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MRI Investigation of the Differential Impact of Left Ventricular Ejection Fraction After Myocardial Infarction in Elderly vs. Nonelderly Patients to Predict Readmission for Heart Failure

Víctor Marcos-Garcés, MD, PhD,[1,2] Héctor Merenciano-González, MD,[1,2] José Gavara, PhD,[2,3*] Ana Gabaldón-Pérez, MD,[1,2] María P. López-Lereu, MD, PhD,[4] José V. Monmeneu, MD, PhD,[4] Julio Nuñez, MD, PhD,[1,2,5,6] Nerea Pérez, BSc,[2] César Ríos-Navarro, PhD,[2] Elena de Dios, MSc,[5] Francisco J. Chorro, MD, PhD,[1,2,5,6] Filipa Valente, MD,[7] Daniel Lorenzatti, MD,[8] Blanca Domenech-Ximenos, MD, PhD,[8,9] Albert Alonso Tello, MD,[7] Manel Maymí-Ballesteros, MD,[7] Pau Rello-Sabaté, MD,[7] Carlos Igor Morr, MD,[8,10] Jose T. Ortiz-Pérez, MD, PhD,[8,10] Jose F. Rodríguez-Palomares, MD, PhD,[6,7,11,12] and Vicente Bodí, MD, PhD[1,2,5,6*]

Background: Patients with ST-segment elevation myocardial infarction (STEMI), especially elderly individuals, have an increased risk of readmission for acute heart failure (AHF).
Purpose: To study the impact of left ventricular ejection fraction (LVEF) by MRI to predict AHF in elderly (>70 years) and nonelderly patients after STEMI.
Study Type: Prospective.
Population: Multicenter registry of 759 reperfused STEMI patients (23.3% elderly).
Field Strength/Sequence: 1.5-T. Balanced steady-state free precession (cine imaging) and segmented inversion recovery steady-state free precession (late gadolinium enhancement) sequences.
Assessment: One-week MRI-derived LVEF (%) was quantified. Sequential MRI data were recorded in 579 patients. Patients were categorized according to their MRI-derived LVEF as preserved (p-LVEF, ≥50%), mildly reduced (mr-LVEF, 41%–49%),

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*Address reprint requests to: V.B., Department of Cardiology, Hospital Clínico Universitario de Valencia, Blasco Ibanez 17, 46010, Valencia, Spain. E-mail: vicente.bodi@uv.es, or J.G., INCLIVA Health Research Institute, Blasco Ibanez 17, 46010, Valencia, Spain. E-mail: jose_4_6_90@hotmail.com
Víctor Marcos-Garcés and Héctor Merenciano-González contributed equally to this work.

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From the [1]Department of Cardiology, Hospital Clínico Universitario de Valencia, Valencia, Spain; [2]INCLIVA Health Research Institute, Valencia, Spain; [3]Center for Biomaterials and Tissue Engineering, Universitat Politècnica de València, Valencia, Spain; [4]Cardiovascular Magnetic Resonance Unit, ASCIRES Biomedical Group, Valencia, Spain; [5]Faculty of Medicine and Odontology, University of Valencia, Valencia, Spain; [6]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV), Madrid, Spain; [7]Hospital Universitari Vall d'Hebron, Department of Cardiology, Barcelona, Spain; [8]Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain; [9]Cardiothoracic Imaging -Diagnostic Imaging Center, Hospital Clínic, Barcelona, Spain; [10]Cardiovascular Institute, Hospital Clínic, Barcelona, Spain; [11]Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain; and [12]Universitat Autònoma de Barcelona, Barcelona, Spain

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or reduced (r-LVEF, ≤40%). Median follow-up was 5 [2.33–7.54] years.
Statistical Tests: Univariable (Student's *t*, Mann–Whitney *U*, chi-square, and Fisher's exact tests) and multivariable (Cox proportional hazard regression) comparisons and continuous-time multistate Markov model to analyze transitions between LVEF categories and to AHF. Hazard ratios (HR) with 95% confidence intervals (CIs) were computed. $P < 0.05$ was considered statistically significant.
Results: Over the follow-up period, 79 (10.4%) patients presented AHF. MRI-LVEF was the most robust predictor in nonelderly (HR 0.94 [0.91–0.98]) and elderly patients (HR 0.94 [0.91–0.97]). Elderly patients had an increased AHF risk across the LVEF spectrum. An excess of risk (compared to p-LVEF) was noted in patients with r-LVEF both in nonelderly (HR 11.25 [5.67–22.32]) and elderly patients (HR 7.55 [3.29–17.34]). However, the mr-LVEF category was associated with increased AHF risk only in elderly patients (HR 3.66 [1.54–8.68]). Less transitions to higher LVEF states ($n = 19$, 30.2% vs. $n = 98$, 53%) and more transitions to AHF state ($n = 34$, 53.9% vs. $n = 45$, 24.3%) were observed in elderly than nonelderly patients.
Data Conclusion: MRI-derived p-LVEF confers a favorable prognosis and r-LVEF identifies individuals at the highest risk of AHF in both elderly and nonelderly patients. Nevertheless, an excess of risk was also found in the mr-LVEF category in the elderly group.
Evidence Level: 2.
Technical Efficacy: Stage 2.

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Cardiovascular disease, and among it, ischemic heart disease (IHD) is the leading cause of death worldwide[1] and ST-segment elevation myocardial infarction (STEMI) represents its most severe clinical presentation.[2] While STEMI has traditionally been associated with younger patients, a paradigm shift is occurring toward an increased prevalence of elderly individuals amongst STEMI patients. Nowadays, patients over 75 years represent more than a third of the STEMI population.[3] Besides often presenting with atypical ischemic symptoms and altered baseline ECG that complicates STEMI identification, elderly patients also have a 4-fold increased risk of death or rehospitalization for acute heart failure (AHF).[4,5] Moreover, age-related factors such as comorbidities and geriatric syndromes further aggravate the prognosis of STEMI patients.[6,7]

AHF is one of the most frequent complications after STEMI[8] and substantially worsens long-term prognosis in contemporary registries.[9,10] Identifying patients at higher risk of this event is important for prescribing tailored guideline-directed medical therapies and organizing structured follow-up healthcare routes for early detection and treatment of decompensations. However, even though several predictors of post-STEMI AHF such as advanced age, diabetes, female sex or chronic kidney disease have been described,[11] identifying high-risk patients is challenging, especially in elderly individuals.

Among currently available techniques, MRI is the most reliable and reproducible method for a comprehensive evaluation of structural consequences after STEMI.[12,13] Of the many MRI-derived parameters, left ventricular ejection fraction (LVEF) is the most accurate predictor of adverse events during follow-up, including AHF.[14–16] Compared to echocardiography-derived LVEF, MRI provides precise measurement of this key parameter, which is especially relevant in patients with segmental wall motion abnormalities.[14]

MRI studies, and specifically those on MRI-LVEF, to predict AHF in STEMI patients according to age are lacking. Thus, the aim of this study was to explore the differential value of MRI-derived LVEF to predict AHF in elderly and nonelderly patients after STEMI and also to investigate the effect of transitions between LVEF categories (reduced, mildly reduced, and preserved) during follow-up in these two groups.

