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ORIGINAL ARTICLE

Long-term mortality after acute coronary syndromes among patients with normal, mildly reduced, or reduced ejection fraction

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Abstract

Aims Left ventricular ejection fraction (LVEF) ≤ 40% is a well-established risk factor for mortality after acute coronary syndromes (ACS). However, the long-term prognostic impact of mildly reduced ejection fraction (EF) (LVEF 41–49%) after ACS remains less clear.

Methods and results This was a retrospective study enrolling patients admitted with ACS included in a single-centre databank. LVEF was assessed by echocardiography during index hospitalization. Patients were divided in the following categories according to LVEF: normal (LVEF ≥ 50%), mildly reduced (LVEF 41–49%), and reduced (LVEF ≤ 40%). The endpoint of interest was all-cause death after hospital discharge. A multivariable Cox model was used to adjust for confounders. A total of 3200 patients were included (1952 with normal EF, 375 with mildly reduced EF, and 873 with reduced EF). The estimated cumulative incidence rates of mortality at 10 years for patients with normal, mildly reduced, and reduced EF were 24.8%, 33.5%, and 41.3%, respectively. After adjustments, the presence of reduced EF was associated with higher mortality compared with normal EF [adjusted hazard ratio (HR) 1.64; 95% confidence interval (CI) 1.36–1.96; $P < 0.001$], as was mildly reduced EF compared with normal EF (adjusted HR 1.33; 95% CI 1.05–1.68; $P = 0.019$). The presence of reduced EF was not associated with a statistically significantly higher mortality compared with mildly reduced EF (adjusted HR 1.23; 95% CI 0.96–1.57; $P = 0.095$).

Conclusions In patients with ACS, mildly reduced EF measured in the acute phase was associated with higher long-term mortality compared with patients with normal EF. These data emphasize the importance of anti-remodelling therapies for ACS patients who have LVEF in the mildly reduced range.

Keywords ACS; Long-term mortality; Left ventricular ejection fraction; Mildly reduced ejection fraction

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Introduction

Among patients admitted with acute coronary syndromes (ACS), left ventricular ejection fraction (LVEF) remains a strong predictor of survival after discharge from the hospital. Pivotal studies have suggested a steep increase in mortality when LVEF reaches values equal to or below 40%, with death rates as high as 15% at 6 months in this population.[1–3] Therefore, this LVEF cut-off was used to select patients for some pivotal randomized clinical trials testing anti-remodelling therapies after myocardial infarction (MI), such as renin-angiotensin system (RAS) inhibitors, mineralocorticoid receptor antagonists (MRAs), and beta-blockers.[4–6]

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Recently, patients with LVEF below the normal range, but above 40%, have emerged as a group of interest in heart failure (HF) and may also be after acute MI. These patients have been variously described as having 'mid-range', 'mildly reduced', or 'borderline' ejection fraction (EF) in current guidelines,[7,8] and recent data suggest that prognosis in this subgroup is worse than among patients who present with a normal LVEF, that is, ≥55%, after an acute MI.[9,10] Moreover, therapies tested in patients with HF and 'preserved' EF (HFpEF), defined as LVEF > 40%, appeared to be more effective in the mildly reduced subgroup than in patients with a higher LVEF, thus fostering the debate about which is the optimum cut-off to identify patients with systolic dysfunction who might benefit from neurohumoral blockade.[11,12] Whereas some guidelines have defined mildly reduced EF as LVEF between 40% and 50%,[7,8] others have chosen different thresholds.[13,14] These cut-offs are often arbitrary,[15] and few reports in the literature have analysed which is the ideal cut-off that best discriminates survivors from non-survivors after MI. Additionally, the long-term prognosis of patients discharged alive after ACS according to EF is poorly understood, because most of the reports in the literature have comprised shorter than 5 years of follow-up.[1–3,10]

Therefore, we performed a study analysing the long-term survival of patients presenting with low, mildly reduced, or normal EF after ACS. We hypothesized that mildly reduced EF would be associated with higher mortality compared with EF in the normal range in patients with ACS. Furthermore, we aimed to validate the optimum LVEF threshold for risk stratification.

Methods

Study design and selection of patients

This was a retrospective, single-centre, cohort study enrolling patients admitted to the Coronary Care Unit (CCU) from the Heart Institute (InCor) of Sao Paulo University Medical School. All patients with a definitive diagnosis of ACS were included consecutively in a prospective dedicated databank. This databank is intended mainly for administrative and quality of care assessment purposes. For the current study, we included patients admitted from 1 February 1998 until 1 August 2016. Variables concerning ACS type, that is, ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA), as well as baseline demographic characteristics, risk factors, past coronary artery disease (CAD) history, or procedures and ongoing medications at the time of admission and discharge were collected. The variables from the databank were collected by the attending physicians as a standard of care in the CCU.

