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Long-Term Prognostic Value of Infarct Transmurality Determined by Contrast-Enhanced Cardiac Magnetic Resonance after ST-Segment Elevation Myocardial Infarction

In Young Choi[1], Hyun-Wook Kim[2], Dong Hyun Gim[1], Young-Jae Ki[1], Hyun Kuk Kim[1], Sung Soo Kim[1], Keun-Ho Park[1], Heesang Song[3], and Dong-Hyun Choi[1,*]

[1]Department of Internal Medicine, Chosun University School of Medicine, [2]Department of Internal Medicine, Kwangju Christian Hospital, [3]Biochemistry and Molecular Biology, Chosun University School of Medicine, Gwangju, Korea

The long-term prognostic significance of maximal infarct transmurality evaluated by contrast-enhanced cardiac magnetic resonance (CE-CMR) in ST-segment elevation myocardial infarction (STEMI) patients has yet to be determined. This study aimed to see if maximal infarct transmurality has any additional long-term prognostic value over other CE-CMR predictors in STEMI patients, such as microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH). The study included 112 consecutive patients who underwent CE-CMR after STEMI to assess established parameters of myocardial injury as well as the maximal infarct transmurality. The primary clinical endpoint was the occurrence of major adverse cardiac events (MACE), which included all-cause death, non-fatal reinfarction, and new heart failure hospitalization. The MACE occurred in 10 patients over a median follow-up of 7.9 years (IQR, 5.8 to 9.2 years) (2 deaths, 3 nonfatal MI, and 5 heart failure hospitalization). Patients with MACE had significantly higher rates of transmural extent of infarction, infarct size >5.4 percent, MVO, and IMH compared to patients without MACE. In stepwise multivariable Cox regression analysis, the transmural extent of infarction defined as 75 percent or more of infarct transmurality was an independent predictor of the MACE after correction for MVO and IMH (hazard ratio 8.7, 95% confidence intervals [CIs] 1.1-71; p=0.043). In revascularized STEMI patients, post-infarction CE-CMR-based maximal infarct transmurality is an independent long-term prognosticator. Adding maximal infarct transmurality to CE-CMR parameters like MVO and IMH could thus identify patients at high risk of long-term adverse outcomes in STEMI.

Key Words: *ST Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Magnetic Resonance Imaging*

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Corresponding Author:
Dong-Hyun Choi
Department of Internal Medicine,
Chosun University School of Medicine,
375 Seoseok-dong, Dong-gu,
Gwangju 501-759, Korea
Tel: +82-62-220-3773
Fax: +82-62-222-3858
E-mail: dhchoi@chosun.ac.kr

INTRODUCTION

Over the last several decades, advances in percutaneous coronary intervention (PCI) and medical treatment have resulted in a dramatic improvement in the outcome of patients with ST-elevation myocardial infarction (STEMI). In around half of the patients with ST-elevation myocardial infarction, despite the effective opening of the culprit artery by the primary percutaneous coronary intervention (PPCI), myocardial tissue perfusion does not improve completely.[1,2] Even after surviving an acute infarction, an increasing percentage of patients are at long-term risk of sudden cardiac death or heart failure.[3] As a result, early risk stratification is recommended for all patients, and the best way to estimate prognosis following STEMI is still being researched.[4]

Contrast-enhanced cardiac magnetic resonance (CE-CMR) imaging is well suited to determine structural and functional changes following STEMI because it provides

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great tissue characterization without exposing the patient to radiation. Several CE-CMR parameters have been shown to have prognostic significance in post-infarction patients in previous research. These include morphological changes (infarct size, area at risk [AAR], myocardial salvage index [MSI]), microvascular injury such as microvascular obstruction (MVO) and/or intramyocardial hemorrhage (IMH), and functional impairment (left ventricular ejection fraction [LVEF], myocardial strain).[5-15] Previous CE-CMR studies in STEMI patients, on the other hand, were limited by a lack of long-term follow-up and the use of soft clinical end-points. As a result, long-term follow-up data and hard clinical end-points are hard to come by.

The transmurality of myocardial infarction can be accurately assessed using CE-CMR,[16] and the transmurality predicts improvement in contractile function.[10] However, the long-term prognostic value of transmurality has not been examined in over two decades, as far as we know.

This study aimed to see if maximal infarct transmurality has any additional long-term prognostic value in STEMI patients over other CE-CMR predictors such as MVO and IMH.

