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MAGNETIC RESONANCE

Prognostic value of a new semiquantitative score system for adenosine stress myocardial perfusion by CMR

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Abstract

Objectives Cardiovascular magnetic resonance (CMR) provides information on myocardial ischemia through stress perfusion studies. In clinical practice, the grading of induced perfusion defects is performed by visual estimation of their extension. The aim of our study is to devise a score of the degree of ischemia and to test its prognostic value.

Methods Between 2009 and 2011, patients with diagnosed or suspected coronary artery disease underwent stress perfusion CMR. A score of ischemic burden was calculated on the basis of (1) stress-induced perfusion defect, (2) persistence, (3) transmurality, and (4) stress-induced contractile defect. Follow-up was censored after 4 years and primary end-point was defined by a composite of death, heart failure episode, acute coronary syndrome, and ventricular arrhythmias. Univariate and multivariate logistic regressions were used to assess the strength of the association between the CMR ischemic variables, and the composite outcome.

Results Forty-four of the 128 patients (34%) presented with adverse events, while 84 (66%) did not. Sixty-one patients (48%) had negative perfusion studies while 67 (52%) showed perfusion defect. Patients with positive perfusion studies and adverse events ($n = 39$) had higher number of segments with persistent defect (3.3 vs 1.3, $p = 0.001$) and highest score (19.6 vs 13.3 $p = 0.012$) than patients with positive perfusion studies and absence of events ($n = 28$). The number of segments with persistent defect showed the strongest predictive value of adverse events (OR 1.54; CI 1.19–2.00; $p < 0.001$).

Conclusions The score of ischemic burden proposed herein has prognostic value. Persistence of a perfusion defect has the strongest impact on prognosis.

Key Points

- *Cardiovascular magnetic resonance provides information on myocardial ischemia by visual estimation of the presence of perfusion defects induced by stress.*
- *There is not a standardized method for grading perfusion defects which, in practice, is performed by visual estimation of their extension.*
- *As proven in this study, the integration of several parameters of perfusion defects (in addition to extension) into a semiquantitative score has prognostic value.*

Keywords Myocardium · Perfusion · Adenosine · Prognosis

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Abbreviations

CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance
CV	Cardiovascular
FFR	Fractional flow reserve
IHD	Ischemic heart disease
IQR	Interquartile range
LV	Left ventricular
MR	Magnetic resonance

PET Positron emission tomography
ROC Receiver operating characteristic
SD Standard deviation
SIB Score of ischemic burden
WMA Wall motility alteration

Introduction

One of the main indications of cardiovascular magnetic resonance (CMR) in our media is the study and stratification of risk in ischemic heart disease (IHD) [1]. A unique asset of CMR in the study of IHD lies in its ability to provide information on ventricular function, presence of necrosis, myocardial viability, and, also, inducible myocardial ischemia in a single test [2].

Adenosine stress myocardial perfusion by CMR, in particular, has shown, in studies performed over the last decade, a fairly high diagnostic accuracy for the detection of significant coronary artery stenosis, comparable to positron emission tomography (PET), and superior to conventional nuclear techniques [3–5]. Values of nearly 80% of diagnostic sensitivity and 90% of specificity have been shown in studies with invasive angiography as a reference [6, 7] and, interestingly, diagnostic specificity has improved significantly when CMR has been compared with fractional flow reserve (FFR), instead of simple quantitative coronary angiography, as a measure of the degree of coronary stenosis [8, 9]. Additionally, the adverse prognostic value of stress-induced CMR perfusion defects has been shown in follow-up studies on large series of patients [10, 11]. Accordingly, stress CMR is considered in clinical guidelines as a first-line test in those patients with suspected stable coronary artery disease (CAD), and at least an intermediate pre-test probability, provided its availability and a reasonable local expertise on the technique [12].

