [97–209]	0.27	171 [108–263]	126 [87–186]	0.51

ASA-PS = American Society of Anesthesiologists Physical Status; BMI = body mass index; IQR = interquartile range; SMD = standardized mean difference; TIVA = total intravenous anesthesia

In addition, we performed sensitivity analyses using different definitions of hypotension and various subgroup analyses. All *P* values < 0.05 were considered statistically significant. Data preprocessing and model constructions were performed with Python 3.8.13 (Python Software Foundation, Wilmington, DA, USA) and scikit-learn 1.1.1,[A] and statistical analyses were performed with R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

From the AIMS, 16,104 patients with 19,255 surgical records were initially extracted (Fig. 1). After excluding 1,894 patients, 14,210 were finally analyzed (ESM eTable 1). In an overall cohort, 82% and 84% of patients experienced PIH and IOH, respectively. Patient characteristics are shown in Table 1.

The 30-day and 90-day postoperative mortality rates were 0.4% (52/14,210) and 1.0% (138/13,334), respectively. We found no differences in hypotensive indices for PIH between the groups with or without 30-day postoperative mortality (Table 2).

The multivariable logistic regression models revealed that 30-day postoperative mortality positively correlated with IOH (adjusted odds ratio [aOR], 1.19; 95% confidence interval [CI], 1.12 to 1.27; $P < 0.001$) but not with PIH (aOR, 1.03; 95% CI, 0.93 to 1.13; $P = 0.60$; Table 3). Moreover, 90-day postoperative mortality was also associated with three out of the four IOH indices but not with PIH.

[A] *Pedregosa F, Varoquaux G, Gramfort A, et al.* Scikit-learn: machine learning in Python. J Mach Learn Res 2011; 12: 2825–30. Available from URL: https://scikit-learn.org/stable/about.html#citing-scikit-learn (accessed August 2023).

Table 2 Number of hypotensive events and hypotension indices of the groups with and without 30-day and 90-day postoperative mortality

	Postoperative 30-day mortality			Postoperative 90-day mortality		
	No *N* = 14,158	Yes *N* = 52	*P* value	No *N* = 13,196	Yes *N* = 138	*P* value
Postinduction						
Any, *n*/total *N* (%)	11,583/14,158 (82%)	44/52 (85%)	0.72[a]	10,829/13,196 (82%)	117/138 (85%)	0.50[a]
Total duration (min), median [IQR]	11 [2–20]	13 [4–27]	0.17[b]	11 [2–20]	12 [4–23]	0.19[b]
Proportion (%), median [IQR]	27 [6–49]	31 [11–54]	0.25[b]	27 [6–49]	31 [9–52]	0.21[b]
AUC (mm Hg·min^{-1}), median [IQR]	53 [5–136]	98 [12–172]	0.07[b]	54 [6–137]	84 [14–162]	0.02[b]
Proportion of AUC (mm Hg), median [IQR]	1.31 [0.14–3.29]	2.01 [0.29–4.52]	0.08[b]	1.32 [0.14–3.29]	1.93 [0.33–4.01]	0.01[b]
Intraoperative						
Any, *n*/total *N* (%)	11,928/14,158 (84%)	47/52 (90%)	0.34[a]	11,139/13,196 (84%)	122/138 (88%)	0.24[a]
Total duration (min), median [IQR]	27 [5–71]	78 [14–138]	0.001[b]	27 [5–71]	56 [8–117]	< 0.001[b]
Proportion (%), median [IQR]	16 [3–43]	40 [10–82]	< 0.001[b]	16 [3–43]	31 [8–66]	< 0.001[b]
AUC (mm Hg·min^{-1}), median [IQR]	95 [10–328]	370 [31–899]	< 0.001[b]	96 [10–328]	281 [30–751]	< 0.001[b]
Proportion of AUC (mm Hg), median [IQR]	0.55 [0.06–1.89]	1.74 [0.33–5.83]	< 0.001[b]	0.56 [0.06–1.86]	1.44 [0.15–3.68]	< 0.001[b]

All models were calculated using the hypotensive definition as mean arterial pressure < 65 mm Hg

[a]Fisher's exact test

[b]Mann–Whitney *U* test

AUC = area under the curve; IQR = interquartile range

Sensitivity analyses

For the analyses using the PSM and RUSBoost models, 13,563 patients were included (Fig. 1). Missing blood-test data were imputed by mean values in 8% (1,099/13,563) patients (ESM eTable 2). In the sensitivity analyses of the cohorts, the 30-day and 90-day postoperative mortality rates were 0.4% (48/13,563) and 1.0% (132/12,763), respectively.

