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Correlation between Myocardial Microalternans Index and Left- Ventricular Ejection Fraction in Stable Coronary Artery Disease

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Short Report

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Abstract

Background

Left ventricular ejection fraction (LVEF) is a widely accepted prognostic marker in coronary artery disease (CAD), yet echocardiography is only available in specialized settings. The Myocardial Microalternans Index (MMI), derived from ECG-dispersion mapping, may offer a simple screening tool. We evaluated the correlation between MMI and echocardiographic LVEF and determined an MMI threshold to identify reduced LVEF (< 40%).

Methods

We conducted a single-centre, cross-sectional study of patients with stable CAD. MMI was measured using the HealthEXPRESS™ system (Medical Computer Systems, Russia). LVEF was obtained by transthoracic echocardiography (biplane Simpson). We assessed the correlation using Spearman correlation and a prespecified partial rank correlation adjusting for clinical covariates. Discrimination for LVEF < 40% was evaluated by ROC analysis.

Results

Among 146 patients (median age 60 years; 82% male), 64% had prior myocardial infarction and 70% had left ventricular hypertrophy. Median LVEF was 48% (IQR 35–60) and median MMI 19% (IQR 16–30). Reduced LVEF (< 40%) occurred in 36% patients. MMI showed a significant, moderate inverse correlation with LVEF (Spearman $r = -0.524$; $p < 0.001$), which remained significant after adjustment with history of myocardial infarction and presence of left ventricular hypertrophy (partial $r = -0.46$; $p < 0.001$). The ROC AUC for MMI to classify LVEF < 40% was 0.78. An MMI cutoff ≥ 24% yielded 63.3% sensitivity and 80.4% specificity.

Conclusion

MMI is moderately and inversely associated with LVEF, and an MMI ≥ 24% moderately discriminates reduced LVEF in stable CAD, MMI could support triage and referral in resource-limited settings. Validation in multicentre and prospective cohorts is warranted.

Background

Left ventricular ejection fraction (LVEF) is one of the most widely accepted prognostic indicators in patients with coronary artery disease (CAD) [1]. In large cohorts, each 10-percentage-point decrease in LVEF < 45% is associated with 39% higher all-cause mortality [2]. Indonesia ranks sixth globally in

cardiovascular disease burden and contributes a substantial share within Southeast Asia, highlighting the need to extend cardiovascular care across all levels of the health system [3]. Although earlier identification of left ventricular dysfunction enables guideline-directed therapy that improves outcomes, diagnosis is often delayed because patients are frequently not screened in specialized centre using echocardiography until symptoms develop [4]. Developing accessible screening tools suitable for primary care settings may improve early detection of left ventricular dysfunction in Indonesia [5].

Technological innovations involving computer-based algorithms, machine learning, and artificial intelligence (AI) have garnered interest for their potential to enable cardiovascular assessment in remote and resource-limited settings [6]. Recent AI-enabled electrocardiography (ECG) models can screen for reduced ejection fraction (LVEF < 40%) with AUC: 0.90–0.93 and sensitivity/specificity around 85–86% illustrating a credible benchmark for non-echocardiographic screening [7]. The HealthEXPRESS™ (Medical Computer Systems, Russia) system takes different approach; it integrates ECG with algorithm-based ECG dispersion mapping to quantify micro-fluctuations in cardiac electrical activity during depolarization and repolarization phases. The resulting parameter, termed the Myocardial Microalternans Index (MMI), is intended to reflect myocardial electrical instability and is displayed in a color-coded, patient-friendly format (3–5-minute recordings [8]. Presenting results in such an easy-to-read format may enhance patients awareness and engagement with care [9].

While small experimental and clinical studies suggest that MMI has association with myocardial ischemic abnormalities and prognosis in patient with critically ill [10]. However, the correlations between MMI and LVEF in stable CAD are under-characterized. This study aims to investigate the correlation between MMI and LVEF in individuals with stable CAD and evaluate its correlation after prespecifying adjustment for key confounders. We therefore evaluate the diagnostic performance of MMI to predict LVEF < 40%. Given its portability and simplified user interface, we assess whether MMI could serve as an accessible, user-friendly, non-invasive surrogate for LV systolic function in primary care.