We defined an ACS case as any patient presenting with new-onset ischaemic symptoms at rest or worsening exertional ischaemic symptoms requiring urgent hospital admission within the first 7 days of symptoms onset. MI was defined according to the current ACS Guidelines or Universal Definition of MI (from 2007 on) at the time of the data collection. STEMI was defined as persistent ST-elevation of at least 1 mm in two or more contiguous leads (except V2–V3, where at least 1.5 mm was required in women and men older than 40 years and at least 2 mm in men younger than 40 years) or new/presumably new left bundle branch block at admission electrocardiogram (ECG). Cases not fulfilling criteria for MI were classified as UA.

Left ventricular ejection fraction assessment

As part of standard of care, all patients had LVEF measured during hospitalization and, whenever possible, within 48 h from hospital admission. LVEF was measured by two-dimensional transthoracic echocardiography, with the Simpson method (preferred), or, if not feasible due to acoustic window issues, LVEF was visually estimated. Some patients also had LVEF assessed by left ventricular (LV) angiogram performed during invasive coronary angiography. If more than one LVEF echocardiographic assessment has been performed, the information from the first was collected in the databank.

Outcomes ascertainment

The primary outcome of interest was all-cause mortality after discharge. In-hospital death was not included in the present analysis to avoid immortal time bias (because patients who died within the first 48 h were less likely to have LVEF assessment). After discharge, all patients, whether treated in our institution or not, were followed by yearly telephone contacts performed by a team of medical students especially trained and supervised by two authors (RHMF and JCN). Those interviews had the purpose of determining the vital status and ascertaining long-term adherence to outpatient visits. No adjudication of cause of death was performed.

Statistical analysis

We classified the patients into three groups of interest according to LVEF: normal EF (EF ≥ 50%), mildly reduced EF (41–49%), or low EF (≤40%).[7,8] As a sensitivity analysis, we also classified patients according to other cut-offs, based on the guidelines from the British Society of Echocardiography: normal EF (≥55%), impaired EF (35–54%), or severely impaired EF (<35%).[13] An additional sensitivity analysis was

also performed using LVEF obtained by invasive left ventriculography.

Categorical variables are described as counts and percentages, and continuous variables as means and standard deviations (SDs), if normally distributed, or median and interquartile ranges (IQRs), if not normally distributed. Baseline variables were compared among the three groups of interest by the χ^2 test or Fisher's exact test, for categorical variables, or by one-way ANOVA or the Kruskal–Wallis test, as appropriate, for continuous variables. For the comparison of continuous variables between survivors and non-survivors to hospital discharge, independent samples Student's *t*-test or Wilcoxon's rank-sum tests were used, as appropriate. The Shapiro–Wilk test was used to assess the normality of distributions.

Mortality after discharge was analysed as a time-to-event variable, with patients censored at the date of last available contact. Cumulative incidence rates were estimated by the Kaplan–Meier product-limit method, and corresponding graphs were generated. Event curves were compared among the groups of interest by the non-stratified log-rank test.

To adjust for potential confounders, multivariable Cox proportional hazards models were fit with time to death as the dependent variable and LVEF category (low, mildly reduced, or normal) as the explanatory variable. Three different models were implemented. In Model 1, the covariates used in the adjustments were baseline variables with a *P*-value < 0.10 different among groups by univariate analyses: sex, ACS phenotype (STEMI vs. non-ST-elevation ACS), age, history of diabetes mellitus, dyslipidaemia, prior HF, prior MI, prior coronary artery bypass graft (CABG), prior stroke, Killip class II or more (Killip class I: no clinical signs of HF; Killip class II: basal crackles, an S3, and elevated jugular venous pressure; Killip class III: acute pulmonary oedema; and Killip class IV: cardiogenic shock),[16] history of kidney disease, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) at discharge, and use of beta-blockers at discharge. A second model (Model 2) included the same covariates from Model 1 plus the presence of multivessel CAD and GRACE (Global Registry of Acute Coronary Events) score.[17] A third model (Model 3) included as covariates all available baseline variables (including GRACE score and history of multivessel CAD), and a stepwise selection procedure was performed. A *P*-value threshold < 0.05 was used to include and a threshold of 0.10 to exclude from the model. A fourth model (Model 4) included same variables from Model 1 but retained only variables that were considered[18] confounders as depicted in a directed acyclic graph (DAG).[17] Accordingly, the variables Killip class II or more, use of ACEI or ARB, and use of beta-blockers were excluded from the model because they were mediators, and history of kidney disease and prior stroke were excluded because they were competing exposures rather than confounders (Supporting Information, *Figure S1*). Proportional hazards assumption was checked in all models by the Schoenfeld residuals.

As a sensitivity analysis, we investigated trends over time analysing patients according to three periods of time span: 1998 to 2004, 2005 to 2010, and 2011 to 2016, corresponding to tertiles of years of inclusion in the cohort. Moreover, in another sensitivity analysis, patients with prior history of HF before index admission were excluded. Finally, a third sensitivity analysis was done including levels of B-type natriuretic peptide (BNP) obtained during index hospitalization as a covariate.

