Association between intraoperative hyperglycemia and postoperative end-organ dysfunctions after cardiac surgery: A retrospective observational study

Shinsaku Matsumoto[1, 2], Hiroki Omiya[1], Waso Fujinaka[1], Hiroshi Morimatsu[2]

[1]Department of Anesthesiology and Intensive Care, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan

[2]Department of Anesthesiology and Resuscitology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Correspondence to: Shinsaku Matsumoto, Department of Anesthesiology and Intensive Care, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan. Tel: +81-82-221-2291, Fax: +81-82-223-5514, e-mail: shinsaku823@yahoo.co.jp

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Abstract

Purpose: Hyperglycemia has been associated with postoperative morbidity in patients who undergo cardiac surgery. However, it remains unclear whether the duration of hyperglycemia is as important as its magnitude in the development of postoperative end-organ dysfunction (PEOD). This retrospective study investigated the hypothesis that the intraoperative blood glucose (BG) exposure index (GE index), calculated by the product of the magnitude and duration of BG concentration ≥180 mg/dL, which is an integration of the severity and duration of hyperglycemia, is associated with the incidence of PEOD in patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods: The primary outcome in this study was PEOD within 72 h of surgery, which was defined as a composite of postoperative acute kidney injury, delirium, myocardial injury, and prolonged mechanical ventilation. The GE index (the magnitude of BG concentration deviation ≥180 mg/dL×duration of BG concentration ≥180 mg/dL) of each patient was calculated based on the intraoperative BG concentration. The relationship between the GE index and the primary outcome was examined via logistic regression model with adjustment for potential confounders.

Results: Within 72 h of surgery, 301 patients (54.5%) developed PEOD. PEOD was more common in patients with greater GE index quartiles (first versus third quartile;

adjusted odds ratio, 5.65, 95% confidence interval (95%CI), 2.94–10.90; *P* <0.001; first versus forth quartile, adjusted odds ratio, 20.80; 95%CI, 8.01–54.00; *P* <0.001).

Conclusion: In patients undergoing cardiac surgery with cardiopulmonary bypass, the GE index was an independent predictor of PEOD.

Introduction

During cardiac surgery with cardiopulmonary bypass (CPB), patients are at risk of a systemic inflammatory response due to by surgical trauma, contact with the foreign surface of the extracorporeal circuit, ischemic-reperfusion injury, and blood cell transfusions [1, 2]. Consequently, cardiac surgery patients are susceptible to postoperative end-organ dysfunction (PEOD), such as acute kidney injury (AKI) [3–5], postoperative cognitive dysfunction and delirium (POCD) [6], myocardial injury (MI) [7], and prolonged mechanical ventilation (PMV) [8]. These end-organ dysfunctions are associated with increased short- and long-term mortality and morbidity [9–11]. Preventing PEOD in the early postoperative phase is important for improving patient outcomes and preserving medical resources. However, the methodology has not been fully established.

Over 60 % of patients undergoing cardiac surgery experience hyperglycemia [12] due to a combination of surgical stressors, catecholamine release, increased catabolism, the use of corticosteroids or inotropic agents, and the administration of glucose-containing cardioplegic solutions [13, 14]. Hyperglycemia induces oxidative stress and upregulates pro-inflammatory factors, exacerbating the inflammatory response and subsequent endothelial injury [15–17]. Consequently, hyperglycemia contributes to endothelial dysfunction and exacerbates PEOD [17, 18]. Accumulating

evidence indicates that hyperglycemia in cardiac surgery negatively affects diabetic and non-diabetic patient outcomes [19, 20]. Currently, the American Society of Thoracic Surgery recommends maintaining perioperative blood glucose (BG) concentration of ≤180 mg/dL in cardiac surgery patients [21]. Additionally, several studies have indicated that the glucose variability is associated with morbidity and mortality in the intensive care unit (ICU) or during cardiac surgery [22–25].

However, little is known about the duration of intraoperative hyperglycemia and its adverse effects in cardiac surgery. In patients with chronic diabetes, an elevated blood hemoglobin A1c concentration, which indicates longstanding uncontrolled hyperglycemia, reflects a risk for developing or worsening diabetes complications such as retinopathy, neuropathy, and nephropathy. There is a profound difference in the effect of glucose toxicity between patients undergoing cardiac surgery and those with chronic diabetes. Whether the duration of intraoperative hyperglycemia, a relatively shorter duration than in other clinical settings, affects the outcomes of patients who undergo cardiac surgery with CPB remains unknown. Additionally, few investigations [18, 26] have been conducted to assess the effects of cardiac surgery-associated hyperglycemia on multiple end-organ systems including AKI, POCD, MI, and PMV.

This retrospective study investigated the relationship of the magnitude and duration of intraoperative hyperglycemia, defined as the product of the magnitude and duration of a BG concentration ≥180 mg/dL, with the incidence rate of PEOD in patients undergoing cardiac surgery with CPB.

Methods

This single-center retrospective observational study was conducted at a specialized tertiary referral hospital. The tenets of the Declaration of Helsinki were adhered to. The Ethical Review Committee of Hiroshima City Hiroshima Citizens Hospital, Hiroshima, first provided ethical approval (IRB No. 2020-126) on January 8, 2021. Because the study protocol was altered, the Ethical Review Committee approval was obtained again on August 10, 2021 (IRB No.2021-61). The requirement for written informed consent was waived because of the retrospective nature of this study. Instead, opt-out consent documents were presented on the Hiroshima City Hiroshima Citizens Hospital website for patients who did not wish to participate.

Patient population

Patients aged ≥20 years who underwent cardiac surgery with CPB between May 2015 and December 2019 were included. The exclusion criteria were as follows: surgery with circulatory arrest, use of extracorporeal membrane oxygenation or a left ventricular assist device, transcatheter aortic valve replacement, kidney disease requiring preoperative renal replacement therapy, pregnancy, and missing primary outcome values. Only the first surgery was considered for patients requiring more than one cardiac surgery with CPB during the same hospitalization period.