In clinical practice, the estimation of the degree of impairment of myocardial perfusion by any stress imaging technique is essential, as current guidelines require a certain ischemia threshold for an interventional procedure to be indicated [13]. Although sophisticated methods for CMR quantification of myocardial perfusion have been developed [14], the assessment of stress CMR studies largely relies, in practice, on a visual estimation of the presence of perfusion defects [15], while its extension to a number of myocardial segments is used as a measure of severity [16].

The aim of the present study is to test the prognostic value of a new semiquantitative score and its components as indicators of the degree of inducible ischemia. The score was devised on the basis of a series of variables obtainable from adenosine stress perfusion CMR exams. The subsequent hypothesis is, thus, that patients with higher values of this score of ischemic burden (SIB) should present with a worse prognosis at follow-up, this proving its value as a risk stratification tool.

Methods

Study design and population

Studies of stress adenosine perfusion CMR performed at our Cardiac Imaging Unit between 2009 and 2011 were included into this study. Patients studied had proven or clinically suspected CAD, the reason for the test being diagnostic, prognostic, and/or treatment planning. A history of chronic infarction or revascularization, either surgical or percutaneous, was not a cause of exclusion.

CMR study

All studies were performed on a 1.5 T scan (Magnetom Avanto®, Siemens Healthineers) according to the protocol of the Cardiac Imaging Unit [17]. Patients were continuously monitored for heart rate, blood pressure, and oxygen saturation throughout the study. After obtaining scout images, steady-state-free-precession cine MR sequences were planned on longitudinal and transverse planes of the ventricles for study of global and regional ventricular function. A myocardial perfusion study with a saturation recovery gradient-echo sequence was then obtained on three equidistant short-axis planes of the left ventricle during the first pass of a bolus of 0.1 mmol/kg of gadobutrol (Gadovist 1.0®, Bayer Global) at an infusion rate of 3 ml/s. The perfusion study was performed twice: first, after 4 min of an infusion of adenosine triphosphate (Atepodín®, Medix Laboratories) at the dose of 160 mcg/kg/min and, then, 10 min later, at rest. A requisite for a study to be included in the analysis was evidence for an adequate hemodynamic response to adenosine, which was considered to be present when the patient had reported side effects and/or when heart rate increased > 10 beats/min or systolic blood pressure decreased > 10 mmHg [18]. A series of fast cine MR sequences oriented on three short-axis slices was also obtained immediately after the stress perfusion study, with the adenosine infusion still flowing, in order to detect stress-induced regional wall motion abnormalities. Finally, a delayed contrast enhancement study was performed by means of inversion recovery sequences 5–10 min after the rest perfusion study and, thus, when a total 0.2 mmol/kg of the gadolinium compound had been given, aimed to detect the presence of areas of myocardial scarring due to previous infarction.

Analysis of CMR data

All CMR studies were re-analyzed by two observers, one of them (G.P.), with > 20 years of experience on the technique, including > 3000 adenosine perfusion studies. Dedicated software Q-Mass® version 7.5 (Medis medical imaging systems) was used for the analyses.

Cine MR sequences were used to derive ventricular volumes and function and, also, to calculate an index of regional wall motion based on the 17-segment model of the left ventricle [19], where each segment is assigned a value (1 = normal motion; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia), the mean of which is considered as the index.

Myocardial perfusion exams were visually analyzed to judge upon the presence or not of inducible first-pass perfusion defects. Perfusion images were acquired in each cardiac cycle for a total of 50 measures which is equivalent to a maximum duration of 1 min. Those linear, subendocardial defects present both in the rest and stress studies were considered as artifacts. Also, a perfusion defect at a myocardial region with a previous necrosis (as detected in the delayed enhancement study) was not considered as an inducible one. Then, the SIB was calculated as described in detail on the following section.