The predictive ability of long-term mortality according to different cut-offs for defining LV dysfunction was analysed by receiver operating characteristic (ROC) curves. Logistic regression models were fit with death during follow-up as the dependent variable, and the presence of LV systolic dysfunction as the explanatory variables, adjusted for baseline covariates as in Model 1 described above. Different cut-offs of LVEF for defining LV dysfunction were applied: ≤35%, ≤40%, ≤45%, ≤50%, and ≤55%, and ROC curves generated for each model, with each corresponding areas under the curve (AUCs).

All analyses are two-tailed and a *P*-value < 0.05 was considered as statistically significant. Because the percentage of missing data for all the baseline characteristics (except GRACE score and multivessel CAD) were <5%, no imputation for missing data was performed. Because this study is observational and exploratory by nature, there was no adjustment for multiplicity. Statistical software used was Stata™ Version 13.1 (StataCorp, College Station, Texas).

Compliance with ethical standards

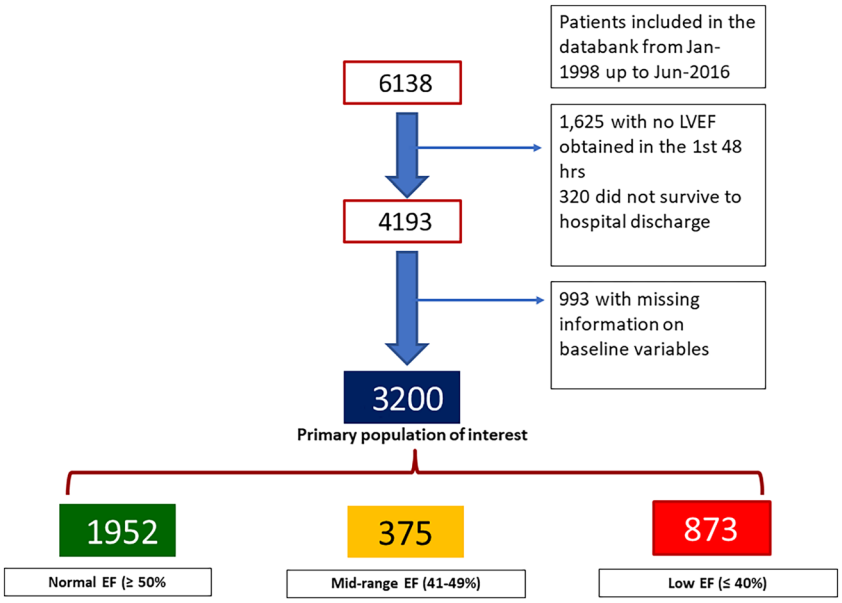
This study conformed to the International Council on Harmonization norms on medical research in humans. The study was approved by the ethics committee from clinics hospital. Because the data are based on individual information obtained for administrative purposes, informed consent was waived, according to local regulations.

Results

Descriptive statistics

From a total of 6138 patients collected in our databank, 1625 did not have available LVEF measured within the first 48 h. Additionally, 320 patients did not survive until hospital discharge and 993 patients did not have complete information regarding baseline variables, rendering 3200 patients eligible for the present analyses. Out of those, 1952 (61.0%) had normal EF (LVEF ≥ 50%), 375 (11.7%) mildly reduced EF (LVEF 41–49%), and 873 (27.3%) low EF (LVEF ≤ 40%) (*Figure 1*).

Figure 1 Study flow chart. EF, ejection fraction; LVEF, left ventricular ejection fraction.



The baseline characteristics of patients who died before discharge and those who survived are depicted in Supporting Information, *Table S1*.

Patients with mildly reduced and reduced EF were more likely to be male and have STEMI as the index ACS event, prior MI, diabetes, prior HF, and kidney disease. There was a graded increase in the proportion of patients with prior MI, prior HF, and presenting with Killip class II or higher from normal until mildly reduced and reduced EF groups, as well as a graded increase in the GRACE risk score across these categories (*Table 1*).

Considering in-hospital medications within the first 24 h of admission, the use of oral beta-blockers was more common among patients with normal EF. Use of ACEIs or ARBs was similar among the three groups. After discharge, patients with low/mildly reduced EF were more frequently treated with beta-blockers, ACEIs/ARBs, and MRAs (*Table 2*).

Long-term mortality after discharge by left ventricular ejection fraction categories

After discharge, the median (IQR) follow-up time was 4.3 (2.3–8.6) years, and the maximum follow-up time was 17.6 years. Overall, 705 (22.0%) patients died during the follow-up. The estimated cumulative incidence rates of mortality at 10 years for patients with normal, mildly reduced, and reduced EF were 24.8%, 33.5%, and 41.3%, respectively ($P < 0.001$ by log-rank test). The unadjusted hazard ratios (HRs) for death comparing reduced EF and mildly reduced EF with normal EF were, respectively, 1.93 [95% confidence interval (CI) 1.64–2.27; $P < 0.001$] and 1.51 (95% CI 1.20–1.90; $P < 0.001$), whereas HR for reduced EF vs. mildly reduced EF was 1.28 (95% CI 1.01–1.62; $P = 0.043$).

