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Cardiac power output associated with hospitalization and mortality in coronary artery disease patients at stage B heart failure

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ABSTRACT

Background: Cardiac power output (CPO) predicts outcomes in advanced heart failure (HF) and cardiogenic shock, but its role in early HF stages is unclear. This study assessed the prognostic value of CPO in coronary artery disease patients with asymptomatic left ventricular systolic dysfunction (ALVSD) at stage B HF.
Methods: We conducted a retrospective analysis of coronary artery disease patients who underwent coronary and pulmonary artery catheterization between 2006 and 2016. Stage B HF with ALVSD was defined as left ventricular ejection fraction < 50 %, without HF symptoms, signs, or prior HF hospitalization. CPO was derived from invasive hemodynamic parameters. Endpoints included HF hospitalization, cardiovascular mortality, and all-cause mortality over a 5-year follow-up.
Results: A total of 783 coronary artery disease patients with ALVSD at stage B HF were enrolled. Incidence rates (per 1000 person-years) were 13.9 for HF hospitalization, 14.5 for cardiovascular mortality, and 23.7 for all-cause mortality.Multivariate analysis adjusting for covariates demonstrated that CPO was independent associated with all endpoints. Patients with a low CPO (<0.97 Watts) were at significantly higher risk for HF hospitalization (adjusted hazard ratio [HR]: 4.04; 95 % CI: 1.53 – 10.6; p = 0.005), cardiovascular mortality (adjusted HR: 2.73; 95 % CI: 1.19 – 6.27; p = 0.018), and all-cause mortality (adjusted HR: 1.86; 95 % CI: 1.05 – 3.30; p = 0.035) compared to those with higher CPO, regardless of subgroup classification.
Conclusion: Resting CPO in patients with ALVSD is significantly associated with adverse events, including HF hospitalization and mortality, highlighting its value in early-stage HF management.

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by structural cardiac abnormalities and elevated intraventricular filling pressure, resulting in symptoms or signs that may manifest at rest or during physical exertion [1]. To elucidate the trajectory of HF development, the American College of Cardiology/American Heart Association classified HF into A, B, C, and D stages [2]. Stage A comprises individuals with underlying diseases at risk of future HF development but without any structural changes or symptoms. Stages C and D are classic symptomatic HF. Stage B heart failure is marked by an abnormal heart structure and potentially elevated filling pressures, but individuals typically do not exhibit current or prior symptoms of heart failure, often described as asymptomatic or pre-clinical HF. In post-myocardial infarction (MI) patients with asymptomatic left ventricular systolic dysfunction (ALVSD) at stage B HF, compensatory physiological mechanisms oppose the decline in ventricular function, thereby sustaining an asymptomatic presentation [3]. Identifying high-risk populations among patients with ALVSD at stage B HF is crucial to prevent progression to stage C or D.

Cardiac power output (CPO), which integrates both pressure and

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ALVSD, asymptomatic left ventricular systolic dysfunction; ARB, angiotensin receptor blocker; BMS, bare-metal stents; CI, confidence intervals; CPO, cardiac power output; DAPT, dual-antiplatelet therapy; DES, drug-eluting stents; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LAD, left anterior descending artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAC, pulmonary artery catheterization; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure.

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flow to measure cardiac hydraulic pumping performance, was first introduced in 2004 as a prognostic predictor for MI with complicated cardiogenic shock. Thereafter, its clinical application has expanded to HF with complicated cardiogenic shock, regardless of baseline left ventricular ejection fraction (LVEF) [4,5]. CPO can be measured via invasive pulmonary artery catheterization (PAC) or non-invasive echocardiography, and previous studies have demonstrated its prognostic value in patients with various types of heart failure. Resting CPO measured by PAC can predict mortality, the need for heart transplantation, or the requirement for a ventricular assist device in individuals with stage C or D advanced HF [6–8]. Non-invasive CPO measurement has independently and incrementally predicted mortality and HF hospitalization in HF with preserved ejection fraction [9]. However, the predictive value of CPO in the pre-clinical stage of HF remains uncertain. Given that CPO reflects a general hemodynamic response to impaired left ventricular systolic function, we hypothesized that CPO could predict stage progression-related HF hospitalization and mortality in pre-clinical HF after long-term follow-up.

2. Methods

2.1. Patient population

This retrospective study screened consecutive patients who were admitted for elective coronary catheterization and received concurrent PAC at a tertiary care academic center from January 2006 to December 2016. Patients who presented with recent MI or unstable angina and underwent elective coronary catheterization were included. A recent MI was defined according to elevated cardiac enzymes or abnormal imaging findings (new occurrence of ST-T changes on electrocardiography, akinesis or scarring myocardium on echocardiography, or evidence of infarction on myocardial perfusion screen) associated with the onset of clinical symptoms 3 to 30 days prior to coronary catheterization. Those who presented with acute coronary syndrome and required emergency or urgent coronary interventions were excluded prior to study screening.

The definition of complete or incomplete revascularization in this study is based on the final coronary angiography. All patients in this study underwent percutaneous coronary interventions with either drug-eluting stents (DES) or bare-metal-stents (BMS) to treat stenotic coronary arteries. Incomplete revascularization was defined as the presence of any coronary artery measuring more than 2.25 mm in diameter with residual stenosis exceeding 50 % as determined by final quantitative coronary angiography. The decision to perform complete or incomplete revascularization and to use DES or BMS was made by attending physician overseeing the case.

In our routine practice, echocardiography data were acquired within 14 days prior to elective coronary catheterization to assess cardiac structure and function. For patients with impaired LVEF (< 50 %) or moderate or severe valvular heart diseases identified by echocardiography, PAC was performed via the right internal jugular vein or common femoral vein to assess hemodynamic data during the index catheterization procedure. Baseline clinical characteristics were determined at the time of the index catheterization based on diagnoses and medical records. CPO was calculated utilizing catheterization data through the formula: [(Mean Arterial Pressure − Right Atrial Pressure) × Cardiac Output)]/451Watts.

