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Association between preoperative autonomic nervous system function and post-induction hypotension in elderly patients: a protocol for a cohort study

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ABSTRACT

Introduction Post-induction hypotension (PIH), which is prevalent among elderly patients, is associated with adverse perioperative outcomes. As a critical part of blood pressure regulation, baroreflex control is believed to be closely related to intraoperative blood pressure fluctuations. Spontaneous baroreflex sensitivity and heart rate variability measurement can aid evaluation of patients' autonomic function. This study aims to determine the association between preoperative decreased baroreflex function and PIH in elderly patients.

Methods and analysis This prospective cohort study will enrol patients who are 65 years old and above, scheduled for elective non-cardiac surgery under general anaesthesia, and American Society of Anesthesiologists physical status I–III (n=180). Baseline assessment will include routine preoperative evaluations as well as symptoms and anamneses associated with baroreflex failure. Preoperative autonomic function monitoring will be performed through 20 min of continuous beat-to-beat heart rate and blood pressure monitoring using LiDCO rapid (Masimo Corporation, USA). The primary outcome will be PIH. Detailed use of anaesthetic agents during induction and maintenance will be documented for adjustment in multivariable analyses.

Ethics and dissemination The Research Ethics Committee of Peking Union Medical College Hospital approved the study protocol (I-22PJ008). We aim to publish and disseminate our findings in peer-reviewed journals.

Trial registration number NCT05425147.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Baroreflex sensitivity is a quantitative marker of baroreflex function and can be measured non-invasively therefore has the potential of being used as prediction tool for post-induction hypotension (PIH).
⇒ Our baseline assessment includes symptoms and anamneses associated with baroreflex failure, which is more effective in assessing a patient's autonomic function than autonomic monitoring alone.
⇒ Passive leg raising will be used to evaluate patients' preoperative volume status, to exclude possible confounding effect of hypovolaemia on PIH.
⇒ The anaesthesiological management will not be strictly standardised, and therefore we can only attempt to correct for confounding factors such as anaesthesia agent and depth of anaesthesia, which might have influenced intraoperative blood pressure.

INTRODUCTION

Intraoperative hypotension (IOH) is a common event during general anaesthesia, occurring in approximately 40% of patients.[1] Low arterial pressure is associated with perioperative mortality and ischaemia of vital organs, including the brain, heart and kidneys in a 'dose-dependent' manner.[2 3] Advanced age is one of the risk factors for IOH.[4] As an increasing number of elderly people receive surgery under general anaesthesia, IOH in elderly patients becomes an urgent issue.[5]

Hypotension can happen throughout perioperative period but is most prevalent during post-induction phase, which refers to the time frame between anaesthesia induction and skin incision. During this phase, arterial hypotension is associated with anaesthesia induction, baseline haemodynamic status and other patient-related factors rather than surgical factors, such as bleeding and surgical interventions.[6] It is widely recognised that the risk of post-induction hypotension (PIH) increases with age.[7]

Apart from senior age, risk factors for PIH includes the American Society of Anesthesiologists (ASA) Physical Status classification ≥3 and low preoperative mean arterial pressure (MAP), which are all non-modifiable in nature.[8] Preoperative hypovolaemia, a potentially modifiable factor, has also been widely studied in PIH-related research. Preoperative echocardiographic assessment and preoperative fluid replenishment strategies have been put forward to achieve euvolaemia.[9 10]

