ORIGINAL ARTICLE

Association of ejection fraction with mortality and cardiovascular events in patients with coronary artery disease

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Abstract

Aims   Recent studies suggested that both left ventricular ejection fraction (LVEF) lower than 60% or higher than 65% were associated with an increased mortality in the general population. Uncertainty remains regarding adverse outcomes across LVEF in coronary artery disease (CAD). The common understanding was that LVEF <40% was associated with an increased risk of mortality. But the threshold at LVEF of 40% was arbitrary because quite a lot of adverse outcomes existed in patients with ejection fraction >40%. We aimed to evaluate the relationship between LVEF and mortality or adverse events in CAD patients undergoing percutaneous coronary intervention (PCI).

Methods and results   A total of 10 252 CAD patients undergoing PCI from an observational cohort were studied. All-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE) were set as outcomes. Kaplan–Meier curves, adjusted Cox regression models, and restricted cubic spline analyses were used for evaluation. A total of 137 (1.3%) patients had all-cause mortality, and 816 (8.0%) patients had MACCE during a median of 2.4 years of follow-up. The median LVEF was 64%. All-cause mortality and MACCE rates changed substantially across LVEF categories, and a linear inverse relationship of LVEF with all-cause mortality and MACCE risk was observed. All-cause mortality or MACCE risk increased significantly below an LVEF of 55 or 65%, respectively. Patients with LVEF <55% had a more than 3.5-fold higher mortality than those with LVEF ≥55%. Patients with LVEF <65% had a more than 1.3-fold higher MACCE than those with LVEF ≥65%. Below 55 or 65%, there was a rise in mortality or MACCE. A gradient–response relationship was observed, with an all-cause mortality risk range between 8.6-fold and 3.0-fold increase from LVEF <40 to 50–54.9% and MACCE risk range between 2.4-fold and 1.4-fold from LVEF <40 to 60–64.9%.

Conclusions   In CAD patients undergoing PCI, LVEF lower than 55% or LVEF lower than 65% was correlated with increased all-cause mortality and MACCE respectively, whereas higher LVEF was not.

Introduction

Left ventricular ejection fraction (LVEF) is a well-recognized measurement for cardiac function and has been widely utilized as a risk stratification tool in heart failure (HF), valvular disease, and coronary artery disease (CAD).[1–4] Reduced LVEF (<40%) is a marker of contractile dysfunction and predicts mortality and adverse events in a variety of clinical settings.[1,2] Many randomized controlled trials (RCTs) for heart diseases designated reduced ejection fraction as the

inclusion criterion,[5–8] but the chosen cut-off at an LVEF of 40% is arbitrary and mainly concluded from evidence in HF.[9]

In contrast with the prior agreement that only severely low levels of LVEF are related to increased mortality, the recent cohort studies reported conflicting findings, with both LVEF lower than 60% or higher than 70% associated with an elevated risk of mortality.[10,11] These studies were conducted in the general population undergoing echocardiography, but the heterogeneity inherent to these studies required further investigation in the specific population. The association between LVEF and adverse events in patients with CAD undergoing percutaneous coronary intervention (PCI) is not completely clear. Few studies have a large enough population to accurately define the relationship. The largest cohort in previous studies had 5127 patients, with all women aged >65 years diagnosed with acute coronary syndrome.[12] The largest pool analysis of RCTs had 6198 patients, but the patients were crudely divided into three groups (<40, 40–50, and ≥50%).[3] Besides, the RCTs do not reflect the real-world practice, because enormous patients in the general population were excluded by the strict entry and exclusion criteria of RCTs.[13]

In the present study, we endeavoured to identify the relationship between LVEF and the risk of mortality and cardiovascular events in CAD patients undergoing PCI in a large observational cohort from the National Center for Cardiovascular Diseases in China. We assessed whether or not there is a threshold above or below which there is no relationship between LVEF and mortality and cardiovascular events.

Methods

Study cohort

The present cohort study included 10 724 consecutive CAD patients undergoing PCI at the National Center for Cardiovascular Diseases in China (Fuwai Hospital) from January 2013 to December 2013. Clinical data were prospectively collected. Among them, 472 patients were excluded due to missing LVEF data and having a perioperative myocardial infarction (PMI). We excluded patients with PMI because it could affect subsequent ejection fraction or MACCE. PMI was defined by SCAI definition.[14] Finally, a total of 10 252 patients were enrolled in the study. All participants had written informed consent before the enrolment. The study complied with the Declaration of Helsinki and was approved by the ethical review board of Fuwai Hospital. The LVEF was measured by transthoracic echocardiography at admission before PCI. The PCI procedures were performed in the current standard manner, and the use of stents and equipment was at the discretion of the treating cardiologist.

