

Perioperative adverse cardiac events predict post-discharge mortality after fragility hip fracture in elderly patients without cardiovascular disease

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ABSTRACT

Background Perioperative adverse cardiac events (PACs) in elderly patients with hip fractures are associated with perioperative mortality. We investigated the relationship of PACE with post-discharge mortality and further explored whether it differs between patients with and without cardiovascular disease (CVD).

Methods We retrospectively analyzed data from patients aged ≥ 65 years who underwent fragility hip fracture surgery from September 2016 to December 2021. PACE was defined as a composite of congestive heart failure, cardiogenic shock, myocardial injury after non-cardiac surgery, arrhythmic event, ischemic stroke, or acute pulmonary thromboembolism during hospitalization or within the 30-day postoperative period. Patients with 30-day mortality were excluded. The primary endpoint was all-cause mortality after hospital discharge.

Results Of the 446 patients (133 patients in the CVD group and 313 patients in the non-CVD group), 14.8% experienced PACE, and overall mortality during a median of 15.9 months (interquartile range: 6.6–27.0 months) was 20.9% [CVD (26.3%) vs. non-CVD (18.5%), $P = 0.064$]. Patients with PACE demonstrated a significantly worse survival rate than those without PACE in both groups (all log-rank $P < 0.05$). After adjustment for confounders, PACE was an independent predictor of mortality in the overall population [hazard ratio (HR) = 3.01, 95% CI: 1.69–5.35, $P < 0.001$]. Its prognostic impact was significant in patients without CVD (HR = 2.69, 95% CI: 1.35–5.38, $P = 0.005$) but not in those with CVD (HR = 1.20, 95% CI: 0.41–3.50, $P = 0.735$).

Conclusions PACE was associated with increased post-discharge mortality after fragility hip fracture, especially in elderly patients without CVD.

The increasing age and comorbidities in patients undergoing major noncardiac surgery increase the risk of perioperative cardiac complications.^[1,2] Although the overall incidence of perioperative adverse cardiac event (PACE) has declined over the past decades,^[3] PACE still accounts for a substantial proportion of perioperative deaths.^[4] In addition, PACE showed significant associations with one- and three-year mortality after noncardiac surgery.^[5,6]

Fragility hip fracture is a common injury among older people, resulting from a low-energy fall at or below standing height or without identifiable trauma. With an in-

creasingly aging population, the incidence of fragility hip fracture is rising,^[7] and the socioeconomic burden associated with its significant morbidity and mortality is an important public health issue.^[8–10] The one-year mortality of elderly patients with hip fractures is estimated to be 20% to 40%,^[9,10] and major adverse cardiovascular events (MACEs) have been the leading cause of death.^[11] In a large population-based cohort study, frail older people with hip fractures were more likely to experience myocardial infarction (MI) and stroke compared to those without hip fractures, even during the perioperative period.^[12] A previous study reported a relatively high incidence of

heart failure (HF) during hospitalization after hip fracture surgery.^[13] Acute trauma and poor surgical tolerability combined with chronic comorbid conditions in this population are thought to increase the risk of PACE.^[14] PACE in elderly patients with hip fracture has been described as one of the main contributors to perioperative mortality,^[15,16] but there is a paucity of studies assessing the effect of PACE on post-discharge mortality.

Cardiovascular diseases (CVDs) are frequently seen in elderly patients with hip fracture,^[17] and have also been associated with an increased risk of hip fracture.^[18] Earlier studies conducted in elderly patients undergoing hip fracture surgery have indicated that patients with prior CVD had a higher risk of PACE and a higher mortality rates than those without prior CVD.^[19,20] However, the risk of mortality in relation to PACE in each group of patients with or without prior CVD has not been determined. Given that elderly patients with hip fracture are at high risk of CVD death for many years thereafter,^[9-11] identification of early predictors of mortality, especially in individuals without prior CVD is important. In the present study, we investigated the clinical impact of PACE on mortality after hospital discharge, and further examined whether this significance differs between patients with or without prior CVD.

