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Clinical predictors and prognostic role of high Killip class in patients with a first episode of anterior ST-segment elevation acute myocardial infarction

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Aims **Killip classification is a simple and fast clinical tool for risk stratification of patients presenting with acute coronary syndrome (ACS). However, the clinical features and predictors of high Killip class at admission, and its prognostic impact in patients presenting with anterior ST elevation MI (STEMI) as first clinical cardiovascular event are still poorly known. The aim of this study was to identify the predictors of high Killip class and its impact on in-hospital and follow-up outcomes.**

Methods **We prospectively enrolled patients with unheralded anterior STEMI because of proximal or mid left anterior descending (LAD) artery categorized according to Killip classification. Patients' characteristics, in-hospital complications and major adverse cardiovascular events (MACEs; composite of all-cause death, heart failure hospitalization and new-onset ACS) at follow-up were collected.**

Results **We enrolled 147 patients [age 66.16±13.33, 113 male patients (76.9%)]. Killip class III–IV occurred in 22 (15%) patients. The median duration of follow-up was 12 [6–15.1] months. At multivariate analysis age [hazard ratio 1.137, 95% CI (1.068–1.209), $P < 0.001$], prehospital cardiac arrest [hazard ratio 12.145, 95% CI (1.710–86.254), $P = 0.013$] and proximal LAD lesion [hazard ratio 5.066, 95% CI (1.400–18.334), $P = 0.013$] were predictive of Killip class III–IV at admission. At multivariate analysis, Killip class III–IV was an independent predictor of in-hospital mortality [hazard ratio 7.790, 95% CI (1.024–59.276], $P = 0.047$ and of MACEs [hazard ratio 4.155 (1.558–11.082), $P = 0.004$) at follow-up.**

Conclusion **Killip classification performed at the time of admission is a simple and useful clinical marker of a high risk of early and late adverse cardiovascular events.**

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Introduction

Acute myocardial infarction (AMI) represents a major health problem and a leading cause of morbidity and mortality worldwide. Despite a lower incidence in recent years, acute heart failure and cardiogenic shock at admission or during hospitalization are still frequent complications following AMI.[1] Killip classification is a simple clinical tool based on the physical examination at admission of patients presenting with ST elevation myocardial infarction (STEMI) that has been demonstrated to be useful for risk stratification being an independent predictor of worse in-hospital complications and long-term mortality, and extensively employed for clinical and academic applications.[2–6] The risk of acute heart failure following AMI is the result of the interaction between baseline patient characteristics, early pharmacological management, extent of myocardial ischemia and concomitant mechanical or arrhythmic complications. Previous studies showed that advanced age, female sex, comorbidities, prior history of heart failure, lack of early reperfusion, multivessel coronary artery disease (CAD) and anterior location of the infarct were predictors of early acute HF, some of which may be not only preventable but also modifiable (i.e. early and effective reperfusion).[4,5] Furthermore, acute heart failure in the setting of AMI also confers adverse long-term prognosis, with higher mortality rates during follow-up.[6,7]

However, these data are mainly derived from studies including patients suffering from AMI in different locations and often including patients with history of cardiovascular diseases and in which Killip classification was applied at different times from the revascularization procedure.[4–9] Therefore, the clinical features and

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predictors of high Killip class at admission, and its prognostic impact in patients presenting with anterior STEMI as first clinical cardiovascular event are still poorly known. The aim of this study was to evaluate in a selected cohort of patients without history of cardiovascular diseases presenting with anterior STEMI as first cardiovascular event: the clinical characteristics and predictors of worse clinical presentation (i.e. high Killip class III–IV) at the time of the admission; differences and predictors of intrahospital complications and differences and predictors of clinical outcomes at follow-up between patients presenting with Killip class I–II vs. III–IV.

Methods

Study population and design

We prospectively enrolled consecutive patients admitted to the Emergency Department of Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, with diagnosis of anterior STEMI in which the culprit vessel was the proximal or mid left anterior descending (LAD) artery, undergoing primary percutaneous coronary intervention (pPCI) within 24 h from symptom onset. Enrolment period was from January 2016 to September 2019. The diagnosis of STEMI was based on the following definition: typical chest pain lasting more than 30 min and unresolved by isosorbide dinitrate intravenous administration (2–4 mg); ST-segment elevation at least 0.2 mV in at least two contiguous leads or new-onset left bundle branch block in the initial electrocardiogram (ECG); elevated serum troponin I levels.[10]

Patients with a prior history of heart failure of any type, coronary revascularization and systemic diseases (e.g. acute/chronic infections, autoimmune diseases, liver diseases, neoplasms, blood diseases) were excluded. Furthermore, those receiving fibrinolysis, rescue PCI, late presentation (>24 h from symptoms onset) and those whom the mode of presentation of AMI was cardiac arrest and remained comatose or intubated upon arrival at the hospital were excluded (Figure, Online Appendix, http://links.lww.com/JCM/A357).

Patients were stratified according to Killip classification[2] by a cardiologist at the time of presentation in emergency room just before the coronary angiography. Killip class I was defined by the absence of signs of pulmonary congestion or systemic hypoperfusion; Killip class II was defined by the presence of rales in the lower half of the lung fields, or by the presence of gallop heart sounds; Killip class III was defined by the presence of rales in the upper half of the lung fields; Killip class IV was cardiogenic shock (significant hypotension: SBP <90 mmHg requiring inotropes and/or vasopressors). In all patients, medical history, home therapy, laboratory data and cardiovascular risk factors were carefully examined, including history of diabetes, family history of CAD, dyslipidemia, smoking habits, hypertension, chronic kidney disease (CKD, >III stage according to KDIGO classification). Preinfarction angina was defined as one or more occurrences of chest pain similar to their STEMI pain that occurred within 24 h on infarct onset. Data regarding use of ventricular mechanical support were also obtained.