Methods

Study design and setting

We conducted a single-centre, cross-sectional study of consecutive adults attending the outpatient cardiology clinic of Dr. Hasan Sadikin General Hospital (Bandung, Indonesia), a tertiary referral hospital, between **February 1, 2021 and July 31, 2025**.

Participants

Patients were eligible if aged 18–80 years and had **stable CAD** confirmed by prior invasive coronary angiography (≥50% stenosis in ≥1 major epicardial vessel), with no ischemic symptoms or acute coronary syndrome within the preceding **30 days**. We excluded permanent atrial fibrillation, pacemaker

or cardiac resynchronization therapy, primary valvular heart disease or prior valve replacement, hemodynamic instability, inability to provide consent, and **incomplete key data** (MMI or LVEF).

Variables and operational definitions

Myocardial Micro-alternans Index (MMI, %) recorded with HealthEXPRESS™ (Medical Computer Systems Ltd., Moscow). After a 15–30-min seated or supine rest, four limb electrodes were placed (deriving the six limb leads I, II, III, aVR, aVL, aVF). A 3-min recording at rest was obtained; patients were instructed to remain still and silent. Dispersion mapping is obtained based on mapping data in changes in the magnitude of electrical micro-voltages from ECG signals; then micro-vibration analysis is performed on changes in amplitude levels when approaching the point where myocardial stability is compromised. Electrophysiological abnormalities in pathological conditions will cause amplitude changes and precede conventional ECG changes. The electrocardiographic characteristics of dispersion mapping are described in 9 analyzed sections, namely G1–G9, which reflect the magnitude and localization of electrophysiological disturbances in the atrial and ventricular myocardium in the depolarization and repolarization periods. The device outputs an index from 0–100%; we used the average across artifact-free segments. Devices were **daily-calibrated** per manufacturer guidance. the HealthEXPRESS™ sytem sets cut off of MMI ranges of normal (< 15%), borderline (15–21%), and pathological (> 21%) [11].

Left ventricular ejection fraction (LVEF, %) data taken from the most recent transthoracic echocardiogram within **≤30 days** of the MMI measurement was used, quantified using **biplane Simpson's method** and averaged across three cardiac cycles. The LVEF was analyse by echocardiography consultant that **blinded to MMI**. The analysis was performed in GE EchoPAC workstation. LVEF was analysed as continuous and, secondarily, categorised as **<40% (reduced), 40–49%, ≥50%**.

Prespecified covariates: age (years), sex (male/female), body mass index (BMI) (kg/m²), hypertension (prior diagnosis or antihypertensive use), diabetes (prior diagnosis, or glucose-lowering therapy), dyslipidaemia (diagnosis or lipid-lowering therapy), smoking (never/former/current), prior myocardial infarction (MI) (>30 days), prior percutaneous coronary intervention (PCI) and prior coronary artery bypass graft (CABG) (yes/no), Presence of three vessel disease (yes/no), presence of left main disease (yes/no), presence of significant proximal left anterior descending artery lesion (yes/no), presence of chronic total occlusion, and presence of left ventricular hypertrophy.

Statistical analysis

Baseline characteristics are summarized as mean±SD or median (IQR) and n (%). Normality was assessed by Shapiro–Wilk. Primary association: Spearman's rank correlation (r) between MMI and LVEF. Multiple linear regression conducted to found the key confounder associated with MMI and LVEF. Partial Rank Spearman correlation between MMI and LVEF adjusting for prespecified covariates (prior MI and presence of left ventricular hypertrophy). We evaluated MMI for classifying reduced LVEF (<40%) using

ROC analysis with AUC and 95% CI by DeLong. The optimal threshold was selected by Youden's J with 95% CI obtained via bootstrap. All tests are two-sided, α=0.05. Analyses were performed in IBM SPSS v25.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and applicable institutional regulations. Ethical approval was granted by the Research Ethics Committee (Komite Etik Penelitian) of Dr. Hasan Sadikin General Hospital (RSUP Dr. Hasan Sadikin), Bandung, Indonesia, under Ethical Approval No. DP.04.03/D.XIV.6.5/10/2026