Materials and Methods

Study Group

Our study was derived from an ongoing prospective, multicenter registry of 759 patients discharged from three university hospitals for a first STEMI and treated with primary percutaneous coronary intervention (PCI) from 2007 to 2017. Previous analyses of this registry have been published.[14,15] Baseline clinical data, echocardiography during admission, and early (1-week) MRI were performed in all patients. Additionally, 579 patients underwent at least one follow-up MRI >3 months after STEMI, which were also analyzed. Patient characteristics including Killip class at admission, peak creatine kinase MB mass, thrombolysis in myocardial infarction (TIMI) flow grade in the culprit artery (before and after reperfusion) and Global Registry of Acute Coronary Events (GRACE) and TIMI scores were recorded. Written informed consent was provided, the research conforms to the principles of the Declaration of Helsinki and the respective local Ethics Committees approved the protocol. The flowchart of patients is shown in Fig. S1 in the Supplemental Material.

Echocardiography

Echocardiography was performed in all patients at predischarge (5 ± 2 days post-STEMI) before MRI. Local cardiologists with more than 5 years (5–35 years) of experience carried out studies, quantified parameters and prospectively included echo data in the respective databases. Left ventricular (LV) ejection fraction (LVEF, [%]), LV end-diastolic volume (mL), and LV end-systolic volume (mL) were assessed using the biplane method of disks (modified Simpson's rule). Tricuspid annular plane systolic excursion, as a proxy of the right ventricle function, was measured in the apical four-chamber view by means of the M-mode. A wave velocity (m/sec), E wave velocity (m/sec), and left atrium diameter (mm) were also measured.

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Magnetic Resonance Imaging

MRI was performed predischarge or shortly after discharge (7 ± 2 days post-STEMI) in all patients. Additionally, 579 patients underwent at least one follow-up MRI >3 months (median of 27.6 [24.6–32.1] weeks) after STEMI.

Local cardiologists specialized in MRI with a high level of experience (MPLL: 22 years, JVM: 16 years, JTOP: 18 years, and JFRP: 16 years) carried out studies and quantified parameters using customized software (QMASS MR, 6.1.5, Medis, Leiden, The Netherlands). Images were acquired by phased-array body surface coil during breathholds and were triggered by retrospective electrocardiography gating. A 1.5 T MAGNETOM® Sonata scanner (Siemens, Erlangen, Germany) was used in Hospital Clínico Universitario de Valencia – ASCIRES Biomedical Group (Valencia) and Hospital Universitari Vall d'Hebron (Barcelona), a 1.5 T MAGNETOM® Avanto scanner (Siemens) was used is Hospital Universitari Vall d'Hebron (Barcelona), and a 1.5 T MAGNETOM® Aera (Siemens) was used in Cardiothoracic Imaging – Diagnostic Imaging Center, Hospital Clínic (Barcelona). The same MRI study protocol was used, as described elsewhere.[14,15]

Cine images were acquired in two-, three-, and four-chamber views and in short-axis views using a balanced steady-state free precession sequence (repetition time/echo time: 2.8/1.2 msec; flip angle: 58°; matrix: 256 × 300; field of view: 320 × 270 mm; slice thickness: 7 mm; slice gap: 3 mm). Two hundred and fifty-six lines of k-space were acquired per cardiac phase in each cardiac cycle and 30 cine phases were reconstructed.

Late gadolinium enhancement imaging was performed 10 minutes after administering gadolinium-based contrast in the same locations as in the cine images using a segmented inversion recovery steady-state free precession sequence triggered by retrospective electrocardiography gating (repetition time/echo time: 750/1.26 msec; flip angle: 45°; matrix: 256 × 184; field of view: 340 × 235 mm; slice thickness: 7 mm; 65 phase encoding lines acquired per cardiac cycle). Inversion time was adjusted to null the signal from normal myocardium. Dimeglumine gadopentetate (Magnevist®, Bayer Pharma AG, Berlin, Germany), gadodiamide (Omniscan®, GE Healthcare, Madrid, Spain), gadobutrol (Gadovist®, Bayer Pharma AG) or dimeglumine gadobenate (Multihance®, Bracco Imaging SpA, Milan, Italy) at 0.1 mmol/kg or gadoteric acid (Dotarem®, Guerbet SA, Roissy, France) at 0.15 mmol/kg were used throughout.

LVEF (%), LV end-diastolic and end-systolic volume indexes (mL/m^2), and LV mass index (g/m^2) were calculated by manual planimetry of endocardial and epicardial borders in short-axis view cine images by the same operators. Infarct size (IS) was defined as the percentage of LV mass showing an intensity >5 standard deviations in comparison with the remote noninfarcted territory; cases were visually revised and quantified by manual planimetry. Microvascular obstruction (MVO) was defined as an area with lack of contrast uptake in the core tissue showing late gadolinium enhancement and was expressed as number of segments using the 17-segment model.[17] Interobserver and intraobserver variability for all MRI indices used in the present study are <5%.[18]

LVEF Categorization

Patients were categorized according to their MRI-derived LVEF as preserved LVEF (p-LVEF, ≥50%), mildly reduced LVEF (mr-LVEF, 41%–49%), or reduced LVEF (r-LVEF, ≤40%), following the latest guidelines on heart failure.[19] Specific analyses were performed to explore the prognostic value of these categories to predict AHF.

Endpoint and Follow-Up

The endpoint of our study was readmission for acute decompensated heart failure (AHF) after initial admission for STEMI. A total of 21 patients died before AHF occurred and were censored at that time. Events were prospectively adjudicated by clinical cardiologists via periodic review of electronic clinical records. Indications for hospitalization were worsening symptoms, signs of the disease and administration of parenteral diuretics, and patient symptoms were classified as AHF if clearly described as such by the physicians in charge.

Statistical Methods

The one-sample Kolmogorov–Smirnov test was used to test normal data distribution. For continuous parametric variables, data are expressed as mean ± standard deviation and analyzed by Student's t test. Continuous nonparametric variables are shown as median plus interquartile range and compared with Mann–Whitney U test. Qualitative variables are presented as percentages and compared by chi-square test or Fisher's exact test. Variables achieving $P < 0.1$ in univariable analysis comparing AHF and non-AHF subgroups were added as cofactors in a multivariable Cox proportional hazard regression model to predict time to AHF. A hierarchical forward stepwise model was used to avoid overfitting of variables. First, clinical baseline variables were selected for model 1. Next, model 2 included clinical baseline variables that were predictors of AHF in model 1, plus echo indices. Finally, model 3 included baseline and echo variables that were predictors of AHF in model 2, plus 1-week MRI indices. Hazard ratios (HR) with the corresponding 95% confidence intervals (CIs) were computed. The collinearity of variables tested in the final multivariable model was assessed using the variance inflation factor (inflated if >5) and its tolerance statistic (inflated if <0.20).

