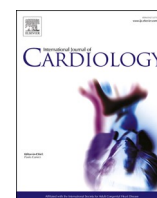




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Short communication

## Risk score for early risk prediction by cardiac magnetic resonance after acute myocardial infarction



Víctor Marcos-Garcés<sup>a,b,1</sup>, Nerea Perez<sup>b,1</sup>, Jose Gavara<sup>b,c</sup>, Maria P. Lopez-Lereu<sup>d</sup>, Jose V. Monmeneu<sup>d</sup>, Cesar Rios-Navarro<sup>b</sup>, Elena de Dios<sup>e</sup>, Hector Merenciano-González<sup>a</sup>, Ana Gabaldon-Pérez<sup>a</sup>, Joaquim Cànoves<sup>a</sup>, Paolo Racugno<sup>a</sup>, Clara Bonanad<sup>a,b,e</sup>, Gema Minana<sup>a,b,e,f</sup>, Julio Nunez<sup>a,b,e,f</sup>, David Moratal<sup>c</sup>, Francisco J. Chorro<sup>a,b,e,f</sup>, Filipa Valente<sup>g</sup>, Daniel Lorenzatti<sup>h</sup>, Jose T. Ortiz-Pérez<sup>h,i</sup>, Jose F. Rodríguez-Palomares<sup>f,g,j,k,\*\*</sup>, Vicente Bodi<sup>a,b,e,f,\*</sup>

<sup>a</sup> Department of Cardiology, Hospital Clínico Universitario de Valencia, Valencia, Spain<sup>b</sup> Health Research Institute - INCLIVA, Valencia, Spain<sup>c</sup> Center for Biomaterials and Tissue Engineering, Universitat Politècnica de València, Valencia, Spain<sup>d</sup> Cardiovascular Magnetic Resonance Unit, ERESA, Valencia, Spain<sup>e</sup> Faculty of Medicine and Odontology, University of Valencia, Valencia, Spain<sup>f</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV), Madrid, Spain<sup>g</sup> Hospital Universitari Vall d'Hebron, Department of Cardiology, Barcelona, Spain<sup>h</sup> Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain<sup>i</sup> Cardiovascular Institute, Hospital Clínic, Barcelona, Spain<sup>j</sup> Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain<sup>k</sup> Universitat Autònoma de Barcelona, Barcelona, Spain

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## ABSTRACT

**Background:** Cardiac magnetic resonance (CMR) performed early after ST-segment elevation myocardial infarction (STEMI) can improve major adverse cardiac event (MACE) risk prediction. We aimed to create a simple clinical-CMR risk score for early MACE risk stratification in STEMI patients.

**Methods:** We performed a multicenter prospective registry of reperfused STEMI patients ( $n = 1118$ ) in whom early (1-week) CMR-derived left ventricular ejection fraction (LVEF), infarct size and microvascular obstruction (MVO) were quantified. MACE was defined as a combined clinical endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (NF-MI) or re-admission for acute decompensated heart failure (HF).

**Results:** During a median follow-up of 5.52 [2.63–7.44] years, 216 first MACE (58 CV deaths, 71 NF-MI and 87 HF) were registered. Mean age was  $59.3 \pm 12.3$  years and most patients (82.8%) were male. Based on the four variables independently associated with MACE, we computed an 8-point risk score: time to reperfusion  $>4.15$  h (1 point), GRACE risk score  $> 155$  (3 points), CMR-LVEF  $<40\%$  (3 points), and MVO  $>1.5$  segments (1 point). This score permitted MACE risk stratification: MACE per 100 person-years was 1.96 in the low-risk category (0–2 points), 5.44 in the intermediate-risk category (3–5 points), and 19.7 in the high-risk category (6–8 points):  $p < 0.001$  in multivariable Cox survival analysis.

**Conclusions:** A novel risk score including clinical (time to reperfusion  $>4.15$  h and GRACE risk score  $> 155$ ) and CMR (LVEF  $<40\%$  and MVO  $>1.5$  segments) variables allows for simple and straightforward MACE risk stratification early after STEMI. External validation should confirm the applicability of the risk score.