After adjustments for baseline characteristics, the presence of reduced EF was associated with higher mortality compared with normal EF (adjusted HR 1.64; 95% CI 1.36–1.96; $P < 0.001$), as was mildly reduced EF compared with normal EF (adjusted HR 1.33; 95% CI 1.05–1.68; $P = 0.019$). Conversely, there was no statistically significant difference in mortality comparing reduced to mildly reduced EF categories (adjusted HR 1.23; 95% CI 0.96–1.58; $P = 0.095$; *Figure 2*).

From the overall population, 2725 (85.2%) patients had available GRACE score, and 2475 (77.3%) patients had information about the presence of multivessel CAD collected in the databank. The association between mildly reduced EF (vs. normal EF) and a higher risk of death remained when other different models were considered, including Model 2, which included presence of multivessel disease and GRACE score (adjusted HR 1.47; 95% CI 1.08–1.99; $P = 0.014$); Model 3, which included all available covariates with a stepwise selection procedure (adjusted HR 1.43; 95% CI 1.06–1.95; $P = 0.021$); and Model 4, where covariates were selected from the DAG (adjusted HR 1.32; 95% CI 1.05–1.67; $P = 0.019$). Of note, when multivessel CAD and the GRACE score were included as covariates (Model 2), there was no difference in mortality between patients with reduced vs. mildly reduced EF (adjusted HR 1.02; 95% CI 0.75–1.41; $P = 0.86$; *Table 3*).

Table 1 Baseline characteristics according to left ventricular ejection fraction categories

Characteristics	Normal EF (LVEF ≥ 50%) (*N* = 1952)	Mildly reduced EF (LVEF 41–49%) (*N* = 375)	Reduced EF (LVEF ≤ 40%) (*N* = 873)	*P*-value
Age in years, median (IQR)	63.0 (55–72)	63.0 (55–73)	65.0 (56–73)	0.057
Female sex (%)	668 (34.2%)	94 (25.1%)	222 (25.4%)	<0.001
LVEF in %, median (IQR)	60.0 (55–66)	45.0 (45–45)	35.0 (30–40)	<0.001
ACS phenotype				<0.001
STEMI (%)	648 (33.2%)	188 (50.1%)	421 (48.2%)	
NSTEMI (%)	552 (28.3%)	90 (24.0%)	252 (28.9%)	
Unstable angina (%)	752 (38.5%)	97 (25.9%)	200 (22.9%)	
White race (%)	1653 (84.7%)	317 (84.5%)	739 (84.8%)	0.99
History of hypertension (%)	1457 (74.6%)	275 (73.3%)	652 (74.7%)	0.86
History of diabetes (%)	588 (30.1%)	131 (34.9%)	310 (35.5%)	0.009
History of dyslipidaemia (%)	1151 (59.0%)	220 (58.7%)	472 (54.1%)	0.047
Current smoking (%)	477 (24.4%)	80 (21.3%)	214 (24.5%)	0.41
Kidney failure at admission[a] (%)	532 (28.6%)	120 (32.9%)	328 (39.1%)	<0.001
Killip class II or higher[b] (%)	167 (8.9%)	56 (15.2%)	248 (28.9%)	<0.001
Prior MI (%)	549 (28.1%)	137 (36.5%)	359 (41.1%)	<0.001
Prior stroke (%)	78 (4.0%)	17 (4.5%)	61 (7.0%)	0.003
Prior HF (%)	72 (3.7%)	43 (11.5%)	194 (22.2%)	<0.001
Prior PCI (%)	413 (21.2%)	84 (22.4%)	177 (20.3%)	0.70
Prior CABG (%)	326 (16.7%)	85 (22.7%)	168 (19.3%)	0.013
Multivessel CAD (%)[c]	1096 (71.3%)	228 (77.8%)	480 (74.2%)	0.048
GRACE score, median (IQR)[d]	114 (95–135)	123 (102–146)	135 (111–162)	<0.001
BNP in pg/mL, median (IQR)[e]	121 (56–256)	202 (97–449)	579 (234–1002)	<0.001

ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; EF, ejection fraction; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

[a]This variable was not available for 71 patients (56 patients with normal EF, 5 patients with mildly reduced EF, and 10 patients with reduced EF).

[b]This variable was not available for 85 patients (64 patients with normal EF, 7 patients with mildly reduced EF, and 14 patients with reduced EF).

[c]This variable was not available for 723 patients (415 patients with normal EF, 82 patients with mildly reduced EF, and 226 patients with reduced EF).

[d]This variable was not available for 475 patients (303 patients with normal EF, 58 patients with mildly reduced EF, and 114 patients with reduced EF).

[e]This variable was available only for 333 patients (193 patients with normal EF, 37 patients with mildly reduced EF, and 103 patients with reduced EF).