METHODS

Study Population and Data Collection

This was a single-center, retrospective observational cohort study. We retrospectively identified 522 consecutive patients undergoing hip fracture surgery at our institution between September 2016 and December 2021. Of these patients, we excluded those younger than 65 years old ($n = 51$) or with a pathologic fracture ($n = 5$), in-hospital death or death within the 30 days after surgery ($n = 13$), and presence of solid or hematological malignancy ($n = 10$). The remaining 446 patients were enrolled in this study and were categorized into the CVD group (133, 29.8%) and the non-CVD group (313, 70.2%) based on medical history at admission (Figure 1). The CVD group included subjects with investigator-reported history of coronary artery disease (defined as previous MI or coronary revascularization or the presence of luminal stenosis $\geq 50\%$ in at least one major epicardial vessel on angiography), ischemic stroke (IS), atrial fibrillation (AF), HF [defined as a clinical syndrome consisting of symptoms

(e.g., breathless, ankle swelling, and fatigue) and/or signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) due to a structural and/or functional abnormality of the heart],^[21] or peripheral artery disease.

Baseline demographic and clinical data included age; gender; body mass index (BMI); Koval grade; comorbidities of diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, dementia, and chronic pulmonary disease; medications at discharge; hospitalization period related to COVID-19 pandemic (March 11, 2020); and laboratory and echocardiographic findings. Also, data on intra- or peri-operative factors including type of surgery, total operation time, blood loss during the operation, and length of hospital stay were collected. Perioperative cardiac risk was estimated using the Revised Cardiac Risk Index according to the Canadian Cardiovascular Society guidelines for patients undergoing noncardiac surgery. All data were extracted from the hospital electronic health records and were reviewed by independent investigators who were blinded to survival outcomes. Our study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (PC22RISI0041). Written informed consent from participants was waived due to the retrospective and observational nature of this study.

Definitions of PACE and Study Outcome

PACE was a composite of congestive HF (CHF), cardiogenic shock (CS), myocardial injury after non-cardiac surgery (MINS), arrhythmic event, IS, or acute pulmonary thromboembolism (PTE) during hospitalization or within the 30-day postoperative period. CHF was defined as new-onset or worsening symptoms and signs of HF requiring additional urgent treatment, including intravenous therapy (i.e., diuretics, vasodilators, and inotropes); mechanical circulatory support or surgical intervention; or the use of ultrafiltration, hemofiltration, or dialysis.^[21] Criteria for CS were: (1) sustained hypotension (systolic blood pressure ≤ 90 mmHg for > 30 min or need for pharmacological or mechanical circulatory support to maintain systolic blood pressure > 90 mmHg), (2) clinical signs of pulmonary congestion, and (3) signs of impaired end-organ perfusion. The presence of at least one of the following manifestations was required for diagnosing impaired end-organ perfusion: (1) altered mental status, (2) cold or clammy skin and extremities, (3) decreased urine output (< 30 mL/h), and (4) elevated ar-



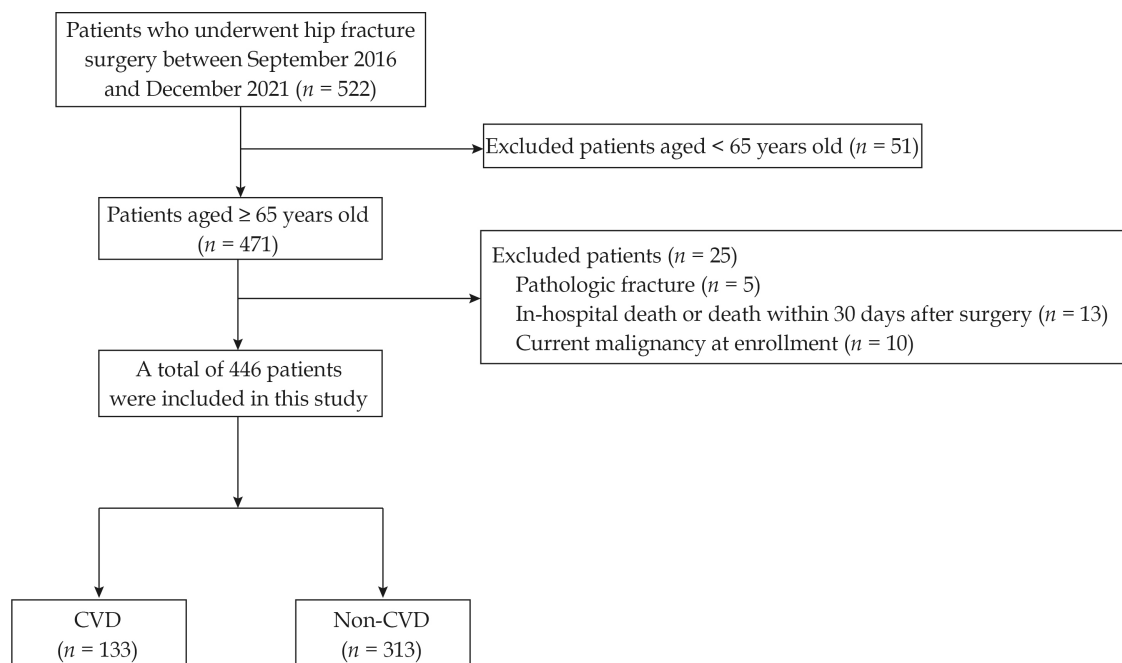


Figure 1 Study flow chart. CVD: cardiovascular disease.