\* Correspondence to: Prof. V. Bodi, Department of Cardiology, Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria del Hospital Clínico Universitario de Valencia (INCLIVA), Universidad de Valencia, Blasco Ibañez 17, 46010, Valencia, Spain.

\*\* Correspondence to: J. F. Rodríguez-Palomares, Hospital Universitari Vall d'Hebron, Department of Cardiology, CIBER-CV, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain.

E-mail addresses: [jfrodri@vhebron.net](mailto:jfrodri@vhebron.net) (J.F. Rodríguez-Palomares), [vicente.bodi@uv.es](mailto:vicente.bodi@uv.es) (V. Bodi).

<sup>1</sup> These authors contributed equally.

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## 1. Introduction

Despite significant improvement in survival following ST-segment elevation myocardial infarction (STEMI) in recent decades [1], subsequent risk of death, re-infarction or heart failure is not negligible [2,3].

Early risk stratification is systematically recommended to identify patients at higher risk of major adverse cardiovascular events (MACE) [4]. Thorough clinical assessment and pre-discharge left ventricular ejection fraction (LVEF) by echocardiography are traditionally considered the cornerstone of non-invasive risk stratification [4].

Use of cardiac magnetic resonance (CMR) in this setting has increased exponentially this century. CMR performed early after the acute event permits comprehensive evaluation of the structural consequences of myocardial infarction and can improve risk prediction by means of accurate LVEF, microvascular obstruction (MVO) and infarct

size (IS) measurement [5–7]. Exploring the prognostic value of novel predictive scores including CMR parameters is therefore an essential undertaking.

In our large, multicenter registry, we aimed to construct a simple risk score including clinical, echocardiographic and CMR variables for straightforward early MACE risk stratification before discharge in STEMI patients.

## 2. Methods

### 2.1. Study group

The study group comprised 1118 patients discharged from hospital for a first STEMI treated with percutaneous coronary intervention and submitted to CMR from 2007 to 2017. Patients were prospectively

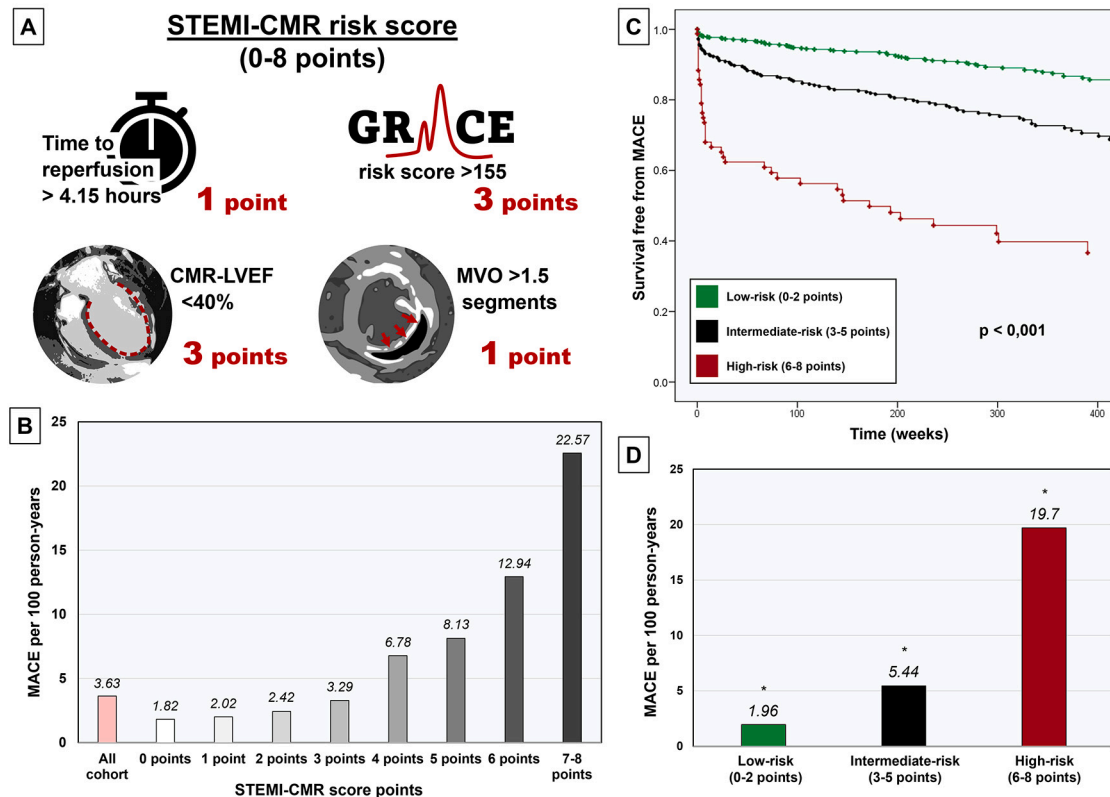
**Table 1**  
Baseline, echocardiography and CMR characteristics of the entire cohort and of patients with and without MACE.

