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ORIGINAL RESEARCH

Association Between Perioperative Adverse Cardiac Events and Mortality During One-Year Follow-Up After Noncardiac Surgery

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BACKGROUND: Cardiac complications are associated with perioperative mortality, but perioperative adverse cardiac events (PACEs) that are associated with long-term mortality have not been clearly defined. We identified PACE as a composite of myocardial infarction, coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, or stroke during the 30-day postoperative period and we compared mortality according to PACE occurrence.

METHODS AND RESULTS: From January 2011 to June 2019, a total of 203 787 consecutive adult patients underwent noncardiac surgery at our institution. After excluding those with 30-day mortality, mortality during a 1-year follow-up was compared. Machine learning with the extreme gradient boosting algorithm was also used to evaluate whether PACE was associated with 1-year mortality. After excluding 1203 patients with 30-day mortality, 202 584 patients were divided into 7994 (3.9%) patients with PACE and 194 590 (96.1%) without PACE. After an adjustment, the mortality was higher in the PACE group (2.1% versus 7.7%; hazard ratio [HR], 1.90; 95% CI, 1.74–2.09; $P<0.001$). Results were similar for 7839 pairs of propensity-score-matched patients (4.9% versus 7.9%; HR, 1.64; 95% CI, 1.44–1.87; $P<0.001$). PACE was significantly associated with mortality in the extreme gradient boostingmodel.

CONCLUSIONS: PACE as a composite outcome was associated with 1-year mortality. Further studies are needed for PACE to be accepted as an end point in clinical studies of noncardiac surgery.

Key Words: cardiac event ■ mortality ■ noncardiac surgery

More than 200 million noncardiac surgeries are performed worldwide every year.[1] As the average age and risk of these patients increase,[2] perioperative mortality rates increase, making it one of the leading causes of death in developed countries.[3] Previous studies have stratified complications after noncardiac surgery and adopted it as a relevant end point. Clavien-Dindo classification is the most widely used method and has been validated in a large number of patients.[4] However, it does not specifically account for cardiac events that are common and fatal.[5]

Major adverse cardiac events, a composite of major end points including death or cardiac death, myocardial infarction, and stroke, are commonly used in clinical studies evaluating cardiovascular outcomes.[6] Although the association with mortality is firmly established for major adverse cardiac events, their incidence is decreasing with advances in perioperative care, which limits their use as study end points.[7] And by accounting only for major outcomes, various perioperative cardiac events that are not considered major may be neglected. Although other minor perioperative cardiac events were also reported alongside increased

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CLINICAL PERSPECTIVE

What Is New?

- A composite of perioperative adverse cardiac events was shown to be associated with long-term mortality of noncardiac surgery.

What Are the Clinical Implications?

- With further verifications, this may be used as a composite outcome in future studies.

Nonstandard Abbreviations and Acronyms

PACE	perioperative adverse cardiac events
SHAP	Shapley additive explanations

mortality during the follow-up period,[8] some studies showed that these events may be self-limiting and have no significant effect on long-term mortality.[9] Therefore, it is unclear to what extent perioperative adverse cardiac events (PACE) in noncardiac surgery portends a higher mortality risk. In this study, we enrolled consecutive adult patients who underwent noncardiac surgery and divided them into 2 groups according to occurrence of cardiac events during the first 30 days after surgery. By comparing 1- and 3-year mortalities of these patients, we aimed to provide evidence for the association between PACE and long-term mortality.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Samsung Medical Center at jong-hwan.park@samsung.com. The Institutional Review Board of Samsung Medical Center granted a waiver for protocol approval and the requirement for written informed consent for this study (SMC 2021-06-078) because the study registry was curated in de-identified form. Our study was conducted in accordance with the Declaration of Helsinki, and the report was organized according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data Curation and Study Population

The SMC-NoCop (Samsung Medical Center-Non Cardiac operation, KCT 0006363) registry consists of 203 787 consecutive adult patients who underwent noncardiac surgery at Samsung Medical Center, Seoul, Korea, between January 2011 and June 2019. SMC-NoCop is a large, single-center, de-identified cohort that was extracted from the institutional electronic archive system using the "Clinical Data Warehouse Darwin-C," a system built for investigators to search and retrieve de-identified medical records. It contains medical information from electronic hospital records of over 4 million patients with more than 900 million laboratory findings and 200 million prescriptions. In patients with multiple surgeries, only the first surgery was retained in the registry. For mortality outside the institution, this system uses a unique personal identification number to consistently update and confirm data with the National Population Registry of the Korea National Statistical Office. All relevant preoperative variables including demographic data, underlying disease, and laboratory blood tests were recorded on preoperative evaluation sheets, which were reviewed by independent investigators who were blinded to mortality data. The Charlson comorbidity index was estimated from preoperative diagnoses according to *International Classification of Diseases, Tenth Revision (ICD-10)* codes.[10] Postoperative diagnoses were separately recorded and also based on *ICD-10* codes. Postoperative events were organized by reviewing extracted in-hospital progress notes, nursing charts, discharge notes, and results from cardiac examinations.