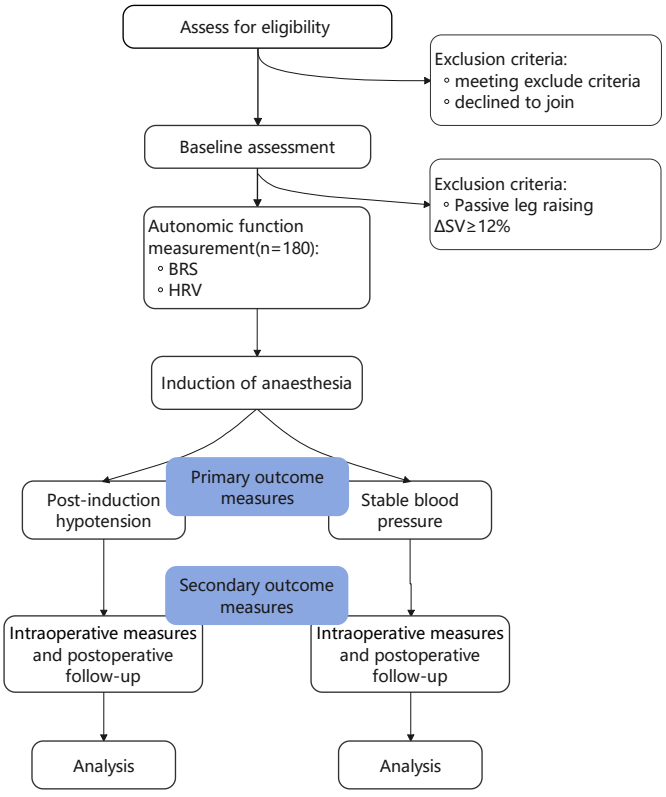

Figure 1 Flow chart of enrolment and measures. BRS, baroreflex sensitivity; HRV, heart rate variability; SV, stroke volume.

However, fluid optimisation before induction fails to maintain haemodynamic stabilisation, suggesting that immediate preoperative volume status could not fully account for PIH. Other key mechanisms are at play. It is possible that autonomic nervous system (ANS) plays an essential role in the adjustment of intravascular volume after anaesthesia induction.[11–13]

Cardiovascular autonomic function is important in blood pressure regulation. The pressure sensor of the cardiovascular system sends the blood pressure signal to the central nervous system, and regulates the blood pressure to an appropriate level through a compensatory reflex (ie, baroreflex).[14] Baroreflex function can be quantified by observing the RR interval response to an arterial blood pressure change and the results are expressed as baroreflex sensitivity (BRS).[15] Originally, BRS has been assessed through vasopressor-induced blood pressure variation, which is still the gold standard of baroreflex control assessment.[16] Considering these methods are invasive and technically difficult, researchers have now chosen non-invasive methods to assess BRS based on the spontaneous swings of blood pressure.[17] BRS can be used in risk stratification of hypertension, myocardial infarction and arterial fibrillation, and can act as a useful tool in diabetic autonomic neuropathy staging.[18–20] However, there are few studies investigating the relationship between baroreflex function and PIH; therefore, the role of baroreflex function in PIH is still unclear. It is widely recognised that ageing is closely related to decreased baroreflex function.[21] Since PIH is prevalent in elderly patients and is associated with adverse postoperative outcomes, we postulate that measurement of BRS in preoperative period may serve as a surrogate marker of individual baseline baroreflex control, and provide information on haemodynamic management among elderly patients undergoing general anaesthesia.

In addition to BRS, heart rate variability (HRV) can also be used to assess ANS. Several studies have revealed the relationship of low HRV and IOH, but the preoperative fluid status assessment was missing in these studies.[22 23] Time, frequency and non-linear analysis measures were all considered to be related to IOH.[23]

We hypothesise that decreased baroreflex function in elderly patients plays a significant role in PIH. This study will enable us to explore whether perioperative short-time BRS and HRV assessment can help to identify elderly patients at high risk of PIH. We will also perform frailty assessment in elderly patients to explore the role of frailty in the association of autonomic regulation and PIH.[24] Overall, this cohort study will provide the relationship between perioperative assessment of autonomic function and outcomes.

METHODS

Study design and setting

Our study is a single-centre prospective cohort study to investigate the potential impacts of preoperative autonomic function on haemodynamic stabilisation after induction. This study will be conducted at Peking Union Medical College Hospital (PUMCH), Beijing, China. This study has been approved by the Research Ethics Committee of PUMCH (reference number: I-22PJ008) and has been registered in ClinicalTrials.gov (registration number: NCT05425147).

Participants

Enrolled patients will be at least 65 years old, scheduled for major elective non-cardiac surgery under general anaesthesia (estimated operation time ≥2 hours) and ASA physical status I–III. The airway management tool during operation will be endotracheal tubes.

Exclusion criteria will be severe vascular disease, secondary hypertension, Parkinson's disease, or other conditions that cause tremors, persistent atrial fibrillation, inability to measure upper extremity blood pressure and mental disorders.

Protocol

Our study includes baseline assessment, autonomic function measurement, intraoperative monitoring and postoperative follow-up (figure 1). All collaborators will be trained on autonomic function measurement. All data will be recorded in the Clinical Report Form (see online supplemental material 1) and kept securely.