Electronic Supplementary Material eTables 3 and 4 show the characteristics before and after the PSM for 30-day and 90-day postoperative mortality. Electronic Supplementary Material eFigs 1–4 show the balance of covariates and the distribution of propensity scores before and after the PSM. After the PSM, we found no differences in 30-day (0.4% *vs* 0.3%; $P = 1$) and 90-day (1.1% *vs* 0.9%; $P = 0.38$) postoperative mortality between patients who experienced < 10 minutes and ≥ 10 minutes of PIH. Postinduction hypotension duration had sufficiently high correlation coefficients with the other three hypotensive indices (ESM eTable 5).

The performance of the RUSBoost models is summarized in ESM eTable 6. The feature importance values of the RUSBoost model for predicting 30-day and 90-day mortality are shown in Fig. 2 and ESM eFigs 5–11. The feature importance of IOH was higher than that of PIH in all evaluated models (Table 4). The five most important features in the 30-day prediction model using the hypotensive proportion of AUC were albumin, height, age, platelet, and prothrombin international normalized ratio (PT-INR; Fig. 2).

The results of the other sensitivity analyses are shown in ESM eTables 7–18 and ESM eFigs 12 and 13. Although the age < 60 yr subgroup showed no association between IOH and mortality (ESM eTable 10), the other subgroups showed trends consistent with the main results. The results were also consistent across a range of hypotensive definitions (ESM eTables 12–17).

Discussion

In this study, we evaluated the association between the timing of hypotension and postoperative mortality using a single-centre, seven-year electronic database with 14,210 patients. In the multivariable logistic regression analyses, 30-day and 90-day postoperative mortality rates were associated with IOH but not with PIH. The PSM models and feature importance of the machine-learning models

Table 3 Adjusted odds ratios of hypotension indices in the groups with 30-day and 90-day postoperative mortality

	Postoperative 30-day mortality[a] *n/N* = 52/14,210		Postoperative 90-day mortality[b] *n/N* = 138/13,334	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Postinduction				
Total duration (min)	1.00 (0.98 to 1.03)	0.69	1.00 (0.98 to 1.01)	0.60
Proportion (%)	1.19 (0.38 to 3.70)	0.77	0.86 (0.41 to 1.79)	0.69
AUC (mm Hg·min^{-1}/100)	1.04 (0.87 to 1.25)	0.65	1.01 (0.89 to 1.14)	0.89
Proportion of AUC (mm Hg)	1.03 (0.93 to 1.13)	0.60	1.01 (0.94 to 1.07)	0.82
Intraoperative				
Total duration (min)	1.00 (1.00 to 1.01)	< 0.001	1.00 (1.00 to 1.00)	0.12
Proportion (%)	5.2 (2.12 to 12.6)	< 0.001	2.42 (1.33 to 4.39)	0.004
AUC (mm Hg·min^{-1}/100)	1.06 (1.03 to 1.08)	< 0.001	1.03 (1.00 to 1.05)	0.02
Proportion of AUC (mm Hg)	1.19 (1.12 to 1.27)	< 0.001	1.12 (1.06 to 1.19)	< 0.001

All models were calculated using the hypotensive definition as mean arterial pressure < 65 mm Hg

[a]The multivariable logistic regression model with the explanatory variables including age, American Society of Anesthesiologists Physical Status (dichotomized as < 3 and ≥ 3), emergency, and surgical risk (dichotomized as low risk and others)

[b]The multivariable logistic regression model with the explanatory variables including age, sex, body mass index, American Society of Anesthesiologists Physical Status (I–IV, as four classes), emergency, surgical risk (1–3, as three classes), anesthesia type (intravenous or inhalational), and neuraxial anesthesia

aOR = adjusted odds ratio; AUC = area under the curve; CI = confidence interval

revealed similar trends, thereby supporting the lack of a significant effect of PIH on postoperative mortality.

As opposed to our hypothesis, PIH was not associated with postoperative mortality. Maheshwari *et al*. reported that PIH and IOH increased the risk of AKI, with increasing duration and AUC of hypotension (MAP < 65 mm Hg).[5] The discrepancy between our findings and those of Maheshwari *et al*. suggests different mechanisms between postoperative mortality and the pathogenesis of AKI. Although postoperative AKI increases mortality,[31] other factors such as myocardial injury,[32] delirium,[33] and respiratory failure,[34] can also affect a patient's prognosis. Postinduction hypotension might have been less associated with prognostic factors other than AKI compared with IOH and did not result in postoperative mortality.

In contrast to PIH, IOH was associated with postoperative mortality, which is consistent with the findings of several studies.[1,4,7,9] Thus, PIH and IOH may affect patients differently despite having the same degree of hypotension. The conflicting results between PIH and IOH may be largely due to different causes behind hypotension. Postinduction hypotension is caused by decreased preload and afterload from vasodilation and cardiac depression after the administration of anesthetics. By contrast, IOH is related to various factors, including bleeding, surgical manipulation, and systematic inflammatory response.[14] Differentiating the effects of PIH and IOH is crucial in anesthesiology research and practice for physiologic interpretation and management strategy. Our findings suggest the importance of managing circulation by addressing the underlying causes rather than merely maintaining BP levels.