Definitions and Study End Points

PACE was defined as a composite of myocardial infarction, coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, or stroke during hospital stay within 30 days after surgery.[8,11] Myocardial infarction was defined as cardiac marker elevation with symptom presence or new electrocardiographic changes compatible with myocardial infarction following the Fourth Universal Definition of Myocardial Infarction.[12] Heart failure was when the patient exhibited new or worsening symptoms on presentation, received treatment initiation or intensification specifically for heart failure, or showed objective evidence of new or worsening heart failure.[6] Arrhythmic attack included rapid atrial fibrillation, ventricular tachycardia, and bradycardia that required medical intervention such as administration of an antiarrhythmic agent, electrical shock, or temporary cardiac pacing. Stroke was defined as neurological function loss caused by an ischemic or hemorrhagic event with symptoms persisting at least 24 hours. Surgical risk was stratified according to the European Society of Cardiology/European Society of Anaesthesiology guidelines on noncardiac surgery.[5]

The primary end point was mortality during the first year, and mortality was also compared for the 3-year

follow-up. Additionally, we identified variables associated with 1-year mortality using machine learning.

Statistical Analysis

Mean±SD or median with interquartile range for baseline characteristics of each group are presented for continuous variables and numbers and percentages are presented for categorical variables. The chi-square or Fisher's exact test was used to compare differences between the groups for categorical variables, and the *t* test or the Mann-Whitney test was used for continuous variables. Mortalities were compared by Cox regression analysis and multivariable adjustment included the following variables: male sex, age, diabetes, current alcohol use, chronic kidney disease, Charlson comorbidity index, stroke, coronary artery disease, heart failure, arrhythmia, peripheral artery disease, aortic disease, valvular heart disease, European Society of Cardiology/European Society of Anaesthesiology intermediate-to-high surgical risk, emergency operation, and operation duration. Cox regression analysis results are reported as hazard ratios (HRs) with 95% CIs. Considering the enormous differences in variables between the groups, we additionally generated a matched population from a propensity score, wherein we used 0.1 caliber widths of the pooled SD of the logit of the propensity score on all available variables and generated 1:1 individually matched populations without replacement. After propensity-score matching, an absolute standardized difference of <10% represented successfully balanced variables between the groups, and we conducted stratified Cox regression analysis to compare mortality. We generated the pairs according to the propensity score and used these pairs as strata. We also generated Kaplan-Meier curves for mortalities in the crude and matched populations and compared mortalities using the log-rank test. Based on the sample size, our analysis power was 0.82 when HR=1.2, and it was 0.99 when HR >1.3.[13] A subgroup analysis was performed to evaluate whether the observed association interacted with relevant variables such as sex, hypertension, coronary artery disease, diabetes, chronic kidney disease, European Society of Cardiology/European Society of Anaesthesiology intermediate-to-high surgical risk, and emergency operation. We also calculated the effects of unmeasured confounding factors. In this method, we evaluated the significance of the observed association between PACE and mortality, assuming a 40% prevalence of unmeasured confounding factors.[14] As an additional analysis, we used machine-learning techniques to validate whether PACE was one of the perioperative factors that are related to 1-year mortality. We also evaluated preoperative factors that are associated with the development of PACE using the same method. For machine-learning techniques, we chose the extreme gradient boosting algorithm, which is a decision-tree-based ensemble model using a gradient boosting framework and the Shapley value framework,[15,16] and the feature interpretation is presented as a Shapley additive explanations (SHAP) summary plot. Analyses were performed with R 4.1.0 (Vienna, Austria; http://www.R-project.org/).

RESULTS

Baseline Characteristics

A total of 203 787 patients were in the SMC-NoCop registry, and we excluded 1203 (0.6%) patients with 30-day mortality. The remaining 202 584 patients were enrolled into the study and divided into 2 groups according to PACE presence during the 30 days after surgery: 7994 (3.9%) patients in the PACE group and 194 590 (96.1%) in the no PACE group. Baseline characteristics of the 2 groups are summarized in Table 1. The median duration from surgery to PACE was 2 days (interquartile range: 1–4 days). The incidence for each PACE component are summarized in Table 2. Additionally, we also provided the incidences for each composite of PACE according to 1-year mortality. Preoperatively, the PACE group tended to include more men and have higher incidence of risk factors such as old age and comorbidities. The PACE group also underwent higher risk surgery with longer operation durations. Surgery types are summarized in Table S1.

Mortality

The median follow-up durations were 1125 days (interquartile range: 406–1959 days) in the no PACE group and 1063 days (interquartile range: 412–1824 days) in the PACE group, and all patients finished 1-year follow-up without censoring. Overall mortality was 2.4% (4852/202 584) during first-year follow-up and the number of observed death was 11 165 during 3-year follow-up. After adjustment, the PACE group showed significantly increased risk of mortality during the first year after surgery (2.1% versus 7.7%; HR, 1.90; 95% CI, 1.74–2.09; *P*<0.001 for all-cause mortality and 0.9% versus 3.4%; HR, 1.81; 95% CI, 1.58–2.08; *P*<0.001 for cardiovascular mortality; Table 3, Figure 1). The risk of 3-year mortality was also higher in the PACE group (9.0% versus 24.3%; HR, 1.73; 95% CI, 1.62–1.84; *P*<0.001 for all-cause mortality and 4.7% versus 13.3%; HR, 1.64; 95% CI, 1.50–1.79; *P*<0.001 for cardiovascular mortality; Table 3).