Baseline assessment

In addition to routine preoperative clinical and laboratory evaluations, we also specifically assess patients for

Table 1 Medical history, symptoms and medications related to autonomic function

Medical history	
Afferent baroreflex failure	Radiation therapy for head and neck cancer
	Resection of neck tumours (bilateral)
	Carotid endarterectomy
Central baroreflex failure	Multiple system atrophy
Efferent baroreflex failure	Diabetic neuropathy
	Parkinson's disease
Symptoms	
Blood pressure	Orthostatic hypotension or syncope
	Hypertensive crisis
	Hypotensive episode
Heart rate	Tachycardia at rest, during exercise or orthostasis
Vasomotion	Heat/cold intolerance
	Skin colour change
Medications	Anticholinergics
	Sympathomimetics
	Parasympathomimetics
	Mineralocorticoids
	Adrenergic antagonists
	Diuretics

*Patients with Parkinson's disease are usually excluded in our study because of tremor.

autonomic function. As is shown in table 1, the symptoms and anamneses associated with baroreflex failure will be taken.[25 26] Medications that may affect autonomic regulation will also be inquired. We will also perform frailty phenotype assessment using FRAIL Scale and Fried phenotype.[27 28]

Autonomic function measurement

Autonomic function monitoring will be performed approximately 40 min before the start of anaesthesia on the day of surgery (figure 2). Patients will be monitored for 20 min using LiDCO rapid (Masimo Corporation, USA) to obtain continuous heart rate and beat-to-beat blood pressure measurement. The measurement will be performed in the pre-anaesthesia waiting room with an ambient temperature of 25°C and constant lighting status. All included patients will have been fasted for at least 8 hours before the test. Patients will be in supine position and undergo the following instructions.[14 29]

1. Baseline monitoring for 2 min.
2. Passive leg raising will be performed to predict central hypovolaemia. LiDCO rapid will be used to measure stroke volume (SV) non-invasively. If ΔSV ≥12%, the patient will be suspected for hypovolaemia and excluded.[30] Fasting time and preoperative intravenous fluid volume will also be recorded.
3. Spontaneous baroreflex function will be monitored for 15 min during which time patients will be instructed to relax and breathe spontaneously.
4. Enhanced baroreflex function will be measured for 1 min during which time patients will be instructed to do pursed-lips breathing at a frequency of 0.1 Hz, to induce periodical fluctuations of heart rate and blood pressure.[31]

Matlab programs will be used to calculate BRS and HRV measures from the continuous heartbeat and blood pressure recordings. BRS is expressed as milliseconds change in RR interval per mm Hg in response to changes in systolic blood pressure (SBP). The sequence method will be used for assessment of baroreflex function, which identifies SBP and RR interval have both progressively increased over three or more consecutive beats.[19 32] The threshold values for SBP and RR interval changes will be set at 1 mm Hg and 6 ms, respectively. BRS will be obtained by calculating the slope of the regression line relating changes in SBP to changes in RR interval. Baroreflex Effectiveness Index (BEI) will be defined as the percentage of progressive increase/decrease swings in SBP that are effectively regulated by heart rate, that is, RR interval changes.[33] We define the increase in RR interval with rising SBP as BRS+/BEI+, and vice versa as BRS−/BEI−.

The RR interval data collected during BRS monitoring will also be used for HRV measurement. We will perform time and frequency domain analysis according to the standards of HRV published by the American Heart Association. Time domain analysis, which reflects overall variability of RR intervals, includes indicators such as SDNN (SD of the normal-to-normal intervals),

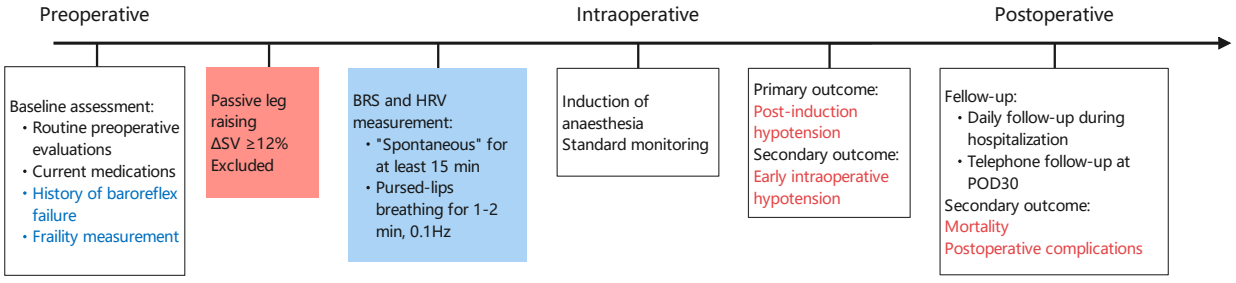

Figure 2 Timeline of measures. BRS, baroreflex sensitivity; HRV, heart rate variability; POD, postoperative day.