Anesthetic and perioperative management

Standard anesthetic management included the use of intravenous midazolam (0.1–0.2 mg/kg) or propofol (1–2 mg/kg), rocuronium (0.6–0.9 mg/kg), and fentanyl (2–5 μg/kg) for induction. General anesthesia was maintained with intravenous remifentanil (0.05–0.25 μg/kg/min) and 1–2 % sevoflurane in a carrier gas of 40–60 % inspired oxygen. During surgery, intravenous fentanyl (15–20 μg/kg) was administered. During CPB, before cessation of mechanical ventilation, propofol (4–8 mg/kg/h) was administrated intravenously according to the BIS Monitor (Medtronic; Minneapolis, Minnesota, United States). Standard monitoring was performed for each patient, including pulse oximetry, end-tidal capnography, electrocardiography, noninvasive blood pressure, and invasive arterial blood pressure. A central venous catheter or pulmonary artery catheter, if suitable, was inserted into the right jugular vein, and a 10 % glucose solution (0.5–1.0 mL/kg/h) was continuously infused as maintenance fluid. No set protocol for insulin administration was followed, and bolus and continuous intravenous insulin for hyperglycemia were administered at the discretion of the anesthesiologist. The inflammatory response was attenuated with intravenous methylprednisolone (1500 mg), which was administered to all patients before the incision according to our institutional policy. The BG concentration was measured at least five times (before induction, before incision, at CPB initiation, just after CPB cessation, and around sternum closure) using a blood gas analyzer (GEM

Premier 4000; Instrumentation Laboratory, Bedford, Massachusetts, United States). During CPB, samples were taken from a CPB reservoir every 30 min after CPB initiation for additional BG measurements. Patients were managed with an alpha-stat and given St. Thomas' hospital cardioplegic solution No 2 for myocardial protection during the aortic cross-clamp, if necessary.

After surgery, all patients were sedated and mechanically ventilated, administered propofol (2–4 mg/kg/h) and dexmedetomidine (0.4 μg/kg/h), and transferred to the ICU. After ICU physicians confirmed hemodynamic stability, all patients underwent spontaneous awaking and breathing trials, and the mechanical ventilation weaning potential was assessed at least once every 12 h. If the trials were successful, mechanical ventilation was discontinued.

Data collection

Data regarding patient demographics, comorbidities, medications, preoperative laboratory findings, and pre- and intraoperative variables were extracted from the electronic medical records (HOPE/EGMAIN-GX; FUJITSU, Tokyo, Japan) and the operating room database (ORSYS; Philips Electronics Japan, Tokyo, Japan). Patient prognostic data, such as postoperative new-onset atrial fibrillation, postoperative infections (the composite event of surgical site infection, deep sternal infection, urinary tract infections, pneumonia, and septicemia), length of mechanical

ventilation, ICU stay, and hospitalization, and 90-day all-cause mortality, were also obtained.

To evaluate the magnitude and the duration of hyperglycemia exposure, the glucose exposure (GE) index was calculated using the intraoperative BG concentrations. The GE index is defined as the products of the magnitude and duration of a BG concentration ≥180 mg/dL. The magnitude of the deviation of individual values of BG concentration above 180 mg/dL was considered the magnitude of BG concentration. BG concentration values less than 180 mg/dL were considered to have a magnitude 0 mg/dL. Duration of BG concentration ≥180 mg/dL was the duration for which the BG concentration as equal to or above 180 mg/dL, calculated as the intervals between a sampling point and one succeeding it, from beginning of the anesthesia induction to the ICU admission. For example, if the BG concentration was 250 mg/dL at 13:00 hours, 200 mg/dL at 14:00 hours, and 170 mg/dL at 15:00 hours, the GE index was calculated as follows: $(250 - 180) \times 1 + (200 - 180) \times 1 = 90\ mg/dL \times hr$. In addition, the glucose coefficient of variation (CV; standard deviation/mean $\times$ 100%), an accepted measure of glucose variability [22], was calculated from all intraoperative glucose values.

Study protocol

The primary outcome was postoperative PEOD, defined as the composite event of postoperative AKI, POCD, MI, and PMV within 72 h after the surgery. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes criteria using the serum creatinine level [27], and POCD was defined as an Intensive Care Delirium Screening Checklist (ICDSC) score ≥4 [28]. MI was defined as a serum creatine kinase MB isoenzyme level elevation to greater than five times the upper normal-range limit [29]. PMV was defined as failure of weaning from the ventilator within 24 h after cardiac surgery [8].

Patients were allocated based on their primary outcome incidence into non-PEOD and PEOD groups. Patient characteristics and perioperative variables, including mean magnitude and duration of BG concentration ≥180 mg/dL, GE index, and CV, were compared between the groups.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR), depending on the data distribution. Categorical data are reported as absolute numbers with percentages (%). Univariate analysis was performed to identify potential candidate variables for multivariable analysis. Based on previous studies about postoperative AKI, POCD, MI, and PMV [3–7, 30], the following variables were screened with univariate analysis: baseline characteristics:

age, sex, body mass index (BMI), American Society of Anesthesiology Physical Status classification ≥3 (ASA-PS ≥3), New York Heart Association functional classification ≥3 (NYHA ≥3), European System for Cardiac Operative Risk Evaluation II (EuroSCOREⅡ) [31]; comorbidities: hypertension, diabetes, diabetes on insulin therapy, atrial fibrillation, acute myocardial infarction, peripheral arterial disease (PAD), current smoking habits, chronic lung disease (COPD), active infectious endocarditis, critical preoperative state, dementia; medication: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers use (ACEi/ARB), beta-blockers use (BetaB); preoperative laboratory and physiological data: hemoglobin level (Hb), serum creatinine (sCr), estimated glomerular filtration rate calculated by revised equations from Japanese serum creatinine (eGFR) [32], total bilirubin, left ventricular ejection fraction (LVEF), estimated pulmonary artery systolic pressure ≥30 mmHg, N-terminal prohormone of brain natriuretic peptide (NTproBNP); surgical characteristics: urgent surgery, type of surgery, surgery requiring more than 2 procedures, duration of anesthesia, surgery, CPB, and aortic cross-clamp (ACC), intra-aortic balloon pumping (IABP), intraoperative catecholamine index (CAI): dopamine dose+dobutamine dose+(noradrenaline dose+adrenaline dose)×100 (μg/kg/min), vancomycin, red blood cell concentrates (RBC), CV, and quartiles of GE index. In univariate analysis, the aforementioned

variables were compared between the two groups using Student's t-test or Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, as appropriate.

Multivariate logistic regression models were used to estimate the adjusted association between postoperative PEOD and the GE index. Variables with *P*-values <0.1 in the univariable analysis were included in the models. For variables which were considered clinically correlated (e.g., duration of anesthesia and duration of surgery), a variable considered more essential in developing PEOD was included in the model on the basis of previous studies. Multicollinearity of the final model was checked using the variance inflation factor (VIF). If the VIF scores were 10 or more, then multicollinearity was considered to exist in the model. The accuracy of the model was validated using the C-index.