Using propensity-score matching, 7839 pairs of patients were generated, and similar results were observed for all-cause mortality (4.9% versus 7.9%; HR, 1.64; 95% CI, 1.44–1.87; *P*<0.001 for 1-year follow-up

Table 1. Baseline Characteristics According to Perioperative Adverse Cardiac Event

	Entire population				Propensity-score-matched population		
	No PACE (n=194 590)	PACE (n=7994)	*P* value	ASD	No PACE (n=7839)	PACE (n=7839)	ASD
Male sex	82 622 (42.5)	4754 (59.5)	<0.001	34.5	4780 (61.0)	4645 (59.3)	3.5
Age, y	62.2 (±15.1)	64.8 (±12.7)	<0.001	89.8	65.5 (±12.2)	64.6 (±12.7)	7.5
Hypertension	47 486 (24.4)	3883 (48.6)	<0.001	51.9	4031 (51.4)	3771 (48.1)	6.6
Diabetes	21 372 (11.0)	2009 (25.1)	<0.001	37.4	1938 (24.7)	1947 (24.8)	0.3
Current alcohol	39 429 (20.3)	1023 (12.8)	<0.001	20.2	946 (12.1)	1014 (12.9)	2.6
Current smoking	15 059 (7.4)	484 (6.1)	<0.001	6.7	421 (5.4)	472 (6.0)	2.8
Chronic kidney disease	2948 (1.5)	417 (5.2)	<0.001	20.6	327 (4.2)	390 (5.0)	3.8
Previous disease							
Charlson comorbidity index	0.25 (±0.78)	0.70 (±1.48)	<0.001	37.6	0.67 (±1.37)	0.68 (±1.45)	0.9
Stroke	3509 (1.8)	674 (8.4)	<0.001	30.4	627 (8.0)	627 (8.0)	<0.1
Coronary artery disease	3075 (1.6)	1035 (12.9)	<0.001	44.9	941 (12.0)	976 (12.5)	1.4
Heart failure	361 (0.2)	248 (3.1)	<0.001	23.1	155 (2.0)	192 (2.4)	3.2
Arrhythmia	1882 (1.0)	1055 (13.2)	<0.001	49.1	694 (8.9)	915 (11.7)	9.3
Peripheral artery disease	470 (0.2)	96 (1.2)	<0.001	11.4	80 (1.0)	90 (1.1)	1.2
Aortic disease	547 (0.3)	131 (1.6)	<0.001	14	119 (1.5)	122 (1.6)	0.3
Valvular heart disease	229 (0.1)	86 (1.1)	<0.001	12.5	55 (0.7)	68 (0.9)	1.9
Chronic obstructive pulmonary disease	3170 (1.6)	420 (5.3)	<0.001	20	410 (5.2)	404 (5.2)	0.3
Operative variables							
Intermediate-to-high surgical risk	117 239 (60.2)	6189 (77.4)	<0.001	37.7	6163 (78.6)	6048 (77.2)	3.5
General anesthesia	168 286 (86.5)	7065 (88.4)	<0.001	5.7	6914 (88.2)	6923 (88.3)	0.4
Emergency operation	13 011 (6.7)	923 (11.5)	<0.001	16.9	837 (10.7)	872 (11.1)	1.4
Operation duration, min	129 (±102)	163 (±129)	<0.001	29.3	173 (±134)	166 (±119)	5

Data are presented as n (%) or mean (±SD). Surgical risk was stratified according to 2014 European Society of Cardiology/European Society of Anaesthesiology guidelines. The multivariable analysis retained male sex, age, diabetes, current alcohol, chronic kidney disease, Charlson comorbidity index, stroke, coronary artery disease, heart failure, arrhythmia, peripheral arterial occlusive disease, aortic disease, heart valve disease, intermediate-to-high surgical risk, emergency operation, and operation duration. ASD indicates absolute standardized difference; and PACE, perioperative adverse cardiac events.

and 15.3% versus 24.4%; HR, 1.51; 95% CI, 1.38–1.66; *P*<0.001 for 3-year follow-up; Figure 2, Table 3) and cardiovascular mortalities (2.1% versus 3.4%; HR, 1.48; 95% CI, 1.38–2.04; *P*<0.001 for 1-year follow-up and 8.5% versus 13.4%; HR, 1.49; 95% CI, 1.31–1.69; *P*<0.001 for 3-year follow-up). The risk of 1-year

Table 2. Incidence for Each Composite of Perioperative Adverse Cardiac Event

	Study patients (n=202 584)	One-year survivor (n=19 733)	One-year mortality (n=4751)
PACE	7994 (3.9)	7380 (3.7)	614 (12.9)
Myocardial infarction	1054 (0.5)	959 (0.5)	95 (2.0)
Unstable angina	63 (0.03)	62 (0.0)	1 (0.0)
Coronary revascularization	138 (0.1)	130 (0.1)	8 (0.2)
Congestive heart failure	320 (0.2)	294 (0.1)	26 (0.5)
Arrhythmic attack	6285 (3.1)	5829 (2.9)	456 (9.6)
Acute pulmonary embolism	281 (0.1)	250 (0.1)	31 (0.7)
Cardiac arrest	77 (0.03)	65 (0.0)	12 (0.3)
Stroke	544 (0.3)	501 (0.3)	43 (0.9)

Data are presented as n (%). PACE indicates perioperative adverse cardiac events.