	All patients (n = 1118)	MACE (n = 216)	No MACE (n = 902)	p-Value
<b>Clinical variables</b>				
Age (years)	59.3 ± 12.3	63 ± 13.7	58.4 ± 11.7	<0.001
Male sex (%)	926 (82.8)	172 (79.6)	754 (83.6)	0.19
Diabetes mellitus (%)	229 (20.5)	52 (24.1)	177 (19.6)	0.16
Hypertension (%)	524 (46.9)	110 (50.9)	414 (45.9)	0.2
Hypercholesterolemia (%)	470 (42)	96 (44.4)	374 (41.5)	0.44
Smoker (%)	707 (63.2)	129 (59.7)	578 (64.1)	0.24
Heart rate on admission (beats per min)	76.5 ± 19.1	81 ± 20.4	75.5 ± 18.6	<0.001
Systolic pressure (mmHg)	131 ± 30.4	130.6 ± 32	131.1 ± 30	0.83
Killip class (%)				<0.001
1	928 (83)	161 (74.5)	767 (85)	
2	141 (12.6)	33 (15.3)	108 (12)	
3	28 (2.5)	13 (6)	15 (1.7)	
4	21 (1.9)	9 (4.2)	12 (1.3)	
Time to reperfusion (hours)	3 [2–4.75]	3.33 [2.18–5.48]	3 [2–4.67]	0.03
Peak creatine kinase MB mass (ng/ml)	184 [85.5–300]	203.3 [92.3–328.4]	181.5 [83.8–289.9]	0.11
Anterior infarction (%)	560 (50.1)	131 (60.6)	85 (39.4)	0.001
TIMI flow grade before PCI (%)				0.21
0	702 (62.8)	136 (63)	566 (62.7)	
1	76 (6.8)	10 (4.6)	66 (7.3)	
2	113 (10.1)	18 (8.3)	95 (10.5)	
3	227 (20.3)	52 (24.1)	175 (19.4)	
TIMI flow grade after PCI (%)				0.04
0	14 (1.3)	5 (2.3)	9 (1)	
1	7 (0.6)	2 (0.9)	5 (0.6)	
2	83 (7.4)	24 (11.1)	59 (6.5)	
3	1014 (90.7)	185 (85.6)	829 (91.9)	
ST-segment resolution at 90 min (%) <sup>a</sup>	55.56 [23.41–90.23]	57.14 [32.58–88.89]	55.56 [21.64–91.99]	0.44
BARI angiographic score	25 [12.5–37.5]	25 [12.5–50]	25 [12.5–37.5]	0.005
GRACE risk score	132.5 ± 31.3	146.2 ± 36.2	129.2 ± 29.1	<0.001
TIMI risk score	2 [1–4]	3 [1–5]	2 [1–4]	<0.001
<b>Echo indices at 1 week</b>				
Echo-LVEF (%)	50.4 ± 11.3	47.2 ± 12.1	51.1 ± 11	<0.001
Echo-LV end-diastolic volume (ml)	109.5 ± 35.6	114.3 ± 36.3	108.6 ± 35.5	0.26
Echo-LV end-systolic volume (ml)	53.6 ± 23.7	62 ± 25.1	51.9 ± 23.1	0.003
TAPSE (mm)	21.4 ± 3.9	20.7 ± 3.1	21.5 ± 4	0.11
E wave velocity (m/s)	0.7 ± 0.3	0.74 ± 0.26	0.7 ± 0.35	0.38
A wave velocity (m/s)	0.7 ± 0.2	0.78 ± 0.25	0.72 ± 0.2	0.01
Left atrium diameter (mm)	37 [33–40.3]	38 [34–41]	36 [33–40]	0.04
<b>CMR indices at 1 week</b>				
CMR-LVEF (%)	50.2 ± 12	45.1 ± 13.7	51.4 ± 11.2	<0.001
CMR-LV end-diastolic volume index (ml/m <sup>2</sup> )	80.1 ± 20.7	81.8 ± 23.3	79.7 ± 20	0.24
CMR-LV end-systolic volume index (ml/m <sup>2</sup> )	41 ± 18.2	46.6 ± 21.5	39.7 ± 17	<0.001
LV mass (g/m <sup>2</sup> )	71 ± 18	76.3 ± 20.6	69.8 ± 17.1	<0.001
Microvascular obstruction (n of segments)	0 [0–2]	1 [0–3]	0 [0–2]	<0.001
Intramycardial hemorrhage (n of segments)	0 [0–1]	0 [0–2]	0 [0–1]	0.07
Area at risk (% of LV mass)	28.08 ± 16.55	32.43 ± 18.3	26.81 ± 15.8	0.001
Infarct size (% of LV mass)	18.8 [10.4–29.7]	26.1 [13.7–38.4]	17.6 [10–27.7]	<0.001
Myocardial salvage index (%)	23 [3.06–45.34]	18.39 [2.25–40.48]	25.24 [3.16–46.15]	0.25