Receiver operating characteristic (ROC) curves were constructed to evaluate the GE index as a predictor of PEOD. The optimal cut-off point was identified using the Youden index [33]. The areas under the curve (AUCs) were compared between the ROC curves for CV and GE index.

Results of the logistic regression model are expressed as odds ratios (ORs) and 95 % confidence intervals (CIs). All *P*-values were two-sided, and values <0.05 were considered statistically significant. All statistical analyses were performed with

EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6-3) designed to add statistical functions frequently used in biostatistics [34].

A power study was not performed because of the lack of knowledge of the effect of the duration of hyperglycemia exposure in cardiac surgery. Instead, for an accurate estimation of regression coefficients, a standardized policy that at least 10 events per variable should be required in a logistic regression model [35] was followed in this study. The number of events was defined as the number of subjects in the smaller of two outcome groups.

Results

During the study period, 553 of the 1360 patients who underwent cardiac surgery with CPB were eligible for the final analysis (Fig. 1). Patient and surgical characteristics are summarized in Table 1 and Table 2, respectively. Within 72 h postoperatively, PEOD occurred in 54.4 % (301/553) of patients, AKI in 40.0 % (221/553), POCD in 20.8 % (115/553), MI in 2.2 % (12/553), and PMV in 14.3 % (79/553; Table 3). The patient prognostic variables are presented in Table 4. The PEOD group had significantly longer mechanical ventilation, ICU stay, and hospitalization durations and a higher 90-day all-cause mortality rate compared with the non-PEOD group.

GE index and PEOD after cardiac surgery

In univariable analysis, the PEOD group had a significantly higher median GE index (170.7 mg/dL×h, IQR 61.1–372.3 mg/dL×h) than the non-PEOD group (26.6 mg/dL×h, IQR 0.0–67.8 mg/dL×h; P <0.001; Table 2). The GE index quartiles were 0–15.4, 15.7–71.4, 72.3–220.8, and 221.1–2569.3 mg/dL×h. Additionally, the PEOD group had a significantly higher median CV (26.8, IQR 20.1–32.9) than the non-PEOD group (24.3, IQR 20.1–30.0; P = 0.005). The following possible confounders were revealed on univariable analysis (P <0.1): age, BMI, ASA-PS ≥3, NYHA ≥3, EuroSCOREⅡ, hypertension, diabetes, PAD, COPD, ACEi/ARB, BetaB, Hb, sCr,

eGFR, LVEF, NTproBNP, surgery requiring more than 2 procedures, duration of anesthesia, surgery, CPB, and ACC, IABP, CAI, RBC, CV, and quartiles of GE index. Among these, the following variables were considered clinically correlated: sCr and eGFR; duration of anesthesia and duration of surgery; duration of CPB and duration of ACC. These variables were confirmed of strong correlations using bivariate correlation analyses (Supplemental Fig.1). Based on the previous studies regarding postoperative mortality and morbidity [36–38], eGFR and duration of surgery were included in the model. Duration of ACC was excluded from the model because previous studies demonstrated that not duration of ACC but duration of CPB was associated with an increase of proinflammatory cytokine and PMV [39, 40]. The variables included in the model are shown in Table 5. After adjusting for possible confounders, the multivariable logistic regression model identified that BMI, PAD, eGFR, CAI, and GE index were independent predictors of PEOD. (Table 5). Patients in the third (adjusted OR, 5.65, 95% CI, 2.94–10.90; P <0.001) or fourth (adjusted OR, 20.80, 95% CI, 8.01–54.00; P <0.001) quartile of GE index had a greater risk of PEOD than those in the first quartile. Multicollinearity was not observed in the final models (all VIFs <10). The C-statistics for the final model was 0.86 (95 % CI, 0.83–0.89).

The optimal GE index cut-off value for predicting PEOD was 91.6 mg/dL×h, with a sensitivity of 68.1%, specificity of 83.7%, and AUC of 0.80 (95% CI, 0.76–0.83). When compared with CV, GE index showed a significantly larger AUC (Fig. 2).

Discussion

The adverse effects of the duration of hyperglycemia exposure on cardiac surgery patient outcomes have not been fully elucidated. To explore this, we integrated the magnitude and duration of the BG concentration ≥180 mg/dL into the GE index. In this study, GE index was found to be an independent predictor of PEOD, while CV, an accepted surrogate of glucose variability, was not. In addition, the third and fourth quartiles showed greater ORs for PEOD than the first quartile of GE index. This indicates that the greater the magnitude and longer the duration of hyperglycemia, the more end-organs are likely to be injured in patients undergoing cardiac surgery with CPB.

Multiple studies have shown that acute hyperglycemia is associated with increased morbidity and mortality, prolonged need for mechanical ventilation, and increased length of ICU stay and hospitalization [8, 14]. From a cardiac standpoint, acute hyperglycemia is associated with increased risk of myocardial dysfunction, impairment of ischemic preconditioning, and cardiac arrythmias. Neurologically, acute hyperglycemia is associated with cerebral edema and disruption of the blood-

brain barrier [41]. Acute hyperglycemia also is associated with renal tubular injury [42]. Numerous studies have concluded that acute hyperglycemia exaggerates impairment of end-organ function in cardiac surgery patients. Most of these studies included measurements of the magnitude of hyperglycemia, such as peak or mean BG concentration; however, few studies have focused on the duration of hyperglycemia. Two studies in pediatric congenital cardiac surgery patients demonstrated that the duration of postoperative hyperglycemia was associated with increased morbidity and mortality [43, 44]. van der Horst et al. reported that persistent hyperglycemia in patients with myocardial infarction patients was strongly associated with major adverse cardiac events within 30 days of myocardial infarction [45]. In addition, Wu et al. demonstrated that persistent hyperglycemia was associated with mortality in patients with intracerebral hemorrhage [46]. We demonstrated that not only the magnitude but also the duration of hyperglycemia should be considered during cardiac surgery with CPB. The median GE index of the PEOD group was approximately 170 mg/dL×h in this study. This means that, on average, a patient in the PEOD group had a BG concentration of 350 mg/dL for 1 hour and a BG concentration of 214 mg/dL for 5 hours intraoperatively. Although the GE index is the product of the magnitude and the duration of BG concentration ≥180 mg/dL, it remains unclear whether a tremendous increase in BG concentration for a

relatively short duration has the same adverse effect as a mild increase for a long duration. In the former case, both the CV and the GE index should increase. However, CV was not found to be a significant predictor of the PEOD in this study. Future research should be investigated whether long durations of mild hyperglycemia, which may be occasionally overlooked intraoperatively, has an unignorable effect on the development of PEOD.