MATERIALS AND METHODS

1. Study population

A total of 515 consecutive patients with STEMI who underwent PPCI between November 2010 and July 2014 were enrolled in this study. Patients were included if they were older than 18 years and had undergone PPCI within 12 hours after symptom onset. Patients who refused to consent to undergo CE-CMR imaging or who had contraindications for CE-CMR imaging were eventually excluded; 112 patients were finally included. The Chosun University Hospital Research Ethics Committee approved the current study protocol (approval CHOSUN 2014-12-001).

2. Definition of STEMI

STEMI was defined as (1) at least 1 mm ST-segment elevation in two or more standard leads, at least 2 mm in two or more nearby precordial leads, or suspected new-onset left bundle branch block, (2) typical chest symptoms that lasted for at least 30 minutes, (3) and troponin I levels above the upper limit.

3. Percutaneous coronary intervention

Before the intervention, all patients were given a dual oral antiplatelet medication (300 mg aspirin, 600 mg clopidogrel), followed by maintenance dosages of aspirin (100–200 mg daily) and clopidogrel (75 mg daily). Standard interventional techniques were used for coronary angiography and stent implantation. Glycoprotein IIb/IIIa receptor antagonists were given intravenously as needed.

4. The primary clinical endpoint

The primary clinical endpoint (major adverse cardiac events [MACE]) was defined as a composite of all-cause death, non-fatal reinfarction, and the occurrence of new heart failure hospitalization following hospital discharge for the index event. Each patient only contributed once to the MACE endpoint (death > reinfarction > congestive heart failure) to avoid double-counting of patients who had multiple events.

5. CE-CMR imaging protocol and analysis

The CE-CMR process and imaging techniques have been described in detail elsewhere,[17-20] and are discussed here. Myocardial infarction and cardiac function were assessed using a comprehensive CE-CMR study. A 1.5-T MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) and a 3.0-T MR scanner (Magnetom Skyra, Siemens Medical Solutions, Erlangen, Germany) with dedicated cardiac surface coils were used for the examinations.

T2- and T1-weighted images were acquired as a stack of contiguous 8-mm-thick images in the cardiac short-axis view. Cine images were obtained by a fast gradient-echo sequence (steady-state free precession) in the short-axis, 2-chamber, and 4-chamber views. Short-axis images of the LV were acquired from the apex to the base to contain the entire LV volume, with the slice thickness fixed at 8 mm without gaps. Following scouting and cine imaging, stress perfusion imaging was performed. Adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered for 6 minutes. Following that, a dose of 0.2 mmol/kg gadolinium-diethylene triamine pentaacetic acid (Magnevist, Bayer Schering Pharma, Berlin, Germany) was administered intravenously at a rate of 3 mL/s followed by a 20-mL saline flush for 4 minutes under adenosine infusion. Delayed hyperenhancement and the amount of MVO were accessed 5 min and 15 minutes after contrast administration in 10-12 contiguous 8-mm-thick slices with no gap. The field-of-view and image matrix were 224×340 mm (230×350 mm in 3T MR) and 256×146 (256×156 in 3T MR), respectively.

All of the cardiac MR image parameters were determined at our MRI core laboratory. The LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were measured. By multiplying the myocardial volume by the myocardial density (1.05 g/mL), the myocardial mass was calculated. LV mass was indexed to the body surface area. The LV infarct size and volume were calculated using delayed enhancement. The volume and the extent of MVO, defined as a late hypo-enhanced zone within the infarcted myocardium on the delayed enhancement image, were determined in the same way as the infarct volume. The myocardial AAR was defined as myocardium with signal intensity greater than two standard deviations (SDs) above the mean signal intensity of a distant normal myocardium and expressed as a percentage of LV myocardial volume. The following formula was used to determine the myocardial salvage index: myocardial salvage index=(AAR−infarct size)×100/AAR. By dividing the greatest hyper-enhanced thickness by the whole myocardial thickness in each segment, we calculated infarct transmurality for all segments. The transmural extent of infarction was defined

as 75 percent or more of maximal infarct transmurality.[21] A region of the hypointense core within the infarcted area with a reduction of T2-signal intensities below 20 ms was designated as an IMH.

6. Statistical analysis

All values are expressed as means±standard deviations (SDs), medians (interquartile ranges [IQRs]), or numbers (percentages). The chi-square or Fisher's exact test was used to compare baseline characteristics between groups for non-continuous variables.