RMSSD (the square root of mean squared differences of normal-to-normal intervals), NN50 (the number of normal-to-normal intervals greater than 50 ms), pNN50 (the proportion of NN50). Frequency domain analysis, which provides information on the power distribution in different frequencies, which include the power of high frequency (HF), low frequency (LF) and very low frequency, will be calculated.[34] Furthermore, Poincaré plot widths (SD1 and SD2) and frequency bands in LF–HF scatter plots, the measures of non-linear analysis, will also be computed to further evaluate the variation.[35 36]

Intraoperative measures and anaesthetic agents use

All enrolled patients will receive standard monitoring with a torso-positioned limb leads ECG, pulse oximetry, a peripheral intravenous line and an automated non-invasive blood pressure (NIBP) according to ASA Standards for Basic Anaesthetic Monitoring.[37] NIBP will be measured every 2 min during post-induction period and every 3 min during intraoperative period. Bispectral index monitoring (BIS; Medtronic, Dublin, Ireland) will be used to maintain the proper depth of anaesthesia, with a BIS target range of 40–60.

Intravenous anaesthesia induction will be used for all patients. For pragmatic reasons, anaesthesia agents used (propofol or etomidate) in the induction and maintenance phase are not strictly regulated and will be chosen at the discretion of the anaesthesiologist in charge who is independent from the study. However, during induction, anaesthetic and other accompanying medications will be given according to the following institutional protocol: fentanyl (1–3 µg/kg), propofol (1.5–2.5 mg/kg) or etomidate (0.1–0.3 mg/kg) and rocuronium (0.5–0.9 mg/kg). Total intravenous anaesthesia will be induced with fentanyl (1–3 µg/kg), propofol (target control infusion with a targeted plasma concentration of 6 µg/mL) and rocuronium (0.5–0.9 mg/kg). We will record anaesthetic agents used during anaesthesia and correct for confounding factors through multivariable analysis. Vasopressors will be allowed during post-induction and intraoperative periods. Patients will receive boluses of ephedrine 6 mg or phenylephrine 100 µg whenever patients meet the standards of hypotension. Pre-emptive vasopressors will not be used.

Postoperative follow-up

We will conduct daily follow-up of patients until hospital discharge and a telephone follow-up at 30 days after surgery. Postoperative recovery, complications and routine laboratory test results will be recorded.

Study outcomes

Primary outcomes

The primary outcome in this study is PIH, occurring within 20 min after induction or before incision. Hypotension is defined as SBP <90 mm Hg, MAP <65 mm Hg or a decrease of more than 30% of baseline.

Table 2 Power calculation according to a previous study on HRV

	Power
Time domain analysis	
Mean RR (ms)	0.84
SDNN (ms)	1.00
RMSSD (ms)	1.00
Frequency domain analysis	
LF (ms^2)	1.00
HF (ms^2)	1.00
Total power (ms^2)	1.00
LF/HF ratio	0.99

HF, high frequency; HRV, heart rate variability; LF, low frequency; RMSSD, square root of mean squared differences of normal-to-normal intervals; SDNN, SD of the normal-to-normal intervals.

Secondary outcomes

The secondary outcomes include:

1. Early intraoperative hypotension, occurring within 30 min of surgery.
2. Mortality within 30 days after surgery.
3. Postoperative complications in accordance with the European Perioperative Clinical Outcome definitions. Postoperative complications will be classified according to the Clavien-Dindo system.[38 39]

Sample size consideration

To investigate the association between BRS, HRV and outcomes, we used the HRV results in the literature to estimate the sample size, considering few previous studies have explored the correlation between BRS and PIH.[23] Our preliminary study suggested that around 33% of elderly patients in our centre developed PIH.[40] Based on the study by Padley and Ben-Menachem[23] and considering the need for a multivariable analysis according to the induction strategy in our study, to achieve a 95% power and a significance level of 5%, 180 patients will be required (60 with PIH and 120 with stable blood pressure). A drop-out rate of 10% is assumed in sample size calculation. The statistical power of various HRV metrics is shown in table 2.

Previous studies have shown that elderly women had lower BRS compared with elderly men.[41] To reduce the impact of differences in sex distribution on measures and outcomes, we included patients in a specific sex ratio. From 2014 to 2022, 41.1% of the elderly patients who received elective non-cardiac surgery under general anaesthesia in our centre were female. We will include patients in a ratio of 6:4 male to female (108 male and 72 female).