Results

Patient Characteristics

A total of 146 patients with stable CAD underwent MMI evaluation using the HealthEXPRESS™ system. The median age was 60 years, and the majority of patients were male (82%). A history of myocardial infarction was present in 93 patients (64%). About 33 patients (22%) not undergo revascularization. Significant proximal left anterior descending (LAD) artery lesions were observed in 118 patients (81%). No left ventricular hypertrophy (LVH) observed in 39 pateints (27%). The median LVEF was 48%, with 53 patients (36%) demonstrating reduced LVEF. The median MMI was 19, with 50 (37%) has pathologic MMI >21. Patient characteristics are summarized in Table 1.

Table 1. Patient Characteristics

Variable	Total (n=146)
Age, years (median, IQR)	60 (53 - 65)
Male	120 (82%)
BMI (mean, ± SD)	24,7 ± 3,98
Cardiovascular Disease History	
Hypertension	92 (63%)
Diabetes	34 (23%)
Dyslipidaemia	76 (52%)
Smoking	107 (73%)
History of myocardial infarction	93 (64%)
History of revascularization	
PCI	64 (44%)
CABG	49 (34%)
Not undergo revascularization	33 (22%)
Coronary Lesion Characteristics	
Three Vessel Disease	93 (64%)
Left Main Disease	44 (30%)
Significant Proximal LAD Lesion	118 (81%)
Chronic Total Occlusion Lesion	47 (32%)
LVH	
No LVH	44 (30%)
LVH	102 (70%)
LVEF (median, IQR)	48 (35 - 60)
LVEF Categories	
LVEF >=50	68 (47%)
LVEF 41-49	25 (17%)
LVEF =<40	53 (36%)
MMI (median, IQR)	19 (16 - 30)
MMI < 15	6 (4%)

MMI 15 - 21	90 (59%)
MMI >21	50 (37%)

- *Note:* Values presented are median (Interquartile range), mean ± standard deviation, or frequency (percentage).
- Abbreviations: BMI, body mass index; CABG, Coronary Artery Bypass Graft; LAD, Left Anterior Descending artery; LVEF, Left Ventricular Ejection Fraction; LVH, Left Ventricular Hypertrophy. PCI, Percutaneous Coronary Intervention.

Correlation Between MMI and Patient Characteristics

Correlation test was conducted using Spearman test, There was a significant negative correlation between MMI and LVEF. There was a weak relationship between MMI with BMI (Spearman r = −0.208), history of myocardial infarction (Spearman r = 0.235), and presence of LVG (Spearman r = 0.175). There was a moderate relationship between MMI and EF (Spearman r = −0.524, p < 0.001) (Table 2), indicating that higher myocardial electrical instability was associated with lower ejection fraction. A linear regression analysis also revealed a weak to moderate inverse linear relationship (R^2 = 0.215) (Figure 1). Multiple linear regression conducted to evaluate key confounder associated with MMI and LVEF. We found that history of myocardial infarction (B = −7.797, p = .004, -13.018 - -2.576 95%CI) and the presence of LVH (B = −7.997, p = .003, - 13.283 - -2.711 95%CI) considered as key confounders (Table 3). After adjusting with confounders, the correlation between MMI and LVEF remained significant (Partial rank correlation r=-0.461, p<0.001) (Figure 2), suggesting an independent correlation between MMI and LVEF.