Abbreviations. BARI = Bypass Angioplasty Revascularization Investigation. CMR = Cardiovascular magnetic resonance. Echo = Echocardiography. GRACE = Global Registry of Acute Coronary Events. LV = Left ventricular. LVEF = Left ventricular ejection fraction. MACE = Major adverse cardiac events. PCI = Percutaneous coronary intervention. TAPSE = Tricuspid annular plane systolic excursion. TIMI = Thrombolysis in Myocardial Infarction.

In patients with atrial fibrillation at the moment of the echocardiography E and A wave velocities were not considered for analyses.

<sup>a</sup> Percentage reduction of the summatory of ST-segment elevation in mm between initial and post-reperfusion (after 90 min) ECG.



**Fig. 1.** A: STEMI-CMR risk score calculation (0–8 points). B: MACE per 100 person-years according to STEMI-CMR score in the 0 to 8 points categories. C: Adjusted survival curves. Risk of MACE according to STEMI-CMR score risk categories (low, intermediate, and high risk). D: MACE per 100 person-years according to STEMI-CMR score risk categories (low, intermediate, and high risk). \*: all comparisons between groups with  $p < 0.001$ .

Abbreviations. CMR = Cardiovascular magnetic resonance. GRACE = Global Registry of Acute Coronary Events. LVEF = Left ventricular ejection fraction. MACE = Major adverse cardiac events. MVO = Microvascular obstruction. STEMI: ST-segment elevation myocardial infarction.

included in a multicenter registry of three University Hospitals after informed consent was provided. Baseline characteristics were recorded. The investigation conforms to the principles of the Declaration of Helsinki and was approved by the respective local Ethics Committees. The flowchart of patients is shown in Supplementary Fig. 1.