Table 3. Mortalities According to Perioperative Adverse Cardiac Event

	No PACE	PACE	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Entire population	n=194 590	n=7994				
1-y mortality	4137 (2.1)	614 (7.7)	3.51 (3.23–2.82)	<0.001	1.90 (1.74–2.09)	<0.001
Cardiovascular death	1820 (0.9)	275 (3.4)	3.58 (3.15–4.06)	<0.001	1.81 (1.58–2.08)	<0.001
3-y mortality	9911 (9.0)	1251 (24.3)	3.06 (2.89–3.25)	<0.001	1.73 (1.62–1.84)	<0.001
Cardiovascular death	4978 (4.7)	635 (13.3)	3.11 (2.86–3.37)	<0.001	1.64 (1.50–1.79)	<0.001
Propensity-score-matched population	n=7839	n=7839				
1-y mortality	384 (4.9)	616 (7.9)			1.64 (1.44–1.87)	<0.001
Cardiovascular death	161 (2.1)	268 (3.4)			1.48 (1.38–2.04)	<0.001
3-y mortality	850 (15.3)	1222 (24.4)			1.51 (1.38–1.66)	<0.001
Cardiovascular death	430 (8.5)	617 (13.4)			1.49 (1.31–1.69)	<0.001

Data are presented as n (%). Multivariable analysis included male sex, age, diabetes, current alcohol use, chronic kidney disease, Charlson comorbidity index, stroke, coronary artery disease, heart failure, arrhythmia, peripheral artery disease, aortic disease, valvular heart disease, European Society of Cardiology/European Society of Anaesthesiology intermediate-to-high surgical risk, emergency operation, and operation duration. MINS was presented with OR, and mortalities were presented as HR. HR indicates hazard ratio; MINS, myocardial injury after noncardiac surgery; OR, odds ratio; and PACE, perioperative adverse cardiac events.

mortality for each composite of PACE is summarized in Table S2.

In subgroup analyses, diabetes had a significant interaction on the association between 1-year mortality and PACE. During the first 30 days after surgery, PACE was associated with 1-year mortality in patients without diabetes but not in those with diabetes (HR, 1.82; 95% CI, 1.56–2.13; *P*<0.001 and HR, 1.25; 95% CI, 0.98–1.59; *P*=0.08, respectively, and *P* for interaction=0.01; Figure 3). The significance of the observed association between PACE and mortality was maintained under all circumstances with unmeasured confounding factors (Table S3).

The SHAP summary plot shows results of the extreme gradient boostingmodel (Figure 4). Features are arranged in descending order where the model contributes to data classification. Each patient is represented by a single dot on each variable line. Each dot in the horizontal line represents an association between the effect of a variable and a higher or lower probability of 1-year mortality of a single study patient. The full-size image file of the SHAP summary plot is available at https://storage.googleapis.com/pace_shap/outcome_pace.pdf. A SHAP value greater than zero on the right side indicates an increased risk of death and the left side indicates lower risk. Age had the greatest importance for 1-year mortality with a score of 0.490, indicating that 1-year mortality increased with older age. Among categorical variables, PACE had a score of 0.073, making it fifth among binary variables after operation risk, sex, alcohol, and emergency operation. Based on plot color, distribution, and low PACE incidence, PACE showed the second largest impact following emergency operation.

Additionally, the effects of preoperative factors on development of PACE are demonstrated as the SHAP summary plot (Figure 5) with the full size provided at https://storage.googleapis.com/pace_shap/

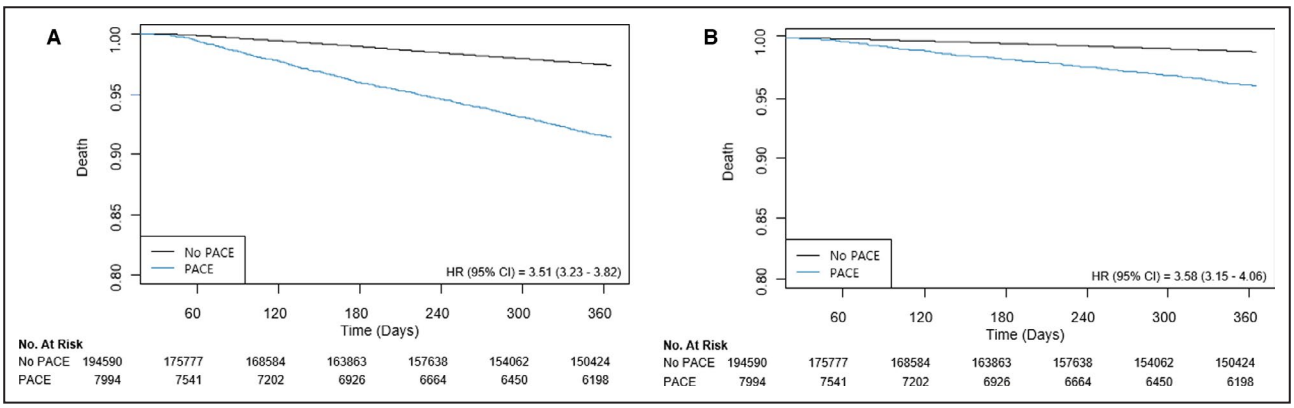

Figure 1. Kaplan-Meier curves of the entire population for (A) all-cause mortality and (B) cardiovascular mortality in 1-year follow-up.
HR indicates hazard ratio; and PACE, perioperative adverse cardiac events.