The use of medications, including dual antiplatelet therapy (DAPT), statin, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), was recorded according to hospital discharge note. During the patient enrollment period, aspirin plus clopidogrel was the only available DAPT regimen in our institution. At that time, Taiwan national healthcare insurance regulations mandated a prescribed duration of 9 months for DAPT in patients receiving DES and 6 months for those with BMS. The mean duration of DAPT use during follow-up period was recorded in this study.

Stage B HF with ALVSD was defined as patients who presented with coronary symptoms and an LVEF of less than 50 %, but without HF symptoms or signs, such as general weakness, dyspnea, leg edema, jugular vein engorgement, or pulmonary congestion visible on a chest X-ray. Those with previous HF symptoms or signs, or who had been hospitalized for HF before the index procedure, were classified as having stage C or D HF.

2.2. Study endpoints and follow-up

The primary endpoint of this study was stage progression-related HF hospitalization, and the secondary endpoints were cardiovascular and all-cause mortality during 5 years of follow-up. Stage progression-related HF hospitalization was defined as admission to a ward or intensive care unit, or a visit to the emergency room for fatigue, short of breath, fluid overload, pulmonary edema, or cardiogenic shock during the follow-up period. Comprehensive medical records encompassing clinical status, medical management, and adverse event occurrences were collected. Individuals underwent regular clinical follow-ups through outpatient visits, occurring every three months from the index procedure date until the occurrence of HF hospitalization, death, or the completion of the 5-year follow-up. The research adhered to the principles outlined in the Declaration of Helsinki, and the Research Ethics Committee institutional review board of Chang Gung Medical Foundation has approved this study protocol (Approved No. 202301045B0).

2.3. Statistical analysis

All statistical analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as means ± standard deviation or percentages, while categorical data are presented as numbers. Categorical variables were compared using Chi-squared or Fisher's exact tests. In the multivariate Cox regression analysis, baseline characteristics, comorbidities, echocardiographic and hemodynamic parameters including LVEF, left ventricular end-diastolic volume (LVEDV), pulmonary artery systolic pressure (PASP) and pulmonary capillary wedge pressure (PCWP), were adjusted along with CPO. Relative hemodynamic parameters used in the calculation of CPO were not adjusted in the multivariate analysis to avoid multicollinearity. CPO levels were evaluated as both continuous and categorical variables, based on a cutoff point determined using Youden's index. Kaplan-Meier curves and log-rank tests were used to assess clinical outcomes based on the CPO cutoff value. Stratified analyses were performed based on age, sex, diabetes mellitus, hypertension, recent MI, LVEF, eGFR, PASP, PCWP and complete revascularization. Statistical significance was defined as $p < 0.05$ (two-sided).

3. Results

3.1. Patient enrollment and outcomes after 5-year follow-up

A total of 1,201 consecutive patients with coronary artery disease who underwent elective coronary catheterization and concurrent PAC were screened. After excluding patients with stage C or D HF (n = 232), those with moderate or severe valvular heart diseases (n = 154), and those on chronic dialysis (n = 32), a final cohort of 783 patients with ALVSD at stage B HF was retained for further analysis. A flowchart of the study enrollment is shown in Fig. 1.

The baselines characteristics of this study cohort are shown in Table 1. The cohort had a mean age of 62.6 ± 12.0 years, with 16.3 % being women. The prevalence of diabetes mellitus was 36.1 %, hypertension 54 %, hyperlipidemia 49.9 %, recent MI 59.9 % and previous stroke 4.9 %. The mean estimated eGFR in the study cohort was 93.3 ± 24.7 ml/min/1.73 m^2, and the mean LVEF was 41.5 ± 8.1 %, with 40.1 % of patients having an LVEF ≤ 40 %. Multivessel coronary artery disease was present in 66.7 % of patients, with 59.1 % having a lesion in the left anterior descending artery (LAD) lesion, and 65.1 % achieving

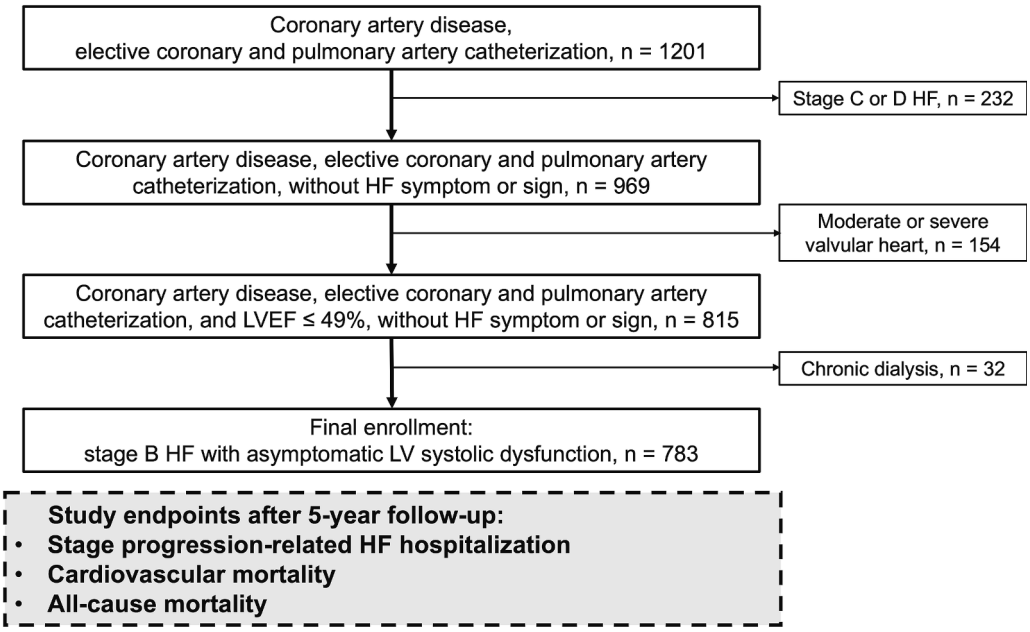

Fig. 1. Flowchart of enrollment.

Table 1
Baseline characteristics of study cohort.