Endpoint and follow-up

All patients received follow-up at regular intervals through telephone or outpatient clinic visits. The outcomes were all-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE). MACCE was composed of cardiac death, myocardial infarction (MI), stent thrombosis (ST), target vessel revascularization (TVR), and stroke.

Statistical analysis

Description of continuous variables was presented as mean ± SD and compared using analysis of variance (ANOVA); categorical variables were presented as numbers with percentages and compared using the chi-square test. Adjusted Cox proportional hazards regression and Kaplan–Meier survival curves analyses were performed to assess the association between LVEF and endpoints. The adjusted variables used in multivariate models were selected and chosen based on the variables with P values < 0.05 in the univariable analysis for mortality (*Supplemental Table 1*), including age, BMI, chronic kidney diseases (CKD, i.e. eGFR below 60), total occlusion, previous cerebrovascular disease, moderate to severe calcification, and baseline TIMI 3. Considering the clinical relevance, sex, lesion length, successful revascularization, and clinical presentation for PCI [stable coronary artery disease (stable CAD) and acute coronary syndrome (ACS)] were also used in multivariate models. Restricted cubic spline (RCS) analysis based on Cox proportional hazards models was used to assess the levels of LVEF on a continuous scale. In addition, LVEF were stratified by 5% width interval into eight groups: <40, 40–44.9, 45–49.9, 50–54.9, 55–59.9, 60–64.9, 65–69.9, and ≥70%. The reference group was the one associated with the lowest risk of all-cause mortality or MACCE. SPSS Version 24.0 (Chicago, USA) and R statistical software version 4.0.3. (https://www.r-project.org/) were used to conduct statistical analyses. All P values were two-sided, and a P value < 0.05 was considered statistically significant.

Results

A total of 10 252 patients with a median follow-up period of 2.4 years were included in the current study. Seven thousand nine hundred (77.1%) of them were men, and the mean age was 59 years. *Table 1* displays that patients with low LVEF were more frequently men and current smokers, had longer lesion lengths, were older ages, and were more likely to have total occlusion and multivessel diseases. Alternatively, hypertension and hyperlipidaemia were more frequent in high LVEF. During the median 2.4 years of follow-up, 137 (1.3%)