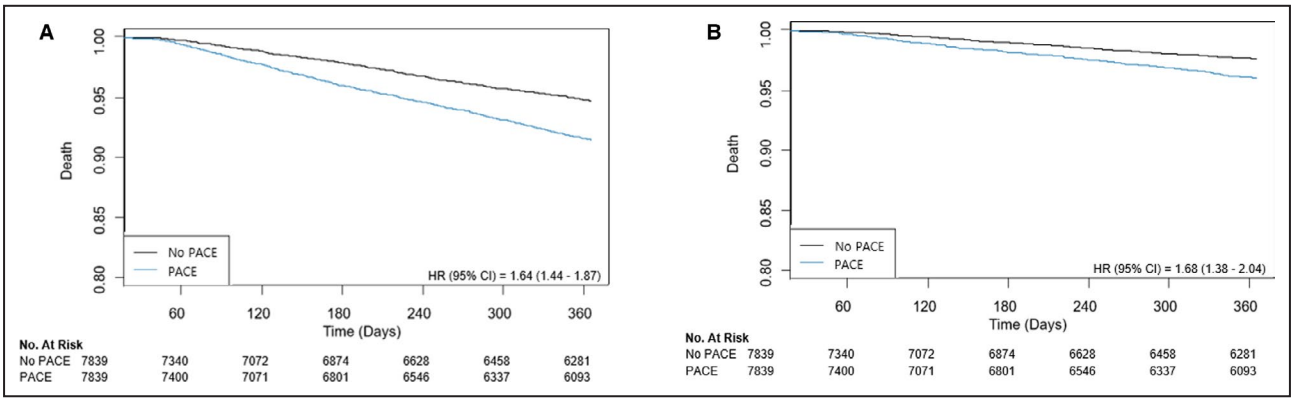

Figure 2. Kaplan-Meier curves of the propensity-score-matched population for (A) all-cause mortality and (B) cardiovascular mortality in 1-year follow-up.
HR indicates hazard ratio; and PACE, perioperative adverse cardiac events.

pace_factor.pdf. Age showed the greatest effect also for the development of PACE with a score of 0.642. It was followed by operation duration, surgical risk, male sex, and Charlson comorbidity index.

DISCUSSION

In this study, we identified PACE, defined as a composite of myocardial infarction, coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, or stroke during a 30-day postoperative period after noncardiac surgery. The incidence was 3.9%, and it was associated with mortality after 1- and 3-year follow-ups. Machine learning with the extreme gradient boosting method algorithm also showed that PACE had an impact on 1-year mortality.

Considering the enormous number of patients undergoing noncardiac surgery and the impact of cardiac complications in these patients, more clinical studies are necessary.[1–3,7] One of the integral strategies in clinical study design is to set a single primary end point that is clinically relevant and, for an end point to be valid in clinical studies, it also needs to be readily available for statistical analysis.[17] Thus, the challenge is to select an optimal end point that is both clinically relevant and not