Table 2. Correlation Between MMI and Patient Characteristics

Variable	*r*	p value
Age	0.037	0.661
Gender	0.027	0.748
BMI	-0.208	0.015
Cardiovascular Disease History		
Hypertension	-0.014	0.870
Diabetes	0.095	0.252
Dyslipidaemia	-0.085	0.304
Smoking	0.012	0.887
History of myocardial infarction	0.235	0.004
History of revascularization	-0.029	0.728
LVH	0.175	0.035
Lesion Characteristics		
Three Vessel Disease	0.029	0.724
Left Main Disease	-0.023	0.781
Significant Proximal LAD Lesion	0.088	0.288
Chronic Total Occlusion Lesion	0.116	0.162
LVEF	-0.524	<0.001

- Abbreviations: BMI, body mass index; LAD, Left Anterior Descending artery; LVEF, Left Ventricular Ejection Fraction.

Table 3. Correlation Coefficients of Patients Characteristic

Variables	Standardized Cofficients	p
Age	0.147	0.068
Gender	0.029	0.725
BMI	0.136	0.095
Hypertension	0.81	0.314
Diabetes	-0.117	0.107
Dyslipidaemia	0.153	0.050
Smoking	-0.30	0.736
History of myocardial infarction	-0.236	0.004
History of revascularization	0.087	0.227
LVH	-0.226	0.003
Three Vessel Disease	-0.089	0.251
Left Main Disease	-0.011	0.889
Significant Proximal LAD Lesion	0.091	0.248
Chronic Total Occlusion Lesion	-0.05	0.947

- Abbreviations: BMI, body mass index; LAD, Left Anterior Descending artery; LVEF, Left Ventricular Ejection Fraction..

Prediction of Reduced Left Ventricular Ejection Fraction

Receiver Operating Characteristic (ROC) analysis demonstrated a good discriminative ability of MMI in predicting severely reduced ejection fraction (EF < 40), with an AUC of 0.78. The optimal cutoff value was identified at MMI ≥ 24, yielding a sensitivity of 63.3% and a specificity of 80.4%, indicating a balanced performance with emphasis on ruling out false positives (Figure 3).

Discussion

In this single-centre, cross-sectional study of patient with stable CAD, higher MMI showed a moderate inverse correlation with LVEF after adjustment for history of myocardial infarction and presence of LVH (partial rank correlation r=-0.461, p<0.001). Using ROC analysis, MMI >24% could discriminated reduced LVEF <40% with an AUC of 0.78 (sensitivity 63.3%, specificity 80.4%).

Our study extend prior work that primarily linked the Myocardial Microalternans Index (MMI) to myocardial ischemia by showing that higher MMI also tracks impaired left-ventricular systolic function in

stable CAD. The HealthEXPRESS systems produces MMI that integrates standard ECG signals with dispersion mapping via algorithmic analysis. In a prioneer studies, the HealthEXPRESS system result as color coded heart portrait output detected ischemia with 79% sensitivity and 63% specificity [12]. By translating the color coded to MMI value in ischemic event, elective PCI studies showed that balloon inflations demonstrating significant changes in MMI values from baseline level [13]. In pilot population study with suspected CAD, an MMI >21 combined with other abnormal HealthEXPRESS parameters predicted a positive treadmill ischemic response (sensitivity 83%, specificity 82%), potentially shifting pretest probability for CAD [14]. Taken together, along with our study, this findings suggests that dispersion-based electrical instability indexed by MMI reflects not only inducible ischemia but also reduced LV systolic function.

Ventricular systolic function depends on adequate perfusion, oxygen delivery, and mitochondrial ATP production that couples cellular energetics to contraction (mechano-energetic coupling) [15]. Under ischemic stress, reduced oxygen shifts metabolism toward anaerobic pathways, lowers ATP, increases reactive oxygen species (ROS), and disrupts ionic currents and calcium handling, which increases the spatial and beat-to-beat dispersion of ventricular depolarization and repolarization [16]. In parallel, heart-failure remodeling adds mitochondrial dysfunction, oxidative and endothelial stress, and contractile inefficiency [17]. These electrophysiologic consequences manifest as beat-to-beat microvariability in ventricular activation and recovery, which ECG dispersion mapping quantifies; accordingly, greater dispersion presents as a higher Myocardial Microalternans Index (MMI) [8]. Consistent with this mechanism, animal models show increased activation/repolarization dispersion during coronary occlusion, providing a mechanistic substrate for elevated MMI [18]. Taken together, elevated MMI can be interpreted as a noninvasive electrophysiologic marker of ischemia-related mitochondrial dysfunction that accompanies impaired systolic performance.