Statistical analysis

Statistical analysis will be performed using the SPSS V.22.0 for Windows (IBM). Quantitative variables will be reported as the mean±SD or median (25th–75th IQR). BRS and

HRV measures will be compared in elderly patients with and without PIH. Categorical variables will be compared using $\chi 2$ or Fisher's exact test. Differences in mean or median values between PIH and stable groups were compared using Student's t-test or the non-parametric Mann-Whitney U test to explore the association between PIH and preoperative ANS function. Logistic regression will be used to estimate the relationship between frailty, BRS and PIH. Since different anaesthetic agents (mainly propofol vs etomidate) used for induction might bring in confounding factors, we will use logistic regression to adjust for confounding. We will consider $p<0.05$ as statistical significance.

Ethics and dissemination

The Research Ethics Committee of PUMCH approved the study and the reference number was I-22PJ008 (approved on 10 June 2022). The investigator will comprehensibly explain the study to patients before recruitment. A written informed consent form will be obtained from all patients. Patients will be informed that they may decline to participate or withdraw from the study at any time.

The study was registered with the National Institutes of Health, US National Library of Medicine at ClinicalTrials.gov (NCT05425147, registered on 15 June 2022).

We aim to publish and disseminate our findings in peer-reviewed journals. Our findings will also be presented at Chinese and international conferences.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

This study aims to find out the association between decreased baroreflex function and PIH or other adverse events in elderly patients. Through preoperative non-invasive BRS and HRV measurement, we can obtain information on the patient's preoperative baroreflex function and sympathetic/parasympathetic tone from real-world evidence.

Considering the impact of PIH on prognosis, the mechanism of PIH has attracted attention of investigators. Previous studies have confirmed that absolute volume status could not explain the complete picture of PIH. Blood pressure rhythms, which are regulated by autonomic nerves, are thought to be a potentially critical link in PIH.[42 43] However, to our knowledge, the study on the association between PIH and baseline BRS is still missing. Accordingly, performing preoperative BRS assessment is an effective way to identify this association. Furthermore, through passive leg raising, we can exclude the effect of hypovolaemia on PIH. Like many studies focused on PIH, anaesthetic agents used during induction cannot be strictly standardised due to clinically practical reasons.[4] To reduce the bias caused by them, we will attempt to correct for confounding factors by statistical methods. In conclusion, despite the limitations, this study might help with early identification and precaution of PIH mediated by impaired autonomic function in elderly patients.

Contributors Concept, study design and first draft of the manuscript—QC, LC and LX. Manuscript review and data collection—HZ, JY, LX and YH. Editing and critical review—LC and LX. All (QC, LC, HZ, JY, LX, YH) authors have given final approval for manuscript submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Clinical Report Form

Date of Recruitment:

CRF Number: ID: Age: Department:

Physical examination	Height_____cm Weight _____kg NBP ____/____HHmg HR _____bpm		
ASA classification		MET	
Allergic history: Smoking ( ) Drinking ( )			
Past medical history			
Cardiovascular: Normal ( ) Hypertension ( ) Coronary artery disease ( ) Valvular heart disease ( ) Arrhythmia( ) Others ( )			
Respiratory: Normal ( ) COPD ( )Asthma ( )Others ( )			
Endocrine: Normal ( ) Diabetes ( ) Hyperthyroidism ( ) Others ( )			
Digestive: Normal ( ) IBD ( ) Hepatitis ( ) Cirrhosis ( ) Others ( )			
Nervous system: Normal ( ) Stroke ( ) Alzheimer's disease ( ) Parkinson's disease ( ) Others ( )			
Urinary system: CKD ( ) Others ( )			
Symptoms related to autonomic function: Orthostatic hypotension or syncope ( ) Hypotensive episode ( ) Tachycardia during exercise or orthostasis ( ) Heat/cold intolerance ( )			
Note:			
Current medications:			
□Anticholinergics □Sympathomimetics □Parasympathic mimetics □Mineralocorticoids □Adrenergic antagonists □Diuretics			
Other medications:			
Preoperative testing:			
ECG/ECHO: Normal ( ) Abnormal ( ) Diagnosis_____			
Pulmonary function test: Normal ( ) Abnormal ( ) Diagnosis_____			
Blood routine examination: HGB ( ) WBC ( ) NEUT% ( ) PLT ( )			