This study showed that the cut-off value of GE index for predicting PEOD was 91.6 mg/dL×h. This value should be used to predict PEOD rather than as a treatment criterion for acute hyperglycemia. Although GE index was independently associated with adverse patient outcomes, it is impossible to determine whether a high GE index is a risk factor for adverse outcomes or merely a marker for severity of patient condition from our observational study. However, using the GE index, we could demonstrate the clinical importance of both the magnitude and duration of hyperglycemia. Ideally, the perioperative BG concentration should be consistently below 180 mg/dL. This could be achieved through the measurement of BG concentration every few minutes and constant intensive insulin treatment. A closed-loop artificial pancreas device, such as the STG-55 (Nikkiso Co. Ltd., Tokyo, Japan), could decrease the GE index more efficiently and safely during cardiac surgery with CPB [47].

Glucose variability, represented as CV, was not an important predictor of POED in this study. Several studies have reported an association between increased glucose variability and mortality or morbidity in cardiac surgery and the ICU setting [23–25]. Glucose variability is likely to increase intraoperatively in cardiac surgery patients due to the acute development of hyperglycemia, insulin resistance, and administration of glucose-containing cardioplegic solutions [22]. In this study, relatively higher levels of intraoperative glucose variability were observed in both the PEOD and non-PEOD groups than those reported in previous studies [22, 23, 25]; therefore, it was potentially impossible to distinguish between its effect on the outcome in both groups. If excessive glucose variability can be decreased intraoperatively, it may be identified as an independent predictor of PEOD.

In this study, BMI, PAD, eGFR, and CAI were also identified as predictors of PEOD. It is plausible that these covariates were associated with the severity of patient illness, thus contributing to PEOD.

The primary outcome of this study was the composite event of four vital organ dysfunctions: the heart, lung, brain, and kidney. These organs are vulnerable to ischemic, inflammatory, and oxidative stress caused by cardiac surgery with CPB [1, 2]. In this study, each organ dysfunction was identified according to its definitive criteria or to a surrogate that was considered to be the most common clinical

manifestation. Regarding the lungs, PMV over 24 h was used as the surrogate marker of respiratory dysfunction because one study identified PMV over 24 h to be the strongest predictor of risk-adjusted mortality in cardiac surgery [8]. The ratio of the arterial partial pressure of oxygen and fraction of inspiratory oxygen was not used because fraction of inspiratory oxygen measurement has been found to be inaccurate [48] in patients receiving low-flow oxygen therapy via nasal cannula, which was used in many patients who were weaned from mechanical ventilation in this study. Other surrogates, such as postoperative pulmonary complications, were difficult to evaluate because of the retrospective study design.

Other scoring systems commonly used to evaluate multiple organ dysfunction in the ICU, such as the Multiple Organ Dysfunction Score [49] or the Sequential Organ Failure Assessment score [50], were not used in this study. It would have been inappropriate to assess neurologic function using the Glasgow Coma Scale because all patients are sedated and intubated in the early postoperative period. Cardiac assessment using the “pressure-adjusted heart rate” or “mean arterial pressure under 70 mm Hg” cardiac assessment may be inappropriate for evaluating postoperative myocardial injury; dopamine is rarely used at our institution, and platelet concentrate transfusion or renal replacement therapy may cause underestimation during scoring. Thus, we used validated assessment

tools for vital organ dysfunction to accurately evaluate early postoperative PEOD caused by cardiac surgery with CPB.

This study has several limitations. First, since this was a retrospective study, there could be unmeasured confounders or inherent biases. Specifically, we excluded the cases that contained missing primary outcome values from the analysis, making this study potentially subject to selection bias. However, data were missing in only 1.2% of all patients who met the inclusion criteria. Second, we used both intermittent dosing and continuous infusion of regular insulin to control the intraoperative BG concentration, and initiating insulin therapy was left to the anesthesiologist's discretion. Moreover, the total intraoperative insulin administered was not included in the analysis; reliable data were not available because of electronic medical record system shortcomings. Third, we did not consider the association between postoperative BG concentrations and PEOD or ICU treatment. By setting an observational period limit of 72 h on the primary outcome, we eliminated postoperative effects as much as possible, focusing only on the relationship between the GE index and PEOD in the early postoperative period. Fourth, the preoperative mental status or cognitive dysfunction of the patient, which may affect the incidence of POCD, was not assessed because of the retrospective nature of the study. Moreover, this study adopted the ICDSC to detect POCD

because of our institutional policy; however, the well-recognized Confusion Assessment Method for the Intensive Care Unit is a more sensitive and specific screening tool for diagnosing POCD [51]. Fifth, GE index was calculated based on the assumption that the magnitude of BG concentration remained unchanged between measurements. Fluctuations in BG concentration between measurements were not considered; therefore, the GE index might be inaccurate if large fluctuations in BG concentration occurred during these blind periods. Continuous monitoring of BG concentration could provide a different perspective on the management of BG concentration during cardiac surgery. Finally, the urine output criteria for an AKI diagnosis were not used in this study because non-protocolized administration of diuretics may obscure AKI incidences.

Conclusion

Intraoperative GE index, the products of the magnitude and duration of BG concentration ≥180 mg/dL, was an independent predictor of end-organ damage within 72 h postoperatively, defined as a composite event of AKI, POCD, MI, and PMV. Not only is the magnitude of hyperglycemia associated with PEOD, but also the duration of hyperglycemia. Thus, the GE index could serve as a predictor of PEOD and could possibly help develop a more time-conscious algorism for BG concentration control in cardiac surgery with CPB. It is of great interest to establish whether a shorter duration, or ideally no occurrence, of hyperglycemia leads to a reduction in morbidity and mortality in cardiac surgery. However, this hypothesis should be verified in large prospective trials.

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Figure legend

Fig. 1 The study population flowchart

In total, 1360 who underwent cardiac surgery with cardiopulmonary bypass were evaluated, and 553 patients were included in this study.