Patient number, n	783
Age, years	62.6 ± 12.0
Female sex, n (%)	128 (16.3)
Diabetes mellitus, n (%)	283 (36.1)
Hypertension, n (%)	423 (54.0)
Hyperlipidemia, n (%)	391 (49.9)
Recent myocardial infarction	469 (59.9)
Previous stroke, n (%)	38 (4.9)
Chronic kidney disease, stage ≥ 3, n (%)	67 (8.6)
eGFR, ml/min/1.73 m^2	93.3 ± 24.7
LVEF, %	41.5 ± 8.1
LVEF ≤ 40 %, n (%)	314 (40.1)
LVEDV, mL	152.9 ± 42.5
Calcified lesions, n (%)	156 (19.9)
Multivessel disease, n (%)	522 (66.7)
LAD lesion, n (%)	463 (59.1)
DES/BMS, n/n (%/%)	693/90 (88.5/11.5)
Complete revascularization, n (%)	510 (65.1)
ACEi or ARB, n (%)	547 (69.9)
Beta-blocker, n (%)	677 (86.5)
DAPT, n (%)	771 (98.5)
Statin, n (%)	780 (99.6)
Duration of using DAPT, months	7.7 ± 2.4
Systolic blood pressure, mmHg	140.4 ± 25.2
Diastolic blood pressure, mmHg	74.5 ± 13.6
Mean blood pressure, mmHg	96.5 ± 15.3
Heart rate, beat/min	72.5 ± 12.7
Right atrial pressure, mmHg	9.6 ± 4.7
PASP, mmHg	38.5 ± 12.7
PCWP, mmHg	18.3 ± 8.2
Cardiac output, L/min	4.8 ± 1.3
Cardiac power output, Watt	0.93 ± 0.32

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare-metal stenting; CPO, cardiac power output; DAPT, dual-antiplatelet therapy; DES, drug-eluting stenting; eGFR, estimated glomerular filtration rate; LAD, left anterior descending artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure.

complete revascularization. DES were used in 88.5 % of cases, while BMS were used in the remaining cases. DAPT was prescribed at discharge for 98.5 % of patients, with a mean DAPT duration of 7.7 ± 2.4 months. Beta-blockers were used by 86.9 % of patients, and ACEi or ARB were used by 69.9 %. The mean blood pressure was 96.56 ± 15.3 mmHg, the mean PASP was 38.5 ± 12.7 mmHg, the mean PCWP was 18.3 ± 8.2 mmHg, the mean cardiac output was 4.8 ± 1.3 L/min, and the mean CPO was 0.93 ± 0.32 W.

During a mean follow-up of 4.2 ± 1.6 years, 51 patients (6.5 %) experienced stage progression-related HF hospitalization, 53 patients (6.8 %) succumbed to cardiovascular mortality, and 87 patients (11.1 %) encountered all-cause mortality. The incidence rates of HF hospitalization, cardiovascular mortality, and all-cause mortality were 13.9, 14.5, and 23.7 per 1000 person-years, respectively.

3.2. Predictors of adverse events in multivariate cox-regression analyses

Table 2 showed the results of independent predictors of adverse events in multivariate cox-regression model. The significantly predictors of stage progression-related HF hospitalization were continuous CPO, per watt increasing (Hazard ratio [HR], 0.23; 95 % Confidence Intervals [CI], 0.07–0.79; p = 0.019), eGFR per ml/min/1.73 m^2 increasing (HR, 0.99; 95 % CI, 0.98–0.99; p = 0.003), and hypertension (HR, 0.49; 95 % CI, 0.26–0.92; p = 0.026).

CPO, per watt increasing (HR, 0.28; 95 % CI, 0.09–0.90; p = 0.033) and age per year increasing (HR, 1.04, 95 % CI, 1.01–1.07; p = 0.010) were independent predictors of cardiovascular mortality. The independent predictors of all-cause mortality were continuous CPO (HR, 0.41; 95 % CI, 0.17–0.97; p = 0.043), age per year increasing (HR, 1.04, 95 % CI, 1.01–1.06; p = 0.002), and using of beta-blockers (HR, 0.55; 95 % CI, 0.32–0.95; p = 0.033).

3.3. Baseline characteristics according to CPO levels

In the multivariate analysis, where CPO emerged as the sole independent predictor of all evaluated outcomes, patients in this cohort were categorized into high or low CPO groups using a threshold of 0.97 Watt, determined by Youden's index from the primary endpoint analysis. Table 3 displays baseline characteristics comparisons between low CPO (<0.97 Watt) and high CPO (≥0.97 Watt) groups within this stage B HF cohort. The mean CPO values in the low and high CPO groups were 0.74 ± 0.15 and 1.25 ± 0.26 Watts, respectively. Individuals in the low CPO group exhibited several distinguishing characteristics, including advanced age, female sex, recent MI, LVEF ≤ 40 % and lower eGFR,

Table 2
Multivariate Cox regression of variables in prediction of clinical outcomes.