In the PSM models, postoperative mortality was not different between patients with < 10 or ≥ 10 minutes of PIH. Several variables, including patient characteristics, preoperative medications, and blood testing data that could not be used in the primary analysis, were used, and the PSM models were designed to create a pair of patients with similar probabilities of having ≥ 10 minutes of PIH. Thus, we could evaluate the difference in postoperative mortality between patients who experienced or did not experience ≥ 10 minutes of PIH with similar susceptibility to PIH. This reinforces our results that PIH was not associated with mortality even further.

We used a machine-learning algorithm to classify imbalanced data to investigate important variables and predict postoperative mortality. The feature importance values of decision tree-based machine-learning models have been used as explainable artificial intelligence (AI).[35] Our models showed that the importance of IOH was greater than that of PIH, supporting our primary analysis. The results for variables with high feature importance are clinically understandable. Mortality increases with advancing age. Being underweight also increases postoperative mortality.[36,37] Clinically, albumin, platelet,

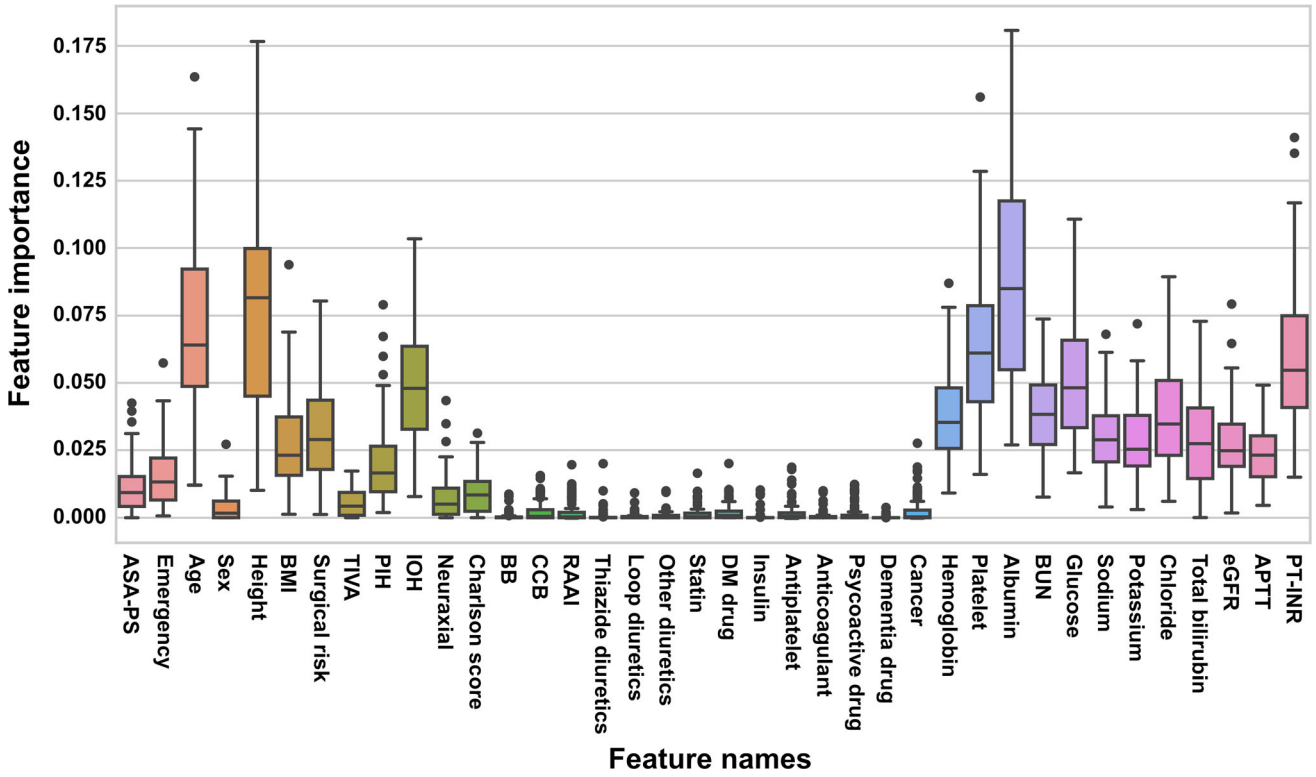

Fig. 2 Feature importance of variables in the RUSBoost model for predicting 30-day postoperative mortality using hypotensive proportion of area under the curve. The boxes' lower and upper edges represent the 25th and 75th percentiles, respectively. The medians are represented by the horizontal lines that run across the boxes. The whiskers represent the lowest and highest values from the 25th and 75th percentiles within a 1.5-box length. Outliers (extreme points beyond whiskers) are shown as dots.
APTT = activated partial thromboplastin time; ASA-PS = American Society of Anesthesiologists Physical Status; BB = beta-blockade; BUN = blood urea nitrogen; BMI = body mass index; CCB = calcium blockade; DM = diabetes mellitus; eGFR = estimated glomerular filtration ratio; IOH = intraoperative hypotension; PIH = post-induction hypotension; PT-INR = prothrombin-international normalized ratio; RAAI = renin-angiotensin-aldosterone system inhibitors; TIVA = total intravenous anesthesia

Table 4 Feature importance of postinduction and intraoperative hypotension indices for predicting 30-day and 90-day postoperative mortality using the RUSBoost models

Hypotensive indices	30-day mortality		90-day mortality	
	PIH	IOH	PIH	IOH
Duration, median [IQR]	0.025 [0.016–0.034]	0.062 [0.049–0.081]	0.029 [0.022–0.042]	0.047 [0.035–0.056]
Proportion, median [IQR]	0.024 [0.016–0.033]	0.050 [0.035–0.066]	0.032 [0.021–0.048]	0.037 [0.028–0.044]
AUC, median [IQR]	0.018 [0.010–0.028]	0.061 [0.043–0.072]	0.031 [0.022–0.040]	0.042 [0.036–0.053]
Proportion of AUC, median [IQR]	0.017 [0.010–0.026]	0.048 [0.033–0.064]	0.028 [0.020–0.037]	0.041 [0.034–0.055]

AUC = area under the curve; IOH = intraoperative hypotension; IQR = interquartile range; PIH = postinduction hypotension

and PT-INR values may have contributed to mortality prediction, as these values decrease with impaired liver function, chronic inflammation, and aging.[38] Consequently, the feature importance of the RUSBoost model provided valid results for interpreting factors contributing to postoperative mortality.