Table 1 Baseline characteristics by LVEF categories

	LVEF <40 (N = 125)	LVEF 40–44.9 (N = 163)	LVEF 45–49.9 (N = 233)	LVEF 50–54.9 (N = 495)	LVEF 55–59.9 (N = 1269)	LVEF 60–64.9 (N = 3417)	LVEF 65–69.9 (N = 2959)	LVEF ≥70 (N = 1591)	P value
Age, years	60.3 (11.6)	59.5 (11.8)	58.3 (11.2)	57.2 (11.3)	58.9 (10.8)	58.5 (10.3)	58.0 (9.9)	58.5 (9.8)	0.006
Male sex	101 (80.8)	133 (81.6)	196 (84.1)	432 (87.3)	1,050 (82.7)	2,627 (76.9)	2,224 (75.2)	1,137 (71.5)	<0.001
BMI, kg/m²	25.5 (3.1)	25.9 (3.3)	25.7 (3.3)	26.1 (3.3)	26.1 (3.2)	25.9 (3.2)	25.9 (3.1)	25.8 (3.3)	0.046
LVEF, %	35.8 (3.9)	41.5 (1.5)	46.6 (1.4)	52.0 (1.5)	57.3 (1.5)	61.8 (1.6)	66.6 (1.5)	72.5 (2.5)	<0.001
Current smoking	78 (62.4)	99 (60.7)	153 (65.7)	323 (65.3)	808 (63.7)	1931 (56.5)	1,631 (55.1)	821 (51.6)	<0.001
Diabetes mellitus	43 (34.4)	50 (30.7)	85 (36.5)	162 (32.7)	395 (31.1)	1,050 (30.7)	868 (29.3)	464 (29.2)	0.218
Hypertension	78 (62.4)	92 (56.4)	129 (55.4)	280 (56.6)	779 (61.4)	2,199 (64.4)	1950 (65.9)	1,087 (68.3)	<0.001
Hyperlipidaemia	71 (56.8)	103 (63.2)	155 (66.5)	314 (63.4)	840 (66.2)	2,298 (67.3)	2034 (68.7)	1,096 (68.9)	0.023
Peripheral vascular disease	3 (2.4)	2 (1.2)	5 (2.1)	11 (2.2)	43 (3.4)	99 (2.9)	75 (2.5)	34 (2.1)	0.413
Previous cerebrovascular disease	17 (13.6)	19 (11.7)	21 (9.0)	46 (9.3)	150 (11.8)	367 (10.7)	309 (10.4)	166 (10.4)	0.663
Multivessel disease	96 (76.8)	130 (79.8)	181 (77.7)	388 (78.4)	994 (78.3)	2,579 (75.5)	2,174 (73.5)	1,166 (73.3)	0.005
Left main disease	7 (5.6)	13 (8.0)	11 (4.7)	25 (5.1)	94 (7.4)	207 (6.1)	174 (5.9)	105 (6.6)	0.407
Total occlusion	43 (34.4)	54 (33.1)	79 (33.9)	171 (34.5)	313 (24.7)	574 (16.8)	392 (13.2)	174 (10.9)	<0.001
Lesion length, mm	30.1 (19.8)	29.9 (17.9)	31.1 (19.0)	32.2 (19.5)	29.7 (20.0)	29.0 (21.0)	28.5 (18.3)	27.5 (16.6)	<0.001
Moderate to severe calcification	23 (18.4)	31 (19.0)	43 (18.5)	85 (17.2)	212 (16.7)	532 (15.6)	454 (15.3)	236 (14.8)	0.5
Baseline TIMI 3	67 (53.6)	82 (50.3)	112 (48.1)	252 (50.9)	777 (61.2)	2,354 (68.9)	2,157 (72.9)	1,202 (75.5)	<0.001
ACS presentation	80 (64.0)	101 (62.0)	158 (67.8)	345 (69.7)	844 (66.5)	2,144 (62.7)	1771 (59.9)	925 (58.1)	<0.001
PCI duration, min	38.2 (28.4)	36.6 (26.6)	41.0 (34.6)	40.9 (36.1)	37.7 (33.0)	35.0 (30.3)	34.4 (32.8)	32.2 (25.7)	<0.001
Successful revascularization	118 (94.4)	159 (97.5)	225 (96.6)	473 (95.6)	1,231 (97.0)	3,337 (97.7)	2,872 (97.1)	1,555 (97.7)	0.055

BMI, body mass index; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction. Continuous variables were presented as the mean with standard deviation. Categorical characteristics were described as counts with percentages.