Blood biochemistry test: Alb ( ) Cr(E) ( ) Other abnormality_____

Preoperative monitoring (LiDCO)

	Baseline	Passive leg raising	Deep slow breathing (1min)	End
Time				
Heart Rate				
Blood pressure				
Note		ΔSV= %		

Intraoperative Record

Time		SBP	DBP	MAP	HR	SpO_2				
	Baseline						Vasopressor	Note	MAC	BIS
	Start of induction									
	2min									
	4min									
	6min									
	Intubation /0min									
	2min									
	4min									
	6min									
	8min									
	10min									
	12min									
	14min									
	16min									
	18min									
	20min									
	Incision /0min									
	+3min									
	+6min									

	+9min									
	+12min									
	+15min									
	+18min									
	+21min									
	+24min									
	+27min									
	+30min									
	End of surgery									

PIH	1 Yes □ 11□SBP<90mmHg;12□MAP＜65mmHg;13□MAP decline≥30%Baseline; 0 No □		
Early Intraoperative hypotension	1 Yes □ 11□SBP<90mmHg;12□MAP＜65mmHg;13□MAP decline≥30%Baseline; 0 No □		
Drugs	Induction dosing	Maintenance dosing	Total
Sevoflurane	/	MAC:	/
Propofol			
Etomidate			
Dexmedetomidine			
Midazolam			
Fentanyl			
Remifentanil			
Oxycodone			
Rocuronium			
Lidocaine			
Ephedrine			
Phenylephrine			
Atropine			
Norepinephrine			
Epinephrine			
Esmolol			
Urapidil			
Others			

Date of surgery		Name of surgery	

Combined nerve block	□Yes □No
Output volume	Urine _____ml; Blood loss _____ml Others _____ml
Transfusion volume	Crystalloid fluid _____ml; Colloid fluid _____ml
Intraoperative blood transfusion	☐Yes ☐Whole blood _____ml □RBC_____U ☐Platelet _____U ☐ Fresh frozen plasma ____ml ☐Autotransfusion _____ml □No
Operation time	
Aneasthesia time	
Duration of stay in PACU	_____min Event: Rescue medications: ☐ NSAIDs ☐ Opioids ☐Ondansetron ☐Others
Stay in ICU	□Yes Mechanical ventilation time _____ h ICU staying time _____h ☐No

Postoperative complications (within 30 days)

Respiratory system	
No ☐; Yes ☐: ☐ Mechanical ventilation time≥48 小时; ☐ ARDS; ☐ Pleural effusion; ☐ Atelectasis; ☐ Pulmonary infection; ☐ Pneumothorax; ☐ Aspiration pneumonia; ☐ PE; ☐ Others_____	
Cardiovascular system	
No ☐; Yes ☐: ☐ Non-fatal cardiac arrest; ☐ACS; ☐ Acute congestive heart failure; ☐ Arrhythmias (requiring treatment); ☐ New-onset hypertension; ☐New-onset hypotension; ☐ Others_____	
Urinary system	
No ☐; Yes ☐: ☐ AKI; ☐ UTI; ☐ Acute urinary retention; ☐ Others_____	
Digestive system	
No ☐; Yes ☐: ☐ Intestinal obstruction; ☐ Peritonitis; ☐ GIB; ☐ Hepatic dysfunction; ☐ Anastomotic fistula; ☐ Others_____	
Nervous system	
No ☐; Yes ☐: ☐ Ischemic stroke; ☐ UTI; ☐ Acute urinary retention; ☐ Others_____	
Hematologic system	
No ☐; Yes ☐: ☐ DVT ☐ RBC transfusion ≥4U within 72 hours after surgery; ☐ Others_____	
Infection	
No ☐; Yes ☐: ☐ Sepsis; ☐ Wound infection; ☐ GIB; ☐ Others_____	
Clavien-Dindo classification	
☐ Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions. ☐ anti-emetics ☐ antipyretics ☐ analgesics ☐ diuretics ☐ electrolytes ☐ physiotherapy ☐ wound infections opened at the bedside
☐ Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
☐ Grade III	Requiring surgical, endoscopic or radiological intervention ☐ IIIa: Not under general anaesthesia; ☐ IIIb: Under general anaesthesia
☐ Grade IV	Life-threatening complication (including central nervous system complications) requiring critical care. ☐ IVa: Single organ dysfunction (including dialysis); ☐ IVb: Multi-organ dysfunction
☐ Grade V	Death of a patient.

Death	No ☐; Yes ☐: POD ____ Cause:_____