terial lactate level (> 2.0 mmol/L).^[22] MINS was defined as at least one measured postoperative cardiac troponin I (cTnI) concentration exceeding the 99th percentile of the upper reference limit, with or without ischemic symptoms or signs, in the absence of nonischemic causes^[23]; and the diagnosis of acute MI was based on the fourth universal definition of MI.^[24] Arrhythmic events included new-onset or the first detected episode of rapid AF, ventricular tachycardia, and ventricular fibrillation that needed medical intervention such as administration of an antiarrhythmic drug or electrical shock. AF was defined as an irregular heart rhythm with the absence of P waves on 12-lead electrocardiography.^[25] Ventricular tachycardia was determined by three or more consecutive wide QRS complexes (duration > 120 ms) at ventricular rates ≥ 100 beats/min on electrocardiography. Ventricular fibrillation was defined as wide QRS complexes with a highly variable morphology, axis, and amplitude; no obvious P waves; and irregular ventricular rates ≥ 300 beats/min.^[26] IS was defined as a sudden-onset neurological deficit of presumed ischemic vascular origin lasting ≥ 24 h that was confirmed by a neurologist based on a brain imaging modality.^[27] Acute PTE was defined as a new diagnosis of a fresh blood clot identified in the pulmonary artery by computed tomography pulmonary angiography.

The primary endpoint was all-cause mortality after hospital discharge. The study population was followed

every three to six months at the orthopedic surgery center of our institution, and data on time to the last follow-up or to death were obtained by reviewing the medical records or telephone interviews.

Statistical Analysis

Continuous variables are presented as the mean $\pm$ SD or median with a corresponding interquartile range (IQR) and categorical variables are presented as percentages. Comparisons of the variables between CVD and non-CVD groups were performed using the Student's *t*-test or Mann-Whitney *U* test for continuous variables and the Pearson's Chi-square or Fisher's exact test for categorical variables, as appropriate. The overall survival rate for each group was estimated using Kaplan-Meier curves that were compared statistically with log-rank tests. Cox proportional hazard models using backward elimination method determined the association between PACE and mortality, and hazard ratios (HRs) along with their 95% confidence intervals (CIs) were calculated. Multivariate Cox regression analyses were performed after adjusting for covariates identified as significant in the univariate analysis or known to affect the survival outcome. We adjusted the following parameters: PACE; pre-existing CVD; age; male; BMI; diabetes mellitus; hypertension; dyslipidemia; chronic kidney disease; dementia; medications at discharge (antiplatelet or statin, or anticoagulant); hospitalization period related to COVID-19

pandemic; serum levels of hemoglobin, HbA1c, creatinine, albumin, and cTnI; and left ventricular ejection fraction (LVEF) and E/e' ratio. To evaluate the factors associated with post-discharge mortality in CVD and non-CVD groups, Cox regression analyses were performed separately in the two groups using the clinical variables mentioned above. All statistical analyses were conducted using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA), and statistical significance was set at two-sided P -values < 0.05 .

RESULTS

Patient Characteristics

The median age of the 446 participants was 82.0 (77.0–86.0) years, and 112 participants (25.1%) of them were men. Demographic and clinical characteristics of the overall population and comparisons between patients with or without prior CVD are presented in [Tables 1 & 2](#). Compared with the non-CVD group, the CVD group

tended to be male (33.1% vs. 21.7%, $P = 0.011$) and to have a higher BMI with borderline significance and a higher preoperative Koval grade. Age was similar between the two groups. Among the CVD group, IS was the most common diagnosis (45.1%), followed by AF (30.8%), coronary artery disease (27.1%), HF (16.5%), and peripheral artery disease (1.5%). Diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease were more common in the CVD group than in the non-CVD group. Patients with CVD had higher levels of HbA1c, serum creatinine and cTnI at admission; and these patients showed a higher postoperative peak cTnI level than those without CVD. The proportion of patients with a Revised Cardiac Risk Index score ≥ 1 was significantly higher in the CVD group than in the non-CVD group [CVD (91.0%) vs. non-CVD (14.7%), $P < 0.001$]. All participants underwent echocardiograms before surgery, and patients with CVD had a lower LVEF and a higher E/e' ratio compared to those without CVD. Internal fixation was the most common surgical procedure (59.6%), followed by hemiarthroplasty (31.2%) and total hip arthro-

Table 1 Demographic characteristics.