	HF hospitalization		Cardiovascular mortality		All-cause mortality	
Variable	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value
Age, per year	0.99 (0.97 – 1.03)	0.916	1.04 (1.01 – 1.07)	0.010*	1.04 (1.01 – 1.06)	0.002*
Female sex	1.12 (0.51 – 2.43)	0.785	1.13 (0.51 – 2.49)	0.772	1.10 (0.59 – 2.05)	0.761
Diabetes mellitus	0.87 (0.46 – 1.64)	0.661	1.33 (0.72 – 2.45)	0.368	1.20 (0.74 – 1.94)	0.457
Hypertension	0.49 (0.26 – 0.92)	0.026*	0.81 (0.44 – 1.48)	0.488	0.83 (0.52 – 1.34)	0.453
Hyperlipidemia	0.77 (0.40 – 1.47)	0.421	0.80 (0.44 – 1.48)	0.486	1.11 (0.69 – 1.79)	0.669
Recent MI	1.35 (0.70 – 2.58)	0.372	1.07 (0.57 – 1.99)	0.839	1.01 (0.62 – 1.65)	0.969
Previous stroke	0.96 (0.22 – 4.09)	0.951	1.97 (0.75 – 5.21)	0.171	1.41 (0.60 – 3.34)	0.432
Calcified lesion	1.32 (0.63 – 2.74)	0.463	0.90 (0.46 – 1.74)	0.747	0.91 (0.54 – 1.54)	0.716
Muli-vessel disease	1.47 (0.57 – 3.78)	0.425	0.74 (0.32 – 1.67)	0.463	0.64 (0.34 – 1.20)	0.161
LAD lesion	1.57 (0.81 – 3.05)	0.183	1.01 (0.54 – 1.91)	0.967	1.07 (0.65 – 1.77)	0.782
DES	0.58 (0.17 – 1.95)	0.381	0.90 (0.35 – 2.35)	0.836	1.20 (0.60 – 2.39)	0.612
Complete revascularization	0.58 (0.30 – 1.12)	0.103	0.79 (0.42 – 1.48)	0.457	0.70 (0.42 – 1.17)	0.177
Beta-blockers	0.59 (0.26 – 1.35)	0.213	1.06 (0.46 – 2.44)	0.900	0.55 (0.32 – 0.95)	0.033*
ACEi or ARB	0.90 (0.47 – 1.72)	0.754	1.16 (0.60 – 2.23)	0.666	1.03 (0.62 – 1.70)	0.921
DAPT	0.50 (0.06 – 4.09)	0.518	0.78 (0.09 – 6.51)	0.821	1.12 (0.15 – 8.73)	0.911
eGFR	0.99 (0.98 – 0.99)	0.003*	1.00 (0.99 – 1.02)	0.649	1.00 (0.99 – 1.01)	0.748
LVEF, per %	1.01 (0.98 – 1.07)	0.314	0.99 (0.96 – 1.04)	0.788	0.99 (0.96 – 1.02)	0.565
LVEDV, per mL	1.00 (0.99 – 1.01)	0.730	1.00 (0.99 – 1.01)	0.466	1.00 (0.99 – 1.00)	0.459
CPO, per Watt	0.23 (0.07 – 0.79)	0.019*	0.28 (0.09 – 0.90)	0.033*	0.41 (0.17 – 0.97)	0.043*
PASP, per mmHg	1.01 (0.97 – 1.05)	0.537	1.01 (0.97 – 1.04)	0.780	1.01 (0.98 – 1.04)	0.426
PCWP, per mmHg	0.98 (0.92 – 1.04)	0.462	0.99 (0.93 – 1.05)	0.723	0.98 (0.93 – 1.03)	0.353

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence intervals; CPO, cardiac power output; DAPT, dual-antiplatelet therapy; DES, drug-eluting stenting; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LAD, left anterior descending artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure.
* : P value < 0.05.

LVEF, LVEDV, systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, and cardiac output compared to those in the high CPO group. Conversely, no significant differences were observed between the low and high CPO groups regarding diabetes mellitus, hypertension, hyperlipidemia, smoking, previous stroke, calcified lesions, multivessel disease, LAD lesion, left ventricular end-systolic volume, PASP, PCWP, and the use of stent type, DAPT, ACEi or ARBs, beta-blockers, and complete revascularization.

3.4. Clinical outcomes and relative risk according to high or low CPO groups

Table 4 provides a comprehensive overview of the 5-year outcomes for the entire study cohort, presenting the relative risk among the low and high CPO groups. The incidence rates of HF stage progression hospitalization were 5.0 and 19.5 per 1000 person-years in the low CPO and high CPO groups, respectively. Low CPO group exhibited a significantly higher risk of stage progression related HF hospitalization compared high CPO group, as evidenced by both crude (HR, 3.84; 95 % CI, 1.73–8.54; p = 0.001) and adjusted risk estimates (HR, 4.04; 95 % CI, 1.53–10.6; p = 0.005). The Kaplan–Meier survival curves illustrating the impact of the CPO groups on stage progression-related HF hospitalization revealed a significant difference ($p < 0.001$), as depicted in Fig. 2A.

Similarly, the low-CPO group experienced a higher incidence of cardiovascular mortality (8.9 %, 19.3 per 1000 person-years) than the high-CPO group (3.1 %, 6.5 per 1000 person-years). This disparity translated into a significantly increased risk of cardiovascular mortality in the low CPO group, with both crude (HR, 2.97; 95 % CI, 1.45–6.09; p = 0.003) and adjusted hazard ratios (HR, 2.73; 95 % CI, 1.19–6.27; p = 0.018). Fig. 2B presents the Kaplan–Meier curves for cardiovascular death in the CPO group, highlighting a statistically significant difference (p = 0.002).

These findings were consistent for all-cause mortality as well, with incidence rates per 1000 person-years of 29.0 (13.4 %) in the low CPO group and 15.1 (7.2 %) in the high CPO group. The low CPO group exhibited a significantly higher risk of all-cause mortality, supported by both crude (HR, 1.92; 95 % CI, 1.17–3.14; p = 0.009) and adjusted hazard ratios (HR, 1.86; 95 % CI, 1.05–3.30; p = 0.035). The Kaplan–Meier survival curves for the CPO groups for all-cause mortality demonstrated a significant difference (p = 0.008), as displayed in Fig. 2C.

3.5. Subgroup stratification analysis

We conducted subgroup and interaction analyses to evaluate the robustness of the association between CPO and clinical events. Fig. 3 illustrates the associations between CPO and three outcomes—HF hospitalization, cardiovascular mortality, and all-cause mortality—across various subgroups. These subgroups include age, sex, diabetes mellitus, hypertension, recent MI, LVEF (>40 % or ≤ 40 %), eGFR (≥90 or < 90 ml/min/1.73 m^2), PASP (≥35 or < 35 mmHg), PCWP (≥15 or < 15 mmHg), and complete revascularization. No significant interactions were observed between CPO and any of the subgroups in relation to clinical endpoints (all interaction p-values > 0.05). Additionally, the association between lower CPO and an increased risk of clinical events remained consistent across all subgroups.

4. Discussion

The main finding of the present study was that stage B HF patients with ALVSD had a lower CPO, which was associated with higher risks of stage progression-related HF hospitalization, cardiovascular mortality, and all-cause mortality, regardless of subgroups classification. These findings suggest the potential value of assessing the resting CPO using PAC for risk stratification of long-term outcomes in coronary artery disease patients with ALVSD. To the best of our knowledge, this is the first study extending the predictive potential of CPO from patients with advanced HF to those with early-stage HF.