On delayed contrast enhancement studies, the presence of myocardial necrosis was established based on the detection of a hyperintense signal (> 5 standard deviation values of the signal intensity at a remote area) involving at least the endocardial layer of a myocardial region consistent with the distribution of a coronary artery perfusion area [15]. The global mass of myocardial necrosis was calculated by manual planimetry of the enhanced regions, and its percentage of the total left ventricular mass was calculated. Also, and as a simplified measure of scar burden weighting both extension and transmurality, a necrosis index was obtained as the mean of values assigned to each of the 17 myocardial segments, according to the pattern of enhancement: 1 = absent; 2 = non-transmural (< 50% of wall thickness); and 3 = transmural (> 50% of wall thickness).

Calculation of the score of ischemic burden

We considered a series of variables from the adenosine stress perfusion studies as indicative of the degree of induced perfusion defects and, as such, directly linkable to the severity of myocardial ischemia. Accordingly, the integration of these variables into a final score should constitute a semiquantitative measure of the ischemic burden in individual patients. The SIB was obtained from the assignment of values to 16 of the 17 segments of the left ventricle (the apex is not visualized in the perfusion sequence protocol), depending on the presence or not of the following variables: (1) stress-induced perfusion defect (0 = absent; 1 = present); (2) persistence of the defect through the duration of the whole perfusion sequence (0 = transient; 1 = persistent); (3) transmurality (0 = < 50% of wall thickness; 1 = > 50%); and (4) stress-induced contractile defect (0 = absent; 1 = present). Values should range, thus, between 0 (absent perfusion defect) and 64 (highest theoretical score), the final SIB being given as a percentage of this maximum. Figure 1 shows an example of calculation of the SIB in a case of stress-induced defect.

Follow-up and event definition

The clinical records of the patients were retrieved and analyzed for the occurrence of events. In case of lack of clinical information over the last 3 months at the time of review, patients were contacted by phone. The primary end-point was defined by a composite of all-cause death, heart failure episode, acute coronary syndrome, and ventricular arrhythmias. Follow-up was available in all patients, which was censored after 4 years.

Statistical methods

Categorical variables are presented as frequencies, and the differences between groups were assessed using the chi-squared or Fisher's exact test whenever necessary. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed or as median and interquartile range (IQR) if not, and differences were accordingly compared using the *t* test or the Mann–Whitney *U* test.

Time-to-event distribution using Kaplan–Meier curve was estimated for each parameter, splitting the cohort into two groups for each parameter: (a) for the presence of stress-induced perfusion defect, we stratified the cohort by its mean; (b) for the remaining parameters, we stratified the cohort by those presenting the parameter in one or more segments and those without any alteration. The differences between time-to-event distributions were assessed using the log-rank test.

Univariate logistic regression analysis was used to preliminary assess the predictive value of the CMR ischemic variables. Multivariate logistic regression analyses were performed to identify independent predictors on four separate models: (a) model A included the presence of ischemic defects; (b) model B considered two parameters (presence and persistence); (c) model C included presence, persistence, and transmural defect parameters; and (d) model D included the performance of those four parameters being evaluated (presence of ischemic defects, persistence of ischemic defects, transmural defect parameters, and inducible regional function defects). A receiver operating characteristic (ROC) curve for each model was constructed in order to compare their corresponding area under the dependent ROC.