Variables	Overall (n = 446)	CVD (n = 133)	Non-CVD (n = 313)	P-value
Age, yrs	82.0 (77.0–86.0)*	82.0 (77.0–87.0)*	82.0 (77.0–86.0)*	0.847
Male	112 (25.1%)	44 (33.1%)	68 (21.7%)	0.011
Body mass index, kg/m ²	22.2 (19.6–24.7)*	22.3 (19.9–25.5)*	22.2 (19.2–24.4)*	0.051
Koval grade	2.6 $\pm$ 1.7	3.1 $\pm$ 1.7	2.4 $\pm$ 1.6	< 0.001
Pre-existing CVD				
Coronary artery disease	36 (8.1%)	36 (27.1%)	—	—
Atrial fibrillation	41 (9.2%)	41 (30.8%)	—	—
Heart failure	22 (4.9%)	22 (16.5%)	—	—
Stroke	60 (13.5%)	60 (45.1%)	—	—
Peripheral artery disease	2 (0.4%)	2 (1.5%)	—	—
Other comorbidities				
Diabetes mellitus	179 (40.1%)	65 (48.9%)	114 (36.4%)	0.014
Hypertension	330 (74.0%)	115 (86.5%)	215 (68.7%)	< 0.001
Dyslipidemia	213 (47.8%)	90 (67.7%)	123 (39.3%)	< 0.001
Chronic kidney disease	44 (9.9%)	26 (19.5%)	18 (5.8%)	< 0.001
Dementia	80 (17.9%)	23 (17.3%)	57 (18.2%)	0.817
Chronic pulmonary disease	11 (2.5%)	4 (3.0%)	7 (2.2%)	0.740
Hospitalization period				0.925
Pre-COVID-19	196 (43.9%)	58 (43.6%)	138 (44.1%)	
During/post-COVID-19	250 (56.1%)	75 (56.4%)	175 (55.9%)	

Data are presented as means $\pm$ SD or n (%). *Presented as median (interquartile range). COVID: coronavirus disease; CVD: cardiovascular disease.



Table 2 Clinical characteristics.

Variables	Overall (n = 446)	CVD (n = 133)	Non-CVD (n = 313)	P-value
Laboratory findings				
Hemoglobin, g/dL	11.2 (10.0–12.5)*	10.8 (9.5–12.3)*	11.2 (10.3–12.5)*	0.227
HbA1c, %	5.9 (5.4–6.6)*	5.9 (5.6–6.7)*	5.8 (5.4–6.6)*	0.046
Serum creatinine, mg/dL	0.8 (0.6–1.2)*	1.0 (0.7–1.6)*	0.7 (0.6–1.0)*	< 0.001
Albumin, mg/dL	3.8 (3.5–4.2)*	3.8 (3.5–4.1)*	3.8 (3.6–4.2)*	0.260
Creatine kinase-myoglobin binding, ng/mL	2.2 (1.6–4.0)*	2.2 (1.6–4.7)*	2.2 (1.6–3.8)*	0.978
Troponin I, ng/mL	0.009 (0.005–0.015)*	0.011 (0.009–0.023)*	0.008 (0.005–0.013)*	< 0.001
Troponin I, ng/mL [†]	0.015 (0.009–0.028)*	0.021 (0.012–0.034)*	0.012 (0.008–0.024)*	< 0.001
Revised Cardiac Risk Index score $\geq$ 1	167 (37.4%)	121 (91.0%)	46 (14.7%)	< 0.001
Echocardiographic findings				
LVEF, %	60.9 $\pm$ 8.3	59.2 $\pm$ 9.4	61.6 $\pm$ 7.6	0.015
E/e' avg	8.5 (6.8–10.9)*	9.4 (7.6–11.4)*	8.3 (6.6–10.7)*	0.022
Surgery type				
Total hip arthroplasty	41 (9.2%)	8 (6.0%)	33 (10.5%)	
Hemiarthroplasty	139 (31.2%)	51 (38.3%)	88 (28.1%)	
Internal fixation	266 (59.6%)	74 (55.6%)	192 (61.3%)	
Total operation time, min	85.0 (65.0–110.0)*	88.0 (65.0–112.5)*	85.0 (65.0–110.3)*	0.117
Blood loss during operation, mL	150.0 (100.0–250.0)*	150.0 (100.0–225.0)*	200.0 (100.0–300.0)*	0.368
Composite PACEs	66 (14.8%)	27 (20.3%)	39 (12.5%)	0.033
Congestive heart failure	30 (6.7%)	13 (9.8%)	17 (5.4%)	0.094
Cardiogenic shock	23 (5.2%)	9 (6.8%)	14 (4.5%)	0.316
MINS	9 (2.0%)	1 (0.8%)	8 (2.6%)	0.291
Arrhythmic event	9 (2.0%)	5 (3.8%)	4 (1.3%)	0.134
Ischemic stroke	4 (0.9%)	2 (1.5%)	2 (0.6%)	0.586
Acute PTE	3 (0.7%)	2 (1.5%)	1 (0.3%)	0.213
Length of hospital stay, days	12.0 (9.0–16.0)*	12.0 (9.5–17.0)*	12.0 (9.0–15.0)*	0.010
Medications at discharge				
Angiotensin-converting enzyme inhibitor or Angiotensin II receptor blocker	201 (45.1%)	73 (54.9%)	128 (40.9%)	0.007
Beta-blocker	36 (8.1%)	22 (16.5%)	14 (4.5%)	< 0.001
Calcium channel blocker	173 (38.8%)	62 (46.6%)	111 (35.5%)	0.027
Diuretics	84 (18.8%)	40 (30.1%)	44 (14.1%)	< 0.001
Antiplatelet	165 (37.0%)	79 (59.4%)	86 (27.5%)	< 0.001
Statin	206 (46.2%)	85 (63.9%)	121 (38.7%)	< 0.001
Anticoagulant	38 (8.5%)	28 (21.1%)	10 (3.2%)	< 0.001