The Kaplan–Meier method was used to calculate and visualize MACE-free survival. The potential independent association between transmural extent of infarction/infarct size/MVO/IMH/LVEF and MACE-free survival was investigated using multivariable Cox regression models. A receiver operating characteristic (ROC) curve analysis was used to categorize continuous CE-CMR variables (infarct size and LVEF) as above or below the cutoff values for predicting MACE in this model. We used the term 'triple combination', which means the transmural extent of infarction with all the presence of MVO and IMH. All of the tests were two-tailed, with a significance threshold of 0.05. When the variance inflation factor (VIF) was greater than 10, it was deemed to have multicollinearity; when the VIF was less than 10, there was no multicollinearity. Statistical analysis was performed with SPSS 28.0.0.0 (IBM, Armonk, NY, USA) and MedCalc Version 20.019 (MedCalc Software Ltd., Acacialaan, Ostend, Belgium).

RESULTS

1. Baseline characteristics of the cohort

Tables 1 and 2 summarize the baseline clinical and CMR parameters. The average age of the patients was 59.0 years, and 85.7 percent of them were men. 17.9 percent of the patients had diabetes, and 72.3 percent were smokers. A Killip class II to IV symptom was experienced by 51.8 percent of the patients, with 85.8 percent of the patients having an anterior or inferior STEMI.

The median interval between STEMI and CMR was 41 days (IQR, 31-52 days). Mean LVEF was 49.8%, maximal mean infarct transmurality was 66%, and mean infarct size was 6.88% of LV. MVO was detected in 26 of 112 patients (23.2%), and in these subjects, the mean MVO extent was 1.1% of LV. IMH was found in 30 of the 112 patients studied (26.8%).

2. Clinical follow-up

The median duration of follow-up was 7.9 years (IQR, 5.8 to 9.2 years; total range 1.1 to 10.8 years). The primary endpoint occurred in 10 patients (8.9%). Two patients experienced death (1.8%). Five patients (4.5%) were admitted to the hospital with decompensated heart failure. Three patients (2.7%) had a nonfatal myocardial infarction during follow-up, and 22 patients (19.6%) had coronary revascularization.

3. Clinical outcomes and cutoff values of continuous CE-CMR variables (infarct size, area at risk, myocardial salvage index, and LVEF)

The ROC curve analysis indicated a cutoff value of 5.4% for infarct size, with 90.0% sensitivity (95% CI: 55.5-99.7) and 46.1% specificity (95% CI: 36.2-56.2) (area under the ROC curve [AUC]=0.656, p=0.043), 13.3% for the area at risk, with 70.0% sensitivity (95% CI: 34.8-93.3) and 46.1% specificity (95% CI: 36.2-56.2) (area under the ROC curve [AUC]=0.503, p=0.973), 0.55% for myocardial salvage index, with 70.0% sensitivity (95% CI: 34.8-93.3) and 59.8% specificity (95% CI: 49.6-69.4) (area under the ROC curve [AUC]=0.645, p=0.095), and 50% for EF, with 70.0% sensitivity (95% CI: 34.8-93.3) and 57.8% specificity (95% CI: 47.7-67.6) (area under the ROC curve [AUC]=0.620, p=0.236) as the best cutoff for predicting the primary endpoint.

4. Infarct-related CE-CMR variables according to the primary outcome

Fig. 1 shows representative CE-CMR images of reperfused STEMI patients. The MACE group had greater rates of transmural extent of infarction (90% vs. 42%, p=0.004), infarct size >5.4 percent (90% vs. 54%, p=0.028), MVO (60% vs. 20%, p=0.004), and IMH (60% vs. 24%, p=0.013) than the non-MACE group. LV dysfunction (EF less than 50%) was more common in the MACE group than in the non-MACE group, but the difference was statistically insignificant (70% vs. 42%, p=0.091).

5. Survival analyses

According to the Kaplan–Meier curve analyses, patients with transmural extent of infarction, infarct size >5.4% of LV, MVO, and IMH had a higher risk of experiencing the primary endpoint (Fig. 2). Although patients with an EF of less than 50% were more likely than those with an EF of 50% to experience the primary endpoint, there was no statistically significant difference between the two groups.

6. Univariate Cox regression analysis for the primary endpoint

The occurrence of the primary outcome was strongly linked to transmural extent of infarction (hazard ratio 11.4, 95% CI 1.4-89.9; p=0.021), MVO (hazard ratio 5.1, 95% CI 1.4-18.1; p=0.012), and IMH (hazard ratio 4.3, 95% CI 1.2-15.2; p=0.024). Infarct size >5.4% of LV, area at risk >13.3%, myocardial salvage index of less than 0.55%, and an EF of less than 50% were not significantly associated with the primary outcome (Table 3).