CPB Cardiopulmonary bypass, *ECMO* Extracorporeal membrane oxygenation, *LVAD* Left ventricular assist device, *TAVR* Transcatheter aortic valve replacement, *RRT* Renal replacement therapy

Fig. 2 ROC curve for PEOD of GE index and CV

Compared with CV, GE index has significantly higher accuracy (P <0.001) of predicting PEOD

ROC receiver operating characteristic, *PEOD* postoperative end-organ dysfunctions, *AUC* area under the curve, *GE index* glucose exposure index, *CV* coefficient of variation

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	Univariable Analysis		
	Non-PEOD (n = 252)	**PEOD (n = 301)**	***P*-value**
Age, yr [median (IQR)]	65 [51–72]	72 [65–78]	<0.001
Sex - male [n (%)]	150 (59.5)	198 (65.8)	0.134
BMI, kg/m^2 [mean (SD)]	22.6 (3.4)	23.8 (3.9)	<0.001
ASA-PS ≥3 [n (%)]	122 (48.4)	215 (71.4)	<0.001
NYHA ≥3 [n (%)]	78 (31.0)	156 (51.8)	<0.001
EuroSCOREII [median (IQR)]	1.8 [1.1–3.1]	3.2 [2.0–6.3]	<0.001
Comorbidity			
Hypertension [n (%)]	137 (54.4)	227 (75.4)	<0.001
Diabetes [n (%)]	39 (15.5)	82 (27.2)	<0.001
Diabetes on insulin [n (%)]	9 (3.6)	15 (5.0)	0.531
Atrial fibrillation [n (%)]	31 (12.3)	46 (15.3)	0.327
Acute myocardial infarction [n (%)]	5 (2.0)	11 (3.7)	0.312
Cerebrovascular disease [n (%)]	18 (7.1)	33 (11.0)	0.141
Peripheral artery disease [n (%)]	51 (20.2)	85 (28.2)	0.037
Current smoker [n (%)]	31 (12.3)	47 (15.6)	0.273
Chronic lung disease [n (%)]	7 (2.8)	18 (6.0)	0.099
Active infectious endocarditis [n (%)]	12 (4.8)	16 (38.2)	0.847
Critical preoperative state[a] [n (%)]	4 (1.6)	12 (4.0)	0.126
Dementia [n (%)]	4 (1.6)	6 (2.0)	0.761

	Univariable Analysis		
	Non-PEOD (n = 252)	**PEOD (n = 301)**	***P*-value**
Medication			
ACEi/ARB [n (%)]	98 (38.9)	145 (48.2)	0.032
Beta-blocker [n (%)]	77 (30.6)	119 (39.5)	0.032
Preoperative laboratory and physiological data			
Hemoglobin, g/dL [mean (SD)]	13.1 (1.7)	12.5 (1.9)	<0.001
Creatinine, mg/dL [median (IQR)]	0.80 [0.66–0.93]	0.90 [0.76– 1.09]	<0.001
eGFR, mL/min/1.73m^2 [median (IQR)]	70 [57–83]	58 [47–70]	<0.001
Total bilirubin, mg/dL [median (IQR)]	0.60 [0.20– 2.80]	0.60 [0.50– 4.00]	0.624
LVEF, % [median (IQR)]	66 [61–71]	64 [57–70]	0.005
Pulmonary hypertension[b] [n (%)]	112 (44.4)	155 (51.5)	0.124
NT-proBNP, pg/dL [median (IQR)]	204 [78–677]	633 [272–1982]	<0.001

Table 1. Baseline characteristics, Comorbidities, Preoperative Covariates in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Data are presented as mean (SD), median (IQR), or n = absolute number (%), as appropriate.

PEOD Postoperative end-organ dysfunction, *SD* Standard deviation, *IQR* Interquartile range, *BMI* Body mass index, *ASA-PS* American Society of Anesthesiology Physical Status classification, *NYHA* New York Heart Association functional classification, *EuroSCORE II* The European System for Cardiac Operative Risk Evaluation II, *ACEi / ARB* Angiotensin-converting enzyme receptor inhibitors / Angiotensin II blockers, *eGFR* Estimated glomerular filtration rate calculated by revised equations from Japanese serum creatinine, *LVEF* Left ventricular ejection fraction, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide [a] Ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before operation room, preoperative inotropes or IABP

[b] Estimated pulmonary artery systolic pressure >30 mmHg

	Univariable Analysis		
	Non-PEOD (n = 252)	**PEOD (n = 301)**	***P*-value**
Urgent surgery [n (%)]	9 (3.6)	14 (4.7)	0.67
Type of surgery [n (%)]			
Coronary artery bypass grafting	44 (17.5)	67 (22.3)	0.167
Valve surgery	168 (66.7)	204 (67.8)	0.786
Aortic surgery	28 (11.1)	42 (14.0)	0.369
Others	55 (21.8)	72 (23.9)	0.612
Surgery requiring more than 2 procedures[a]	61 (24.2)	102 (33.9)	0.015
Duration of anesthesia, min [median (IQR)]	430 [369–520]	464 [410–558]	<0.001
Duration of surgery, min [median (IQR)]	340 [277–419]	374 [314–464]	<0.001
Duration of CPB, min [median (IQR)]	160 [126–199]	189 [142–239]	<0.001
Duration of aortic cross-clamp, min [median (IQR)]	108 [77–144]	118 [91–163]	<0.001
Intra-aortic balloon pumping [n (%)]	3 (1.2)	21 (7.0)	<0.001
Intraoperative drugs and transfusion			
Catecholamine index[b], μg/kg/min [median (IQR)]	1.0 [0.0–2.8]	2.4 [0.8–5.1]	<0.001
Vancomycin [n (%)]	6 (2.4)	5 (1.7)	0.559
Red blood cell concentrates, Units [median (IQR)]	0 [0–3.6]	3.6 [0–5.4]	<0.001
Intraoperative blood glucose data			
Mean magnitude of BG concentration ≥180 mg/dL, mg/dL [median (IQR)]	10.6 [0.0–20.5]	44.7 [22.0–75.2]	<0.001
Duration of BG concentration ≥180mg/dL, min [median (IQR)]	60 [20–135]	210 [125–295]	<0.001

	Univariable Analysis		
	Non-PEOD (n = 252)	**PEOD (n = 301)**	***P*-value**
Glucose coefficient of variation (%)	24.3 [20.1–30.0]	26.8 [21.0–32.9]	0.005
Glucose exposure index, mg/dL×h [median (IQR)]	26.6 [0.0–67.8]	170.7 [61.1–372.3]	<0.001
Glucose exposure index, interquartile [n (%)]			<0.001
First quartile	96 (38.1)	43 (14.3)	
Second quartile	97 (38.5)	41 (13.6)	
Third quartile	43 (17.1)	95 (31.6)	
Fourth quartile	16 (6.3)	122 (40.5)	

Table 2. Surgical Characteristics in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Data are presented as mean (SD), median (IQR), or n = absolute number (%), as appropriate.