Data are presented as means $\pm$ SD or n (%). *Presented as median (interquartile range). [†]Presented as follow-up on postoperative day 1. CVD: cardiovascular disease; E/e' avg: the ratio of early diastolic mitral inflow velocity to the averaged value of early diastolic mitral annulus velocities obtained from the septal and lateral side of mitral annulus; LVEF: left ventricular ejection fraction; MINS: myocardial injury after non-cardiac surgery; PACE: perioperative adverse cardiac event; PTE: pulmonary thromboembolism.

plasty (9.2%), and total hip arthroplasty seemed to be less frequently performed in patients with CVD compared to those without CVD (6.0% vs. 10.5%, $P = 0.057$). There were no significant differences in the hospitalization period

related to COVID-19 pandemic, total operation time and blood loss during surgery between the two groups.

The median duration from hospital admission to PACE was 5 (2–7) days. Sixty-six patients (14.8%) experi-



enced PACE; of these, CHF ($n = 30$, 6.7%) was the most common, followed by CS ($n = 23$, 5.2%), MINS ($n = 9$, 2.0%) and arrhythmic event ($n = 9$, 2.0%), IS ($n = 4$, 0.9%), and acute PTE ($n = 3$, 0.7%). Overall, the incidence of PACE was significantly higher in the CVD group than in the non-CVD group [CVD ($n = 27$, 20.3%) vs. non-CVD ($n = 39$, 8.7%), $P = 0.033$]. A similar trend was observed for each PACE, but there was no statistically significant difference between the two groups. Patients with prior CVD had longer hospital lengths of stays; and at discharge, patients without prior CVD were less likely to be treated with CVD drugs than those with prior CVD.

PACE and Mortality

During a median follow-up duration of 15.9 (6.6–27.0) months, death occurred in 93 patients (20.9%). The mortality rate tended to be higher in patients with CVD than in those without, but no significant difference was found between the two groups [CVD ($n = 35$, 26.3%) vs. non-CVD ($n = 58$, 18.5%), $P = 0.064$]. The Kaplan-Meier event-free survival curves significantly differed between patients with or without PACE (Figure 2). In the total study population, patients with PACE demonstrated a significantly lower survival rate than those without PACE (Figure 2A, log-rank $P < 0.001$). In the CVD group, patients with PACE had a lower survival rate compared to those without PACE (Figure 2B, log-rank $P = 0.003$). Similarly, in the non-CVD group, patients who had experienced PACE showed a significantly lower survival rate (Figure 2C, log-rank $P = 0.005$).