7. Multivariate Cox regression analysis for the primary endpoint

The significant univariate variables (transmural extent of infarction, MVO, and IMH) were included in the multivariate logistic regression analysis. After adjusting for the other factors, the variable shown to be an independent risk factor for the primary outcome was transmural extent of infarction (Table 3).

TABLE 1. Baseline characteristics

Characteristic	Total (n=112)	Without MACE (n=102)	MACE (n=10)	p-value
Clinical characteristics				
Age (years)	59.0±10.4	58.6±10.1	62.9±12.8	0.217
Male sex (%)	96 (85.7%)	88 (86.3%)	8 (80.0%)	0.588
Hypertension (%)	46 (41.1%)	41 (40.2%)	5 (50.0%)	0.548
Diabetes mellitus (%)	20 (17.9%)	18 (17.6%)	2 (20.0%)	0.853
Dyslipidemia (%)	13 (11.6%)	12 (11.8%)	1 (10.0%)	0.868
Smokers (%)*	81 (72.3%)	74 (72.5%)	7 (70.0%)	0.863
Prior PCI (%)	6 (5.4%)	5 (4.9%)	1 (10.0%)	0.494
Killip class ≥2 (%)	58 (51.8%)	52 (51.0%)	6 (60.0%)	0.586
Anterior infarction (%)	48 (42.9%)	44 (43.1%)	4 (40.0%)	0.848
SBP at admission (mmHg)	126.1±24.3	125.2±24.8	135.0±17.2	0.225
Initial heart rate (beat/min)	73.5±17.1	73.4±17.4	75.0±13.5	0.388
Door-to-balloon time (min)	79.5±21.3	79.6±22.2	78.3±7.8	0.854
Symptom-to-balloon time (min)	264.9±166.7	260.0±165.7	314.9±178.6	0.322
TIMI risk score	3.5±2.3	3.5±2.3	3.8±2.0	0.669
Peak CK-MB (ng/dL)	222.1±123.5	217.7±124.1	267.0±112.5	0.230
Peak hs-cTnT (ng/mL)	6.39±3.78	6.10±3.59	9.30±4.67	0.010
Creatinine (mg/dL)	1.00±0.19	1.00±0.19	1.00±0.19	0.963
Peak hsCRP (mg/dL)	3.32±4.43	3.02±4.04	6.45±6.82	0.018
Angiographic data				
Culprit artery				
LAD (%)	48 (42.9%)	44 (43.1%)	4 (40.0%)	0.848
LCx (%)	16 (14.3%)	16 (15.7%)	0 (0.0%)	0.176
RCA (%)	48 (42.9%)	42 (41.2%)	6 (60.0%)	0.251
Multivessel disease (%)	63 (56.3%)	59 (57.8%)	4 (40.0%)	0.278
Baseline TIMI flow grade 0-1 (%)	89 (79.5%)	80 (78.4%)	9 (90.0%)	0.387
Final TIMI flow grade 3 (%)	103 (92.0%)	94 (92.2%)	9 (90.0%)	0.811
Angiographic no-reflow (%)	3 (2.7%)	2 (2.0%)	1 (10.0%)	0.133
Thrombus aspiration (%)	26 (23.2%)	25 (24.5%)	1 (10.0%)	0.300
Bare-metal stents (%)	27 (24.1%)	24 (23.5%)	3 (30.0%)	0.648
Stent diameter at culprit artery (mm)	3.13±0.59	3.11±0.60	3.35±0.46	0.216
Stent length at culprit artery (mm)	31.5±18.0	30.8±17.5	38.1±22.6	0.224
Glycoprotein IIb/IIIa inhibitor (%)	64 (57.1%)	60 (58.8%)	4 (40.0%)	0.251
Discharge medications				
Aspirin	112 (100%)	102 (100%)	10 (100%)	N/A
ADP receptor antagonist	112 (100%)	102 (100%)	10 (100%)	N/A
Beta-blocker	106 (94.6%)	96 (94.1%)	10 (100%)	0.430
ACEI or ARB	108 (96.4%)	98 (96.1%)	10 (100%)	0.524
Statin	111 (99.1%)	101 (99.0%)	10 (100%)	0.753

*Active smokers and ex-smokers who quit smoking less than a year before enrolling are both considered smokers. PCI denotes percutaneous coronary intervention. SBP: systolic blood pressure, CK: creatine kinase, hs-cTnT: high-sensitivity cardiac troponin T, hsCRP: high sensitivity C-reactive protein, LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction, ADP: adenosine diphosphate, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker.