For nonelderly patients, variables included in model 1 were male sex, history of chronic coronary syndrome, heart rate on admission, Killip class, time to reperfusion, peak creatine kinase MB mass, anterior infarction, multivessel disease, TIMI flow grade after PCI, GRACE risk score and TIMI risk score. In model 2, we included the following variables: history of chronic coronary syndrome, Killip class, anterior infarction, TIMI flow grade after PCI, Echo-LVEF, E wave velocity, and left atrium diameter. Finally, variables included in model 3 were as follows: Killip class, anterior infarction, E wave velocity, MRI-LVEF, LV mass, MVO and IS.

In elderly patients, variables included in model 1 were heart rate on admission, Killip class, peak creatine kinase MB mass, anterior infarction, GRACE risk score and TIMI risk score. In model 2, we included the following variables: Killip class, peak creatine kinase MB mass and Echo-LVEF. Finally, variables included in model 3 were Echo-LVEF, MRI-LVEF, LV mass, MVO, and IS.

Receiver operating characteristic (ROC) curves to predict AHF were computed using the variables that predicted AHF in multivariable models in nonelderly and elderly patients. An area under the ROC curve (AUC) > 0.8 was considered excellent.[20] AUC were compared by means of Z test. To calculate the risk score in nonelderly patients, points were assigned according to the weight of the

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TABLE 1. Baseline Characteristics of the Entire Cohort and Elderly (>70 years) vs. Nonelderly Patients by Readmission for AHF Subgroup

		Nonelderly (≤70 years) Patients				Elderly (>70 years) Patients				
	All patients ($n = 759$)	All ($n = 582$)	No readmission for AHF ($n = 537$)	Readmission for AHF (n = 45)	*P* value[#]	All ($n = 177$)	No readmission for AHF ($n = 143$)	Readmission for AHF (n = 34)	*P* value[#]	*P* value[†]
Age (years)	59.39 ± 12.46	54.29 ± 9.14	54.14 ± 9.1	56.09 ± 9.57	0.17	76.17 ± 4.85	75.9 ± 4.65	77.26 ± 5.55	0.14	<0.001
Male sex (%)	622 (81.9)	506 (86.9)	471 (87.7)	35 (77.8)	0.07	116 (65.5)	98 (68.5)	18 (52.9)	0.11	<0.001
Diabetes mellitus (%)	152 (20)	97 (16.7)	88 (16.4)	9 (20)	0.53	55 (31.1)	41 (28.7)	14 (41.2)	0.22	<0.001
Hypertension (%)	364 (48)	247 (42.4)	223 (41.5)	24 (53.3)	0.16	117 (66.1)	95 (66.4)	22 (64.7)	0.84	<0.001
Hypercholesterolemia (%)	321 (42.3)	256 (44)	235 (43.8)	21 (46.7)	0.76	65 (36.7)	52 (36.4)	13 (38.2)	0.85	0.1
Smoker (%)	453 (59.7)	412 (70.8)	377 (70.2)	35 (77.8)	0.31	41 (23.2)	34 (23.8)	7 (20.6)	0.82	<0.001
History of chronic coronary syndrome (%)	67 (8.8)	50 (8.6)	43 (8)	7 (15.6)	0.09	17 (9.6)	14 (9.8)	3 (8.8)	1	0.65
Heart rate on admission (beats per min)	77.46 ± 19.41	77.78 ± 19.36	77.09 ± 19.18	86.02 ± 19.73	0.003	76.39 ± 19.59	74.36 ± 17.51	84.85 ± 25.18	0.03	0.4
Systolic pressure (mmHg)	130.23 ± 29.64	129.12 ± 28.78	129.43 ± 28.64	125.44 ± 30.44	0.37	133.88 ± 32.13	134.3 ± 32.28	132.09 ± 31.95	0.72	0.06
Killip class (%)					<0.001				<0.001	<0.001
1	633 (83.4)	506 (86.9)	475 (88.5)	31 (68.9)		127 (71.8)	112 (78.3)	15 (44.1)		
2	91 (12)	55 (9.5)	49 (9.1)	6 (13.3)		36 (20.3)	24 (16.8)	12 (35.3)		
3	20 (2.6)	14 (2.4)	8 (1.5)	6 (13.3)		6 (3.4)	4 (2.8)	2 (5.9)		
4	15 (2)	7 (1.2)	5 (0.9)	2 (4.4)		8 (4.5)	3 (2.1)	5 (14.7)		
Time to reperfusion (hours)	190 [142.75–293]	186 [140–282.5]	181 [135–279]	213.5 [170.75–345]	0.01	200 [145–332.5]	198.5 [145–312.75]	210 [156.5–396]	0.29	0.14
Peak creatine kinase MB mass (ng/mL)	189.5 [75–300]	193.15 [79–301.95]	184.3 [74.05–300]	299.6 [156–380]	0.005	184 [60.3–294.2]	161 [53.75–277.45]	273.1 [90.1–413]	0.02	0.25
Anterior infarction (%)	400 (52.7)	303 (52.1)	265 (49.3)	38 (84.4)	<0.001	97 (54.8)	71 (49.7)	26 (76.5)	0.007	0.55
Multivessel disease (%)	225 (29.6)	155 (26.6)	138 (25.7)	17 (37.8)	0.08	70 (39.5)	55 (38.5)	15 (44.1)	0.56	0.001
TIMI flow grade before PCI (%)					0.2				0.26	0.45
0	454 (59.8)	341 (58.6)	316 (58.8)	25 (55.6)		113 (63.8)	87 (60.8)	26 (76.5)		
1	49 (6.5)	40 (6.9)	34 (6.3)	6 (13.3)		9 (5.1)	9 (6.3)	0 (0)		
2	69 (9.1)	57 (9.8)	51 (9.5)	6 (13.3)		12 (6.8)	10 (7)	2 (5.9)		
3	187 (24.6)	144 (24.7)	136 (25.3)	8 (17.8)		43 (24.3)	37 (25.9)	6 (17.6)		