The cutoff values of CPO, determined through RHC measurements and ranging from 0.53 to 0.6 Watt, have emerged as robust, independent predictors of clinical outcomes in patients experiencing conditions such as cardiogenic shock, acute cardiac issues, and advanced HF [4,7,10]. The severity of HF in this study (stage B) is less pronounced than that in previous studies (stage C or D), so it can be explained why the cutoff

Table 3
Clinical characteristics according to CPO level in patients with asymptomatic left ventricular systolic dysfunction.

Patient group, Mean ± SD, Watt	Low CPO (< 0.97), 0.74 ± 0.15 Watt	High CPO (≥ 0.97), 1.25 ± 0.26 Watt	P value
Patient number, n	493	290	
Age, years	64.6 ± 11.7	52.3 ± 11.9	< 0.001
Female sex, n (%)	99 (20.1)	29 (10.0)	< 0.001
Diabetes mellitus, n (%)	179 (36.3)	104 (35.9)	0.939
Hypertension, n (%)	255 (51.7)	168 (57.9)	0.102
Hyperlipidemia, n (%)	237 (48.1)	154 (53.1)	0.183
Recent MI, n (%)	310 (62.9)	159 (54.8)	0.029
Previous stroke, n (%)	25 (5.1)	13 (4.5)	0.864
Chronic kidney disease, stage ≥ 3, n (%)	48 (9.7)	19 (6.6)	0.146
eGFR, ml/min/1.73 m^2	90.5 ± 26.3	97.9 ± 20.8	< 0.001
LVEF, %	40.8 ± 8.3	42.5 ± 7.7	0.004
LVEF ≤ 40 %, n (%)	216 (43.8)	98 (33.8)	0.007
LVEDV, mL	150.4 ± 42.4	157.0 ± 42.3	0.037
Calcified lesions, n (%)	104 (21.1)	52 (17.9)	0.309
Multi-vessel disease, n (%)	336 (68.2)	186 (64.1)	0.272
LAD lesion, n (%)	293 (59.4)	170 (58.6)	0.822
DES/BMS, n/n (% / %)	435/58 (88.2 / 11.8)	258/32 (89.0 / 11.0)	0.817
Complete revascularization, n (%)	323 (65.5)	187 (64.5)	0.816
ACEi or ARB, n (%)	338 (68.6)	209 (72.1)	0.301
Beta-blocker, n (%)	425 (86.2)	252 (86.9)	0.786
DAPT at discharge, n (%)	484 (98.2)	287 (99.0)	0.550
Duration of using DAPT, months	7.7 ± 2.3	7.8 ± 2.5	0.431
Statin, n (%)	491 (99.6)	289 (99.7)	0.894
Systolic blood pressure, mmHg	132.4 ± 23.0	153.9 ± 23.1	< 0.001
Diastolic blood pressure, mmHg	70.0 ± 12.0	82.2 ± 12.7	< 0.001
Mean blood pressure, mmHg	90.8 ± 13.2	106.1 ± 13.7	< 0.001
Heart rate, beat/min	71.1 ± 12.6	74.8 ± 12.5	< 0.001
Right atrial pressure, mmHg	9.7 ± 4.9	9.3 ± 4.2	0.207
PASP, mmHg	38.7 ± 13.3	38.2 ± 11.8	0.595
PCWP, mmHg	18.3 ± 8.8	18.3 ± 7.1	0.941
Cardiac output, L/min	4.1 ± 0.8	5.9 ± 1.1	< 0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare-metal stenting; CPO, cardiac power output; DAPT, dual-antiplatelet therapy; DES, drug-eluting stenting; eGFR, estimated glomerular filtration rate; LAD, left anterior descending artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure.

value of CPO at 0.97 is higher than the CPO values in previous studies. Nevertheless, despite the elevated CPO value, we noted that the sensitivity and specificity of the CPO cutoff value in this study closely resembled those in prior studies. Mendoza et al. demonstrated that CPO cut-off at 0.53 Watt has a positive predict value 49 % and negative predict value 80 % for in-hospital mortality in patients with acute cardiac diseases [10]. Basir et al. previously reported that, CPO threshold of 0.6 Watt in cardiogenic shock demonstrated a sensitivity of 38 % and a specificity of 88 %, thereby showing potential utility in shock protocols to enhance clinical outcomes [5]. In this study focusing on coronary artery disease patients with ALVSD, the CPO measured via PAC with a threshold of 0.97 Watt demonstrated a sensitivity of 39 % and a specificity of 86 % for the prediction of stage progression-related HF hospitalization, a sensitivity of 39 % and a specificity of 84 % for forecasting cardiovascular mortality, and a sensitivity of 39 % and a specificity of 77 % for predicting all-cause mortality.

ALVSD, classified as stage B HF, represents a pre-clinical phase of HF with a prevalence exceeding three times that of advanced HF [11]. Moreover, individuals with pre-clinical HF demonstrate a significant likelihood of progressing to more advanced stages. Previous investigations have reported an incidence of HF stage progression ranging from 6.0 to 14.0 per 1000 person-years among those with stage B HF [12,13]. In our study cohort, the incidence of HF stage progression for all participants was 13.9 per 1000 person-years, closely aligning with prior research. However, the observed mortality incidence in our study surpassed that reported in previous community studies. Ammar et al. reported sex-specific 5-year mortality rates for individuals with stage B HF, with rates of 7.2 % in men and 2.3 % in women [11]. Conversely, Xanthakis et al. found no significant difference in the mortality rate of stage B HF between men and women, standing at 8.81 per 1000 person-years [12]. Vasan et al. documented event rates for middle-aged African American individuals with stage B HF in the United States, reporting 5.9 and 20.6 per 1000 person-years for cardiovascular and all-cause mortality, respectively [14]. In our study, we found no significant difference in cardiovascular or all-cause mortality between men and women (6.1 % vs. 10.2 %, p = 0.121 for cardiovascular mortality; 10.4 % vs. 14.8 %, p = 0.165 for all-cause mortality). The incidence of cardiovascular mortality and all-cause mortality for all participants was 14.5 and 23.7 per 1000 person-years, respectively. The higher rates of cardiovascular and all-cause mortality in our study compared to prior studies can largely be attributed to the older age and high prevalence of MI within our study cohort. Participants in our present study had an average age of 62.6 years, with 59.9 % presenting with recent MI, in contrast to earlier research involving participants aged 50–59 years, with less than 10 % incidence of MI [12,14].