All patients with STEMI were treated using aspirin (300 mg, except those already in chronic therapy with low-dose aspirin) on admission to the emergency room. A second antiplatelet agent (ticagrelor, prasugrel or clopidogrel, as appropriate) was then administered in the cath lab or in the Intensive Coronary Unit (ICU) according to healthcare provider preference. All pPCIs were performed through a radial or femoral access according to operator's preference, using a 6 French catheter, and only the culprit vessel was revascularized in those with multivessel involvement. A bolus of 5000 IU of heparin was administrated during coronary angiography. Manual thrombus aspiration (Eliminate, Terumo Interventional Systems, Eschborn, German) and glycoprotein IIb/IIIa inhibitors after diagnostic angiogram at the starting of pPCI (intravenous administration of abciximab, bolus 0.25 mg/kg and following 12 h infusion) were used according to operators' decision.

All procedures performed in this study were in accordance with the ethical standards of our institutional committee (Fondazione Policlinico Universitario Agostino Gemelli IRCCS – Università Cattolica del Sacro Cuore) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Angiographic data

Data about lesion location (proximal vs. mid segment of LAD), concomitant presence of multivessel disease and number of diseased vessels were collected. Proximal LAD lesion was defined as a lesion proximal to and including the first major septal branch. Mid LAD lesion was defined as a lesion immediately distal to origin of first septal branch and extending to the point where LAD forms an angle (right anterior oblique view), and if this angle was not identifiable, this segment was considered ended at one half the distance from the first septal to the apex of the heart.[11] Thrombolysis in Myocardial Infarction (TIMI) flow was assessed according to previous studies and reported at baseline and after coronary revascularization.[12] Finally, data on patients with multivessel disease undergoing complete revascularization during index admission and on those with residual CAD (defined as an obstructive lesion causing >50% in a major coronary vessel) at discharge were also collected.

ECG and echocardiography

A 12-lead ECG was performed in all patients at admission, and amplitude of ST-segment elevation, number of leads showing ST-segment elevation and corrected QT interval were manually calculated and reported.

All patients underwent standard comprehensive transthoracic two-dimensional Doppler echocardiogram[13] by an expert operator within 72 h from admission to the ICU after pPCI and at 1-year follow-up. Left end-diastolic and end-systolic volumes and left ventricular ejection fraction (LVEF) were calculated using the modified Simpson's biplane method. Left ventricular diastolic function was evaluated using transmitral diastolic flow tracings assessed with pulsed-wave Doppler from an apical four-chamber view with early (E)-wave and late (A)-wave velocity measurements, pulsed-wave tissue Doppler early diastolic mitral annular velocity (e′) averaged between the lateral and septal annulus, and calculation of the average E/e′ ratio. Right ventricular function was assessed using tricuspid annular plane systolic excursion (TAPSE). Right ventricular systolic pressure (PASP) was calculated by adding the transtricuspid pressure gradient to the right atrial pressure estimate. Presence of valvopathies were also collected. Left ventricle thrombus was defined as an echo-dense mass, contiguous but distinct from the endocardium, located in an area of asynergy that was seen in both systole and diastole in at least two echocardiographic views.

Assessment of clinical outcomes

During index admission, intrahospital complications included new-onset cardiogenic shock during hospitalization, need of O_2 supplementation therapy/intravenous diuretics/inotropes or vasopressors/mechanical support, cardiac arrest requiring resuscitation maneuvers, death, nosocomial infections, ventricular tachycardia (defined as episodes of more than three consecutive premature ventricular complexes), new-onset atrial fibrillation and stroke/transient ischemic event episodes were recorded.

After discharge, occurrence of death from any cause, nonfatal acute coronary syndrome (ACS) [defined as new hospitalization for unstable angina or re-infarction (STEMI or non-STEMI)] recurrence, rehospitalization for heart failure were collected by outpatient clinic visits or by telephone interviews at 6, 12, 24, and 36 months. All patients were also asked about dyspnea perception and classified according to New York Heart Association (NYHA) classification. Major adverse cardiovascular events (MACE) were defined as the composite of death from any cause, nonfatal ACS and rehospitalization for heart failure. Deaths occurred during the index hospitalization have been included in the analysis of MACE at follow-up.

Statistical analysis

Data distribution was assessed according to the Kolmogorov–Smirnov test. Continuous variables were compared using an unpaired Student's *t*-test or Mann–Whitney *U* test, as appropriate, and data were expressed as mean ± standard deviation or as median (range). Categorical data were evaluated using the chi-square test or Fisher's exact test as appropriate. All tests were two-sided, and a P value of less than 0.05 represented statistically significant differences. Univariate logistic regression analysis was applied to assess the relation of all individual clinical and angiographic variables with Killip class III–IV at admission as well as with in-hospital mortality. A multivariate logistic regression model was then performed to identify variables independently associated with Killip class III–IV at admission and in-hospital mortality. With this aim, we included in the multivariate model only variables showing P value 0.1 or less at univariate analysis. Univariable Cox regression analysis was applied to assess the relation of individual variables with MACE at follow-up. Cox regression was then applied to identify variables independently associated with all-cause mortality; with this aim, we included in the multivariable model only variables showing P value 0.1 or less at univariable analysis. Finally, Kaplan–Meier survival curves with log-rank tests were used for comparisons of the occurrence of MACE in patient groups stratified according to Killip class at presentation. All analyses were performed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics according to Killip class at admission