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TABLE 1. Continued

	All patients ($n = 759$)	Nonelderly (≤70 years) Patients				Elderly (>70 years) Patients				
		All ($n = 582$)	No readmission for AHF ($n = 537$)	Readmission for AHF (n = 45)	*P* value[#]	All ($n = 177$)	No readmission for AHF ($n = 143$)	Readmission for AHF (n = 34)	*P* value[#]	*P* value[†]
TIMI flow grade after PCI (%)					0.006				0.82	0.83
0	11 (1.4)	8 (1.4)	7 (1.3)	1 (2.2)		3 (1.7)	2 (1.4)	1 (2.9)		
1	5 (0.7)	3 (0.5)	2 (0.4)	1 (2.2)		2 (1.1)	2 (1.4)	0 (0)		
2	52 (6.9)	40 (6.9)	32 (6)	8 (17.8)		12 (6.8)	10 (7)	2 (5.9)		
3	691 (91)	531 (91.2)	496 (92.4)	35 (77.8)		160 (90.4)	129 (90.2)	31 (91.2)		
GRACE risk score	132.38 ± 32.7	123.33 ± 28.78	121.73 ± 27.7	142.36 ± 34.41	<0.001	162.14 ± 26.66	158.36 ± 25.23	178.03 ± 27.01	<0.001	<0.001
TIMI risk score	3 [1–4]	2 [1–3]	2 [1–3]	3 [2–4.5]	<0.001	5 [4–6]	5 [3–6]	6 [4.75–8]	<0.001	<0.001
Pharmacological treatment[a]										
Aspirin	713 (93.9)	551 (94.7)	508 (94.6)	43 (95.6)	1	162 (91.5)	130 (90.9)	32 (94.1)	0.61	0.07
Clopidogrel	397 (52.3)	279 (47.9)	246 (45.8)	33 (73.3)	0.002	118 (66.7)	90 (62.9)	28 (82.4)	0.02	<0.001
P2Y12 inhibitors	339 (44.7)	290 (49.8)	278 (51.8)	12 (26.7)	<0.001	49 (27.7)	44 (30.8)	5 (14.7)	0.13	0.002
Statins	695 (91.6)	530 (91.1)	490 (91.2)	40 (88.9)	0.84	165 (93.2)	133 (93)	32 (94.1)	0.58	0.37
Beta-blockers	631 (83.1)	493 (84.7)	457 (85.1)	36 (80)	0.2	138 (78)	115 (80.4)	23 (67.6)	0.04	0.02
Angiotensin-converting enzyme inhibitors	460 (60.6)	367 (63.1)	340 (63.3)	27 (60)	0.47	93 (52.5)	77 (53.8)	16 (47.1)	0.48	0.004
Angiotensin II receptor blockers	129 (17)	94 (16.2)	84 (15.6)	10 (22.2)	0.27	35 (19.8)	27 (18.9)	8 (23.5)	0.29	0.15
Mineralocorticoid receptor antagonists	135 (17.8)	91 (15.6)	72 (13.4)	19 (42.2)	<0.001	44 (24.9)	28 (19.6)	16 (47.1)	0.001	0.002
Sacubitril/valsartan	7 (0.9)	3 (0.5)	3 (0.6)	0	1	4 (2.3)	3 (2.1)	1 (2.9)	1	0.14
Loop diuretics	120 (15.8)	65 (11.2)	48 (8.9)	17 (37.8)	<0.001	55 (31.1)	40 (28)	15 (44.1)	0.02	<0.001
Anticoagulation	138 (18.2)	98 (16.8)	85 (15.8)	13 (28.9)	0.02	40 (22.6)	30 (21)	10 (29.4)	0.13	0.02

AHF = acute heart failure; GRACE = Global Registry of Acute Coronary Events; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.
[#]*P* values comparing characteristics in patients with and without readmission for AHF during follow-up within nonelderly and elderly subgroups.
[†]*P* values comparing characteristics between nonelderly and elderly patients.
[a]Pharmacological treatment was not considered for multivariable analyses to avoid protopathic, channeling and disease severity biases (eg mineralocorticoid receptor antagonists, loop diuretics, etc.).

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TABLE 2. Echocardiographic and MRI Characteristics of the Entire Cohort and Elderly (>70 years) vs. Nonelderly Patients by Readmission for AHF Subgroup

	All patients ($n = 759$)	Nonelderly (≤70 years) Patients				Elderly (>70 years) Patients				
		All ($n = 582$)	No readmission for AHF ($n = 537$)	Readmission for AHF (n = 45)	*P* value[#]	All ($n = 177$)	No readmission for AHF ($n = 143$)	Readmission for AHF ($n = 34$)	*P* value[#]	*P* value[†]
Echo indices at 1 week										
Echo-LVEF (%)	53.66 ± 10.44	54.29 ± 10.47	54.95 ± 10.11	47.41 ± 11.71	<0.001	51.72 ± 10.16	53.29 ± 9.54	45.68 ± 10.37	<0.001	0.009
Echo-LV end-diastolic volume (mL)	106.29 ± 33.53	109.4 ± 32.38	109.09 ± 32.63	112.89 ± 29.97	0.63	97.99 ± 35.29	93.79 ± 32.88	115.81 ± 40.55	0.02	0.008
Echo-LV end-systolic volume (mL)	53.3 ± 22.97	54.25 ± 22.97	53.49 ± 22.42	62.94 ± 27.76	0.09	50.79 ± 22.91	47.06 ± 20.17	66.63 ± 27.51	0.02	0.24
TAPSE (mm)	21.39 ± 3.91	21.52 ± 4	21.6 ± 4.08	20 ± 1.96	0.15	21.02 ± 3.61	20.91 ± 3.74	21.56 ± 2.94	0.51	0.29
E wave velocity (m/sec)	0.7 ± 0.21	0.71 ± 0.2	0.7 ± 0.19	0.81 ± 0.27	0.01	0.68 ± 0.24	0.67 ± 0.21	0.73 ± 0.33	0.25	0.14
A wave velocity (m/sec)	0.73 ± 0.21	0.68 ± 0.18	0.69 ± 0.18	0.67 ± 0.21	0.75	0.87 ± 0.23	0.88 ± 0.21	0.86 ± 0.31	0.77	<0.001
Left atrium diameter (mm)	36 [32–41]	36 [32–41]	36 [32–41]	38 [34.5–44]	0.04	36 [32.5–40.5]	36 [32.5–40]	35.5 [32.25–46.25]	0.46	0.84
MRI indices at 1 week										
MRI-LVEF (%)	51.85 ± 12.22	51.72 ± 12.02	52.87 ± 11.26	38.02 ± 12.4	<0.001	52.3 ± 12.9	53.99 ± 11.5	45.2 ± 15.95	0.004	0.58
MRI-LV end-diastolic volume index (mL/m^2)	78.98 ± 21.72	79.95 ± 21.9	78.98 ± 21.25	91.61 ± 26.03	0.003	75.76 ± 20.87	74.83 ± 19.92	79.67 ± 24.39	0.29	0.02
MRI-LV end-systolic volume index (mL/m^2)	39.26 ± 18.86	39.76 ± 19.09	38.18 ± 17.77	58.58 ± 23.97	<0.001	37.61 ± 18.03	35.61 ± 15.93	46.03 ± 23.5	0.02	0.18
LV mass (g/m^2)	74.58 ± 18.52	75.4 ± 19.08	74.26 ± 18.02	89 ± 25.34	<0.001	71.88 ± 16.31	70.78 ± 15.89	76.64 ± 17.49	0.06	0.03
Microvascular obstruction (*n* of segments)	0 [0–2]	0 [0–3]	0 [0–2]	3 [0–7]	<0.001	0 [0–2]	0 [0–2]	1 [0–3.25]	0.08	0.33
Infarct size (% of LV mass)	21.21 ± 14.4	21.22 ± 14.76	20 ± 13.78	35.75 ± 18.11	<0.001	21.18 ± 13.18	19.54 ± 12.13	28.07 ± 15.26	0.001	0.97

AHF = acute heart failure; Echo = echocardiography; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; TAPSE = tricuspid annular plane systolic excursion.

[#]*P* values comparing characteristics in patients with and without readmission for AHF during follow-up within nonelderly and elderly subgroups.