8. Incremental prognostic value of all the transmural extent of infarction, MVO, and IMH

Even though transmural extent of infarction was the only independent predictor of the primary outcome, we performed survival analysis to compare groups of triple-positive (transmural extent of infarction with all the presence of MVO and IMH) and non-triple-positive patients. It exhibited an additional prognostic value of all the transmural extent of infarction, MVO, and IMH (triple combination) for the primary endpoint (Fig. 3). In addition, among patients with transmural extent of infarction, we separated the group into subgroups with triple-positive and non-triple-positive; the rate of long-term primary outcome was greater in the triple-positive subgroup than in the non-triple-positive subgroup (Table 4).

DISCUSSION

The following are the key conclusions of our investigation: (i) After adjusting for other important CE-CMR fac-

TABLE 2. CE-CMR imaging characteristics

Characteristic	Total (n=112)	Without MACE (n=102)	MACE (n=10)	p-value
LVEDV (mL)	140.1±32.9	139.5±33.1	145.6±31.6	0.581
LVESV (mL)	70.4±28.8	69.8±29.3	76.4±22.9	0.494
LV mass index (g/m^2)	89.1±16.2	88.5±15.7	97.5±19.9	0.092
LV ejection fraction (%)	49.8±9.8	50.1±9.9	46.8±9.0	0.313
Infarct size, % of LV	6.88±5.5	6.69±5.5	8.76±4.7	0.255
Area at risk, % of LV	17.4±11.1	17.4±11.2	17.0±11.1	0.896
Myocardial salvage index (%)	0.58±0.26	0.60±0.26	0.46±0.27	0.114
Frequency of IMH (%)	30 (26.8%)	24 (23.5%)	6 (60.0%)	0.013
Frequency of MVO (%)	26 (23.2%)	20 (19.6%)	6 (60.0%)	0.004
MVO area, % of LV*	0.24±0.55	0.21±0.53	0.58±0.62	0.041
Number of segments with transmural extent of infarction	1.45±1.73	1.34±1.73	2.60±1.35	0.028
Maximal infarct transmurality (%)	66.0±29.0	63.9±29.3	87.7±11.9	<0.001
Frequency of transmural extent of infarction (%)	52 (46.4%)	43 (42.2%)	9 (90.0%)	0.004

*In patients with MVO. CE-CMR denotes contrast-enhanced cardiac magnetic resonance. LV: left ventricle, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, MVO: microvascular obstruction.

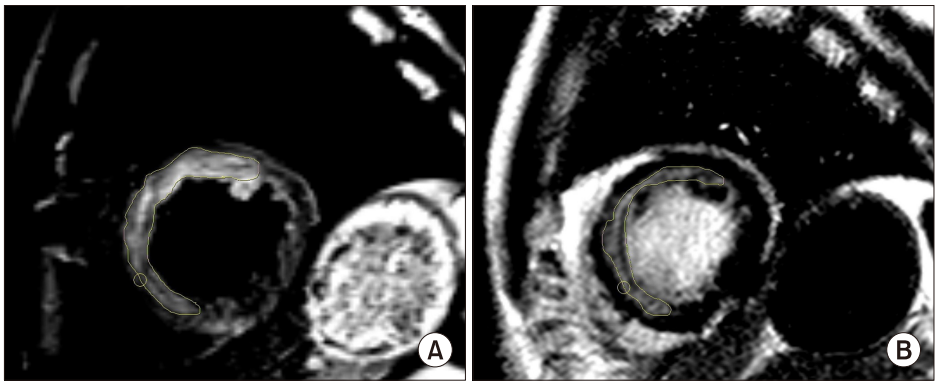

FIG. 1. Short-axis contrast-enhanced magnetic resonance images. T2-weighted short-axis image showing edema (A) and the corresponding delayed enhancement (85% of transmurality) and microvascular obstruction (MVO) (B).

tors (MVO and IMH), maximal transmural infarction detected by CE-CMR was an independent predictor of long-term MACE (all-cause death, non-fatal reinfarction, and the occurrence of new heart failure hospitalization) after STEMI; (ii) transmural extent of infarction was more closely connected with long-term MACE than infarct size; and (iii) when transmural extent of infarction, MVO, and IMH were used together, they provided additive prognostic information. As a result, using CE-CMR imaging to estimate infarct transmurality, MVO, and IMH may help with long-term risk classification and management for STEMI patients. To further elucidate these concepts, larger clinical investigations are required.