We enrolled 147 patients [mean age 66.16 ± 13.333, 113 male patients (76.9%)]. Admission Killip class III–IV occurred in 22 (15%) patients [16 (10.9%) Killip class III and 6 (4.1%) Killip class IV]. Compared with patients with Killip class I–II, those with Killip class III–IV were older (78.91 ± 11.719 vs. 63.92 ± 12.336, $P < 0.001$), had a higher prevalence of female sex [9 (40.1%) vs. 25 (20%), $P = 0.032$ for male sex], prior history of CKD [5 (22.7%) vs. 11 (8.8%), $P = 0.042$], prehospital cardiac arrest [5 (22.7%) vs. 9 (7.2%), $P < 0.001$], a lower incidence of preinfarction angina [5 (22.7%) vs. 58 (46.4%), $P = 0.039$] and a longer symptoms-to-balloon time [7 (4.75–12) vs. 4 (3–8) h, $P = 0.012$]. Patients with Killip class III–IV had a trend for a lower median arterial pressure [80.5 (64.5–99.25) vs. 90 (80.5–103), $P = 0.06$] and a higher heart rate [87 (78–100) vs. 76 (67–87), $P = 0.004$] at admission. There were no significant differences between home medical therapy and ECG features at admission between the two groups (all $P \geq 0.05$). Furthermore, no differences in laboratory tests at admission were detected except for peak serum levels of troponin I [278.56 (85.52–550.0) vs. 106 (44.0–302.8) ng/ml, $P = 0.04$], N-terminal- pro hormone BNP (NT-proBNP levels) [9629 (3328.5–19010.3) vs. 1898.0 (426.0–5560.3) pg/ml, $P = 0.05$], lactate [3.00 (1.50–5.00) vs. 0.90 (0.70–1.00) mmol/l, $P < 0.001$], C-reactive protein (CRP) [31.1 (10.6–163.4) vs. 15.4 (3.5–57.3) mg/l, $P = 0{,}025$] and creatinine [1.04 (0.87–1.28) vs. 0.86 (0.71–1.28), $P = 0.011$]. At coronary

angiography, proximal LAD lesion [16 (72.7%) vs. 62 (49.6%), $P < 0.001$], presence of multivessel disease [15 (68.2%) vs. 52 (41.6%), $P = 0.021$] and postprocedural TIMI flow 0–1 [10 (40.9%) vs. 15 (12%), $P < 0.001$] were more common in those presenting with Killip class III–IV compared with those presenting with Killip class I–II. There were no significant differences with regard to type of stent implanted, preprocedural TIMI flow, and use of intracoronary of glycoprotein IIIb/IIa inhibitors or thrombus aspiration between the two groups (all $P \geq 0.05$). Killip class III–IV patients received more frequently clopidogrel [16 (72.7%) vs. 41 (32.8%), $P < 0.001$] and less frequently prasugrel [5 (22.7%) vs. 41 (32.8%), $P = 0.003$] as part of dual antiplatelet therapy. As expected, Killip class III–IV patients more frequently received inotropes/vasopressors and left ventricular mechanical devices (both $P < 0.001$) with intra-aortic balloon pump representing the most commonly used mechanical support (inserted during pPCI or during hospital stay because of hemodynamic deterioration despite adequate pharmacological therapy). There were no differences in residual CAD at discharge between two groups ($P \geq 0.05$) as well as in pharmacological therapy at discharge (all $P \geq 0.05$) expect for a higher use of diuretics (furosemide and mineralocorticoid receptor antagonist, both $P < 0.001$) and a lower use of prasugrel ($P = 0.007$) in favor of clopidogrel ($P = 0.029$) in those with high Killip class. Killip class III–IV patients compared with Killip class I–II had a lower LVEF [34% (29.75–42.25) vs. 48.5% (40.25–55), $P < 0.001$], higher estimated left ventricular filling pressures [E/e' ratio 14 (8–16) vs. 10 (7.75–12.25), $P = 0.018$] and lower right ventricle performance [TAPSE 19 mm (17–20) vs. 21 mm (19–24), $P < 0.001$]. Clinical, laboratory, echocardiographic and angiographic data are reported in Table 1.

At univariate analysis, age [hazard ratio 1.114, 95% CI (1.061–1.169), $P < 0.001$], female sex [for male: hazard ratio 0.361, 95% CI (0.139–0.940) $P = 0.037$], CKD [hazard ratio 3.239, 95% CI (0.996–10.395) $P = 0.051$], no preinfarction angina [hazard ratio 0.340, 95% CI (0.118–0.978), $P = 0.045$], prehospital cardiac arrest [hazard ratio 3.791, 95% CI (1.135–12.661), $P = 0.030$], CRP at admission [hazard ratio 1.009,95% CI (1.002–1.016), $P = 0.015$], proximal LAD occlusion [hazard ratio 2.710, 95% CI (0.995–7.378), $P = 0.051$] and presence of multivessel coronary disease [hazard ratio 3.008, 95% CI (1.146–7.897), $P = 0.025$] predicted Killip class III–IV. At multivariate analysis, only age [hazard ratio 11.137, 95% CI (1.068–1.209), $P < 0.001$], prehospital cardiac arrest [hazard ratio 12.145, 95% CI (1.710–86.254), $P = 0.013$] and proximal LAD lesion [hazard ratio 5.066, 95% CI (1.400–18.334), $P = 0.013$] remained predictive of Killip class III–IV at admission (Table 2).