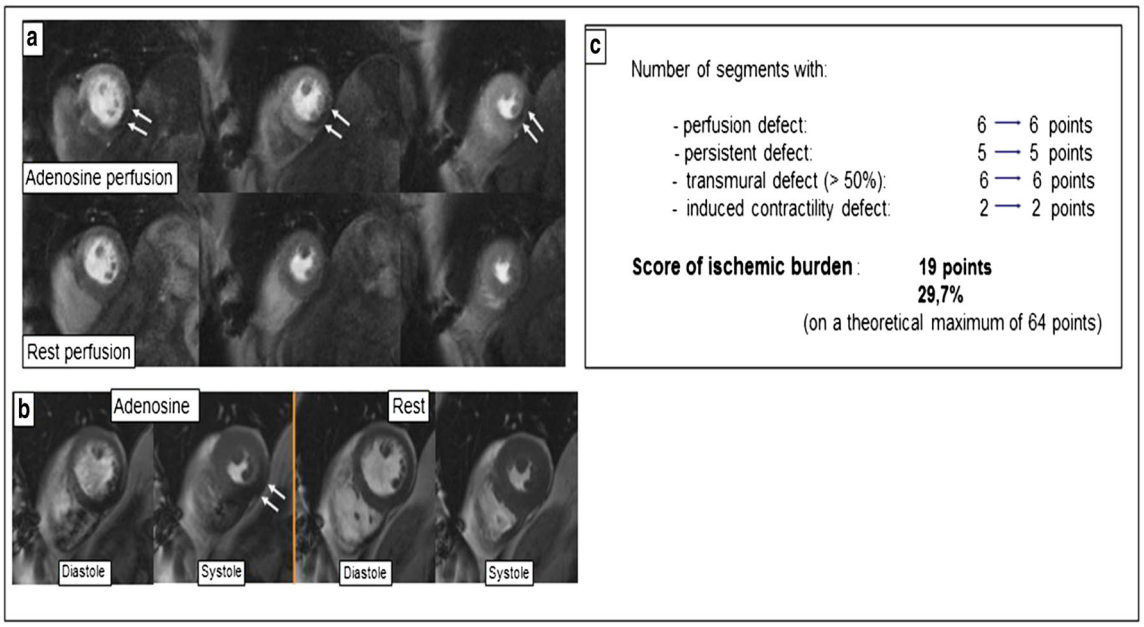

Fig. 1 Example of calculation of the score of ischemic burden, based on the 16 myocardial segment scheme. In the adenosine perfusion sequence (**a**, top panel) a transmural defect is detected (arrows) at the inferior and infero-lateral basal, medial, and apical segments, which is not seen at rest (**a**, bottom panel). Also, a stress-induced contractile defect is visualized (see arrows in the systolic frame during adenosine, in panel **b**), which, again, is not detected at rest (compare with the corresponding systolic frame at rest, also in panel **b**. The calculation of the Score considers also the persistence of the defect throughout the whole duration of the perfusion sequence (not shown), giving in this case an absolute value of 19 (29.7% of the theoretical maximal burden (panel **c**)

Two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS version 20.0 (IBM Analytics). STATA software version 13.1 (Stata Corp LLC) and GraphPad Prism version 6.00 (GraphPad Software) were used to produce the graphs.

Results

A total of 128 patients with technically adequate CMR perfusion studies were identified and selected as study group. Follow-up showed that 44 patients (34%) had presented with adverse events, while 84 (66%) had not.

With respect to demographics and clinical variables (Table 1), patients with a history of smoking and those with previous cardiovascular disease were significantly more prevalent among the group with adverse events at follow-up compared with those without.

With regard to CMR data (Table 2), there were no differences in left ventricular volumes or function between patients with or without adverse events. Patients presenting with adverse events, however, had a larger area of myocardial necrosis compared with those without (10.3 ± 15.3 vs. 5.0 ± 8.9 g, $p = 0.037$) and, in consequence, also higher percentages of infarcted left ventricular mass (6.8 ± 9.6 vs. $3.5 \pm 6.0\%$, $p = 0.047$) and higher necrosis index (1.3 ± 0.3 vs. 1.2 ± 0.2, $p = 0.04$).

CMR stress perfusion studies from the whole study group were negative in 61 patients (48%), while 67 (52%) showed abnormal results (any degree of perfusion defect). Time-to-event analyses using Kaplan–Meier curve estimates showed significant differences between those patients with presence of perfusion defect involving ≥ 3 segments and those without any perfusion defect (Fig. 2a). Similarly, differences were seen when patients with persistent perfusion defects were compared with those with either normal perfusion or with non-persistent defects (Fig. 2b), and, although not significant, also a trend towards statistical significance was observed for the association between the outcome and the presence of transmural defects (Fig. 2c) or with associated inducible regional function defect (Fig. 2d) compared with those with either normal or perfusion defects without these features.