Table 2 In-hospital therapies within the first 24 h according to left ventricular ejection fraction categories

Characteristics	Normal EF (LVEF ≥ 50%) (*N* = 1952)	Mildly reduced EF (LVEF 41–49%) (*N* = 375)	Low EF (LVEF ≤ 40%) (*N* = 873)	*P*-value
In-hospital therapies				
Oral beta-blocker[a] (%)	1364 (70.0%)	243 (65.0%)	563 (64.6%)	0.009
ACEI/ARB[a] (%)	1250 (64.1%)	240 (64.2%)	591 (67.9%)	0.14
Thrombolytic[b] (%)	203 (31.3%)	43 (22.9%)	113 (26.8%)	0.049
Primary PCI[b] (%)	252 (38.9%)	91 (48.4%)	192 (45.6%)	0.020
Non-primary PCI (%)	747 (38.3%)	134 (35.7%)	298 (34.2%)	0.102
CABG for index event (%)	352 (18.0%)	55 (14.7%)	107 (12.3%)	<0.001
Post-discharge therapies				
Beta-blockers[c] (%)	1517 (77.9%)	306 (81.8%)	724 (83.3%)	0.002
ACEI/ARB[c] (%)	1380 (70.8%)	294 (78.6%)	701 (80.7%)	<0.001
MRA[d] (%)	2 (1.37%)	11 (20.4%)	11 (30.6%)	<0.001
Diuretics[c] (%)	321 (16.5%)	90 (20.1%)	362 (41.7%)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; EF, ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention.

[a]This variable was not available for 5 patients (2 patients with normal EF, 1 patient with mildly reduced EF, and 2 patients with low EF).

[b]Among patients with ST-elevation myocardial infarction.

[c]This variable was not available for 9 patients (4 patients with normal EF, 1 patient with mildly reduced EF, and 4 patients with low EF).

[d]This variable was available for only 236 patients (146 patients with normal EF, 54 patients with mildly reduced EF, and 36 patients with low EF).

Figure 2 Cumulative incidence rates for mortality after discharge according to LVEF categories. CI, confidence interval; EF, ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction. Model adjusted for sex, age, ST-elevation myocardial infarction, diabetes, dyslipidaemia, prior heart failure, prior myocardial infarction, prior coronary artery bypass graft, prior stroke, prior kidney disease, Killip class II or higher, use of beta-blocker at discharge, and use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at discharge.

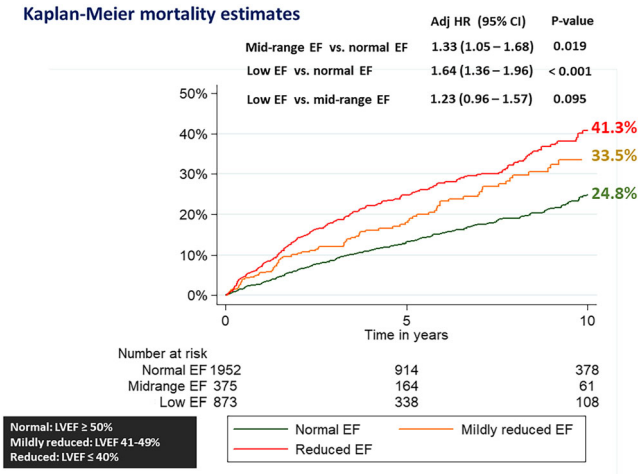


Table 3 Adjusted Cox models for mortality after discharge according to LVEF categories (normal EF: LVEF ≥ 50%; mildly reduced EF: LVEF 41–49%; and low EF: LVEF ≤ 40%)

	Low EF vs. normal EF		Mildly reduced EF vs. normal EF		Low EF vs. mildly reduced EF	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Unadjusted	1.93 (1.64–2.27)	<0.001	1.51 (1.20–1.90)	<0.001	1.28 (1.01–1.62)	0.043
Model 1	1.64 (1.36–1.96)	<0.001	1.33 (1.05–1.68)	0.019	1.23 (0.96–1.57)	0.095
Model 2	1.51 (1.19–1.93)	0.001	1.47 (1.08–1.99)	0.014	1.03 (0.75–1.41)	0.86
Model 3	1.52 (1.20–1.93)	0.001	1.43 (1.06–1.95)	0.021	1.06 (0.77–1.46)	0.72
Model 4	1.70 (1.43–2.02)	<0.001	1.32 (1.05–1.67)	0.019	1.29 (1.01–1.63)	0.040

CI, confidence interval; EF, ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Model 1 was adjusted for sex, age, ST-elevation myocardial infarction (STEMI), diabetes, dyslipidaemia, prior heart failure (HF), prior myocardial infarction (MI), prior coronary artery bypass graft (CABG), prior stroke, prior kidney disease, Killip class II or higher, use of beta-blocker at discharge, and use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) at discharge; Model 2 was adjusted for the same variables in Model 1 plus Global Registry of Acute Coronary Events (GRACE) score and presence of multivessel coronary artery disease (CAD); Model 3 was adjusted for age, kidney disease, GRACE score, STEMI, use of ACEI/ARB at discharge, hypertension, diabetes, multivessel CAD, oral beta-blockers in the first 24 h of hospitalization, prior stroke, prior HF, prior percutaneous coronary intervention, and prior CABG; and Model 4 was adjusted for covariates from the Model 1 that were considered confounders by the directed acyclic graph: sex, age, STEMI, diabetes, dyslipidaemia, prior HF, prior MI, and prior CABG.