Of note, a sensitivity analysis performed including only patients with proximal LAD lesion confirmed that age was an independent predictor of worse Killip class at admission whereas preinfarction angina was protective (Supplementary Tables 1, http://links.lww.com/JCM/A356 and 2, http://links.lww.com/JCM/A356).

Clinical outcomes according to Killip class at admission

Patients with Killip class III–IV at admission had a worse clinical outcome compared with those with Killip class I–II, both during hospital admission and at medium-term follow-up. Indeed, during index admission, patients with Killip class III–IV had a higher rate of intrahospital complications, including all-cause death [5 (22.7%) vs. 2 (1.6%), $P = 0.001$], cardiac arrest requiring resuscitation maneuvers [7 (31.8%) vs. 5 (4%), $P < 0.001$], new episodes of cardiogenic shock [5 (22.7) vs. 2 (1.6), $P = 0.001$]. The length of stay was longer in patients with Killip class III–IV compared with those with Killip class I–II [16.5 (10.5–30) vs. 8 days (6–10.5), $P < 0.001$]. The rate of ventricular arrhythmias and new-onset atrial fibrillation was instead similar between the two groups (all $P \geq 0.05$) (Table 1). At univariate analysis, Killip class III–IV at admission [hazard ratio 18.088, 95% CI (3.250–100.657), $P = 0.001$], ejection fraction [hazard ratio 0.889, 95% CI (0.816–0.969), $P = 0.007$] and peak Troponin I [hazard ratio 1.002, 95% CI (1.000–1.003), $P = 0.017$] were predictive of in-hospital mortality but only high Killip class remained significant at multivariate analysis [hazard ratio 7.790, 95% CI (1.024–59.276), $P = 0.047$] (Supplementary Table 3, http://links.lww.com/JCM/A356).

At follow-up [median 12 (6–15.1) months, without significant differences between the two groups, $P = 0.911$], patients with Killip class III–IV had a significantly higher occurrence of MACE [15 (68.2%) vs. 26 (20.8%), $P < 0.001$], death from any causes [11 (50%) vs. 5 (4%), $P < 0.001$] and heart failure hospitalizations [6 (27.3%) vs. 6 (4.8%), $P < 0.001$] with a similar rate of nonfatal ACS [1 (4.5) vs. 15 (12), $P = 0.468$] compared with Killip class I–II patients. Furthermore, patients with Killip class III–IV at admission experienced worse dyspnea [NYHA class 1 (1–3) vs. 2 (1–2), $P = 0.03$] and lower LVEF [43% (36.25–49.5) vs. 54% (43.25–58.75), $P < 0.001$) values at follow-up (Table 3).

At simple Cox regression analysis age [hazard ratio 1.021, 95% CI (0.997–1.045), $P = 0.088$], Killip class III–IV [hazard ratio 4.627, 95% CI (2.4274–8.822), $P < 0.001$], peak troponin [hazard ratio 1.001, male sex (1.000–1.002), $P = 0.001$] and ejection fraction at admission [hazard ratio 0.959, 95% CI (0.930–0.988), $P < 0.007$] were significant predictors of MACE at follow-up. At multivariable Cox regression, the presence of Killip class III–IV [hazard ratio 4.155 (1.558–11.082), $P = 0.004$] and peak troponin I [hazard ratio 1.001, 95% CI (1.00–1.001), $P = 0.015$] was significantly associated with MACE at follow-up (Table 4).

Finally, comparisons of Kaplan–Meier curves by log-rank test showed that patients with Killip class III–IV at

Table 1 Clinical, ECG, echocardiographic, angiographic and laboratory data of overall population and according to Killip class at presentation