Cox regression analyses for the associations between PACE and the risk of post-discharge mortality in the overall population are presented in Table 3. In univariate analyses, PACE [unadjusted HR = 2.55, 95% CI: 1.63–3.99, $P = 0.001$]; pre-existing CVD (unadjusted HR = 1.55, 95% CI: 1.02–2.37, $P = 0.039$); older age; male gender; lo-

wer BMI; chronic kidney disease; dementia; lower levels of hemoglobin and serum albumin; higher levels of serum creatinine and log-transformed preoperative cTnI; and lower LVEF and higher E/e' ratio was associated with mortality. After adjustment for confounding factors, PACE (adjusted HR = 3.01, 95% CI: 1.69–5.35, $P < 0.001$), chronic kidney disease, and lower LVEF remained as independent predictors of mortality. Additionally, old age, dementia, and low serum albumin level that are known to increase the risk of mortality in older people were weakly associated with mortality in our study population. In Table 4, when analyzing the association of PACE with mortality in the CVD group, lower BMI, prior AF, and higher serum creatinine level, but not PACE (adjusted HR = 1.20, 95% CI: 0.41–3.50, $P = 0.735$), were associated with an increased risk of mortality (supplemental material, Table 1S). However, in the non-CVD group, PACE (adjusted HR = 2.69, 95% CI: 1.35–5.38, $P = 0.005$), along with older age, elevated HbA1c level, and lower albumin level, was a significant predictor of mortality. We also found an association between prior hypertension and post-discharge mortality with borderline statistical significance (supplemental material, Table 2S).

DISCUSSION

The major findings of our study were as follows. First, PACE after fragility hip fracture among elderly patients was not uncommon, and its incidence was higher in patients with prior CVD compared to those without. Second, PACE was independently associated with an increased risk of post-discharge mortality in the overall population; however, its prognostic impact was significant in the non-CVD group but not in the CVD group.

Hip fracture increases the risk of CVD mortality,^[11] and PACE has been largely responsible for in-hospital

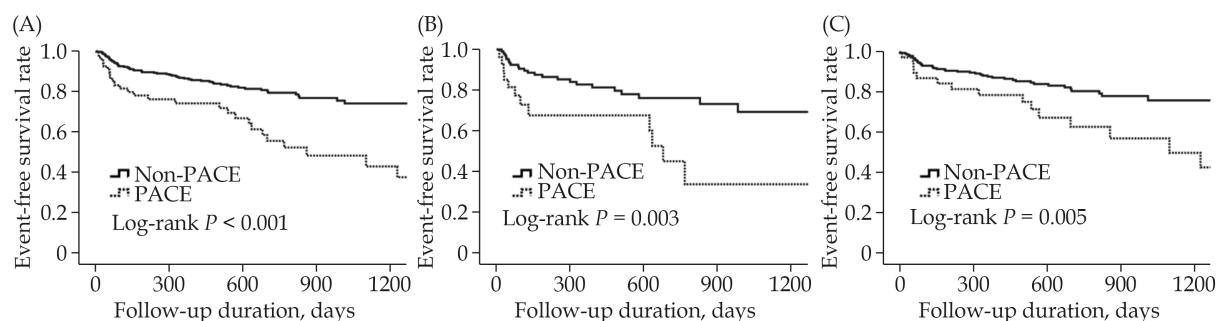


Figure 2 Kaplan-Meier event-free survival curves for post-discharge mortality after fragility hip fracture according to the occurrence of PACE in (A) the overall population ($n = 446$), (B) CVD patients ($n = 133$), and non-CVD patients ($n = 313$). CVD: cardiovascular disease; PACE: perioperative adverse cardiac event.



Table 3 Predictors for post-discharge mortality in the overall population.