This study has some limitations. First, given the retrospective design, establishing causality between hypotension and mortality was limited. To make causal inferences, we adjusted for possible confounders with PSM and produced clinically interpretable results. Nevertheless, PSM cannot adjust for unselected or unmeasured confounders. For instance, vasopressor and inotrope use, intraoperative fluid volume, and estimated blood loss were not included in the models as these variables could be observed after PIH. Patients with high doses of vasopressors may underestimate hypotensive indices. Second, the single-centre setting and the small number of

mortality outcomes are fraught with the potential for selection bias, statistical model instability, and insufficient power. Only a limited number of variables could be put into the logistic regression analyses. Therefore, sensitivity analyses were performed to confirm the robustness of the primary results. Future studies using multicentre or nationwide databases combining laboratory and BP data are warranted. Third, 1,756 patients were excluded because of missing BP values and mortality information, which also led to selection bias. Fourth, the feature importance values for continuous variables tend to be higher than those for categorical variables.[39] Thus, categorical variables, such as emergency surgery and surgical risk, should not be compared with continuous variables, such as blood testing values. Finally, physiologic and imaging data, such as electrocardiogram and chest *x-ray* images, were not used.

Nevertheless, this study has several strengths. First, we examined the previously under-explored relationship between the timing of hypotension and postoperative mortality. Second, PSM models were used for causal inferences and machine-learning models as an explainable AI, and consistent trends in the results were noted. In the sensitivity analyses, as many potentially confounding factors that were electronically available were included, which may strengthen the validity of our findings and facilitate their clinical interpretation. Future studies must establish optimal circulatory management by taking into account the timing of hypotension.

In conclusion, this study revealed that 30-day and 90-day postoperative mortality events were associated with IOH but not with PIH.

Author contributions *TN* contributed to the study conceptualization, study design, data acquisition, data analysis, data interpretation, and manuscript drafting. *TT*, *YS*, *HH*, and *KF* contributed to the study design, data analysis, data interpretation, and reviewing and revising the manuscript. *KS* contributed the study conceptualization, study design, data interpretation, and reviewing and revising the manuscript.

Acknowledgments The authors would like to thank the staff of the Medical Affairs Division of Nagoya City University Hospital for data extraction and Enago (www.enago.jp) for the English language review.

Disclosures None.

Funding statement None.

Prior conference presentations Part of the study was presented at the 70th Annual Meeting of the Japanese Society of Anesthesiologists (1–3 June 2023, Kobe, Japan).

Editorial responsibility This submission was handled by Dr. Philip M. Jones, Deputy Editor-in-Chief, *Canadian Journal of Anesthesia/ Journal canadien d'anesthésie*.

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