	Overall population ($N=147$)	Killip I–II ($N=125$)	Killip III–IV ($N=22$)	P value
Baseline characteristics				
Age (years ± SD)	66.16 ± 13.333	63.92 ± 12.336	78.91 ± 11.719	**<0.001**
Sex (male) [*n* (%)]	113 (76.9)	100 (80)	13 (59.1)	**0.032**
Hypertension [*n* (%)]	86 (58.5)	69 (55.2)	17 (77.3)	0.053
Diabetes type 2 [*n* (%)]	35 (23.8)	30 (24)	5 (22.7)	0.897
Smoking [*n* (%)]	80 (54.4)	69 (55.2)	17 (77.3)	0.168
Hypercholesterolemia [*n* (%)]	53 (36.1)	43 (34.4)	10 (45.5)	0.319
Obesity [*n* (%)]	24 (16.3)	21 (16.8)	3 (13.6)	1
Family history of CAD [*n* (%)]	38 (25.9)	36 (28.8)	2 (9.1)	0.064
BMI (kg/m^2) [median (IQR)]	26 [24–29]	26 [24–29]	24.5 [23–28.5]	0.275
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2) [*n* (%)]	16 (10.9)	11 (8.8)	5 (22.7)	**0.042**
Chronic obstructive pulmonary disease [*n* (%)]	11 (7.5)	9 (7.2)	2 (9.1)	0.670
History of atrial fibrillation [*n* (%)]	5 (3.4)	4 (3.2)	1 (4.5)	0.561
Preinfarction angina [*n* (%)]	63 (42.9)	58 (46.4)	5 (22.7)	**0.039**
Prehospital cardiac arrest [*n* (%)]	14 (9.5)	9 (7.2)	5 (22.7)	**<0.001**
Therapy at admission				
Aspirin [*n* (%)]	12 (8.2)	10 (8)	2 (9.1)	1
Beta-blockers [*n* (%)]	11 (7.5)	10 (8)	1 (4.5)	1
ACE-I/ARB [*n* (%)]	32 (21.8)	26 (20.8)	6 (27.3)	0.498
Statins [*n* (%)]	7 (4.8)	6 (4.8)	1 (4.5)	0.719
Clinical characteristics at admission				
Acute pulmonary edema (Killip III) [*n* (%)]	16 (10.9)	0 (0)	16 (72.3)	**<0.001**
Cardiogenic shock (Killip IV) [*n* (%)]	6 (4.1)	0 (0)	6 (27.3)	**<0.001**
Mean arterial pressure (mmHg) [median (IQR)]	90 [80–103]	90 [80.5–103]	80.5 [64.5–99.25]	0.06
Frequency (bmp) [median (IQR)]	78 [70–90]	76 [67–87]	87 [78–100]	**0.004**
Laboratory data				
HB (g/dl) [median (IQR)]	14.5 [13.0–15.5]	14.6 [13.1–15.6]	13.9 [12.1–15.2]	0.183
WBC (×10^3/l) [median (IQR)]	11.9 [9.22–14.09]	11.5 [9.1–14.0]	12.8 [10.3–16.2]	0.085
PLT (×10^3/l) [median (IQR)]	236 [192.0–289.0]	235 [190.0–286.0]	238.5 [204.3–298.0]	0.676
CRP (mg/l) [median (IQR)]	16.2 [4.8–75]	15.4 [3.5–57.3]	31.1[10.6–163.4]	**0.025**
Total cholesterol [mg/dl ± SD]	177 [144.0–203.0]	177[141.0–202.5]	169.6 [154.5–218.0]	0.535
HDL cholesterol [mg/dl ± SD]	38.5 [32.0–48.3]	38 [31.75–47]	46.5 [33.0–54.8]	0.199
LDL cholesterol [mg/dl ± SD]	110.0 [84.0–134.5]	109 [81.8–134.5]	110.5 [97.0–139.0]	0.459
TG (mg/dl) [median (IQR)]	105.0 [76.0–143.0]	107.0 [76.0–144.0]	102 [75.0–132.8]	0.496
Lactate (mmol/l)	1.00 [0.70–1.20]	0.90 [0.70–1.00]	3.00 [1.50–5.00]	**<0.001**
Creatinin (mg/dl) [median (IQR)]	0.89 [0.73–1.08]	0.86 [0.71–1.28]	1.04 [0.87–1.28]	**0.011**
Peak troponin I (ng/ml) [median (IQR)]	112.43 [49.27–341.53]	106 [44.0–302.8]	278.56 [85.52–550.0]	**0.04**
Peak NTproBNP (pg/ml) [median (IQR)]	2416.5 [679.3–6319.5]	1898.0 [426.0–5560.3]	9629 [3328.5–19010.3]	**0.05**
Angiographic data				
Symptoms to balloon time (hours) [median (IQR)]	4.75 [3–8]	4 [3–8]	7 [4.75–12]	**0.012**
No. of diseased vessels [median (IQR)]	1 [1–2]	1 [1–2]	1 [1–3]	**0.024**
Multivessel disease [*n* (%)]	67 (45.6)	52 (41.6)	15 (68.2)	**0.021**
Culprit segment [*n* (%)]				**0.045**
Proximal LAD	78 (53.1)	62 (49.6)	16 (72.7)	
Mid LAD	69 (46.9)	63 (50.4)	6 (27.3)	
TIMI flow pre-PCI (0–1) [*n* (%)]	147 (100)	125 (100)	22 (100)	1
TIMI flow post-PCI [*n* (%)]				**<0.001**
0–1	25 (16.3)	15 (12)	10 (40.9)	
2–3	123 (83.7)	110 (88)	12 (59.1)	
DES [*n* (%)]	147 (100)	125 (100)	22 (100)	1
Thrombus aspiration [*n* (%)]	72 (49)	54 (43.2)	6 (27.3)	0.412
Use of GP IIb/IIIa inhibitors [*n* (%)]	60 (40.8)	54 (43.2)	6 (27.3)	0.161
Complete revascularization [*n* (%)]	45 (30.6)	38 (30.4)	7 (31.8)	0.894
Residual CAD [*n* (%)]	23 (15.6)	17 (13.6)	6 (27.3)	0.104
DAPT used [*n* (%)]				
Clopidogrel	57 (38.8)	41 (32.8)	16 (72.7)	**<0.001**
Prasugrel	47 (32)	46 (36.8)	1 (4.5)	**0.003**
Ticagrelor	46 (31.3)	41 (32.8)	5 (22.7)	0.347
ECG				
QTc (ms) [median (IQR)]	415 [393.3–430.5]	4141 [393–430]	427 [403–435]	0.159
Number of derivations with ST elevation [*n* (%)]	4 [3–6]	4 [3–5]	4.5 [4–7]	0.192
Amplitude of ST elevation (mm) [median (IQR)]	4.5 [3–8]	4 [2–5]	4 [2–8]	0.947
Echocardiographic data				
LVEDV (ml) [median (IQR)]	91 [78.25–111.0]	91 [78–112]	88 [79–108]	0.476
LVESV (ml) [median (IQR)]	50 [47–54]	47 [38–62]	59 [46.5–70.5]	**0.035**
LVEF (%) [median (IQR)]	47 [38–54]	48.5 [40.25–55]	34 [29.75–42.25]	**<0.001**
E/e' ratio [median (IQR)]	10 [8–13]	10 [7.75–12.25]	14 [8–16]	**0.018**
TAPSE (mm) [median (IQR)]	21 [19–23]	21 [19–24]	19 [17–20]	**<0.001**
PASP (mmHg) [median (IQR)]	25 [25–35]	25 [25–30]	30 [25–41.25]	0.071
Moderate-to-severe mitral regurgitation [*n* (%)]	16 (10.9)	12 (9.6)	4 (18.2)	0.263
LV thrombi [*n* (%)]	17 (11.6)	13 (10.4)	4 (18.2)	0.293
Intrahospital complications				
Length of stay [median (IQR)]	8 [6–12]	8 [6–10.5]	16.5 [10.5–30]	**<0.001**
All-cause mortality [*n* (%)]	7 (4.8)	2 (1.6)	5 (22.7)	**0.001**
Cardiac arrest during hospitalization [*n* (%)]	12 (8.2)	5 (4)	7 (31.8)	**<0.001**