[†]*P* values comparing characteristics between nonelderly and elderly patients. In patients with atrial fibrillation at the time of echocardiography, E and A wave velocities were not considered for analyses.

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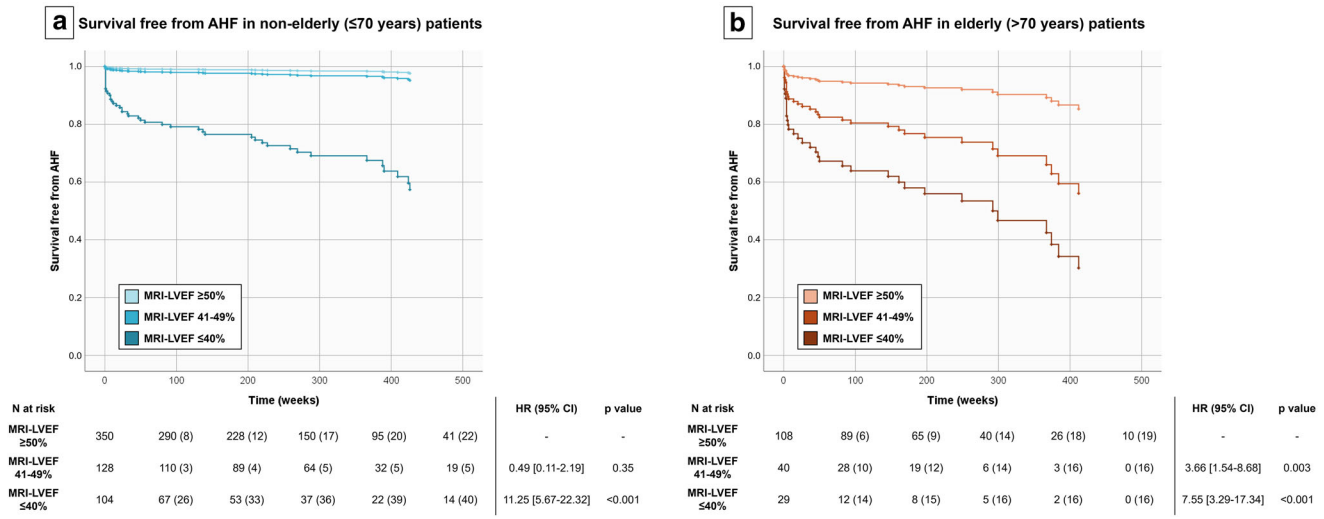

N at risk							HR (95% CI)	p value
MRI-LVEF ≥50%	350	290 (8)	228 (12)	150 (17)	95 (20)	41 (22)	-	-
MRI-LVEF 41-49%	128	110 (3)	89 (4)	64 (5)	32 (5)	19 (5)	0.49 [0.11-2.19]	0.35
MRI-LVEF ≤40%	104	67 (26)	53 (33)	37 (36)	22 (39)	14 (40)	11.25 [5.67-22.32]	<0.001

N at risk							HR (95% CI)	p value
MRI-LVEF ≥50%	108	89 (6)	65 (9)	40 (14)	26 (18)	10 (19)	-	-
MRI-LVEF 41-49%	40	28 (10)	19 (12)	6 (14)	3 (16)	0 (16)	3.66 [1.54-8.68]	0.003
MRI-LVEF ≤40%	29	12 (14)	8 (15)	5 (16)	2 (16)	0 (16)	7.55 [3.29-17.34]	<0.001

FIGURE 1: Survival curves free from AHF by 1-week MRI-LVEF category. (a) Survival curves in nonelderly (≤70 years) patients. (b) Survival curves in elderly (>70 years) patients. The HR with the corresponding 95% CIs are displayed. MRI-LVEF ≥ 50% was set as the normal reference value. AHF = acute heart failure; CIs = confidence intervals; HR = hazard ratios; LVEF = left ventricular ejection fraction.

increase in chi-square value at each step in the multivariable Cox stepwise analysis.

Incidence rates of AHF (expressed as AHF per 100 person-years) were determined. Two-tailed *P* values were obtained using mid-*P* adjustments.

As LVEF may exhibit dynamic behavior after STEMI, the continuous-time multistate Markov model was used to explore patient transition rates between LVEF states assessed by MRI along the entire observation process, and to determine the prognostic value of each LVEF state at any time point assessed to predict subsequent AHF. Patients were categorized into one of the four following states at each time point: state 1 = r-LVEF; state 2 = mr-LVEF; state 3 = p-LVEF; or state 4, if AHF occurred. Estimates from the multistate Markov model are presented as observed transitions, adjusted transition probabilities or transition intensity ratios, the latter two indices with their respective 95% CIs.

Statistical significance was defined as a two-tailed *P* value < 0.05. The SPSS statistical package (version 21.0, SPSS Inc., Chicago, Illinois), STATA (version 14.1.0, StataCorp, College Station, Texas) and R software (R Foundation for Statistical Computing, Vienna, Austria) were used throughout.

Results

Patient Characteristics

The final study group comprised 759 STEMI patients who underwent predischarge Echo and early (1 week) MRI (Fig. S1 in the Supplemental Material) after their baseline clinical characteristics had been collected. Of the entire cohort, 177 (23.3%) patients were elderly (>70 years).

Non-elderly patients were mostly male (81.9%) and smokers (59.7%) and displayed lower risk scores (mean GRACE score: 132.38 ± 32.7 points, and median TIMI score: 3 [1–4] points). Conversely, in elderly patients male sex (65.5%) and smoking habit (23.2%) were less frequent, multivessel disease was more likely (39.5%) and higher risk

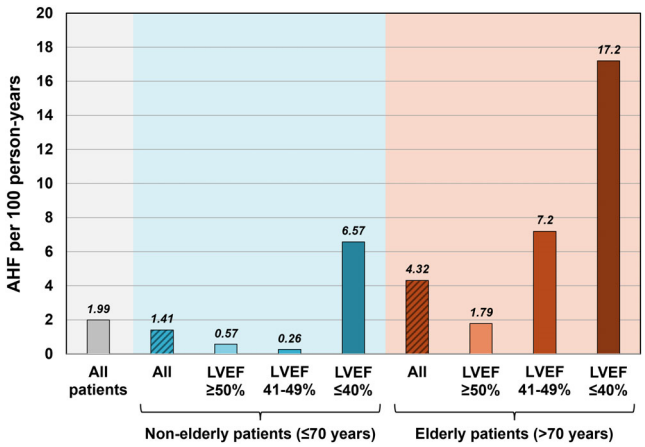

FIGURE 2: Rate of AHF per 100 person-years across 1-week MRI-LVEF categories. Results are shown for nonelderly and elderly patients. AHF = acute heart failure; LVEF = left ventricular ejection fraction.

scores were noted (mean GRACE score: 162.14 ± 26.66 points, and median TIMI score: 5 [4–6] points, Table 1). Regarding Echo and MRI indices, elderly patients depicted lower LVEF by Echo (51.72 ± 10.16 vs. 54.29 ± 10.47%) but not by MRI (52.3 ± 12.9 vs. 51.72 ± 12.02, $P = 0.58$), lower end-diastolic volumes by both Echo (97.99 ± 35.29 vs. 109.4 ± 32.38 mL) and MRI (75.76 ± 20.87 vs. 79.95 ± 21.9 mL/m^2), higher A wave velocities (0.87 ± 0.23 vs. 0.68 ± 0.18 m/s) and lower LV mass (71.88 ± 16.31 vs. 75.4 ± 19.08 g/m^2) (Table 2).