PEOD Postoperative end-organ dysfunction, *SD* Standard deviation, *IQR* Interquartile range, *CPB* Cardiopulmonary bypass, *BG* Blood glucose

[a] Combined surgery including coronary artery bypass grafting, valve surgery, aortic surgery, and others such as Maze surgery

[b] Dopamine dose+dobutamine dose+(noradrenaline dose+adrenaline dose)×100, μg/kg/min

		n = 553
Postoperative end-organ dysfunction		301 (54.4)
Acute kidney injury [n (%)]		221 (40.0)
Acute kidney injury stage [n (%)]	1	187 (33.8)
	2	22 (4.0)
	3	12 (2.2)
Renal replacement therapy [n (%)]		9 (1.6)
Postoperative cognitive dysfunction and delirium [n (%)]		115 (20.8)
Maximum ICDSC score [n (%)]	0	27 (4.9)
	1	74 (13.4)
	2	221 (40.0)
	3	115 (20.8)
	4	45 (8.1)
	5	42 (7.6)
	6	21 (3.8)
	7	6 (1.1)
	8	1 (0.2)
Myocardial injury [n (%)]		12 (2.2)
Prolonged mechanical ventilation [n (%)]		79 (14.3)

Table 3. Severities of PEOD

Data are presented as n = absolute number (%).

PEOD Postoperative end-organ dysfunction, *ICDSC* Intensive Care Delirium Screening Checklist

	Non-PEOD (n = 252)	PEOD (n = 301)	*P*-value
New onset atrial fibrillation [n (%)]	78 (31.0)	125 (41.5)	0.013
Postoperative infection[a] [n (%)]	11 (4.4)	25 (8.3)	0.082
Length of mechanical ventilation, hour [median (IQR)]	7.0 [5.0–13.0]	13.0 [7.0–25.0]	<0.001
Length of ICU stay, day [median (IQR)]	3 [2–5]	5 [3–7]	<0.001
Length of hospitalization, day [median (IQR)]	21 [17–28]	26 [20–36]	<0.001
90-day all-cause mortality, day [n (%)]	0 (0.0)	6 (2.0)	0.034

Table 4. Prognostic Variables between the Non-PEOD and the PEOD group

Data are presented as median (IQR) or n = absolute number (%), as appropriate.

PEOD Postoperative end-organ dysfunction, *IQR* Interquartile range

[a] The composite event of surgical site infection, deep sternal infection, urinary tract infections, pneumonia, and septicemia

	Adjusted Model		
	Odds ratio	**95% CI**	***P*-value**
Age, yr	1.02	1.00-1.04	0.11
BMI, kg/m^2	1.13	1.06-1.21	<0.001
ASA-PS ≥3	1.42	0.88–2.30	0.15
NYHA ≥3	1.03	0.62–1.71	0.91
EuroSCOREⅡ	0.99	0.93–1.05	0.7
Hypertension	1.48	0.86–2.55	0.16
Diabetes	0.60	0.33–1.09	0.093
Peripheral artery disease	1.78	1.02–3.10	0.041
Chronic lung disease	1.73	0.55–5.47	0.35
ACEi / ARB	1.06	0.66–1.71	0.8
Beta-blocker [n (%)	1.16	0.71–1.90	0.55
Preoperative hemoglobin, mg/dL	0.97	0.82–1.15	0.74
Preoperative eGFR, mL/min/1.73m^2	0.98	0.97–1.00	0.045
LVEF, %	0.99	0.96–1.01	0.22
NT-proBNP, pg/dL (every 100 pg/dL increase)	1.00	0.99–1.02	0.46
Surgery requiring more than 2 procedures	1.02	0.59–1.74	0.95
Duration of surgery, min (every 10 min increase)	0.98	0.94–1.01	0.22
Duration of CPB, min (every 10 min increase)	1.04	0.98–1.10	0.2
Intra-aortic balloon pumping	2.93	0.49–17.50	0.24
Catecholamine index[a], μg/kg/min	1.13	1.02–1.26	0.026
Red blood cell concentrates, Unit	1.06	0.95–1.18	0.32

	Adjusted Model		
	Odds ratio	**95% CI**	***P*-value**
Glucose coefficient of variation, %	0.97	0.97–1.02	0.2
Glucose exposure index			
First quartile	Reference		
Second quartile	0.94	0.51–1.75	0.85
Third quartile	5.65	2.94–10.90	<0.001
Fourth quartile	20.80	8.01–54.00	<0.001

Table 5. Logistic Regression[b] for PEOD

CI Confidence interval, *BMI* Body mass index, *ASA-PS* American Society of Anaesthesiology Physical Status classification, *NYHA* New York Heart Association functional classification, *EuroSCORE II* The European System for Cardiac Operative Risk Evaluation II, *ACEi / ARB* Angiotensin converting enzyme receptor inhibitors / Angiotensin II blockers, *eGFR* Estimated glomerular filtration rate calculated by revised equations from serum creatinine in Japan, *LVEF* Left ventricular ejection fraction, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *CPB* Cardiopulmonary bypass

[a] Dopamine dose+dobutamine dose+(noradrenaline dose+adrenaline dose)×100, μg/kg/min

[b] Logistic regression model with the variables whose *P*-values <0.1 in the univariable analysis was applied. Preoperative serum

creatinine and duration of anesthesia were excluded because of their high correlation with eGFR and duration of surgery, respectively. Duration of aortic cross-clamp was also excluded based on the previous study. Multicollinearity was checked and not detected (all variance inflated factors <10). The C-statistics of the model was 0.86.