Long-term risk stratification following STEMI is still critical, even in the era of primary PCI. Pedersen et al.[3] found that death surpassed 7% within the first month after STEMI in a large cohort of STEMI patients treated with primary PCI. After that, mortality gradually reduced, though it remained high. The myocardial function should be determined in all patients with acute STEMI, as recommended by current guidelines.[4]

Because of its unique ability to offer a thorough assessment of LV structure and function as well as quantitative multiparametric characterization of infarcted myocardium, CE-CMR has the potential to become the imaging modality of choice for investigating patients after STEMI. As a result, CMR is widely used to determine LV function, infarct size, transmurality, and microvascular injury following myocardial infarction.[22-24] However, previous CE-CMR investigations in STEMI patients have been restricted by a lack of long-term follow-up and the use of soft clinical end-points. As a result, information on long-term follow-up and hard clinical end-points are scarce.

MVO is related to severe microvascular damage.[25] Nagao et al.[25] showed that MVO is related to a lower myocardial perfusion index, and late enhancement with or without MVO is an important predictor of perfusion status after reperfusion therapy. During a median of 2.7 years, Ahn et al.[15] found that patients with a transmural necrotic segment count of more than 5 had a greater risk of MACE (cardiac mortality, recurrent MI, and heart failure hospitalization). Symons et al.[13] showed that MVO was a strong independent prognosticator of the composite of all-cause mortality and HF hospitalization after a median follow-up of 5.5 years in multicenter registry research that included more than 800 STEMI patients evaluated by CE-CMR fol-