In line with the pathogenic mechanisms driving the progression of HF, myocardial strength biomarkers and noninvasive cardiac imaging are crucial in predicting prognosis in stage B HF [15,16]. In early HF,

Table 4
Incidence and risk of 5-year outcomes in patients with asymptomatic left ventricular systolic dysfunction according to CPO level.

	Patient number, n	Events, n (%)	person-year	Incidence per 1000 person-years	Crude HR (95 % CI)	P value	Adjusted# HR (95 % CI)	P value
HF hospitalizations								
CPO ≥ 0.97	290	7 (2.4)	1401.3	5.0	1.00 [Reference]	–	1.00 [Reference]	–
CPO < 0.97	493	44 (8.9)	2261.6	19.5	3.84 (1.73 – 8.54)	0.001	4.04 (1.53 – 10.6)	0.005
Cardiovascular mortality								
CPO ≥ 0.97	290	9 (3.1)	1392.1	6.5	1.00 [Reference]	–	1.00 [Reference]	–
CPO < 0.97	493	44 (8.9)	2274.1	19.3	2.97 (1.45 – 6.09)	0.003	2.73 (1.19 – 6.27)	0.018
All-cause mortality								
CPO ≥ 0.97	290	21 (7.2)	1392.1	15.1	1.00 [Reference]	–	1.00 [Reference]	–
CPO < 0.97	493	66 (13.4)	2274.1	29.0	1.92 (1.17 – 3.14)	0.009	1.86 (1.05 – 3.30)	0.035

adjusted age per 10 years-old, sex, hypertension, diabetes mellitus, hyperlipidemia, recent myocardial infarction, previous stroke, estimated glomerular filtration rate, calcified lesion, multivessel disease, left anterior descending artery, drug-eluting stenting, left ventricular ejection fraction, left ventricular end-diastolic volume, pulmonary artery systolic pressure, pulmonary capillary wedge pressure, complete revascularization, duration of dual-antiplatelet therapy, use of statin, beta-blockers, angiotensin conversion enzyme inhibitor or angiotensin receptor blockers.

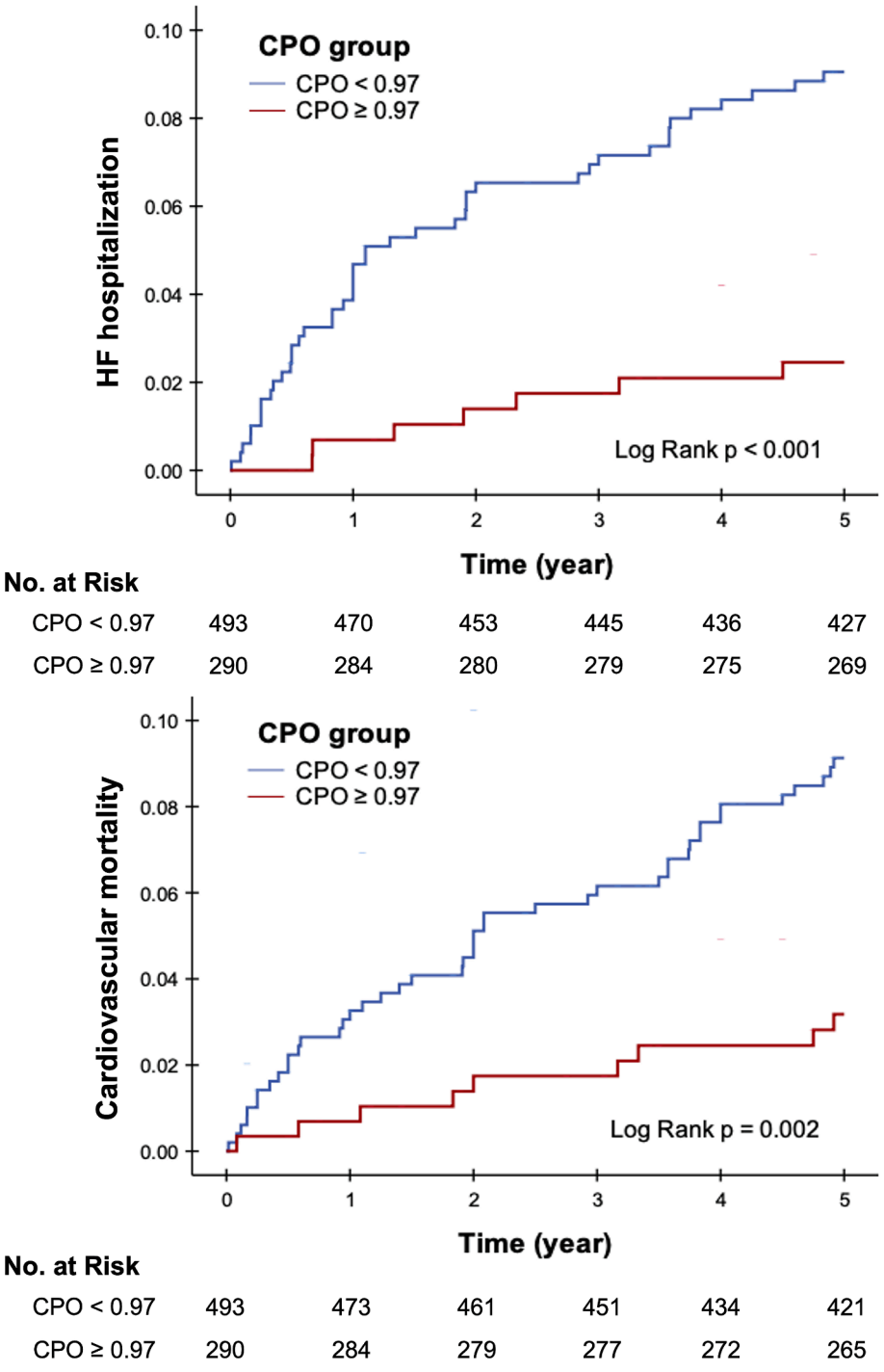

Fig. 2. Kaplan-Meier survival curves of (A) HF hospitalization, (B) cardiovascular mortality, and (C) all-cause mortality among high and low CPO in patients with asymptomatic left ventricular systolic dysfunction.