Table 3 depicts the association between each CMR parameter and adverse outcome in those 67 patients with at least one inducible perfusion defect. There were significant differences regarding the number of segments with persistent defect (mean of 1.3 vs 3.3, $p = 0.001$) and the SIB (mean 13.3 vs 19.6, $p = 0.012$). On the contrary, no differences were shown with respect to the number of segments with defective stress perfusion, the number of segments with transmural defects, or the induction or not of regional function defect during stress.

From univariate logistic regression analysis, the number of segments with persistent perfusion defect showed to be the feature with the strongest association with adverse events (OR 1.54; CI 1.19–2.00; $p < 0.001$) followed by the SIB

Table 1 Demographic and clinical variables of the study group

	All patients ($n = 128$)	Adverse events ($n = 44$)	No adverse events ($n = 84$)	p value
Age (years)	66.9 ± 10.8	69.1 ± 10.6	65.8 ± 10.8	0.106
Male gender, n (%)	98 (76.6)	33 (75)	65 (76.5)	0.853
Diabetes, n (%)	44 (34.4)	20 (45.5)	25 (29.8)	0.077
Hypertension, n (%)	95 (74.2)	36 (81.8)	59 (70.2)	0.155
Dyslipidemia, n (%)	88 (68.8)	35 (79.5)	53 (63.1)	0.057
Smoker, n (%)	58 (48.3)	39 (88.6)	62 (72.9)	0.040
Previous CV disease, n (%)	100 (78.1)	28 (63.6)	38 (44.7)	0.041
Revascularization, n (%)	66 (51.6)	23 (59)	35 (42.7)	0.094

Categorical variables are presented as frequencies, and the differences between groups were assessed using the chi-squared. Continuous variables are expressed as mean ± standard deviation (SD) and compared using the t test

(OR 1.07; 95% CI 1.01–1.12; $p = 0.016$). However, the remaining features of the perfusion studies (i.e., number of segments with defect, segments with transmural defects, or with stress-induced function defect), did not show statistically significant association with adverse prognosis (Fig. 3).

At multivariate analysis, ROC curve for model A (presence of perfusion defect) showed an area under the curve (AUC) of 0.62 (CI 0.49–0.76); for model B (presence and persistence of defect), the AUC was 0.72 (CI 0.59–0.85); for model C (presence, persistence, and transmurality of defect), AUC was 0.74 (CI 0.62–0.86); and for model D (presence, persistence, transmurality, and inducible functional defect), AUC was 0.76 (CI 0.67–0.88). Although no significant differences were shown when AUC from model A was compared with the rest of models (Table 4), the progressive addition of features implies a substantial gain in the predictive value of models that might be clinically relevant in assisting clinicians to better assess the prognostic value of the CMR in this context.

Discussion

The information contained in the CMR sequences of myocardial perfusion can be useful in assessing the severity of inducible defects and their subsequent impact on prognosis. Among a series of parameters considered in the present study, persistent perfusion defects had the strongest predictive value of adverse events.

Several previous studies have proven the prognostic value of the presence of stress-induced CMR perfusion defects [10, 11, 20, 21]. The analysis of first-pass studies in these reports has relied mainly on visual assessment of the extension and transmurality of defects. Based on these results, CMR stress perfusion is a rational choice in current clinical practice and, moreover, it is expected to become a first-line test for purposes of stratification and treatment planning after the results of an ongoing comparison study with invasive angiography including fractional flow reserve [22].