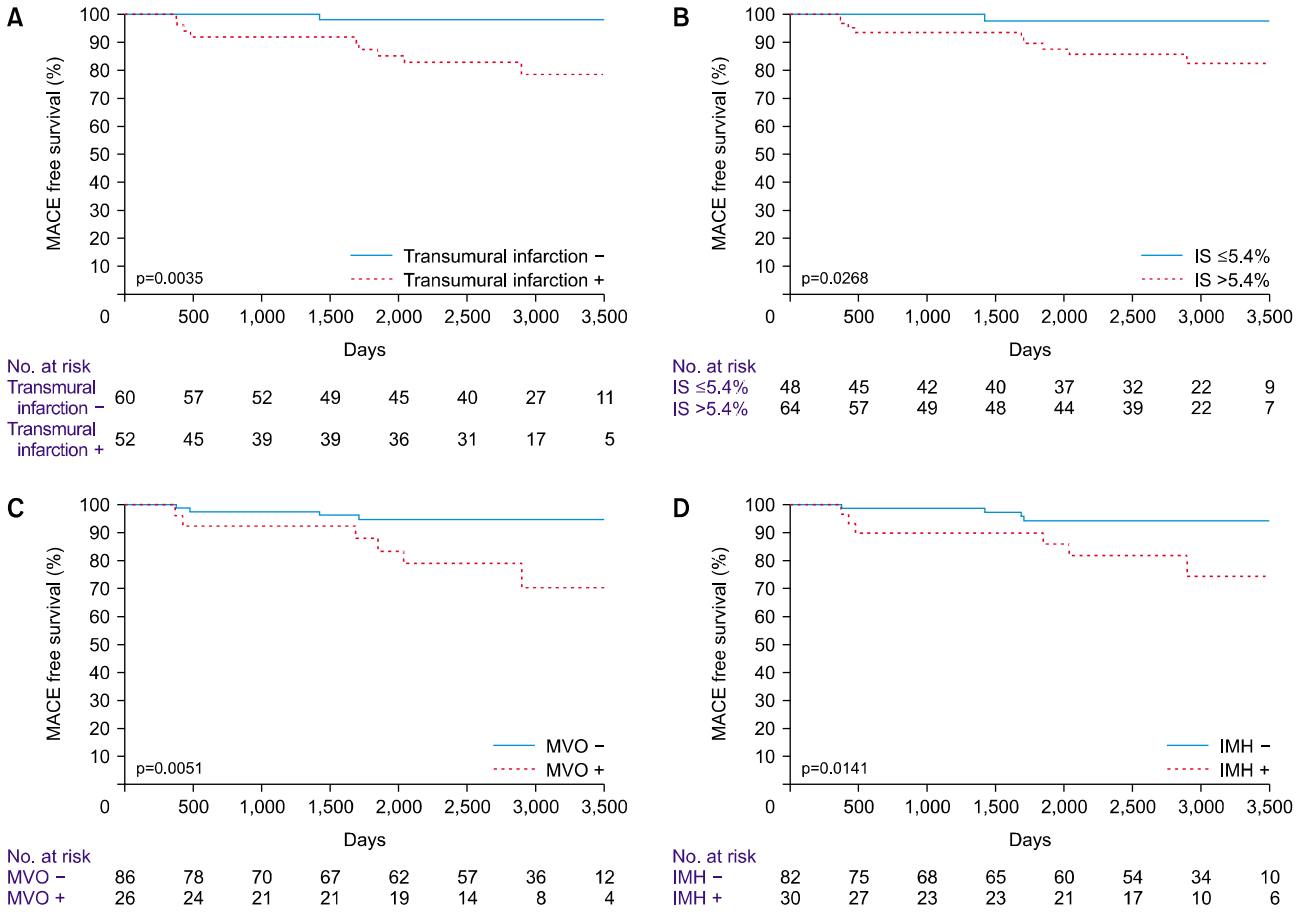

FIG. 2. MACE free survival for the primary endpoint. Kaplan–Meier curves show the time-to-first event for the primary composite endpoint according to the transmural extent of infarction (A), the cutoffs of infarct size (IS) (B), microvascular obstruction (MVO) (C), and intramyocardial hemorrhage (IMH) (D).

TABLE 3. Univariate and multivariate Cox regression analyses determine the significant and independent CE-CMR predictors for the long-term MACE

Factor	Univariate OR (95% CI), p-value	Multivariate OR (95% CI), p-value
Transmural extent of infarction	11.4 (1.44-89.9), 0.021	8.69 (1.07-70.7), 0.043
Infarct size (>5.4%)	7.32 (0.93-57.8), 0.059	
MVO	5.09 (1.43-18.1), 0.012	1.97 (0.43-8.97), 0.382
IMH	4.28 (1.21-15.2), 0.024	2.45 (0.55-11.0), 0.240
Area at riak (>13.3%)	1.95 (0.50-7.54), 0.333	
Myocardial salvage index (≤0.55%)	3.31 (0.86-12.8), 0.083	
Low LVEF (≤50%)	2.90 (0.75-11.2), 0.123	

The reference group was as follows: infarct transmurality <75%, infarct size (5.4%), no MVO, no IMH, area at risk (13.3%), myocardial salvage index (>0.55%), preserved LVEF (>50%). Each level of infarct size, area at risk, myocardial salvage index, and LVEF were cut-off values for the long-term MACE by ROC analysis.

lowing infarction. IMH was an independent prognostic CE-CMR predictor of MACE (all-cause death, non-fatal reinfarction, and the development of new heart failure) in revascularized STEMI patients at 12 months, according to Reinstadler et al.[5] Our analysis now provides significant evidence that CE-CMR-derived infarct transmurality, MVO, and IMH are linked with MACE at long-term follow-up, in line with these and other publications.[5-15] Surprisingly, individuals with transmural extent of infarction had an 11-fold higher risk of death, reinfarction, or being hospitalized for heart failure than those who did not have a transmural extent of infarction. In addition, stepwise inclusion of the relevant dichotomized CE-CMR factors in the multivariate analysis revealed that transmural extent of in-

farction had the best predictive power for predicting the long-term primary outcome, outperforming MVO and IMH.

Stone et al.[26] demonstrated that infarct size, as measured by CMR or technetium-99m sestamibi SPECT within 1 month of primary PCI, was strongly associated with all-cause mortality and hospitalization for heart failure within 1 year in a meta-analysis of 10 studies involving over 2,600 STEMI patients. However, we discovered that infarct size was not an independent predictor of clinical outcomes, which is consistent with previous studies.[13,14,27-29] There are some plausible explanations for why infarct size was not an independent predictor of clinical outcomes, even though infarct transmurality was an independent predictor and had a weak but significant positive correlation with infarct size ($r=0.59$, $p<0.0001$, data not shown). First, it could imply that the depth of the infarction (transmurality), rather than the overall infarct size, has a bigger impact on the long-term prognosis. As a result, infarct size appears to be underpowered in terms of predicting MACE. Second, in this study, the mean infarct size was only 6.88%, and infarct size >5.4% is a determinant to separate with or without MACE, which was a much lower infarct size compared with other studies.[26] However, the exact pathophysiological mechanisms that relate transmurality (rather than infarct size) to poorer outcomes are unknown.