Figure 1 All-cause mortality and MACCE rates according to LVEF categories. LVEF, left ventricular ejection function; MACCE, major adverse cardiovascular and cerebrovascular events.
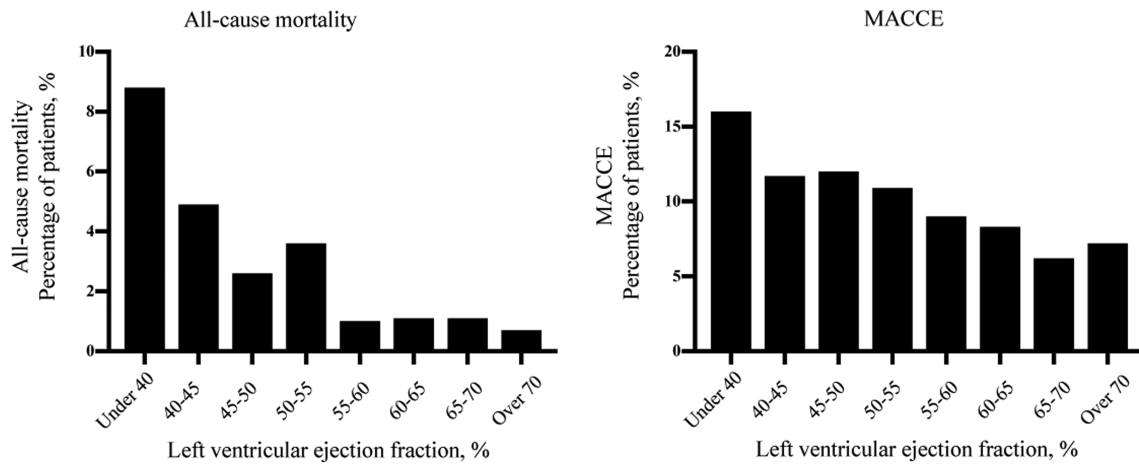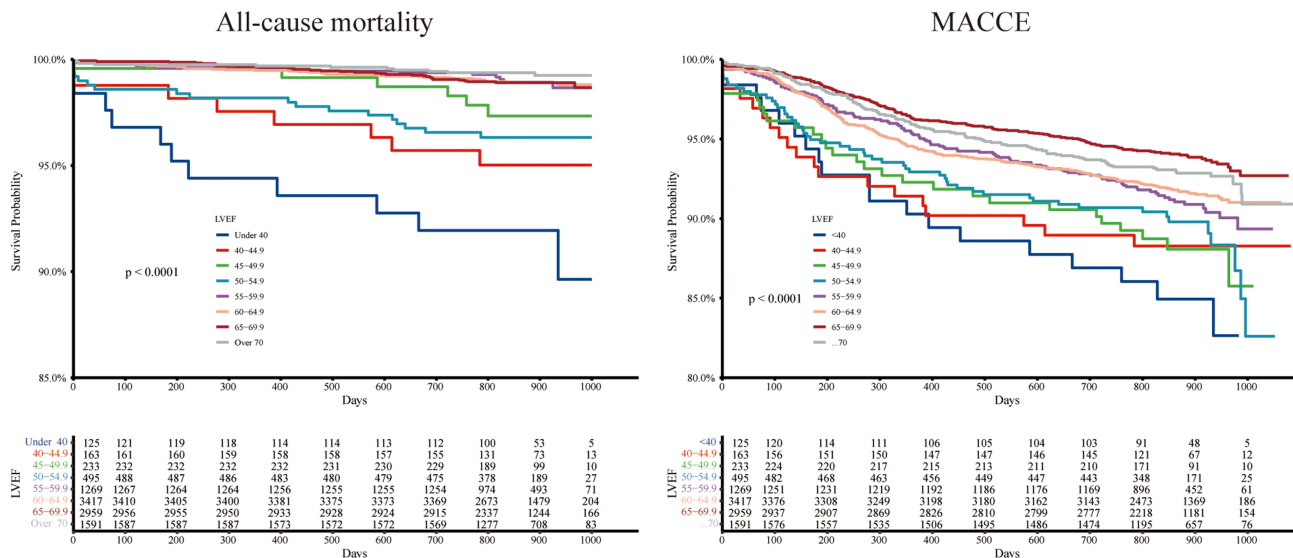

Figure 2 Kaplan–Meier curves by LVEF categories. LVEF, left ventricular ejection function; MACCE, major adverse cardiovascular and cerebrovascular events.

patients had all-cause mortality, and 816 (8.0%) patients had MACCE.

As displayed in *Figure 1*, with a stepwise 5% increase of LVEF from <40 to ≥70%, an inverse association between LVEF and all-cause mortality rates and MACCE rates was observed. In *Figure 2*, Kaplan–Meier survival curves show that LVEF under 55% was correlated with increased all-cause mortality (*P* < 0.001) and LVEF under 65% was correlated with increased MACCE (*P* < 0.001).

The associations of LVEF with all-cause mortality and MACCE are illustrated in *Figure 3*. A significantly higher ad-

justed risk was observed at LVEF <55% for all-cause mortality and at LVEF <65% for MACCE. Patients with LVEF <55% had a more than 3.5-fold higher mortality [adjusted hazard ratio (HR) 3.51, 95% confidence interval 2.41–5.13, *P* < 0.001] than those with LVEF ≥55%. Patients with LVEF <65% had a more than 1.3-fold higher MACCE [adjusted HR 1.33, 95% confidence interval 1.15–1.53, *P* < 0.001] than those with LVEF ≥65%. A gradient–response relationship was observed, with an all-cause mortality risk range between 8.6-fold and 3.0-fold increase from LVEF <40 to 50–54.9% (*P* for trend < 0.001) and MACCE risk range between 2.4-fold and