Advances in the technique and the analysis of CMR perfusion studies should improve the reliability of the method, as has been shown with high resolution sequences [23], or with 3D sequences allowing for a full coverage of the left ventricle [9]. Also, the use of quantitative methods for the analysis of first-pass studies [24] has resulted in an improved diagnostic accuracy of significant coronary artery stenosis when compared with qualitative techniques. Quantitation of myocardial perfusion by CMR, however, is technically demanding and not highly

Table 2 CMR data (excluding perfusion study data)

	All patients ($n = 128$)	Adverse events ($n = 44$)	No adverse events ($n = 84$)	p value
LV end-diastolic volume, ml	157.2 ± 59.9	158.6 ± 52.0	156.1 ± 63.7	0.820
LV end-systolic volume, ml	69.1 ± 51.5	72.3 ± 46.6	67.2 ± 53.8	0.575
LV ejection fraction, %	59.1 ± 15.3	57.6 ± 16.4	54.9 ± 14.6	0.414
Regional Wall motion index	1.5 ± 2.1	2.0 ± 3.7	1.3 ± 0.4	0.266
Necrotic LV mass, g	6.8 ± 11.8	10.3 ± 15.3	5.0 ± 8.9	0.037
Necrotic LV mass percent, %	4.6 ± 7.6	6.8 ± 9.7	3.5 ± 6.0	0.047
Necrosis index	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.2	0.040

All CMR were assessed by two observers, these values illustrate their consensus. Variables are expressed as mean ± standard deviation (SD). Comparisons were performed using the t test