particularly among patients with acutely impaired LVEF, compensatory hemodynamic responses—such as increased sympathetic activity, blood pressure, ventricular size, and stroke volume—can temporarily obscure symptoms, even when filling pressures are elevated. Acanfora D et al. demonstrated the biomechanical and neuroanatomic responses in ischemic HF and underscored the prognostic importance of beta-adrenergic myocardial desensitization [17]. This study showed that the use of beta-blockers and CPO were independent predictors of 5-year all-cause mortality, aligning with Acanfora's findings, reinforcing the view of HF as a systemic disease, and supporting β-blockers as essential for long-term therapy.

Even in patients with acute or chronic HF, congestion is frequently unrecognized, and its impact on outcomes is often overlooked by clinicians. Massari et al. demonstrated that four biomarkers, used as surrogates for congestion, can predict outcomes in patients with acute or chronic HF [18]. For identifying potential prognostic progression in stage B HF, current guidelines recommend routine monitoring of myocardial stretch biomarkers, specifically B-type natriuretic peptide (BNP) and its N-terminal pro-peptide (NT-proBNP) [19,20]. Additionally, echocardiographic parameters such as left ventricular chamber

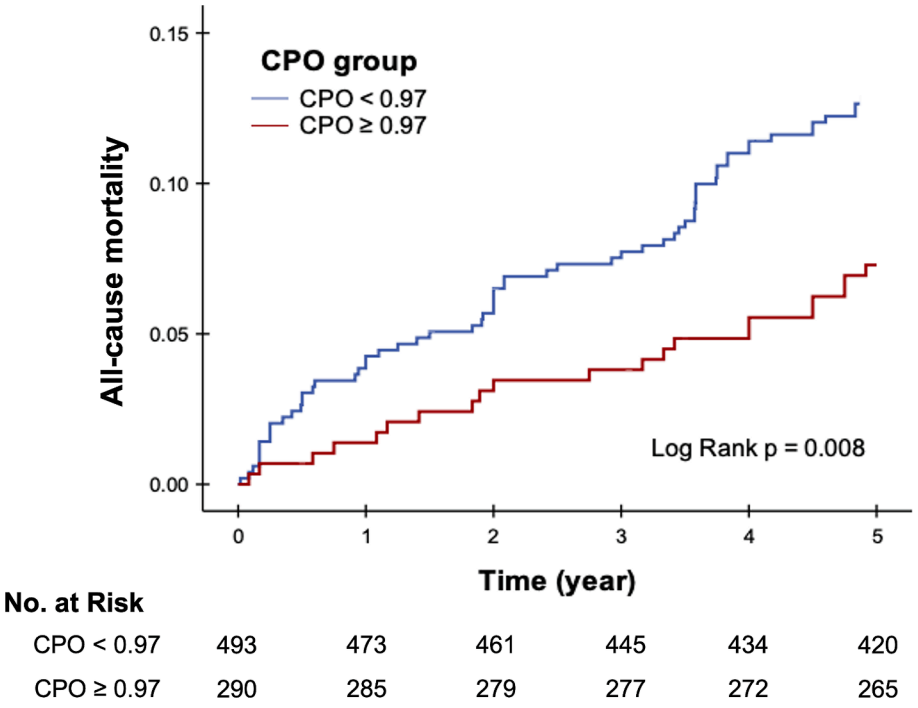

Fig. 2. (*continued*).