Predictors of AHF in Multivariable Analysis

Patients were followed for a median of 5 [2.33–7.54] years, during which 79 (10.4%) AHF events occurred. Nonelderly patients with AHF had a significantly higher proportion of anterior infarction, higher GRACE and TIMI scores, lower

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Echo- and MRI-LVEF, higher LV mass and more extensive MVO and IS (Tables 1 and 2). Similar results were found for elderly patients expect for LV mass and MVO, for which differences between AHF and no AHF subgroups were marginally significant ($P = 0.06$ and p = 0.08, respectively).

On multivariable analysis, in nonelderly patients Killip class at admission (HR 2.05 [1.32–3.17]), anterior infarction (HR 3.43 [1.13–10.36]) and MRI-LVEF (HR 0.94 [0.91–0.98] per increased %) independently predicted AHF during follow-up (Table S1 in the Supplemental Material). In elderly patients, MRI-LVEF was the only predictor of AHF in the final multivariable model (HR 0.94 [0.91–0.97]; Table S2 in the Supplemental Material).

The combined risk score in nonelderly patients comprised the variables that independently predicted the AHF endpoint (Killip class, anterior infarction and MRI-LVEF). This risk score showed an excellent ability to predict AHF but did not outperform MRI-LVEF alone (AUC 0.81 [0.74–0.88] vs. 0.81 [0.73–0.88]). In elderly patients, the predictive power of MRI-LVEF was moderate (AUC 0.68 [0.56–0.80]; Fig. S2 in the Supplemental Material).

Readmission for AHF Across 1-Week MRI-LVEF Categories

Patients were categorized according to 1-week MRI-LVEF as p-LVEF (≥50%), mr-LVEF (41–49%) or r-LVEF (≤40%).

In nonelderly patients, there was no significant difference in AHF-free survival between p-LVEF and mr-LVEF (HR 0.49 [0.11–2.19], $P = 0.35$ compared to p-LVEF), while significantly higher risk of AHF was observed in the r-LVEF category (HR 11.25 [5.67–22.32] compared to p-LVEF, Fig. 1a). In elderly patients, however, a risk gradient was observed for each category. Patients with mr-LVEF had a significantly increased risk of AHF compared with p-LVEF (HR 3.66 [1.54–8.68]), and patients with r-LVEF had the highest risk of AHF (HR 7.55 [3.29–17.34], compared to p-LVEF, Fig. 1b). A significant difference in risk between r-LVEF and mr-LVEF categories was noted in nonelderly patients (HR 22.8 [5.5–95.2]) and in elderly patients (HR 2.74 [1.16–6.46]).

Additionally, compared to nonelderly individuals, elderly patients showed a generalized higher risk of AHF (Fig. S3 in the Supplemental Material). For instance, elderly patients with mr-LVEF had a similar risk of AHF as their younger counterparts with r-LVEF (HR 10.94 [4.73–25.31] compared to nonelderly and p-LVEF).

The AHF rate per 100 person-years was 1.99 in the whole cohort and 1.41 and 4.32 in nonelderly and elderly patients, respectively (Fig. 2). Nonelderly patients with p-LVEF and mr-LVEF showed the lowest rate of AHF (0.57 and 0.26 per 100 person-years). In nonelderly patients with r-LVEF the AHF rate was significantly increased (6.57 per 100 person-years). In contrast, elderly patients generally had a higher AHF rate, and a gradient was observed from p-LVEF (1.79 per 100 person-years) to mr-LVEF (7.2 per 100 person-years) to r-LVEF (17.2 per 100 person-years).

The distribution across MRI-LVEF categories was analyzed in the 79 patients (45 nonelderly and 34 elderly) who presented AHF (Fig. 3). Most nonelderly patients with AHF had r-LVEF ($n = 32$, 71%). However, in elderly patients who presented AHF, LVEF was more evenly distributed between the reduced ($n = 13$, 38%), mildly reduced ($n = 11$, 32%) and preserved ($n = 10$, 30%) categories.

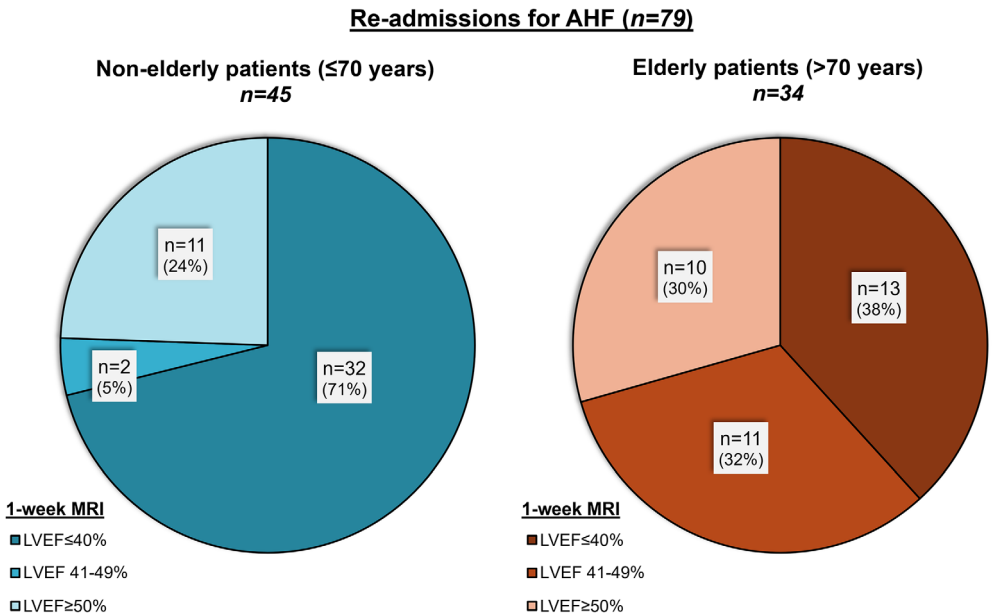

FIGURE 3: Readmissions for acute heart failure and 1-week MRI-LVEF categories. Most nonelderly patients who presented AHF had reduced (≤40%) MRI-LVEF (71%). However, in elderly patients who presented AHF, MRI-LVEF was more equally spread between reduced (≤40%, 38%), mildly reduced (41%–49%, 32%) and preserved (≥50%, 30%) categories. AHF = acute heart failure; LVEF = left ventricular ejection fraction.