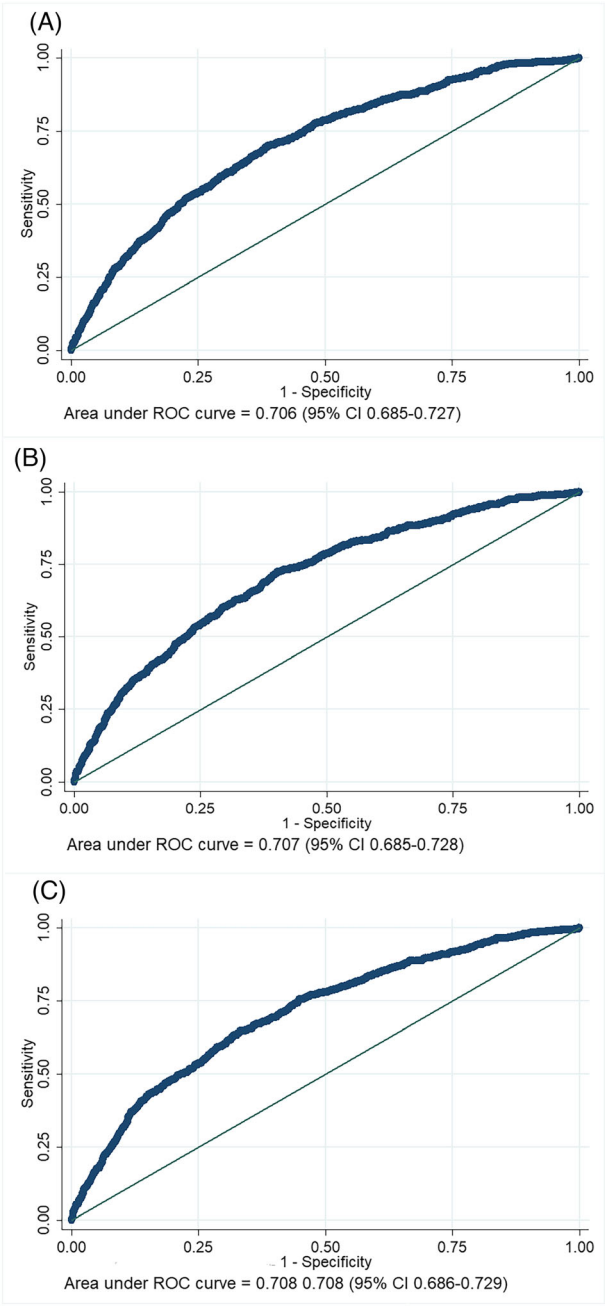
Discriminatory performance of cut-offs of left ventricular ejection fraction for long-term mortality

In the logistic regression models, the presence of LV dysfunction remained associated with higher odds of long-term death, for all cut-offs chosen, with adjusted odds ratios (ORs) of 1.58 (95% CI 1.25–1.98; $P < 0.001$), 1.55 (95% CI 1.27–1.89; $P < 0.001$), 1.52 (95% CI 1.25–1.84; $P < 0.001$), 1.57 (95% CI 1.30–1.90; $P < 0.001$), and 1.34 (95% CI 1.10–1.63; $P < 0.001$), respectively, for cut-offs of LVEF of 35%, 40%, 45%, 50%, and 55%. The AUCs for these models were, respectively, 0.706 (95% CI 0.685–727), 0.707 (95% CI 0.685–0.728), 0.707 (95% CI 0.685–0.728), 0.708 (95% CI 0.686–0.729), and 0.704 (95% CI 0.682–0.725; $P = 0.27$ for comparison among AUCs). These results are shown in *Figure 3*.

Sensitivity analyses

The results were consistent when patients were categorized as normal, impaired, and severely impaired EF, according to the cutpoints of <35%, 35–49%, and >50% LVEF (Supporting Information, *Figure S2*). From the overall population in our study, 407 patients had LVEF also assessed by invasive LV angiogram during hospitalization and the results of analyses using these measurements were also consistent with those

Figure 3 ROC curves for different LVEF cut-offs defining LV dysfunction for estimating mortality at long term. CI, confidence interval; LV, left ventricular; LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic. Models estimated by logistic regression adjusted for the following covariates: sex, age, acute coronary syndrome phenotype, diabetes, dyslipidaemia, prior heart failure, prior myocardial infarction, prior coronary artery bypass graft, prior stroke, use of beta-blocker at discharge, and use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at discharge. (A) LV dysfunction defined as LVEF ≤ 35%. (B) LV dysfunction defined as LVEF ≤ 40%. (C) LV dysfunction defined as LVEF ≤ 50%.



observed with echocardiographic assessment (Supporting Information, *Figure S3*). Supporting Information, *Tables S2* and *S3* show the baseline characteristics for each LVEF category used in these alternative classifications.