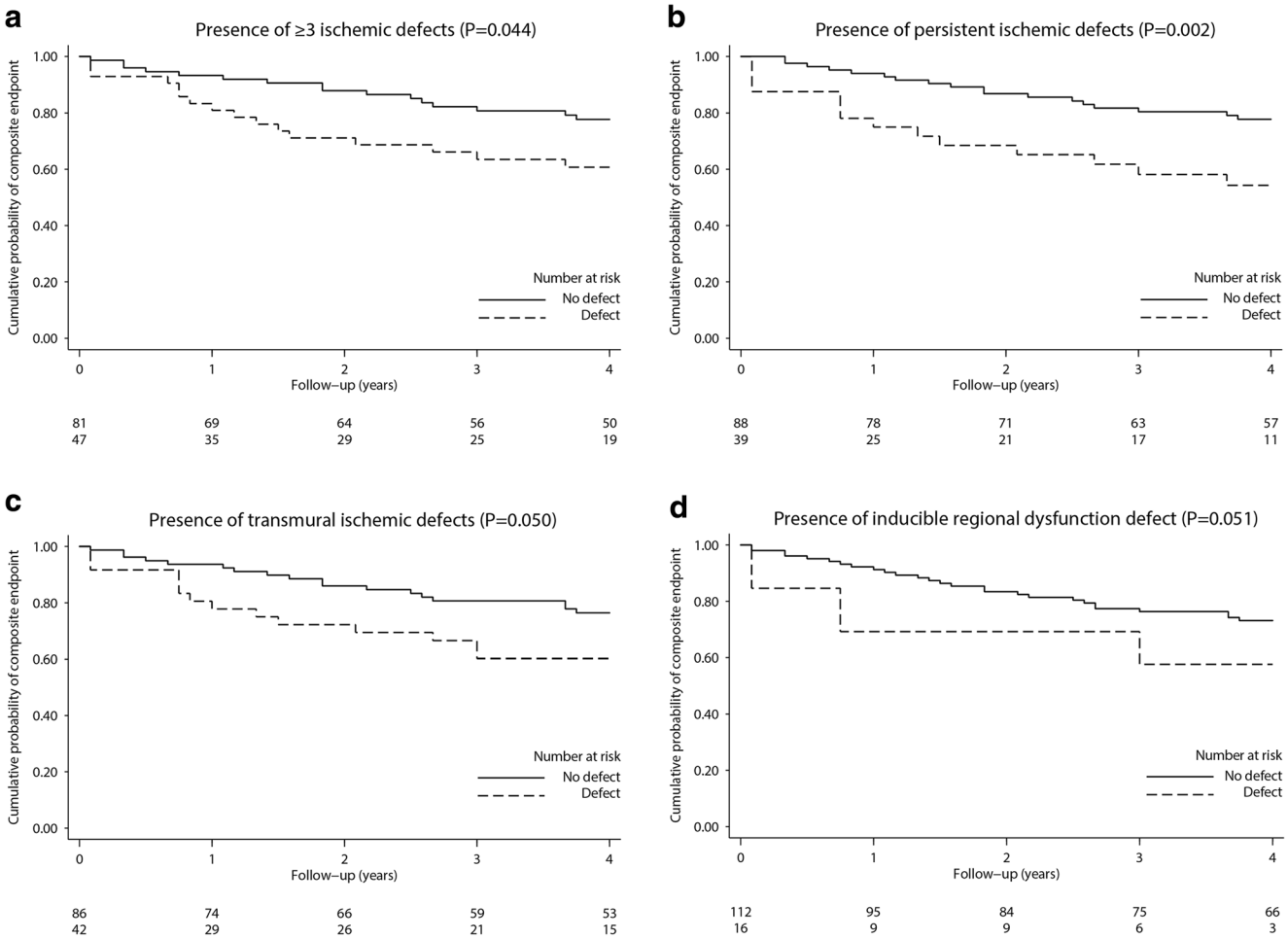

Fig. 2 Kaplan–Meier survival curves for presence (dotted line) vs absence (continuous line) of at least one segment involved in each parameter of the SIB. Kaplan–Meier curve was estimated for each parameter, splitting the cohort into two groups for each parameter: **a** for the presence of stress-induced perfusion defect, we stratified the cohort by its mean; **b** for the remaining parameters, we stratified the cohort by those presenting the parameter in one or more segments and those without any alteration. Comparisons were evaluated using the log-rank test

accurate in practice, as absolute perfusion values have been shown to correlate weakly with PET results [25]. In addition, quantitation of perfusion and calculation of myocardial reserve have shown only a modest inter-study reproducibility [26].

Thus, there is room for further refinement of semiquantitative analysis of first-pass CMR perfusion sequences. Advantages of the conventional perfusion sequences are their wide availability, the large experience of most clinical groups, and the reliability of visually estimated features of the sequence. Among them, we choose to consider, as related with the severity of the defect, its extension, degree of transmurality, persistence, and the association of wall motion abnormalities.

Table 3 CMR perfusion parameters in those patients with positive studies ($n = 67$)

	Adverse events ($n = 39$)	No adverse events ($n = 28$)	p value
Segments with *any* stress perfusion defect	6.4 (3.46)	5.2 (3.33)	0.11
Segments with *persistent* stress perfusion defect	3.3 (2.56)	1.3 (1.62)	0.001
Segments with *transmural* stress perfusion defect	2.3 (2.07)	1.6 (2.07)	0.101
Segments with stress-induced *function* defect	1.1 (2.14)	0.9 (2.24)	0.397
Score of ischemic burden (SIB)	19.6 (10.16)	13.3 (9.59)	0.012

All CMR were assessed by two observers, these values illustrate their consensus. Data are expressed as mean and SD, although their statistical significance was tested using the Mann–Whitney U test

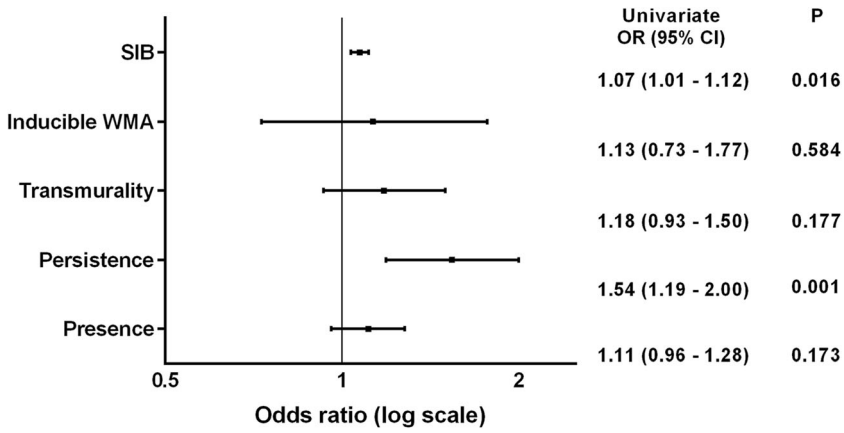

Fig. 3 Univariate logistic regression analysis to assess the prognostic value of each CMR stress perfusion parameters in patients with ischemic defects ($n = 67$). Presence refers to at least one perfusion defect. Univariate logistic regression analysis was used to assess the strength of the association between CMR ischemic variables and the composite outcome