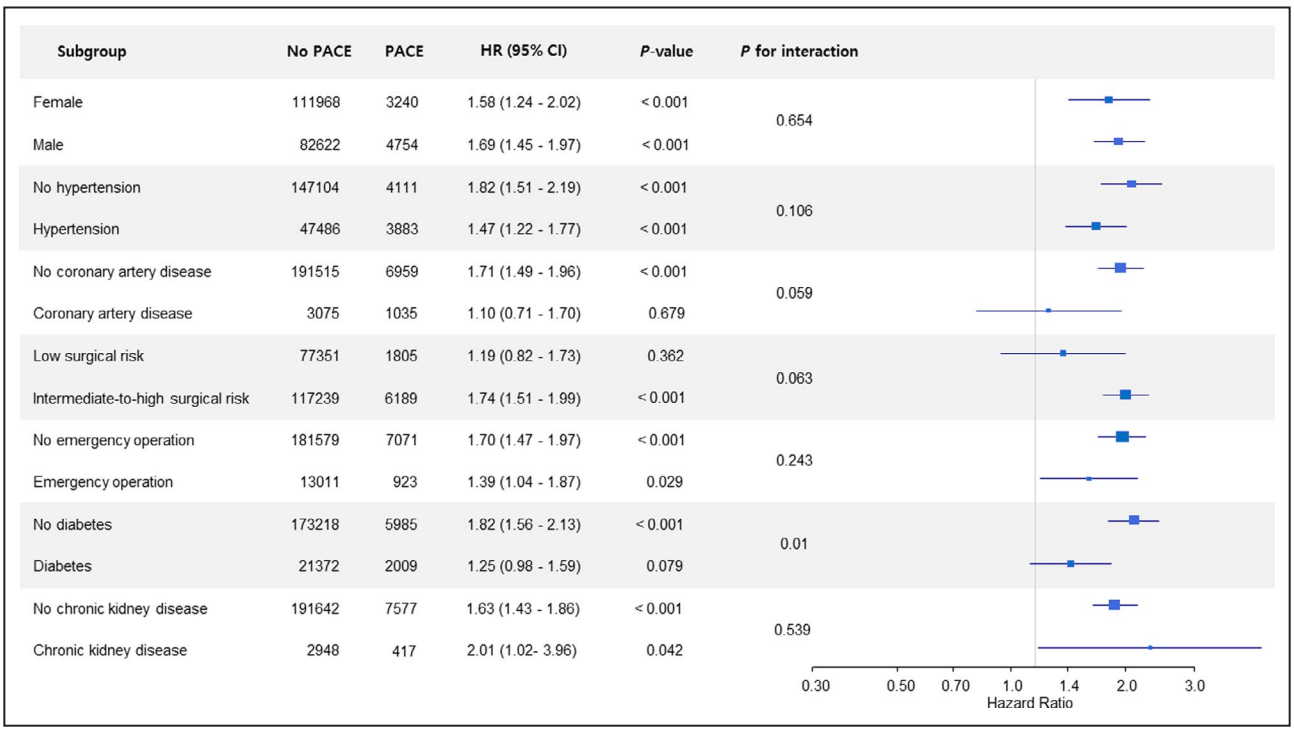

Figure 3. A forest plot of subgroup analysis.
Position of the squares represent HR and vertical lines represent 95% CI. HR indicates hazard ratio; and PACE, perioperative adverse cardiac events.

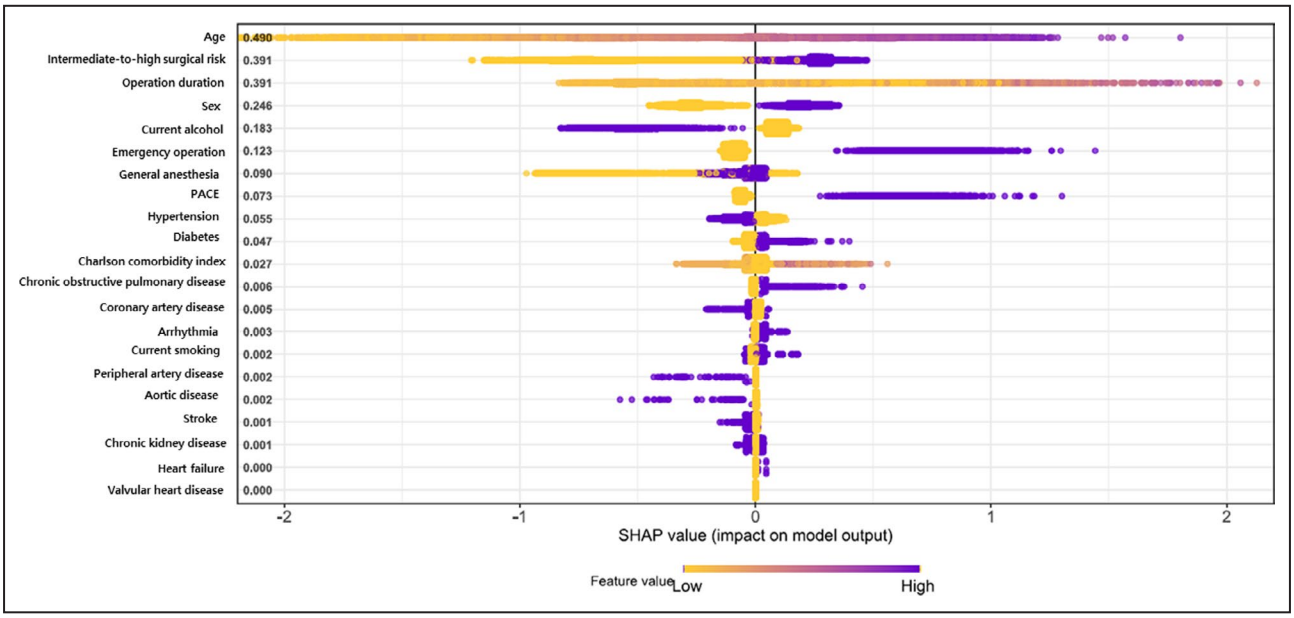

Figure 4. Shapley additive explanations (SHAP) summary plot representing the effects of preoperative variables on 1-year mortality from the extreme gradient boosting (XGB) algorithm of a machine-learning technique.
PACE indicates perioperative adverse cardiac events.

too rare. In this study, we used a large decade-long single-center data set from a tertiary hospital to evaluate an association between mortality and PACE that includes composites that have been considered minor events. Our results for incidence and association with long-term mortality may be helpful for selecting an end point in future studies.