Results remained similar regardless of the period of inclusion in the cohort, as well as when patients with prior history of HF before hospitalization were excluded (Supporting Information, *Figures S4* and *S5*). From the overall population, 333 (10.4%) patients had BNP measured at baseline. When the models were adjusted for BNP as the only covariate, results remained consistent with the main findings (adjusted HR 2.20; 95% CI 0.86–5.70 and adjusted HR 2.19; 95% CI 1.09–4.42, for mildly reduced vs. normal EF, and reduced EF vs. normal EF, respectively).

Discussion

We analysed a retrospective cohort of 3200 after ACS enrolled in an academic tertiary centre and followed up for more than 15 years. We made three important observations. First, patients with mildly reduced EF (i.e. LVEF 41–49%) experienced higher long-term mortality when compared with patients with normal EF. This association persisted despite comprehensive adjustment for differences in baseline characteristics and other prognostic variables. Second, although the long-term survival of patients with mildly reduced EF was higher than that of patients with reduced EF, the numerical difference in mortality risk between the two groups appeared to be attenuated when adjusted models accounted for the GRACE score, a well-established risk score for mortality after ACS,[17] and extent of obstructive CAD. Third, the LVEF cut-off of <50% for discriminating survivors from non-survivors in the long-term after ACS appears to perform as good as the traditional one of LVEF < 40%, according to the ROC curve analysis.

Previous studies have analysed the long-term prognosis of patients after ACS according to baseline LVEF. In pivotal studies from the pre-fibrinolytic era, LVEF equal to or below 40% was associated with mortality rates as high as 15% at 6 months, leading to this threshold being commonly used to define LV systolic dysfunction after MI.[1,19,20] In a secondary analysis of the GISSI-2 trial, among patients with STEMI treated with lytics, investigators observed that the early and late recovery LVEF < 40% was also associated with a worse prognosis.[3] Since then, new therapies aimed at improving survival after MI with LV systolic dysfunction have enrolled mainly patients with LVEF ≤ 40%.

Since 2013, guidelines for HF management have been updated to define a new threshold of LVEF between 41% and 49%, now described as HF with mid-range EF or mildly reduced EF.[7,8,15] This distinct category was justified based on studies in chronic HF suggesting a worse prognosis in these patients than in HF patients with an LVEF above 50%,

although still better than reduced EF (≤40%).[21] However, this new categorization has not been widely evaluated after ACS.[22–24] In a single-centre study from Israel, investigators have observed higher mortality among patients with STEMI (*n* = 2086) undergoing primary percutaneous coronary intervention (PCI) who had mildly reduced EF, as compared with normal EF.[9] Similarly, in another single-centre retrospective cohort study from Northern Ireland (*n* = 533), mildly reduced EF after STEMI was associated with higher composite outcome of death, hospitalization for HF, or ventricular arrhythmias, compared with patients with normal EF.[10] In both studies, patients with reduced EF had a worse prognosis than patients with mildly reduced EF. Subsequent studies in cohorts from other countries have observed similar findings.[25–27] In our study, we did not observe a statistically significantly higher mortality in patients with reduced EF compared with patients with mildly reduced EF after adjustment for baseline covariates. This finding might be explained by the different regions of the world where the studies were performed, or to the more complete adjustment in covariates and the longer follow-up in our study compared with the previous ones. Of note, a longer follow-up may render patients with mildly reduced EF more exposed to non-cardiovascular (CV) deaths.[28] Our findings underscore the need to keep close surveillance on patients with mildly reduced EF, who may be at a higher risk of death compared with patients with normal EF. Despite that, patients with mildly reduced EF are less commonly treated with RAS inhibition or other therapies aimed at reducing adverse LV remodelling in routine clinical practice than patients with reduced EF.[29] However, whether these therapies might also improve long-term mortality specifically in patients with mildly reduced EF remains to be determined.

Based on the ROC curve analyses from our study, the cut-off of LVEF < 40% performed, as well as cut-off of LVEF < 50%, to discriminate survivors from non-survivors in the long-term. This finding builds up on prior observations suggesting that the definition of LV dysfunction after MI might rest upon different cut-offs other than the traditional of <40%. In fact, in a prior study from our group, use of oral beta-blockers was associated with lower long-term mortality among patients with NSTEMI and LVEF < 55%, but not among those with an LVEF ≥ 55%.[30] Among patients with chronic HF, there appears to be a benefit in reducing CV death or hospitalization for HF with different anti-remodelling therapies (such as ARBs, MRAs, and, more recently, angiotensin receptor-neprilysin inhibitors) across the full spectrum of LVEF up to 50%.[11,12,31] Future studies in patients with ACS at risk of LV dysfunction may help to further understand which is the best cut-off to discriminate long-term prognosis among these patients.