Variables	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
PACE	2.55 (1.63–3.99)	< 0.001	3.01 (1.69–5.35)	< 0.001
Pre-existing CVD*	1.55 (1.02–2.37)	0.039		
Age	1.08 (1.04–1.11)	< 0.001	1.04 (1.00–1.08)	0.066
Male	1.87 (1.23–2.84)	0.004		
Body mass index	0.94 (0.88–1.00)	0.039		
Diabetes mellitus	1.18 (0.78–1.77)	0.436		
Hypertension	0.72 (0.46–1.12)	0.140		
Dyslipidemia	0.90 (0.60–1.35)	0.606		
Chronic kidney disease	2.34 (1.37–4.02)	0.002	3.01 (1.49–6.10)	0.002
Dementia	2.22 (1.42–3.45)	< 0.001	1.89 (0.99–3.58)	0.053
Medications at discharge				
Antiplatelet	1.19 (0.79–1.79)	0.416		
Statin	0.85 (0.56–1.28)	0.429		
Anticoagulant	1.64 (0.82–3.26)	0.163		
Hospitalization period				
Pre-COVID-19	1.00 (reference)	Not applicable		
During/post-COVID-19	1.39 (0.87–2.20)	0.170		
Laboratory findings				
Hemoglobin	0.85 (0.76–0.94)	0.002		
HbA1c	1.16 (0.97–1.40)	0.109		
Creatinine	1.19 (1.09–1.31)	< 0.001		
Albumin	0.39 (0.26–0.58)	< 0.001	0.55 (0.29–1.03)	0.064
Log-transformed troponin I	1.42 (1.20–1.67)	< 0.001		
Echocardiographic findings				
LVEF	0.97 (0.95–0.99)	0.004	0.97 (0.95–1.00)	0.036
E/e' _{avg}	1.10 (1.03–1.17)	0.006		

*Presented as ≥ 1 of the coronary artery disease, atrial fibrillation, heart failure, stroke, peripheral artery disease. CVD: cardiovascular disease; COVID: coronavirus disease; E/e'_{avg}: the ratio of early diastolic mitral inflow velocity to the averaged value of early diastolic mitral annulus velocities obtained from the septal and lateral side of mitral annulus; LVEF: left ventricular ejection fraction; PACE: perioperative adverse cardiac event.

death following hip fracture surgery.^[15,16] In a retrospective cohort study of elderly patients with hip fractures, most perioperative deaths occurred during hospitalization; and ischemic heart disease and cardiac failure were predominant causes of death at autopsy.^[16] The incidence of perioperative myocardial injury after hip fracture surgery was about 40%, and its relationship with in-hospital mortality was significant despite no definite evidence of MI.^[28] However, studies on the predictive value of PACE for post-discharge mortality in this population are relatively limited. Although a previous study demonstrated the significant effect of postoperative HF on one year mortality after hip fracture, this group did not provide clear definitions for perioperative cardiac complications. Also, there was a lack of information re-

garding fragile medical conditions of elderly patients.^[29] Recently published studies have shown the association between PACE and long-term mortality in the setting of non-cardiac surgeries and indicated that PACE may be a useful composite outcome measure. However, their studies included various types of non-cardiac surgery,^[5,6] and all orthopedic surgeries were categorized as bone surgeries.^[5] In addition, surgical variables possibly affecting the risk of PACE such as the type of surgical procedure, operation time, and blood loss during operation were not analyzed.^[5,6] Our study was conducted in elderly patients with hip fractures based on detailed demographic and clinical data, and we found a significant impact of PACE on post-discharge mortality following hip fracture surgery.

Osteoporosis and CVD are age-related diseases leading to high morbidity and mortality,^[30,31] and there has been accumulating evidence supporting significant epidemiological links and a possible common pathophysiology between these two disorders.^[32] In a post-hoc analysis of postmenopausal women who were enrolled as a placebo-treated group of the Multiple Outcomes of Raloxifene Evaluation trial, individuals with osteoporosis were at greater risk of CVD events compared to those with low bone mass; and that increased risk was proportional to the severity of osteoporosis.^[33] On the other hand, a long-term follow-up prospective cohort study of 31,936 twins found a significantly increased risk of subsequent osteoporotic hip fracture after a recent diagnosis of CVD.^[18] Some observational studies showed inverse associations between the use or cumulative dose of statin and risk of hip fracture and revealed an osteoprotective effect of statin, the use of which is the gold-standard for primary or secondary prevention of CVD.^[34,35] These findings have been explained by shared regulatory mechanisms between bone and vascular systems in which vascular atherosclerosis/calcification resembles the bone formation process. Indeed, many of the established CVD risk factors have been reported to negatively affect bone remodeling by promoting bone resorption.^[32] A recent study reported that patients with pre-existing CVD had a higher risk of PACE after osteoporotic hip fracture than those without and emphasized the need for CVD screening in this vulnerable population.^[19] Although CVD has been a strong predictor of mortality in elderly patients with hip fractures,^[20] previous studies investigating the relationship between PACE and mortality after hip fracture have been conducted in unselected patients with or without prior CVD.^[15,16,28,29] To our knowledge, this is the first study to determine the differential impact of PACE on the risk of mortality in patients with and without prior CVD.