In this study, the most common PACE component was arrhythmic attack and, within arrhythmic attack, atrial fibrillation made up the largest portion. Postoperative atrial fibrillation is very common, peaking 2 to 4 days after surgery.[8,18] However, postoperative atrial fibrillation incidence after noncardiac surgery has been reported to be highly variable, and its effect

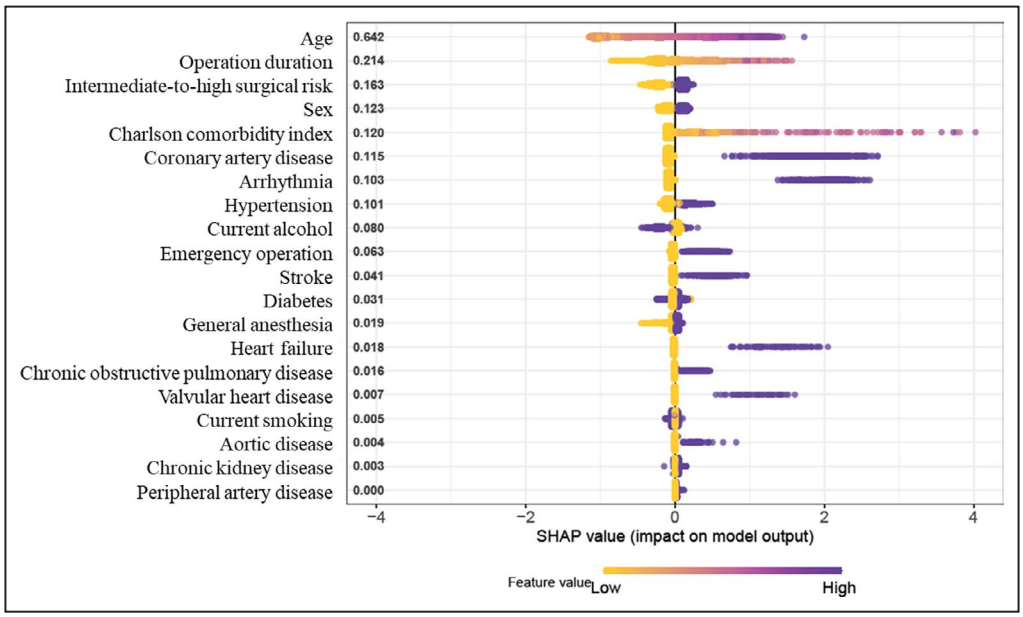

Figure 5. Shapley additive explanations (SHAP) summary plot representing the effects of preoperative variables on perioperative adverse cardiac events (PACEs) from the extreme gradient boosting (XGB) algorithm of a machine-learning technique.

on long-term mortality is still unclear.[9,18,19] In this study, arrhythmic attack was limited to events that needed an additional intervention such as administration of an antiarrhythmic drug or chemical or direct current cardioversion. Applying a strict definition may have provided more prognostic impact, and it was also beneficial for accurately curating retrospective data from electronic hospital records. Along with other cardiac events, atrial fibrillation that required an intervention showed a significant contribution to increased mortality during 1- and 3-year follow-ups.

We further aimed to evaluate whether PACE acts as a risk factor for 1-year mortality or if it is affected by other factors that are directly associated with mortality. Thus, we evaluated whether our results remained consistent when the risk factors for postoperative mortality were identified by a machine-learning method using the extreme gradient boostingalgorithm and SHAP.[15] This algorithm uses explainable artificial intelligence with Shapley values that has shown to be an effective prediction model for a wide range of applications and offers better results than traditional algorithms.[15] An additional benefit of using the SHAP method in this study was that it can be used for data sets with correlated features. Specifically, it can be used for predictability evaluation, even among features that are not guaranteed to be independent of each other.[16] In our results, the feature importance of PACE may seem low, but this is owing to the low PACE incidence. Referring to the impact represented by its SHAP value, PACE was the second largest contributing factor following emergency operation to affect mortality.

We applied the machine-learning technique also to evaluate preoperative factors that are related to the development of PACE. Our result was in line with previously known cardiac risk factors,[20] but variables with the high effects on PACE such as age, operation duration, and the risk of surgical procedure were the ones that are difficult to modify in real-world practice. Also, a definite measure to prevent any component of PACE has not been established.[20] So clinically, our results demonstrating an association between PACE and long-term mortality suggest the need for active treatment followed by close monitoring in patients with PACE. Considering the difference between each composite of PACE, a personalized approach as a perioperative care team may be beneficial. An evaluation by cardiologists was shown to improve outcomes of postoperative cardiovascular complications.[21] Our finding that the risk factors of PACE are in line with the known cardiac rick factors support the potential of PACE as a composite end point of clinical studies.

In our subgroup analyses, no association between PACE and mortality was observed for patients with diabetes. Diabetes is an established strong risk factor for various cardiovascular events from atrial fibrillation to myocardial ischemia,[22] and the risk from diabetes may have outweighed PACE. Another explanation may be associated with the fact that diabetic patients present cardiac symptoms with different patterns.[23] In the perioperative period when cardiac complications are likely to show asymptomatic presentation, the masking effect of diabetes might also have affected our results.