## 2.2. Echocardiography

Transthoracic echocardiography was performed in all patients before discharge ( $5 \pm 2$  days post-STEMI), before CMR. LVEF (%), left ventricular (LV) end-diastolic and end-systolic volumes ( $\text{cm}^3$ ), tricuspid annular plane systolic excursion (mm), E and A wave velocities (m/s), and left atrium diameter (mm) were measured.

## 2.3. CMR

CMR was performed pre-discharge or shortly after discharge ( $7 \pm 2$  days post-STEMI).

LVEF (%), LV end-diastolic and end-systolic volume indices ( $\text{ml}/\text{m}^2$ ) and LV mass index ( $\text{g}/\text{m}^2$ ) were calculated by manual planimetry of endocardial and epicardial borders in short-axis view cine images. Areas showing late gadolinium enhancement were visually quantified by manual planimetry. IS (% of LV mass) and myocardial edema (area at risk) were assessed as the percentage of LV mass showing late gadolinium enhancement and high T2 signal intensity, respectively. Myocardial salvage index was expressed as %. MVO was defined as an area with lack of contrast uptake in the core tissue showing late gadolinium enhancement, and the finding of a low-signal-intensity area surrounded by a high-signal-intensity area in T2 images was considered to indicate an

area of intramyocardial hemorrhage. They were expressed as number of segments using the 17-segment model. Further details on CMR acquisition can be consulted in Supplementary Material.

## 2.4. Endpoint and follow-up

MACE was defined as a combined clinical endpoint including cardiovascular (CV) death, non-fatal myocardial infarction (NF-MI) or re-admission for acute decompensated heart failure (HF), whichever occurred first. All events were prospectively adjudicated by clinical cardiologists.

## 2.5. Statistical methods

Standard tests were used for univariate comparisons of parametric, nonparametric data and group percentages. Variables achieving  $p < 0.1$  significance in univariate analysis comparing MACE and non-MACE subgroups were added as cofactors in a multivariable Cox proportional hazard regression model to predict time to MACE. A forward stepwise model was used to avoid overfitting of variables. Hazard ratios with the corresponding 95% confidence intervals were computed.

Incidence rates of MACE (expressed as MACE per 100 person-years) were determined. Two-tailed  $p$ -values were obtained using mid- $p$  adjustments.

Receiver operating characteristic (ROC) curves to predict MACE were computed, and variables that independently predicted MACE were dichotomized by means of the Youden index. To calculate the STEMI-CMR risk score, points were assigned according to the weight of the increase in chi-square value in the multivariate Cox stepwise analysis.

Statistical significance was achieved at a two-tailed  $p$ -value  $< 0.05$ . The SPSS statistical package (version 15.0, SPSS Inc., Chicago, Illinois) and STATA (version 9.0, StataCorp, College Station, Texas) were used throughout.

### 3. Results

During a median follow-up of 5.52 [2.63–7.44] years, 216 first MACE were registered (58 CV deaths, 71 NF-MI and 87 HF).

Mean age was  $59.3 \pm 12.3$  years, most patients (82.8%) were male, and the most prevalent risk factor was smoking habit (63.2%). Half of patients (50.1%) presented with anterior myocardial infarction, and TIMI grade 3 flow was achieved after reperfusion in most of these cases (90.7%). Mean LVEF by pre-discharge echocardiography and CMR was  $50.4 \pm 11.3\%$  and  $50.2 \pm 12\%$ , respectively (Table 1).

In multivariable, hierarchical Cox regression, four variables (managed as continuous data) were independent predictors of MACE: time to reperfusion (HR 1.03 [1.01–1.05] per hour,  $p = 0.01$ ), GRACE risk score (HR 1.01 [1.01–1.02] per point,  $p < 0.001$ ), CMR-LVEF (HR 0.97 [0.95–0.98] per %,  $p < 0.001$ ) and MVO (HR 1.11 [1.03–1.19] per segment,  $p = 0.008$ ) (Supplementary Table 1).