Table 1 (*continued*)

	Overall population ($N=147$)	Killip I–II ($N=125$)	Killip III–IV ($N=22$)	*P* value
New-onset cardiogenic shock [*n* (%)][b]	7 (4.8)	2 (1.6)	5 (31.5)	**<0.001**
Need of O_2 supplementation therapy [*n* (%)]	45 (30.6)	27 (21.6)	18 (81.8)	**<0.001**
Intravenous diuretics [*n* (%)]	53 (36.1)	35 (28)	21 (95)	**<0.001**
Inotropes/vasopressors [*n* (%)]	12 (8.2)	1 (0.8)	11 (50)	**<0.001**
Mechanical support [*n* (%)]	8 (5.4)	1 (0.8)	7 (31.8)	**<0.001**
IABP [*n* (%)]	6 (4.1)	1 (0.8)	5 (22.7)	**<0.001**
Impella [*n* (%)]	2 (1.3)	0 (0)	2 (9.1)	**0.022**
Ventricular fibrillation [*n* (%)]	9 (7.2)	4 (3.3)	5 (22.7)	**<0.001**
Ventricular tachycardia [*n* (%)]	30 (20.4)	24 (19.2)	6 (27.3)	0.386
Nosocomial infection [*n* (%)]	24 (16.3)	10 (8)	14 (63.6)	**<0.001**
New-onset atrial fibrillation [*n* (%)]	22 (14.9)	16 (12.8)	6 (27.3)	0.079
Stroke/TIA [*n* (%)]	8 (5.4)	6 (4.8)	2 (9.1)	0.342
Therapy at discharge[a]				
Aspirin [*n* (%)]	134 (95.7)	118 (96.7)	16 (88.9)	0.171
Clopidogrel [*n* (%)]	53 (37.9)	42 (34.4)	11 (61.1)	**0.029**
Ticagrelor [*n* (%)]	40 (28.6)	36 (29.5)	4 (22.2)	0.780
Prasugrel [*n* (%)]	46 (32.9)	45 (36.9)	1 (5.6)	**0.007**
Anticoagulants (%)	28 (20)	25 (20.5)	3 (16.7)	1
Beta blockers [*n* (%)]	131 (93.6)	114 (93.4)	17 (94.4)	1
ACE-I/ARBs [*n* (%)]	130 (92.9)	115 (94.3)	15 (83.3)	0.120
MRA [*n* (%)]	41 (29.3)	27 (22.1)	14 (77.8)	**<0.001**
Statins [*n* (%)]	139 (99.3)	121 (99.2)	18 (100)	1
Furosemide [*n* (%)]	51 (36.4)	35 (28.7)	16 (88.9)	**<0.001**

ACE-I, angiotensin-converting enzyme – inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; DES, drug eluting stent; eGFR, estimated glomerular filtration rate; HB, haemoglobin; IABP, intra-aortic balloon pump; IQR, interquartile range; LAD, left anterior descending; LV, left ventricle; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MRA, mineralocorticoid receptor antagonist; PASP, pulmonary arterial systolic pressure; PLT, platelets; TAPSE, tricuspid annular plane systolic excursion; TG, triglycerides; TIMI, thrombolysis in myocardial infarction; WBC, white blood cells. [a] Therapy at discharge was calculated by including only patients still alive at the time of discharge (overall population $n=140$; Killip I–II, $n=122$, Killip III–IV, $n=18$). [b] Cardiogenic shock during hospitalization was calculated by excluding those patients ($n=6$) with cardiogenic shock at admission.
Bold values represent *p* values statistically significant (<0.05).