Fig.1

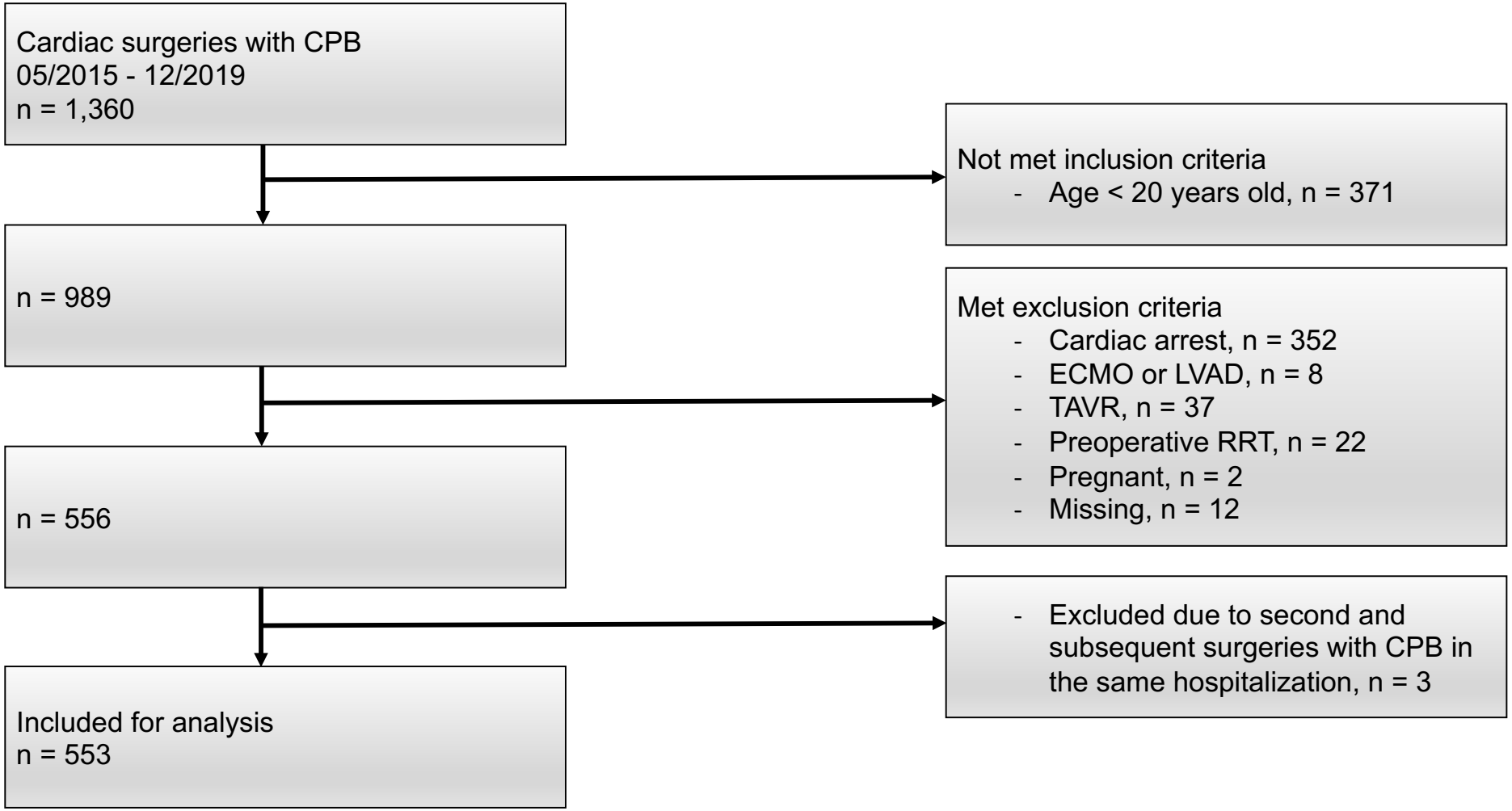
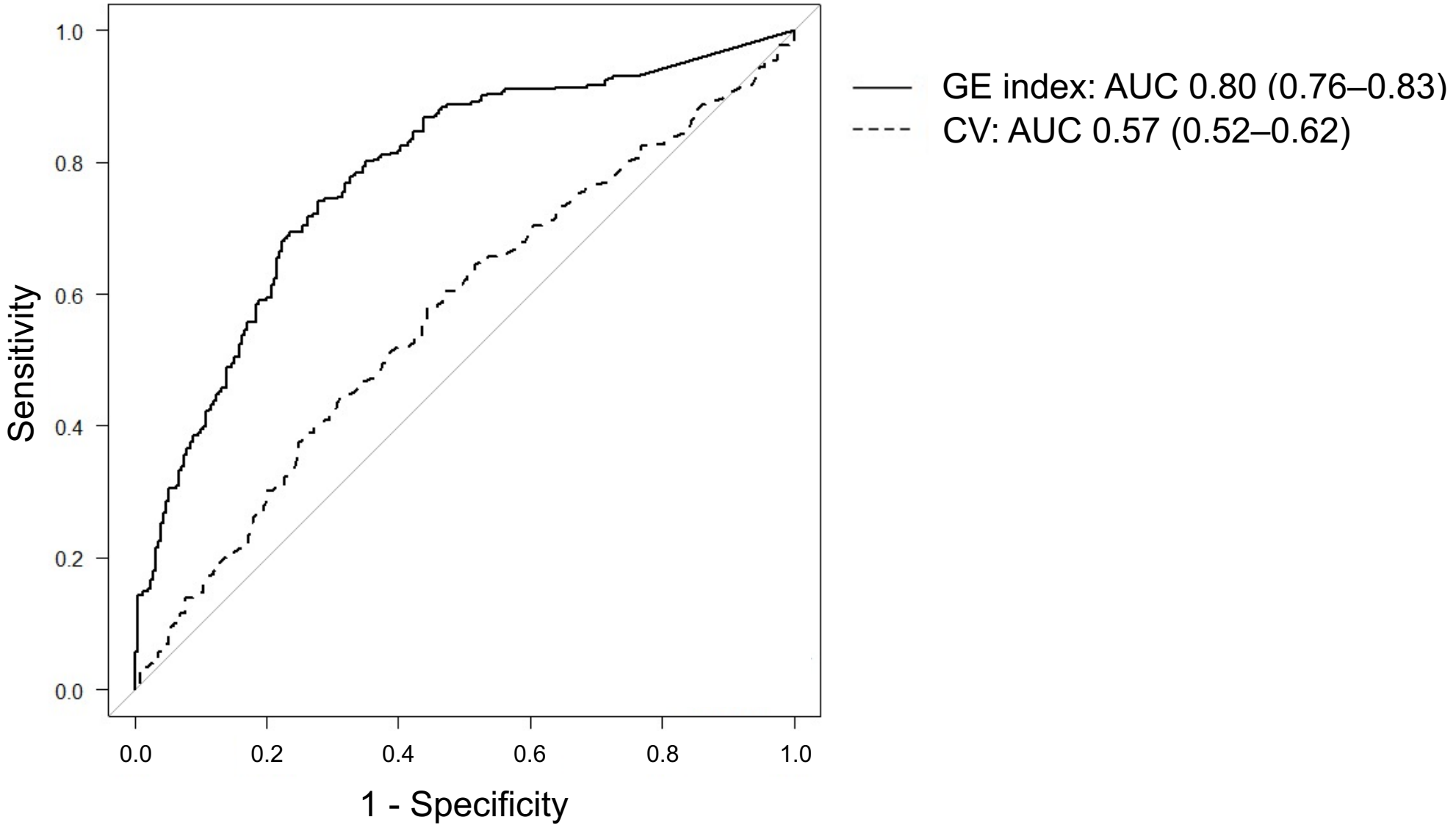
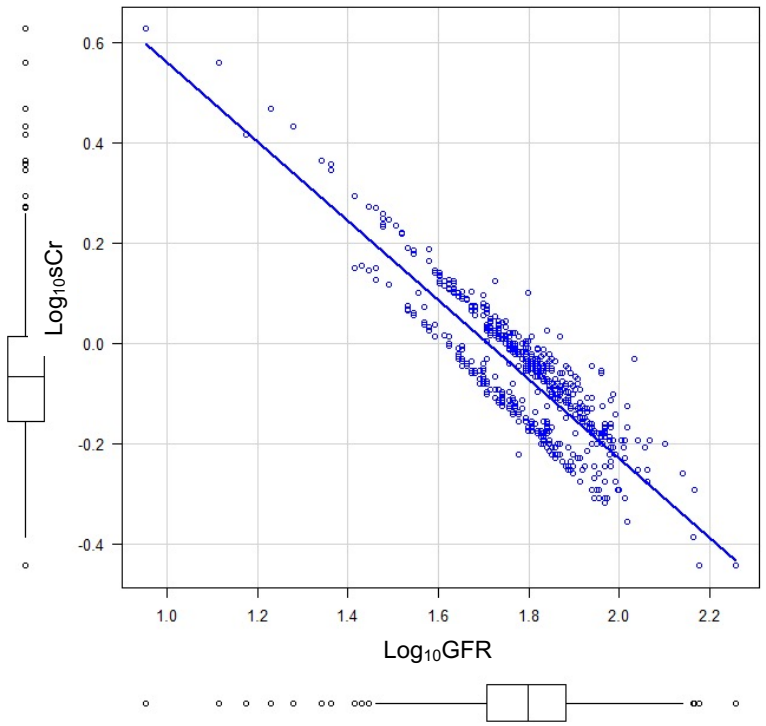