Our study showed a higher incidence of PACE in patients with CVD than in those without CVD, but we found that PACE was not uncommon in patients without CVD. Various factors related to preoperative clinical features, the intraoperative process, and postoperative conditions initiate inflammatory, hypercoagulable, stress, and hypoxic states, which are associated with an increased risk of PACE.^[4,14] Considering that surgical procedures were performed by experienced orthopedic surgeons at one institution and all patients received comprehensive postoperative care, it is speculated that the

fragile conditions of the elderly, such as malnutrition, physical inactivity, and undiagnosed or uncontrolled comorbidities, may contribute to PACE in the non-CVD group. In line with previous research, our study confirmed an increased risk of mortality related to PACE and identified that this risk was significant in the non-CVD group. Given that most deaths after hip fracture have been attributed to MACEs,^[11] our findings suggest that PACE, particularly in the non-CVD group, may represent the older patient's medical vulnerability to future MACEs leading to increased mortality. Hsu, *et al.*^[36] reported the highest HRs for MACEs at 90 days after hospital discharge, and the risk gradually decreased but was significant up to one year following hip fracture. Their study indicated the need for early assessment and management of CVD events after hip fracture to reduce subsequent risk of MACEs, regardless of the presence or absence of CVD risk factors. Our study revealed that PACE was a strong predictor of post-discharge mortality in elderly patients without previously diagnosed CVD. Actually, performing complete CVD evaluations for underlying CVD in asymptomatic elderly patients with no identifiable comorbidities before urgent hip fracture surgery is not practical. Accordingly, our findings suggest that follow-up and monitoring for elderly patients who had experienced PACE after hip fractures is important to improve survival even after post-treatment discharge.

LIMITATIONS

This study has several limitations inherent to a single-center, retrospective study involving a small number of subjects in which there might be potential selection biases that could affect clinical outcome. First, our results were derived from a population-based cohort of hip fracture patients, so information on fasting glucose or lipid profiles at admission was not available. Second, although we confirmed the presence or absence of CVD based on careful review of medical records, there was a possibility that patients with undiagnosed CVD were misclassified. Third, detailed data on intraoperative or peri-operative care that could affect PACEs were not analyzed. Fourth, since our study was conducted between 2016 and 2021, which overlapped with the COVID-19 pandemic period, and regular follow-up at outpatient clinics and monitoring of comorbidities or CVD after hospital discharge were not available for some participants. Nevertheless, we obtained complete survival



Table 4 Association between PACE and post-discharge mortality in patients with and without CVD.

Subjects	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
CVD group (n = 133)*	2.81 (1.39–5.68)	0.004	1.20 (0.41–3.50)	0.735
Non-CVD group (n = 313)**	2.27 (1.26–4.09)	0.006	2.69 (1.35–5.38)	0.005

*Adjusted for age, male, body mass index, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, coronary artery disease, atrial fibrillation, heart failure, stroke, hospitalization period related to COVID-19 pandemic, hemoglobin, HbA1c, serum creatinine, albumin, troponin I, left ventricular ejection fraction. **Adjusted for *covariates except for coronary artery disease, atrial fibrillation, heart failure and stroke. Peripheral artery disease was not analyzed due to small number. CVD: cardiovascular disease; PACE: perioperative adverse cardiac event.

outcome data for all patients through medical record review or telephone interview. Furthermore, in multivariate analysis adjusting hospitalization period related to COVID-19 pandemic, we found an independent strong association between PACE and post-discharge mortality. Finally, the frailty indicators such as nutritional status, sarcopenia, physical activity, cognitive function, or socioeconomic status that have been reported to be associated with mortality were not analyzed. In particular, there may be possibilities that patients with higher socioeconomic status are less likely to have CVD and tends to be better managed after surgery compared to those with lower socioeconomic status. Since our study was conducted in elderly patients admitted to the emergency room with hip fracture and most of them were local residents, unfortunately, there was no way to assess the socioeconomic status in detail.

CONCLUSIONS

In conclusion, PACE was a strong independent predictor of post-discharge mortality in elderly patients with hip fracture. Although PACE was more frequently observed in the CVD group than in the non-CVD group, its prognostic significance on mortality was found in the non-CVD group. Our results suggest that PACE could be a useful surrogate marker for the risk stratification of post-discharge mortality following fragility hip fracture, especially in PACE survivors without prior history of CVD, and simultaneously highlight the importance of continuous surveillance to improve survival among these patients. Further prospective studies with a long-term follow-up and large numbers of patients are needed to establish the prognostic value of PACE and its underlying pathophysiology in this population.

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