Figure 3 Adjusted hazard ratio and 95% confidence interval for all-cause mortality and MACCE by LVEF categories. LVEF, left ventricular ejection function; MACCE, major adverse cardiovascular and cerebrovascular events.
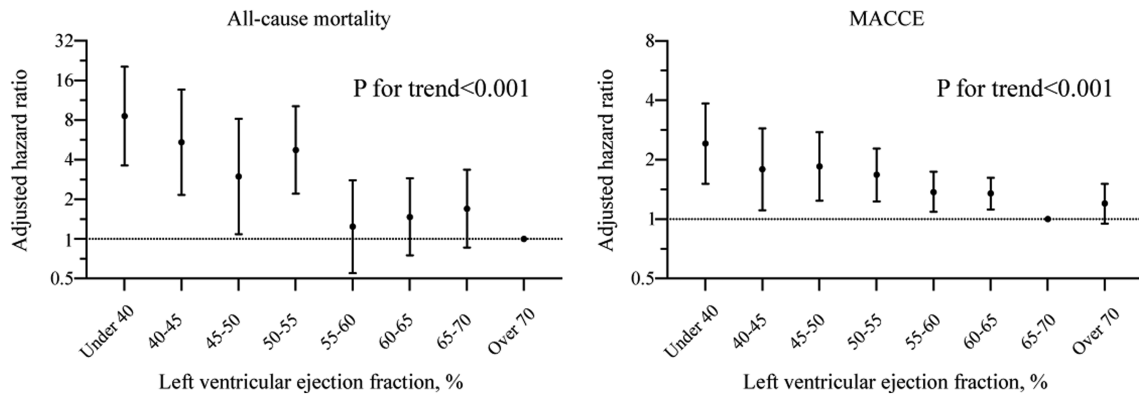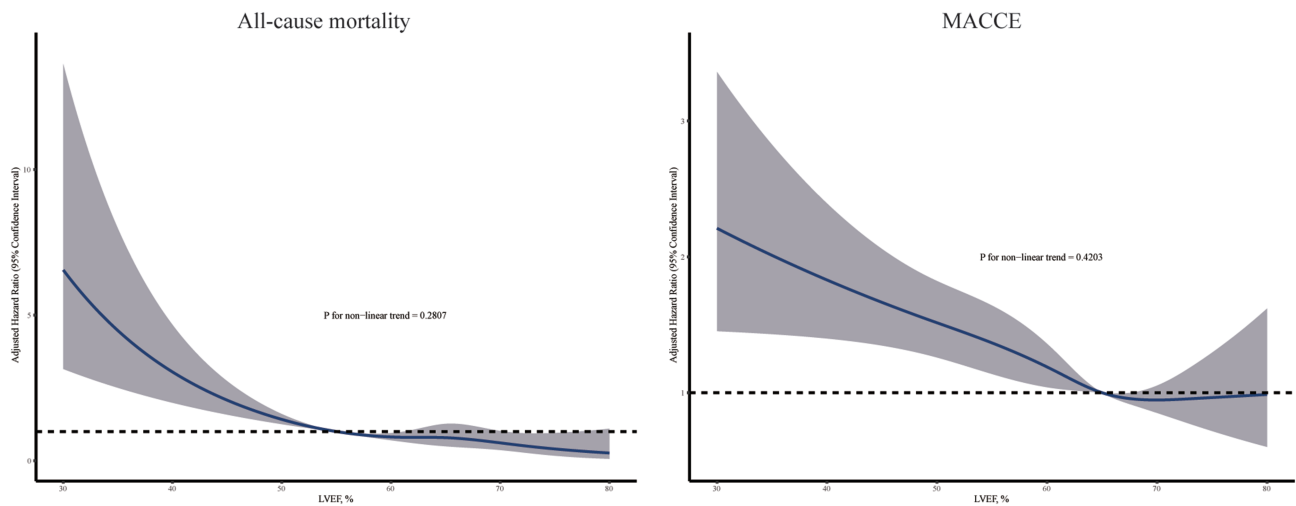

Figure 4 Adjusted restricted cubic spline curves for all-cause mortality and MACCE by LVEF categories. LVEF, left ventricular ejection function; MACCE, major adverse cardiovascular and cerebrovascular events.

1.4-fold increase from LVEF <40 to 60–64.9% (*P* for trend < 0.001). Adjusted RCS for LVEF and events are shown in *Figure 4*. A linear inverse pattern was observed at LVEF <55% for all-cause mortality and at LVEF <65% for MACCE although the risk was comparable at higher LVEF. Similar findings were also seen in stable CAD and acute coronary syndrome (ACS) (*Figure 5*).