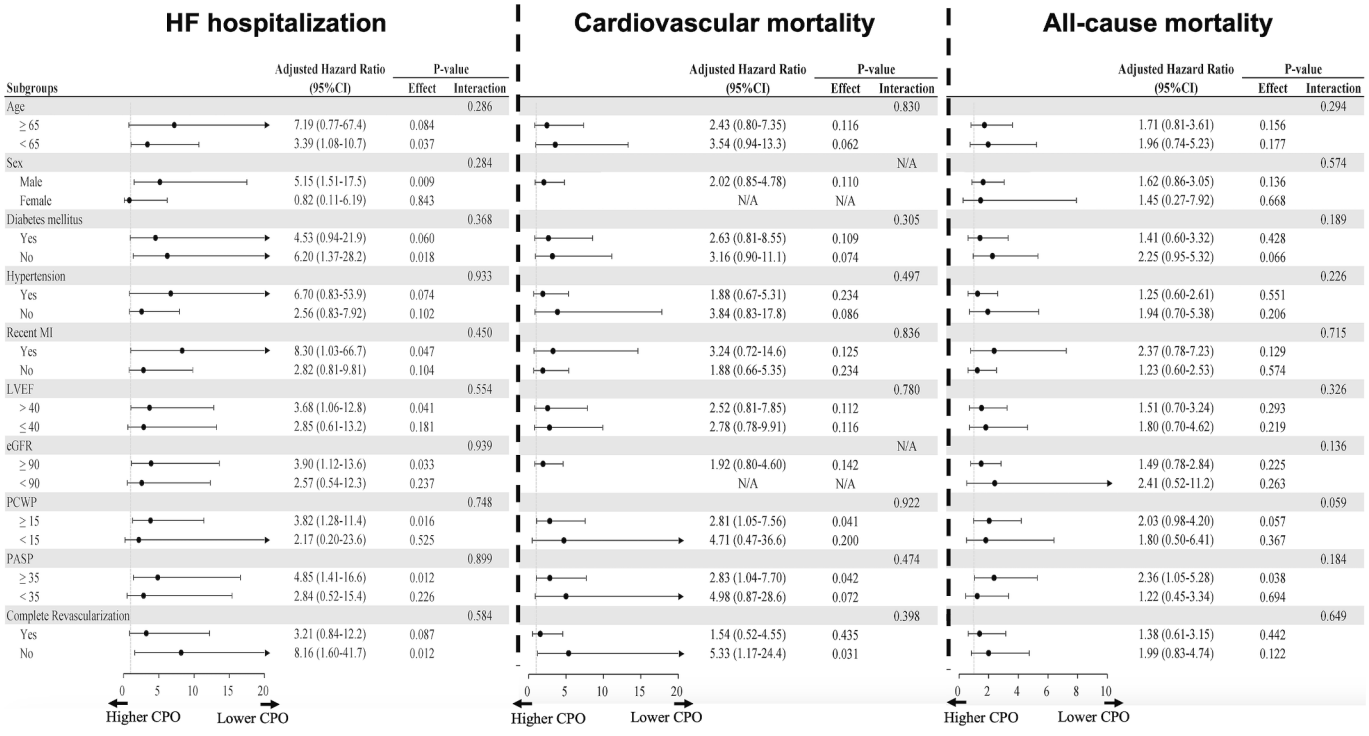

Fig. 3. Subgroup analysis of HF hospitalization, cardiovascular mortality, and all-cause mortality. Each stratification was adjusted for factors using in Table 4, except for the stratification factor itself.

dilation, left ventricular hypertrophy, E/A ratio, E/e', and global longitudinal strain are independent prognostic indicators of heart failure progression. Combining these imaging parameters, considering their interrelated mechanisms in the pathogenesis of HF, provides superior sensitivity in predicting the progression of HF stages [21–23]. In this study, we demonstrated the hemodynamic parameter – CPO could predict long-term HF progression and mortality in patients initially with LVSD and myocardial ischemic presentation. CPO is not only solely the intrinsic property of heart but also the regulation ability of autonomous nervous system and peripheral vasculature [24]. CPO is calculated by substituting the blood flow and pressure exhibited by the organism into the fluid mechanics formula, ultimately deriving the value that signifies cardiovascular energy, and is more accurate in reflecting cardiac work than LVEF [25]. In addition, it has been showed that CPO is the more

powerful adverse outcome predictor than clinical (age, sex, diastolic blood pressure, and atrial fibrillation), and echocardiographic markers (left atrial size, pulmonary pressures, global longitudinal strain, and E/e') in HF reduced EF [6,7]. Therefore, we propose that CPO functions as a comprehensive hemodynamic marker and has the potential to predict prognostic outcomes in individuals with pre-clinical HF. This study finding aligns with prior research in advanced HF, indicating that individuals with lower CPO tend to be older and have a higher proportion of females. Moreover, this group exhibits lower stroke volume, blood pressure, heart rate, and overall cardiac output compared to those in the high CPO group [4]. Individuals with lower CPO may exhibit reduced cardiovascular capacity to respond to stress through a catecholamine-mediated mechanism, limiting their ability to generate the required energy for hemodynamic compensation [26]. Hence this study find that CPO continues to serve as an independent predictor for risk stratification, not only in advanced but also in pre-clinical HF. This observation holds true even after adjusting for clinical characteristics and potential confounding factors.

The main strength of this study lies in its utilization of invasive PAC to gather hemodynamic data from individuals with stage B HF and ALVSD. Our findings revealed that while some patients exhibited elevated filling pressures, they remained clinically asymptomatic. Furthermore, the inclusion of right atrial pressure by PAC within the CPO formula in this study not only enhances the conceptual alignment of CPO as stroke work per unit time but also contributes to improved prognostic performance [27,28]. The recent implications of PAC in HF stages C and D have garnered renewed interest [29–31]. The findings of this study further broaden the scope of PAC's role in the broader HF spectrum. This study had a few limitations that must be considered. First, due to limitation of using PAC in our practice, stage B HF in this study was only focused on participants with coronary artery disease and LVEF $<$ 50 %. Those without coronary artery stenosis or those with LVEF $\geq$ 50 % associated with structural abnormalities were not included in this study. Second, we did not have laboratory data on certain heart-related biochemistry markers, such as B-type natriuretic peptide, because not all participants with pre-clinical HF underwent these tests regularly. Therefore, we could not determine whether there was an interaction between CPO and these biomarkers. Third, CPO was determined just once when the participants were at rest, which might not depict the changes over time. Moreover, we did not investigate how CPO, or the cardiac reserve might change after an exercise test in participants with pre-clinical HF. Fourth, this study retrospectively analyzed patients from 2006 to 2016, which may have introduced inherent differences between the study groups. The choice between complete or incomplete revascularization and the use of DES or BMS was made by the attending physician, introducing potential bias and serving as a limitation of this study. The use of beta-blockers and ACEi/ARBs in this study was 86.5 % and 69.9 %, respectively. During this period, clinical guidelines only recommended beta-blockers and ACEi/ARBs for patients with LVEF $\leq$ 40 % [32], with no clear recommendations for patients with LVEF between 41 % and 49 %. Until recently, beta-blockers and ACEi/ARBs were the recommended treatments for stage B HF, regardless of LVEF, while the role of Sodium-Glucose Cotransporter 2 inhibitors and Angiotensin Receptor-Neprilysin Inhibitors in this population remained uncertain [33]. In addition, for this coronary artery disease-based patient population in this study, the use of DAPT and statins was 99.6 % and 98.5 %, respectively. However, the duration of DAPT was influenced by national healthcare insurance regulations during the study period. Despite using statistical methods to adjust for major baseline characteristics, hidden biases may still persist.

In conclusion, this retrospective study showed lower CPO, particularly in the CPO $<$ 0.97 Watt, significantly predicts increased risks of HF stage progression, cardiovascular mortality, and all-cause mortality in stage B HF patients with ALVSD over a 5-year follow-up. Additional investigations are warranted to assess the potential applicability of these findings in clinical practice.

CRediT authorship contribution statement

Ming-Jer Hsieh: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Jih-Kai Yeh:** Investigation, Funding acquisition, Data curation. **Yu-Chang Huang:** Investigation, Funding acquisition. **Ming-Yun Ho:** Investigation. **Dong-Yi Chen:** Investigation. **Cheng-Hung Lee:** Investigation. **Chao-Yung Wang:** Investigation. **Shang-Hung Chang:** Investigation. **Chun-Chi Chen:** Supervision, Investigation. **I-Chang Hsieh:** Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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