Our study should be interpreted considering inherent limitations. First, this was a retrospective, observational study, so that its design cannot infer causality. Despite adjusting for several important baseline characteristics, residual confounding is possible. However, our results were consistent in several sensitivity analyses using different statistical models, different definitions for mildly reduced EF, and different imaging modalities to assess LVEF. Second, a considerable proportion of patients did not have LVEF available and were then excluded from the current analysis. Third, our databank did not collect some important information, such as the timing of LVEF assessment. Fourth, other CV outcomes such as hospitalization for HF, recurrent MI, or death causes were not captured in our database. However, our endpoint of interest, all-cause mortality, is objective, easy to ascertain, and clinically meaningful. Fifth, we did not have information regarding serial LVEF assessment along the time, so that some patients with initially low EF may have improved due to reverse remodelling. Of note, patients with low EF were more commonly prescribed therapies known to improve LV remodelling, such as ACEIs and beta-blockers. Although our adjusted models accounted for these differences, it remains uncertain whether a higher mortality among patients with reduced EF may have been reduced by more use of these treatments, thus artificially making mortality of patients with mildly reduced EF resembling that one for reduced EF. Moreover, in a statistical model that considered only confounders as covariates based on a DAG (excluding mediators and competing exposures), long-term mortality was higher in patients with low compared with mildly reduced EF. Sixth, our data come from a single centre, so that our findings may not apply to other countries or healthcare systems. However, our population is well representative of other contemporary registries in ACS.[32] Finally, the period of our databank comprised a long-time span, during which the standard of care for patients with ACS and even definitions of ACS phenotypes (especially NSTEMI) have changed substantially. Despite that, our results remained consistent across different time periods of inclusion in the databank.

Conclusions

Among patients with ACS discharged alive from hospital, mildly reduced EF measured in the acute phase was associated with higher long-term mortality compared with patients with normal EF. These data reinforce the need to consider mortality-proven therapies also for ACS patients who have LVEF in the mildly reduced range.

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Conflicts of interest

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Supporting information

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

Table S1. Baseline characteristics of patients who survived until hospital discharge versus patients who did not.
Table S2. Baseline characteristics according to left ventricle ejection fraction categories (according to the British Society of Echocardiography).
Table S3. Baseline characteristics according to left ventricular ejection fraction categories assessed by left ventricle angiogram.
Figure S1. Directed acyclic graph (DAG) representing the variables according to their associations with the main exposure (left ventricle ejection fraction; LVEF) and outcome (mortality) of interest. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; DM = diabetes mellitus; HF = heart failure; MI = myocardial infarction.
Figure S2. Cumulative incidence rates for mortality after discharge according to LVEF categories following the British Society of Echocardiography classifications. CI = confidence interval; HR = hazard ratio; LVEF = left ventricle ejection fraction. Model adjusted for: sex, age, STEMI, diabetes, dyslipidemia, prior HF, prior MI, prior CABG, prior stroke, prior kidney disease, Killip class 2 or higher, use of beta-blocker at discharge and use of ACEI/ARB at discharge.
Figure S3. Cumulative incidence rates for mortality after discharge according to LVEF assessed by left ventricle angiogram. CI = confidence interval; HR = hazard ratio; LVEF = left ventricle ejection fraction. Model adjusted for: sex, age, STEMI, diabetes, dyslipidemia, prior HF, prior MI, prior CABG, prior stroke, prior kidney disease, Killip class 2 or higher, use of beta-blocker at discharge and use of ACEI/ARB at discharge.
Figure S4. Cumulative incidence rates for mortality after discharge according to LVEF assessed by echocardiogram for every period of inclusion of the study. **A.** 1998 to 2004. **B.** 2005 to 2010. **C.** 2011 to 2016. P-interactions in the Cox models for mortality comparing reduced versus normal EF and mildly reduced versus normal of 0.77 and 0.52, respectively. CI = confidence interval; HR = hazard ratio; LVEF = left ventricle ejection fraction. Model adjusted for: sex, age, STEMI, diabetes, dyslipidemia, prior HF, prior MI, prior CABG, prior stroke, prior kidney disease, Killip class 2 or higher, use of beta-blocker at discharge and use of ACEI/ARB at discharge.
Figure S5. Cumulative incidence rates for mortality after discharge according to LVEF assessed by echocardiogram after exclusion of patients with prior history of heart failure (HF). CI = confidence interval; HR = hazard ratio; LVEF = left ventricle ejection fraction. Model adjusted for: sex, age, STEMI, diabetes, dyslipidemia, prior MI, prior CABG, prior stroke, prior kidney disease, Killip class 2 or higher, use of beta-blocker at discharge and use of ACEI/ARB at discharge.

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