Discussion

In the present study, we reported an analysis of 10 252 CAD participants in a PCI cohort. We identified the linear inverse

relationship of LVEF with all-cause mortality and MACCE. The findings demonstrate that all-cause mortality or MACCE was increased in patients with LVEF <55 or <65%, respectively. In contrast, LVEF >55 or >65% were not correlated with significantly higher risk. The cut-off values for increased risk of all-cause mortality and MACCE were at LVEF of 55% and LVEF of 65%, respectively. Patients with LVEF <55% had a more than 3.5-fold higher mortality than those with LVEF ≥55%. Patients with LVEF <65% had a more than 1.3-fold higher MACCE than those with LVEF ≥65%. Below 55 or 65%, there was a rise in mortality and MACCE.

To the best of our knowledge, this is the largest cohort study exploring the association between LVEF and mortality or cardiovascular events in CAD patients. The research is

Figure 5 Adjusted restricted cubic spline curves for all-cause mortality and MACCE by LVEF categories for stable CAD and ACS. ACS, acute coronary syndrome; CAD, coronary artery disease; LVEF, left ventricular ejection function; MACCE, major adverse cardiovascular and cerebrovascular events. [Correction added on 29 July 2022, after first online publication: the text in the lower right corner of every panel in Figure 5 has been deleted in this version.]

Stable CAD All-cause mortality

Stable CAD MACCE

ACS All-cause mortality

ACS MACCE
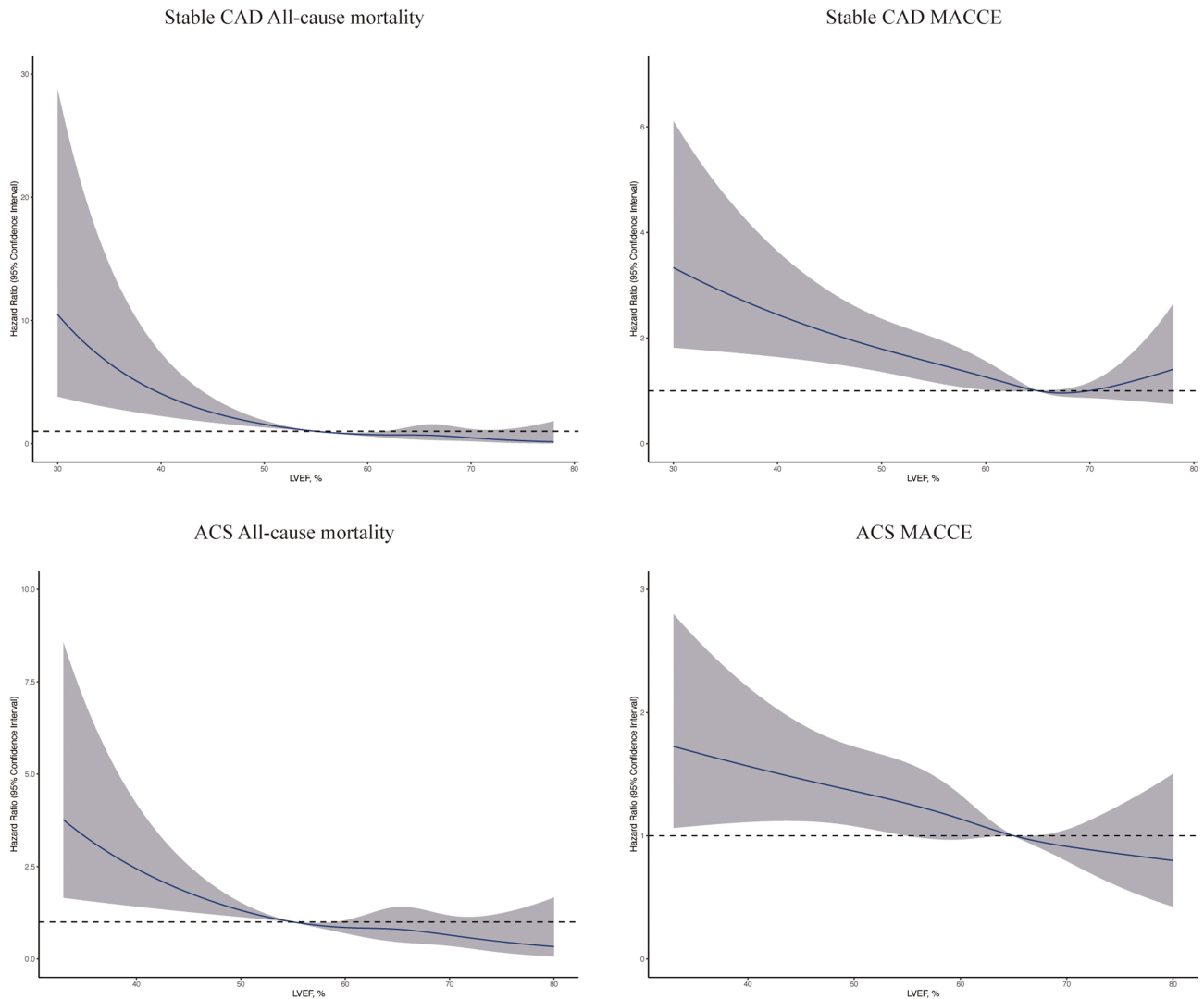
important given the recent yet unexplained finding of excess mortality in subjects with LVEF deviated from 60 to 65% in the general population.[10] Our results are relevant. The findings provide critical evidence for clinical risk evaluation and management. Furthermore, our study has crucial implications for the LVEF threshold used for the entry criterion in CAD-related studies and trials.