Cardiac surgeries with CPB
05/2015 - 12/2019
n = 1,360
Not met inclusion criteria
- Age < 20 years old, n = 371
n = 989
Met exclusion criteria
- Cardiac arrest, n = 352
- ECMO or LVAD, n = 8
- TAVR, n = 37
- Preoperative RRT, n = 22
- Pregnant, n = 2
- Missing, n = 12
n = 556
- Excluded due to second and subsequent surgeries with CPB in the same hospitalization, n = 3
Included for analysis
n = 553

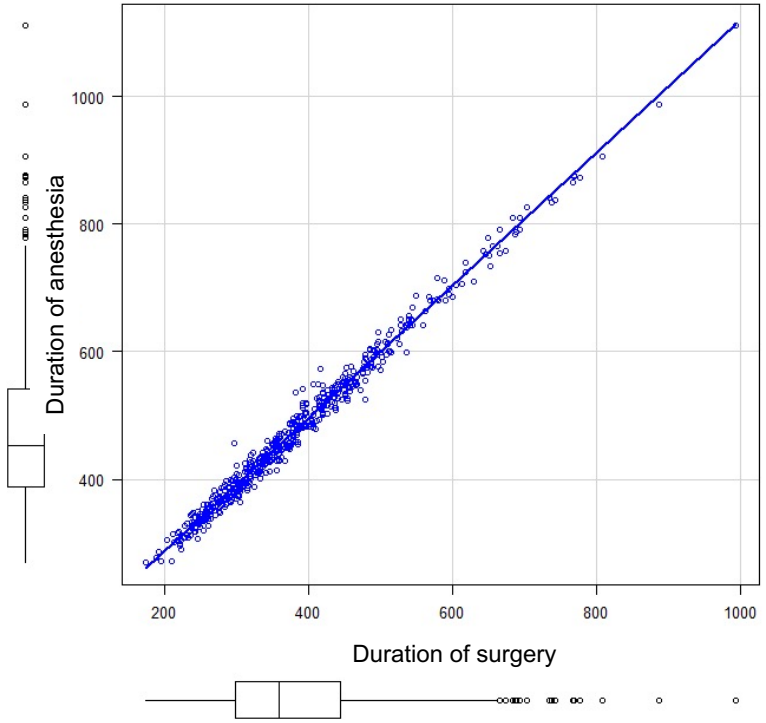
Fig.2


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
GE index: AUC 0.80 (0.76–0.83)
CV: AUC 0.57 (0.52–0.62)

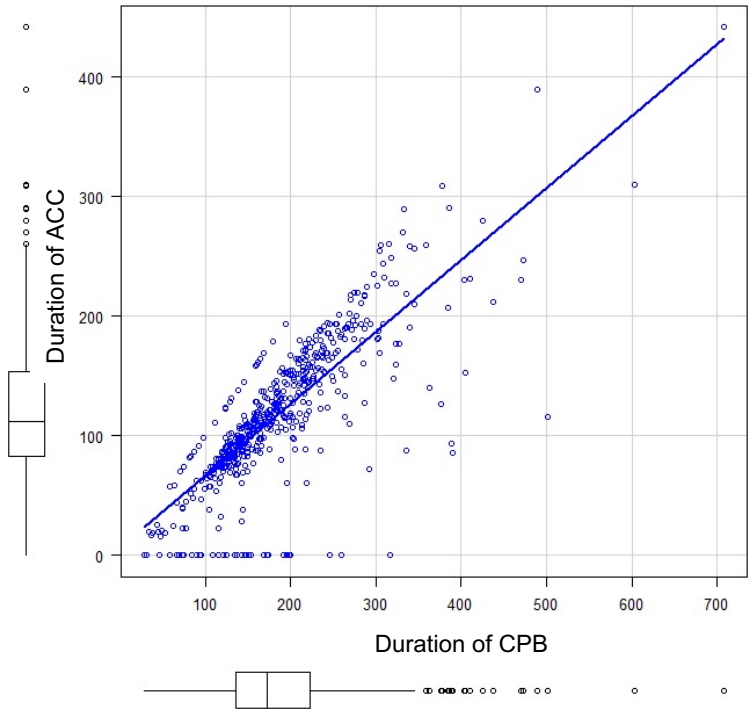
Supplemental Fig. 1 Correlation coefficient between variables considered clinically correlated



sCr and eGFR
Correlation coefficient = -0.96



Duration of anesthesia and
duration of surgery
Correlation coefficient = 0.99



Duration of CPB and
duration of ACC
Correlation coefficient = 0.82

sCr serum creatinine; *eGFR* estimated glomerular filtration rate calculated by revised equations from Japanese serum creatinine; *CPB* cardiopulmonary bypass; *ACC* aortic closs-clamp