Our results should be interpreted as descriptive, considering the limitations of our analysis. This study used a retrospective administrative data set, and unmeasured variables could not be balanced even after rigorous statistical adjustments with propensity-score matching. Our data were from a single center and may not be generalizable. In addition, our study patients were mostly Asian, so our analysis may show different results owing to the ethnic difference. Perioperative care was not controlled. Although clinicians followed institutional protocols based on current guidelines, clinical decisions are often made at the attending clinician's discretion and, over the long study period, some guidelines may have changed. Despite applying several hyper-parameters to avoid overfitting, there is a possibility of overfitting in SHAP because our data set is highly deviated owing to low PACE incidence. Despite these limitations, we demonstrated an association between PACE during the 30 days after noncardiac surgery and long-term mortality in a large clinical data set. Our findings suggest that PACE may be a suitable composite end point for future clinical trials.

CONCLUSIONS

PACE, defined as myocardial infarction, coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, or stroke over a 30-day postoperative period, was associated with mortality during 1- and 3-year follow-up periods. After validation, PACE may be considered an end point for studies in noncardiac surgery.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Types of surgery.

	No PACE (N=194,590)	PACE (N=7,994)
Neuroendocrine	12894 (6.6)	173 (2.2)
Lung	10499 (5.4)	1452 (18.2)
Head & Neck	29675 (15.3)	1139 (14.2)
Breast	17483 (9.0)	184 (2.3)
Stomach	12152 (6.2)	413 (5.2)
Hepatobiliary	16446 (8.5)	633 (7.9)
Colorectal	13222 (6.8)	569 (7.1)
Urology	17862 (9.2)	629 (7.9)
Gynecology	24258 (12.5)	256 (3.2)
Bone & Skin etc	40099 (20.6)	2546 (31.8)

Table S2. Risk of one-year mortality for each composite of perioperative adverse cardiac event (PACE) in the propensity-score-matched population.

	Unadjusted HR (95% CI)	P-value
PACE	3.51 (3.23-2.82)	<0.001
Myocardial infarction	1.86 (1.42-2.44)	<0.001
Unstable angina	0.90 (0.09-8.68)	0.93
Coronary revascularization	1.23 (0.49-3.10)	0.66
Congestive heart failure	1.77 (1.01-3.09)	0.045
Arrhythmic attack	1.68 (1.49-1.90)	<0.001
Acute pulmonary embolism	2.94 (1.74-4.94)	<0.001
Cardiac arrest	5.92 (2.06-16.98)	<0.001
Stroke	2.01 (1.33-3.02)	<0.001

HR, hazard ratio; CI, confidence interval

Table S3. Effect of an unmeasured confounder on hazard ratio of perioperative adverse cardiac event for one-year mortality in the propensity-score-matched population.

		$OR_{ZY\|X}$					
		1.5	2	2.5	3	3.5	4
OR_{zx}	0.3	1.95 (1.70-2.23)	2.15 (1.88-2.47)	2.28 (1.99-2.61)	2.44 (2.13-2.80)	2.53 (2.21-2.89)	2.61 (2.28-2.98)
	0.4	1.85 (1.62-2.11)	2.00 (1.75-2.28)	2.11 (1.84-2.41)	2.18 (1.91-2.49)	2.25 (1.97-2.56)	2.31 (2.02-2.63)
	0.5	1.80 (1.58-2.05)	1.89 (1.66-2.16)	1.97 (1.72-2.24)	2.01 (1.77-2.30)	2.08 (1.82-2.37)	2.12 (1.86-2.42)
	0.6	1.75 (1.53-1.99)	1.81 (1.59-2.07)	1.87 (1.64-2.14)	1.91 (1.67-2.17)	1.94 (1.70-2.21)	1.98 (1.74-2.26)
	0.7	1.72 (1.51-1.96)	1.76 (1.55-2.01)	1.79 (1.57-2.03)	1.84 (1.61-2.09)	1.86 (1.63-2.12)	1.87 (1.64-2.13)
	1.1	1.76 (1.59-1.95)	1.75 (1.58-1.94)	1.75 (1.58-1.93)	1.74 (1.57-1.93)	1.73 (1.57-1.92)	1.74 (1.57-1.93)
	1.2	1.75 (1.58-1.94)	1.73 (1.56-1.92)	1.71 (1.55-1.90)	1.70 (1.54-1.89)	1.70 (1.54-1.89)	1.68 (1.52-1.87)
	1.3	1.74 (1.57-1.92)	1.71 (1.55-1.90)	1.69 (1.52-1.87)	1.68 (1.51-1.86)	1.66 (1.50-1.84)	1.66 (1.50-1.84)
	1.4	1.73 (1.56-1.92)	1.69 (1.52-1.87)	1.67 (1.50-1.85)	1.64 (1.48-1.81)	1.63 (1.47-1.80)	1.61 (1.46-1.79)
	1.5	1.72 (1.55-1.91)	1.67 (1.51-1.85)	1.64 (1.48-1.82)	1.61 (1.46-1.79)	1.59 (1.44-1.77)	1.58 (1.43-1.75)

Prevalence of unmeasured confounder = 40%

Numbers represent HRs (including 95% CIs).

HR, hazard ratio; X: dichotomous exposure measure, y dichotomous outcome measure, z: potential dichotomous confounder.

OR_{zx} indicates the association (OR) between the unmeasured confounder and f perioperative adverse cardiac event.

$OR_{ZY|X}$ indicates the association (OR) between the unmeasured confounder and one-year mortality.