Prior studies mainly focused on the association between LVEF and adverse events in HF patients, coming with various results. An inverse relation between LVEF and mortality or cardiovascular outcomes was observed in chronic or stable HF at LVEF <45%.[15,16] A U-shaped relation for unadjusted mortality was observed in acute HF with a nadir at LVEF of 35%, but the increased risk in high LVEF was attenuated after

adjustment.[17] Recent evidence of heterogeneous population studies found conflicting results. In a cohort of individuals without cardiovascular diseases at baseline from the Multi-Ethnic Study of Atherosclerosis, they found a U-shaped association for the risk of incident chronic HF with a nadir at 62.5%, but not for the risk of mortality with increased risk of mortality only at LVEF <50%.[18] On the contrary, echocardiographic data from the cohort in Geisinger health records in the USA and the registry from the National Echocardiography Database Australia (NEDA) show that both low and high levels of LVEF were associated with increased mortality.[10,11] Few studies have examined the relationship between LVEF and mortality in CAD patients undergoing PCI, with the majority of studies studying LVEF as dichotomization (LVEF

$<$40 and $\geq$40%)[19,20] or as three categories (LVEF $<$40%, 40–50, and $\geq$50).[3,21,22] An interesting study focusing on women aged over 65 years showed that LVEF $>$65% is associated with an increased risk of death.[12] Moreover, most studies were conducted with a modest size of subjects; large enough PCI participants are required for the reliable examination. Based on 10252 participants, our study found that low, but not high, levels of LVEF were associated with increased mortality and MACCE in the large-scale PCI cohort in contemporary practice. Consistent with pool analysis of CAD RCTs and direct analysis of the Multi-Ethnic Study of Atherosclerosis,[3,18] we also found that low normal LVEF, more specifically 55 or 65%, was capable of risk-stratified increased mortality or cardiovascular events.

Our results provide crucial clinical implications for understanding the optimal levels of LVEF in CAD patients. The finding shows that LVEF $\geq$55% or LVEF $\geq$65% is not associated with all-cause mortality or MACCE respectively, which implies that LVEF over this threshold might be relatively optimal. Furthermore, the present study indicates that the LVEF cut-off in CAD might need to be redefined based on findings in the CAD setting.

Limitations

First, our study was a retrospective analysis of prospectively collected data, and the inherent bias associated with this type of study should be carefully considered. However, the present study provided real-world evidence in a non-selected CAD population. Second, we did not have the data of LVEF at discharge or at follow-up or physiological testing data.

Conclusions

Low and low normal, but not high, LVEF was associated with increased risk of all-cause and MACCE in CAD patients undergoing PCI. Patients with LVEF $\geq$55% or LVEF $\geq$65% could be considered as the threshold above which there is no relationship between LVEF and mortality or cardiovascular events. Our findings might help to guide the clinical management and inclusion criterion in clinical trial design.

Acknowledgements

Conflict of interest

Nothing to report.

Funding

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Table 1. Univariable Cox analysis of all-cause mortality.

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