Table 2 Variables associated with Killip class III–IV at presentation by univariate and multivariate logistic regression analysis

	Univariate analysis		Multivariate analysis	
	β (95% CI)	*P*	β (95% CI)	*P*
Age	1.114 (1.061–1.169)	**<0.001**	1.137 (1.068–1.200)	**<0.001**
Sex (male)	0.361 (0.139–0.940)	**0.037**	0.555 (0.157–1.969)	0.362
CKD	3.239 (0.996–10.395)	**0.051**	0.645 (0.120–3.450)	0.608
Preinfarction angina	0.340 (0.118–0.978)	**0.045**	0.339 (0.092–1.225)	0.105
Prehospital cardiac arrest	3.791 (1.135–12.661)	**0.030**	12.145 (1.710–86.254)	**0.013**
Proximal LAD lesion	2.710 (0.995–7.378)	**0.051**	5.066 (1.400–18.334)	**0.013**
Multivessel coronary disease	3.008 (1.146–7.897)	**0.025**	2.598 (0.723–9.289)	0.144
Symptoms-to-balloon time	1.061 (0.986–1.141)	0.112		

CI, confidence interval; CKD, chronic kidney disease; LAD, left anterior descending.

Table 3 Clinical outcomes and echocardiographic data at follow-up of overall population and according to Killip class at admission

	Overall population ($N=147$)	Killip I–II ($N=125$)	Killip III–IV ($N=22$)	*P* value
Follow-up outcomes				
MACE [*n* (%)]	41 (27.9)	26 (20.8)	15 (68.2)	**<0.001**
All-cause mortality [*n* (%)]	16 (10.9)	5 (4)	11 (50)	**<0.001**
HF hospitalization [*n* (%)]	12 (8.1)	6 (4.8)	6 (27.3)	**<0.001**
Nonfatal ACS [*n* (%)]	16 (10.9)	15 (12)	1 (4.5)	0.468
NYHA class [median (IQR)]	2 [1–2]	2 [1–2]	2 [1–3]	**0.03**
Mean follow-up time (months) [median (IQR)]	12 [6–15.1]	12 [6–15.05]	12.1 [4.225–17.25]	0.911
Echocardiographic data				
LVEDV (ml) [median (IQR)]	103 [81–12]	102 [81–129]	120 [91.25–129.5]	0.358
LVESV (ml) [median (IQR)]	50 [40–69]	47 [37–65]	67.5 [52.5–77.5]	**0.049**
LVEF (%) [median (IQR)]	52 [42–58]	54 [43.25–58.75]	43 [36.25–49.5]	**0.008**
E/e' ratio [median (IQR)]	8 [6–10]	8 [6–10]	8 [6.5–12.5]	0.488
TAPSE (mm) [median (IQR)]	21 [20–23.75]	21 [20–24]	20 [19–22.5]	0.431
PAPs (mmHg) [median (IQR)]	27 [25–30]	27 [25–30]	30 [26.5–42.5]	0.356
Moderate-to-severe mitral regurgitation [*n* (%)]	7 (4.8)	6 (4.8)	1 (4.5)	0.959
LV thrombi [*n* (%)]	1 (0.7)	1 (0.8)	0 (0)	1

HF, heart failure; LV, left ventricle; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MACE, major adverse cardiovascular events; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 4 Variables associated with major adverse cardiovascular events at follow-up by univariate and multivariate linear regression analysis

	Univariate analysis		Multivariate analysis	
	β (95% CI)	*P*	β (95% CI)	*P*
Age	1.021 (0.997–1.045)	**0.088**	0.995 (0.969–1.023)	0.995
Sex (male)	0.776 (0.394–1.528)	0.463		
CKD	1.762 (0.736–4.219)	0.204		
Killip class III–IV	4.627 (2.4274–8.822)	**<0.001**	4.155 (1.558–11.082)	**0.004**
Proximal LAD occlusion	0.901 (0.562–1.925)	0.901		
Peak troponin I	1.001 (1.001–1.002)	**<0.001**	1.001 (1.00–1.001)	**0.015**
EF	0.959 (0.930–0.988)	**0.007**	1.001 (0.965–1.039)	0.956
Residual CAD at discharge	1.816 (0.856–3.850)	0.120		

CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; LAD, left anterior descending.

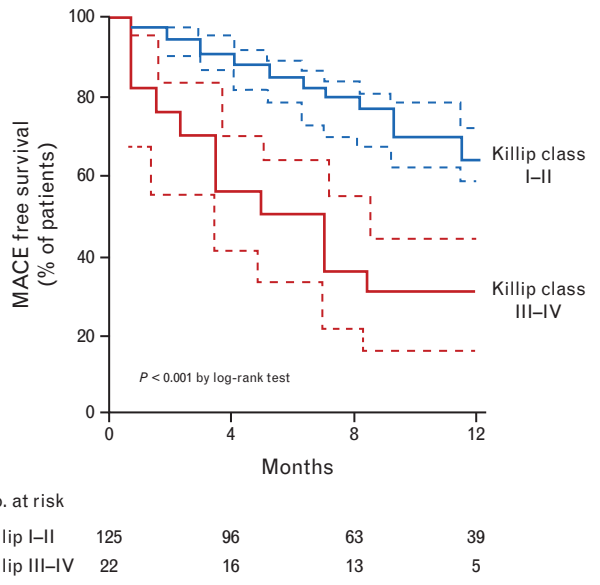
admission had a worse MACE-free survival with Killip class I–II at follow-up ($P < 0.001$) (Fig. 1).

Discussion

In our study, we demonstrated that: high Killip class (III–IV) is present in approximately 15% of patients presenting with anterior STEMI without previous cardiovascular history; compared with those presenting with Killip class I–II, patients with Killip class III–IV at admission have a different baseline clinical profile; older age, history of prehospital cardiac arrest and proximal LAD stenosis (vs. mid LAD) were predictive of worse Killip class at presentation; high Killip class was a significant predictor of in-hospital mortality and worse clinical outcomes at mid-term follow-up.