The perfusion territory of the occluded artery determines the spatial extent of the "at-risk" region after coronary artery occlusion. Necrosis begins in the subendocardium and develops in a wavefront toward the epicardium with increasing occlusion duration within the at-risk zone.[30] CE-CMR can accurately assess the transmurality of myocardial infarction,[16] and the transmurality predicts improvement in contractile function.[10] However, as far as we know, the long-term prognostic utility of transmurality has not been investigated in over two decades. As a result, this is the first study to look at the long-term prognostic usefulness of myocardial infarction transmural extent measured by CE-CMR following STEMI.

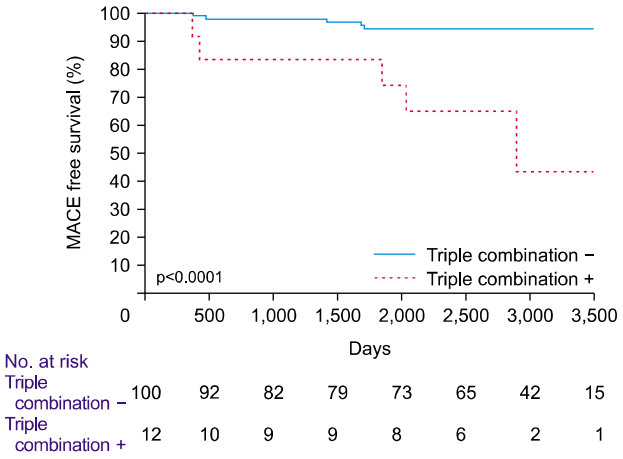

FIG. 3. Impact of outcome predictor combination on long-term prognosis. The Kaplan–Meier curve depicts the time to the first event for the primary composite endpoint when transmural extent of infarction, microvascular obstruction (MVO), and intramyocardial hemorrhage (IMH) are combined.

Even though MVO and IMH were not independent predictors of long-term MACE following transmural extent of infarction adjudication, the combination of MVO, IMH, and transmural extent of infarction had the greater predictive potential for long-term clinical outcomes. Furthermore, the triple-positive (transmural extent of infarction with MVO and IMH) cohort showed a greater rate of long-term primary outcome than the non-triple-positive category among patients with transmural extent of infarction. As a result of these findings, transmural extent of infarction, MVO, and IMH may have incremental prognostic significance; patients who test positive for all three should be treated more aggressively.

1. Limitations

Our study had a small sample size and was conducted in a single center. The number of observed occurrences was modest while being comparable to other studies.[5,13] Moreover, this study refers to the retrospective analysis. As a result, the findings and conclusions are susceptible to the limitations that come with this type of research.

In comparison to other research, the time it took to get CE-CMR images was quite long (median 41 days vs. 3-7 days).[5,13,25] In addition, the T2-weighted image of the myocardium is an unstable image. Therefore, 40 days after MI onset may be late to determine edema. Furthermore, this may be an inappropriate time to evaluate an area at risk or salvage area for acute reperfused MI. In the same context, MVO immediately after onset may also disappear after 40 days; this may underestimate MVO. Nonetheless, in individuals with transmural extent of infarction and non-transmural extent of infarction, the period between infarction and CE-CMR was identical, reducing the possibility of bias.

T2* is optimal for the presence of hemorrhagic infarction; T2-weighted is less sensitive. This is a possible explanation for the outstanding prognostic value of the max-

TABLE 4. Event rates according to triple-positive

Event rate	Total (n=112)	Non-triple-positive (n=100)	Triple-positive (n=12)	p-value
Primary endpoint	10 (8.9%)	5 (5.0%)	5 (41.7%)	<0.001
All-cause death	2 (1.8%)	1 (1.0%)	1 (8.3%)	0.070
Non-fatal reinfarction	3 (2.7%)	1 (1.0%)	2 (16.7%)	0.001
Heart failure hospitalization	7 (6.3%)	4 (4.0%)	3 (25.0%)	0.005

imal infarct transmurality over IMH.

Patients having contraindications to CE-CMR (e.g., unstable hemodynamics or renal insufficiency with creatinine clearance < 30 mL/min) could not be included in the trial, hence this patient group is not represented in the study population.

In conclusion, at long-term follow-up, post-infarction CE-CMR-based maximal transmurality is a robust independent prognosticator in reperfused STEMI patients over and above established CE-CMR markers (MVO and IMH). As a result, adding a transmurality to MVO and IMH assessment can identify patients with the highest risk of long-term adverse outcomes in STEMI.

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CONFLICT OF INTEREST STATEMENT

None declared.

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