A finding from this study that contrasts with previous ones is the lack of prognostic value of the mere presence of perfusion defects by themselves. This may be explained, in our view, by the fact that the present study was not addressed to this aim, as patients were retrospectively selected, and those with potential confounding factors (i.e., myocardial necrosis) were not excluded. However, we demonstrate that patients with greater extension of ischemia (three or more segments with perfusion defect) have a worse prognosis than those with inducible defects limited to one or two myocardial segments. With regard to the features of first pass perfusion studies considered, its progressive inclusion led to an increased prognostic value of the model, as shown at the multivariate analysis, this leading to a significant predictive value of the SIB. One of these features, however, emerges as the strongest in terms of prognosis, as is the persistence of a visually detectable defect along the entire duration of the perfusion sequence, which is roughly 1 min, depending on the heart rate of the patient. The dynamics of the CMR perfusion sequence helps to understand, in our view, this finding, as a persistent first-pass defect should mean a particularly severe impairment in blood inflow to a myocardial bed. Interestingly, as our study shows, this feature has more impact than other seemingly reliable indicators of severity of inducible ischemia, as the extension of the defect or its degree of transmural involvement. As with regard to the induction of contractile defect, and in contrast with previous reports using dipyridamole as stressor agent [27, 28], we did not find this to have prognostic value. When observed, this feature should plausibly indicate a more advanced step in the ischemic cascade and, thus, more severe impairment. Inducible contractile defects, however, are relatively unusual in a 4-min protocol of adenosine perfusion studies, even in cases with extensive defects. We hypothesize that this discrepancy may be due to the much shorter half-life of adenosine in comparison with dipyridamole, which could prevent the ultimate development of contractile dysfunction.

Table 4 Predictive value of four models of defective perfusion studies in a multivariate logistic regression analysis

	Area	CI 95%	*p* value
Model A (defect present)	0.624	0.487–0.761	0.085
Model B (A + persistent)	0.722	0.592–0.851	0.002
Model C (B + transmural)	0.742	0.621–0.864	0.001
Model D (C + contractile defect)	0.764	0.674–0.882	<0.001

A receiver operating characteristic (ROC) curve for each model. The *p* value was constructed in order to compare their corresponding area under the dependent ROC

There is one main limitation inherent to our semiquantitative score, as is the lack of statistical power to better define all those CMR predictors of events within a single risk score. However, the relative weight of different features of myocardial perfusion studies is proven, which may enlighten future research on CMR predictors. Both the importance of persistent perfusion defects and the combination of several CMR features into a single score are novel findings and may help to further develop tools to stratify patients according to their prognosis.

In conclusion, the consideration of several features of myocardial first-pass stress CMR studies allow for the calculation of a global semiquantitative score of ischemic burden which has prognostic value. Among its components, the persistence of a perfusion defect along the whole duration of the sequence has the strongest impact on prognosis.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent ethical approval Written informed consent was not required because our study was designed as a descriptive one with retrospective collection of CMR and follow-up data which were available on the clinical recordings of the center. As such, no therapeutic measures were undertaken on the basis of the data review nor any additional medical visit was elicited as a result of the analyses.

Ethical approval Institutional Review Board approval was not required because our study was designed as a descriptive one with retrospective collection of CMR and follow-up data which were available on the clinical recordings of the center. As such, no therapeutic measures were undertaken on the basis of the data review nor any additional medical visit was elicited as a result of the analyses.

Methodology
- Retrospective
- Observational
- Performed at one institution

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