Our data are partially consistent with prior evidence reporting that advanced age, female sex, comorbidities, multivessel CAD, prehospital cardiac arrest and longer time since symptoms onset are independent predictors of high Killip class at admission in patients with STEMI.[4] Despite the higher prevalence of female sex, CKD, multivessel CAD and a longer symptoms-to-balloon time in patients presenting with Killip class III–IV, we found that age, proximal LAD lesion and prehospital cardiac arrest were independent predictors of worse clinical presentation in our population. Elderly patients may in fact present more often comorbidities and atypical presentation than younger patients, putting them at increased risk for delayed management or misdiagnosis.[14] As expected, proximal LAD segment lesion by subtending a larger area of myocardial ischemia and stunning was associated with increased risk of presenting a high Killip class.[15,16] Patients with history of prehospital cardiac arrest have typically a much higher risk profile resulting in a greater degree of myocardial damage and lower LVEF.[17] Approximately half of patients suffered multivessel CAD at time of coronary angiography with a higher prevalence in patients with high Killip class at admission. However, the presence of multivessel coronary involvement was not an independent predictor of worse clinical presentation; the inclusion of patients with anterior STEMI without history of prior heart failure and/or previous revascularization procedures may have led to the selection a cohort of patients in which the large ischemic area subtended by LAD lesion mitigated the additive contribute of further coronary involvement. Interestingly, symptoms-to-balloon time was longer in patients with higher Killip class but not predictive of worse clinical presentation, suggesting that the interplay between the baseline patient's characteristics may be the most relevant determinant of clinical presentation or alternatively its predictive role may have been diluted by the time lost for patient's stabilization before pPCI is performed. Furthermore, in our study, the protective independent role of preinfarction angina was not confirmed in the overall population but only in the subgroup of patients with proximal LAD lesion. Preinfarction angina is a clinical surrogate of ischemic preconditioning and its protective role may be more apparent in patients with a larger ischemic area.[18] We also found that patients with high Killip class had higher CRP values at baseline compared with those with low Killip class. CRP, a marker

Fig. 1



Survival Kaplan–Meier curves with 95% confidence interval for major adverse cardiovascular events according to the presence of high Killip class III–IV at admission (curves are compared by the log-rank test).

of systemic inflammatory response, has consistently been shown to predict adverse outcomes in patients with AMI as the intensity of the inflammatory response increases the risk of mechanical consequences and complications of ischemic injury.[19]

Furthermore, patients with high Killip class at admission experienced a significantly higher rate of adverse events during both index hospitalization and mid-term follow-up, with high Killip class remaining an independent predictor of intrahospital mortality and of MACEs at follow-up. This is at least partially because of the fact that patients with high Killip class had larger myocardial damage as shown by lower LVEF, higher estimated left ventricular filling pressures, lower postprocedural TIMI flow and higher values of peak troponin I and NT-proBNP values. Patients with high Killip class had also longer hospital length of stay and higher rate of nosocomial infections, with relevant healthcare and socioeconomic-related costs. Furthermore, patients with Killip class III–IV were less often treated with the more potent antiplatelet therapies (i.e. prasugrel), with clopidogrel representing the most common antiplatelet drug used probably because of the greater presence of elderly patients in this subgroup and relative bleeding concerns, and higher use of concomitant anticoagulation therapy for left ventricular mechanical support, atrial fibrillation or presence of LV thrombi. At mid-term follow-up, patients with high Killip class had lower LVEF, more dyspnea perception and experienced a significantly higher rate of MACEs, in particular in terms of all-cause mortality and heart failure hospitalizations. The observation that ejection fraction is not a predictor of worse outcomes in the multivariate analysis is not only surprising but also clinically relevant as it suggests that an integrated clinical marker of risk might be more efficient than a single dimension assessing myocardial performance. It is likely that ejection fraction would re-emerge as an independent predictor of outcome at a longer follow-up. New-onset ACS did not differ between the two groups and this could be at least in part due the fact the residual CAD at the time of discharge did not significantly differ between the two groups.

The main limitation of our study is that is a single center study with a small sample size and a short follow-up time. The small sample size, in particular, of the Killip class III–IV group, might have reduced the chances of detecting statistical differences in our population (type II error). This is, however, the first study including only patients with STEMI in the anterior location and excluding patients with history of cardiovascular diseases in order to reduce the heterogeneity of the population enrolled. At the same, we cannot exclude that the strict inclusion criteria may limit the external validity of the study. Of note, we defined Killip class at presentation before pPCI was performed in order to reduce the confounding effect of pPCI. Finally, the enrollment of patients within the 24 h from symptoms (> 12 h) onset may have led to the inclusion of late presenters with a higher risk of cardiovascular complications.[20]

In our population of patients presenting with an anterior STEMI patients as first cardiovascular event, we did not find any modifiable factors associated with an advanced Killip class at presentation as only advanced age, proximal LAD lesion and prehospital cardiac arrest were predictive of worse Killip class. Despite the introduction of pPCI, more potent antiplatelet and cardioprotective therapies, in the real-word scenario still a high percentage of patients without previous cardiovascular disease may present with Killip class III–IV at admission. Our data support the notion that Killip classification performed at the time of admission, even before pPCI, is an easy, rapid and powerful stratification tool that might help in identifying those patients at higher risk of short-term and long-term adverse events. This is clinically relevant as patients with high Killip class need closer monitoring and intensive preventive and therapeutic measures.[21]

Conflicts of interest

There are no conflicts of interest.

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