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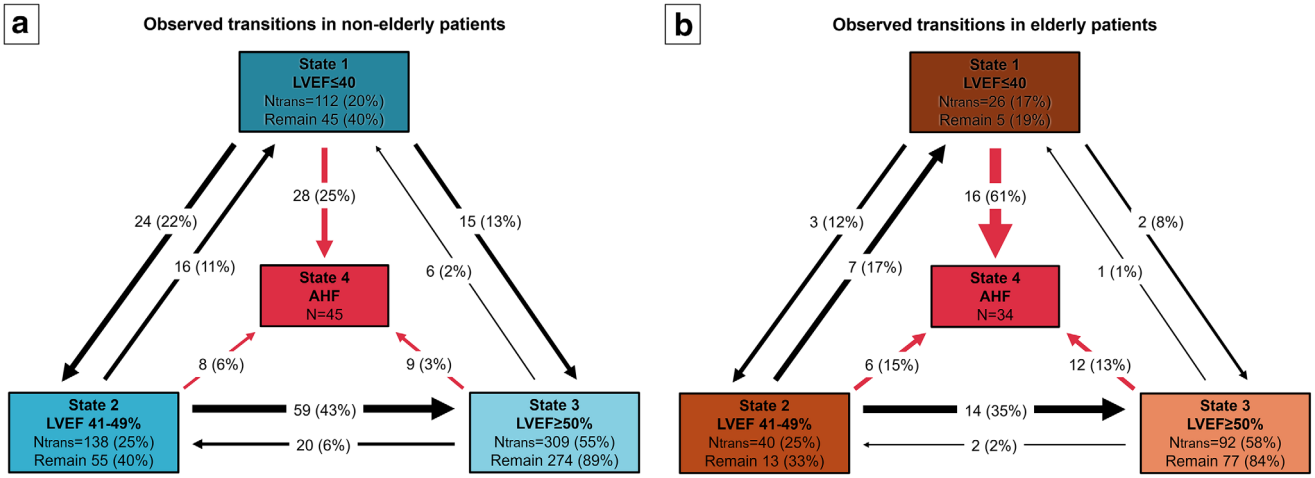

FIGURE 4: Distribution of transitions between LVEF states by follow-up MRI studies in nonelderly and elderly patients. Most transitions occur from more reduced LVEF states to more preserved LVEF states, although LVEF improvement is less frequent in elderly patients, from both state 1 (LVEF ≤40%) and state 2 (LVEF 41%–49%). The most common transition was from state 2 (LVEF 41%–49%) to state 3 (LVEF ≥50%), observed in 43% of nonelderly patients and 35% of elderly patients, whereas elderly patients in state 2 were more likely to transition to state 1 than nonelderly patients (17% vs. 11%). (a) Observed transitions in nonelderly patients. (b) Observed transitions in elderly patients. AHF = acute heart failure; LVEF = left ventricular ejection fraction.

TABLE 3. Intensity Transition Ratios Indicating Likelihood of AHF. Multistate Markov Analysis

Transitions to AHF in nonelderly patients				
Ratios	**ITR**	**Lower [95% CIs]**	**Upper [95% CIs]**	***P* value**
1–4 to 3–4	21.6	6.7	69.1	0.04
2–4 to 3–4	2.82	0.49	16.2	0.13
1–4 to 2–4	7.7	1.9	30.9	0.08
Transitions to AHF in elderly patients				
Ratios	**ITR**	**Lower [95% CIs]**	**Upper [95% CIs]**	***P* value**
1–4 to 3–4	11.65	4.52	30.04	0.02
2–4 to 3–4	2.06	0.36	11.62	0.13
1–4 to 2–4	5.65	0.88	36.37	0.15

AHF = acute heart failure; CIs = confidence intervals; ITR = intensity transition ratio.

Transitions Between MRI-LVEF Categories and Risk of AHF

The continuous-time multistate Markov model was used to analyze the transitions between LVEF categories during follow-up and their association with occurrence of AHF. Most patients (n = 579, 76.3%) underwent at least one additional MRI study >3 months after STEMI.

In nonelderly patients, most transitions occurred toward improvement in LVEF: 22% of patients in state 1 (LVEF ≤ 40%) transitioned to state 2 (LVEF 41%–49%), and 43% of patients in state 2 transitioned to state 3 (LVEF ≥ 50%) (Fig. 4). In elderly patients, transitions from state 2 to state 3 were less frequent (35%) and more patients experienced LVEF worsening from state 2 to state 1 (17%) than improving from state 1 to state 2 (12%).

Adjusted transition probabilities (Fig. S4 in the Supplemental Material) and intensity transition ratios (Table 3) are consistent with an increased risk of transition to AHF (state 4) from state 1 (LVEF ≤ 40%) in both nonelderly (ITR 21.6 [6.7–69.1]) and elderly patients (ITR 11.65 [4.52–30.04]) compared with state 3. In nonelderly patients, a nonsignificant trend was observed toward an increased risk of transition to AHF from state 1 compared to state 2 (LVEF 41%–49%) (ITR 7.7 [1.9–30.9], P = 0.08). However, in elderly patients,

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a similar risk of transition to AHF between r-LVEF and mr-LVEF categories was noted (ITR 5.65 [0.88–36.37], $P = 0.15$).

Discussion

The main findings of this study are that 1) LVEF quantified by MRI soon after STEMI is the most potent predictor of AHF during follow-up in both nonelderly and elderly (>70 years) patients but especially in the former group; 2) elderly patients show a higher risk of AHF across the whole LVEF spectrum compared to younger individuals; 3) in nonelderly patients, AHF risk was only significantly increased in the range of r-LVEF; 4) conversely, in elderly patients both r-LVEF and mr-LVEF at early MRI were associated with an incremental excess of risk of AHF; and 5) transitions between LVEF categories and AHF status indicate a more adverse profile (more transitions to lower LVEF status and to AHF) in elderly patients, which partly explains the increased risk of AHF noted in the mr-LVEF subgroup.

Consequences and Predictors of AHF After STEMI

Improved survival of STEMI patients combined with an aging population has led to an increased number of patients with heart failure, highlighting the key role of secondary prevention after STEMI.[21] Prior to the primary PCI era, AHF rates oscillated between 25% and 35%.[22] In more contemporary registries, however, AHF occurrence has decreased, probably due to the adoption of urgent reperfusion strategies which can decrease the amount of irreversible myocardial damage.[23–25] In 9406 STEMI patients between 2002 and 2008, Kaul et al found that 13.6% of the cohort developed AHF during the index hospitalization and a cumulative rate of 23.4% was noted at 1 year.[25] Other contemporary registries have shown similar AHF incidence after STEMI (9.9%–14.6%),[22–24] consistent with the incidence of this event in our cohort (10.4%).

Irrespective of the timing of presentation, either during index admission (represented by the Killip class classification) or after hospital discharge, AHF development after STEMI associates with worse long-term prognosis,[9,10] including increased mortality during follow-up.[22–24] Given its impact on prognosis, the search for reliable predictors of AHF after STEMI is important to better allocate pharmacological, logistical, and personal resources in the follow-up of patients at higher risk.