These variables were dichotomized by the best cutoff point as per the Youden index, and an 8-point risk score was calculated as derived from the four independent variables included in the final multivariable model (Supplementary Table 2): time to reperfusion  $> 4.15$  h (1 point), GRACE risk score  $> 155$  (3 points), CMR-LVEF  $< 40\%$  (3 points), and MVO  $> 1.5$  segments (1 point) (Fig. 1A). Separately, each of these dichotomized variables was significantly associated with MACE occurrence (Supplementary Fig. 2).

This risk score permitted stratification of MACE occurrence across the continuum of assigned points (Fig. 1B). Additionally, we established three risk categories which also stratified MACE risk: MACE per 100 person-years was 1.96 in the low-risk category (0–2 points), 5.44 in the intermediate-risk category (3–5 points), and 19.7 in the high-risk category (6–8 points),  $p < 0.001$ . Fig. 1C–D illustrates the adjusted survival curves based on these three categories.

### 4. Discussion

In our large multicenter registry, we demonstrate that a novel and simple risk score including clinical (time to reperfusion and GRACE score) and CMR (LVEF and MVO) variables permits early and effective MACE risk stratification soon after STEMI.

Accurate prediction of MACE soon after STEMI is crucial for patients, relatives, and physicians, and is highly appreciated by other players such as employers, health administration and insurance companies. Moreover, it can be helpful to identify the subset of patients that can benefit most from intensive follow-up and specific therapies [4,8]. Clinical variables plus echocardiography-derived LVEF have traditionally proven to yield valuable prognostic information [9,10].

CMR-derived LVEF and MVO have consistently been reported to enhance prognostic stratification of STEMI patients soon after infarction [11–13]. Separately, a number of CMR indexes such as IS, myocardial salvage index, myocardial hemorrhage or strain have also contributed prognostic information [11–14]. The increasing use of CMR in STEMI patients highlights the need for an integrated risk prediction approach that combines conventional prognosticators with the most widely analyzed CMR parameters (namely, LVEF, IS, and MVO).

Based on a simple and straightforward 4-variable score, we were able to effectively discriminate patients in low-, intermediate, and high-risk categories. Two universally available clinical variables (time to reperfusion and GRACE risk score) and two CMR indexes (LVEF and MVO) were selected. Dichotomization of variables was deemed to improve clinical applicability. While a low score translates into a low risk of MACE events during follow-up, and is thus reassuring for both patients and clinicians, a high score should alert the cardiologist in charge, and

allocating available resources to this high-risk population should be a priority [15]. Nonetheless, further research is warranted to explore the potential of this risk score for patient management and decision-making.

Leading on from previous research to determine which patients could benefit most from CMR for prognostic purposes, e.g. those with echocardiography-LVEF  $< 50\%$  [7], the present study focuses on simple risk prediction in patients who undergo CMR. This technique is recommended when echocardiography is suboptimal or inconclusive, and brings the added benefit of additional assessment of residual ischemia and myocardial viability [4]. With increasing availability of CMR comes the need for clinically applicable tools for straightforward risk stratification in STEMI patients submitted to CMR early after the acute event.

Certain limitations of this study should be acknowledged. Several variables which could have played a role in patient prognosis, such as prodromal angina, were not included in the registry. Due to the observational nature of the study, referral and survival bias cannot be excluded. Only patients undergoing CMR early after STEMI were included, so the cohort may not be entirely representative of the whole STEMI population. External validation of the risk score should be performed to confirm its applicability in other populations.

### 5. Conclusions

A novel risk score including clinical (time to reperfusion  $> 4.15$  h and GRACE risk score  $> 155$ ) and CMR (LVEF  $< 40\%$  and MVO  $> 1.5$  segments) variables allows for simple and straightforward MACE risk stratification early after STEMI. External validation of the risk score and the potential impact of this strategy for patient management and decision-making should be further explored.

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### Declaration of Competing Interest

Siemens Healthcare provided financial support to conduct cardiac magnetic resonance studies in 94 subjects of this series.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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None.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2021.11.050>.

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