MRI for AHF Prediction after STEMI

AHF after STEMI occurs as a consequence of a plethora of factors.[8,26] Complications such as atrial fibrillation, ischemic mitral regurgitation, and diastolic dysfunction can contribute to decompensation in some patients. However, in most cases, the most potent underlying mechanism is hypothesized to be systolic dysfunction due to ischemic myocardial damage.[26] Echocardiography-derived LVEF, as the main proxy of systolic function, represents a well-validated predictor of AHF development,[27,28] so all STEMI patients should therefore undergo an echocardiogram before discharge to assess resting ventricular function and exclude mechanical complications.[29]

However, beyond first-line echocardiographic assessment, more advanced imaging techniques such as MRI can also provide additional information.[29] Indeed, MRI permits reliable, reproducible and comprehensive evaluation of structural consequences after STEMI.[12,30] Aside from parameters such as IS and MVO, evaluation of systolic function by LVEF is one of the most useful MRI prognostic markers after STEMI.[14–16] Furthermore, MRI is currently the reference standard for LVEF measurement,[31,32] especially in STEMI patients, in whom the presence of wall motion abnormalities hinders echocardiographic assessment of LVEF.[14]

The prognostic power of MRI-derived parameters in STEMI patients has consistently been shown in several studies. We have previously confirmed that predischarge MRI-derived LVEF outperforms echocardiography for predicting major adverse cardiac events, especially in patients with reduced echo-LVEF.[14] Moreover, using the STEMI-CMR score, we demonstrated that major adverse cardiac events risk can be stratified in STEMI patients by means of MRI-LVEF <40% and MVO in >1.5 myocardial segments, along with two readily available clinical variables (time to reperfusion >4.15 h and GRACE risk score > 155).[16] IS has also been associated with adverse outcomes in several registries.[33–35]

The interplay between LVEF, MVO, IS, and other structural parameters such as left ventricular remodeling is complex and incompletely defined.[36] Specifically for AHF prediction, however, our results suggest that MRI-derived LVEF assessed early after STEMI is the most robust predictor of AHF occurrence, in elderly and particularly in nonelderly patients.

Moreover, LVEF has been shown to exhibit dynamic behavior after STEMI.[15,36] Changes in LVEF generally move toward at least partial recovery, and LVEF dynamics can strongly impact on prognosis, reclassifying patient risk either downward (if LVEF improves) or upward (if LVEF worsens).[15] Indeed, in the present study, most LVEF transitions in nonelderly patients occurred toward improvement. In these patients, a higher risk of transition to AHF was noted in those with r-LVEF, either on initial assessment or during follow-up, but no increased risk of AHF was seen in the mr-LVEF category. This can be partly explained by the high proportion of patients in whom LVEF improved to p-LVEF but also by the more benign prognosis of this category *per se* in nonelderly compared to elderly patients.

AHF in Elderly STEMI Patients

Despite their increased risk of adverse events after STEMI,[4–6] elderly patients have traditionally been underrepresented in

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observational studies and clinical trials. Nonetheless, recent studies have focused on risk prediction in this population by clinical and MRI-derived parameters.[37,38] Both STEMI and AHF are more prevalent in the elderly,[39] and age is among the key clinical risk factors for developing AHF after STEMI.[26] Thus, strategies addressed specifically at identifying patients at risk of this adverse outcome stratified precisely by age are of importance.

In our cohort, 1-week MRI-LVEF was the most robust predictor of AHF. In nonelderly patients, a clear safe threshold could be established (40% MRI-LVEF), with patients having MRI-LVEF above the threshold having a low risk of AHF. This ability to stratify the population into two clearly differentiated risk populations (above vs. below 40%) gives MRI-LVEF excellent prognostic power in nonelderly individuals.

However, irrespective of LVEF category, elderly patients had an increased risk of AHF compared to nonelderly patients with similar LVEF status. Indeed, in this population the detrimental impact of any degree of LVEF worsening after STEMI was much higher, which could in part underlie the moderate predictive power of MRI-LVEF in this subset.

In elderly patients, most AHF (62%) occurred in those with p- or mr-LVEF on early MRI, whereas in nonelderly patients most AHF (71%) occurred in those with r-LVEF on early MRI. In fact, in elderly patients, not only r-LVEF but also mr-LVEF at 1-week MRI conferred an increased risk of readmission for AHF compared to the p-LVEF category. As previously commented, however, the mr-LVEF category was not associated with an increased risk of AHF in nonelderly patients.

MRI-LVEF dynamics can contribute to explaining the differential impact of LVEF on AHF occurrence across age. In elderly patients, fewer transitions occurred toward LVEF improvement, with approximately 20% of patients transitioning from mr-LVEF to r-LVEF and only around 10% improving from r-LVEF to mr-LVEF.

Thus, two factors can account for the increased risk of AHF in elderly patients across the LVEF spectrum: first, underlying structural and functional characteristics of the older heart that make AHF more likely even in mr- and p-LVEF categories, consistent with the increased prevalence of heart failure in elderly patients with mr- and p-LVEF[19,39]; and second, a higher proportion of elderly patients in which worsening (or nonrecovery) of LVEF is noted after STEMI, which places or keeps them in a more adverse risk category.

Several clinical implications of our study should be highlighted. First, early (1-week) MRI after STEMI (specifically through LVEF assessment) can provide valuable risk stratification in this population in terms of AHF prediction. Second, r-LVEF is associated with an increased risk of AHF in both nonelderly and especially in elderly patients, thus providing a rationale for closer follow-up and targeted therapies in this subgroup. Third, whereas an MRI-derived mr-LVEF finding is reassuring in nonelderly patients, elderly patients classified as such also have a statistically significant increased incidence of AHF and LVEF deterioration, which could also justify specific, structured follow-up and treatment. Lastly, given its complexity and costs, further studies should delve deeper into selection of patients eligible for early and/or follow-up MRI studies for prognostic assessment. Our study can provide some foundational evidence for patient selection and differential imaging strategies in elderly and nonelderly patients.

Limitations

Referral and survival bias cannot be excluded due to the observational nature of our study, and patients referred for MRI may not be entirely representative of the whole STEMI population. There is no well-established cut-off value to define elderly population, so a 70-year cutoff was selected in accordance with our previous experience.[7,37] A relatively low incidence of AHF was recorded in our population, although concordant with contemporary registries. Furthermore, several biochemical and clinical variables such as geriatric assessment, frailty evaluation, and other imaging parameters which could have played a role in patient prognosis were not included in the registry. Finally, changes in treatment could have influenced clinical outcomes, but an in-depth analysis of pharmacological variables is beyond the scope of the present study.

Conclusion

LVEF quantified by MRI soon after STEMI has potential to accurately predict the risk of AHF in elderly (>70 years) and especially in nonelderly (≤70 years) patients and identify those individuals at higher risk (i.e., MRI-LVEF ≤40%). Elderly patients show an increased risk of AHF across the LVEF spectrum compared to nonelderly individuals, and in this population an excess of risk is also observed in the mildly reduced LVEF category (41%–49%) on early MRI. Transitions between LVEF categories by subsequent MRI studies and AHF status represent a worse profile (more frequent transitions to lower LVEF status and to AHF) in elderly patients, emphasizing the need for improved predictive strategies in this population.

Conflict of Interest

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

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