While causality cannot be inferred from our cross-sectional design, the observed moderate inverse correlation between MMI and LVEF suggests that MMI indexes dispersion-based electrophysiologic instability that accompanies impaired systolic function. Clinically, LVEF is essential to risk stratification in CAD, and patients with LVEF < 40% have higher mortality [19]. In our study, MMI > 24% discriminated LVEF < 40%. Consistent with our findings, in an acutely ill with mixed etiology patients, has demonstrated MMI values greater than 24% were associated with an increased risk of one-year mortality [20]. Additionally, MMI has been shown to significantly correlate with fibrosis/arrhythmia biomarker ST2 levels in patients with ischemic cardiomyopathy [21]. Given the observed mechanism a study that evaluate combined model of MMI and LVEF to predict major adverse cardiac event is needed. Also, MMI reduction could be studied to measure the treatment effect. These hypotheses are testable in prospective, multicenter cohorts with repeated MMI/LVEF measures and adjudicated outcomes.

In practice, MMI ≥ 24% should prompt expedited echocardiography. Serving as an adjunct rather than a replacement for standard assessment. This approach aligns with efforts to expand early cardiovascular screening using user-friendly technologies to reduce mortality and improve clinical outcomes [22]. Also

color coded heart potrait resulting from Health express could improve patient awareness[9]. Future prospective studies should evaluate the net clinical benefit, and whether MMI-guided pathways improve outcomes.

This study has several limitations that should be acknowledged. This single-center, CAD-only cohort constrains generalizability; however, the narrow setting enhanced protocol uniformity and reflects the intended early use case in primary care. We did not analyze 12-lead ECGs, intentionally avoiding circularity with MMI to test its stand-alone association with LVEF. Electrolyte level were not collected, however participants were clinically stable enrolling. We lacked non-CAD controls because the aim was within-CAD risk stratification. The cross-sectional design precludes causal inference yet is appropriate for first-phase analytical validation; prospective, longitudinal cohorts with repeated MMI/LVEF and outcomes will clarify temporality and clinical utility. Finally, the MMI 24% cutoff was internally derived under a pre-specified rule; external validation and potential recalibration are planned to confirm transportability and net clinical benefit.

Conclusion

This study demonstrates a moderate inverse correlation between MMI and LVEF: higher MMI corresponds to lower left-ventricular systolic function. In our study, an MMI cutoff 24% identified patients with reduced LVEF. Given its user-friendly, color-coded output, MMI could support primary-care screening of CAD patients for reduced LVEF and enable timely referral for echocardiography. Beyond prior links with ischemia, our findings indicate that MMI also reflects systolic function. However, the cross-sectional, single-center design and homogeneous population constrain causal inference and generalizability. Also, the proposed cutoff requires external validation. Prospective, multicenter studies that enroll diverse populations including patient with non-ischemic cardiomyopathy are needed to enhance the correlation between MMI with LVEF. If validated, MMI could complement existing risk-stratification pathways to identify patients who warrant timely imaging.

Declarations

Author Declarations

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and applicable institutional regulations. Ethical approval was granted by the Research Ethics Committee (Komite Etik Penelitian) of Dr. Hasan Sadikin General Hospital (RSUP Dr. Hasan Sadikin), Bandung, Indonesia, under Ethical Approval No. DP.04.03/D.XIV.6.5/10/2026

Consent to Participate

Written informed consent was obtained from all participants prior to data collection.

Consent for Publication

All participants provided consent for the use of anonymized quotes/data for publication.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy restrictions, but are available from the corresponding author on reasonable request and with permission from the ethics committee.

Competing interests

The authors declare no competing interests.

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Authors' contributions

N.F.T and B.B.T wrote the main manuscript text, C.J.C and D.P.W prepared the figures and tables, M.R.A and C.A sharpening the discussion and conclusion. All authors reviewed the manuscript.

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Figures

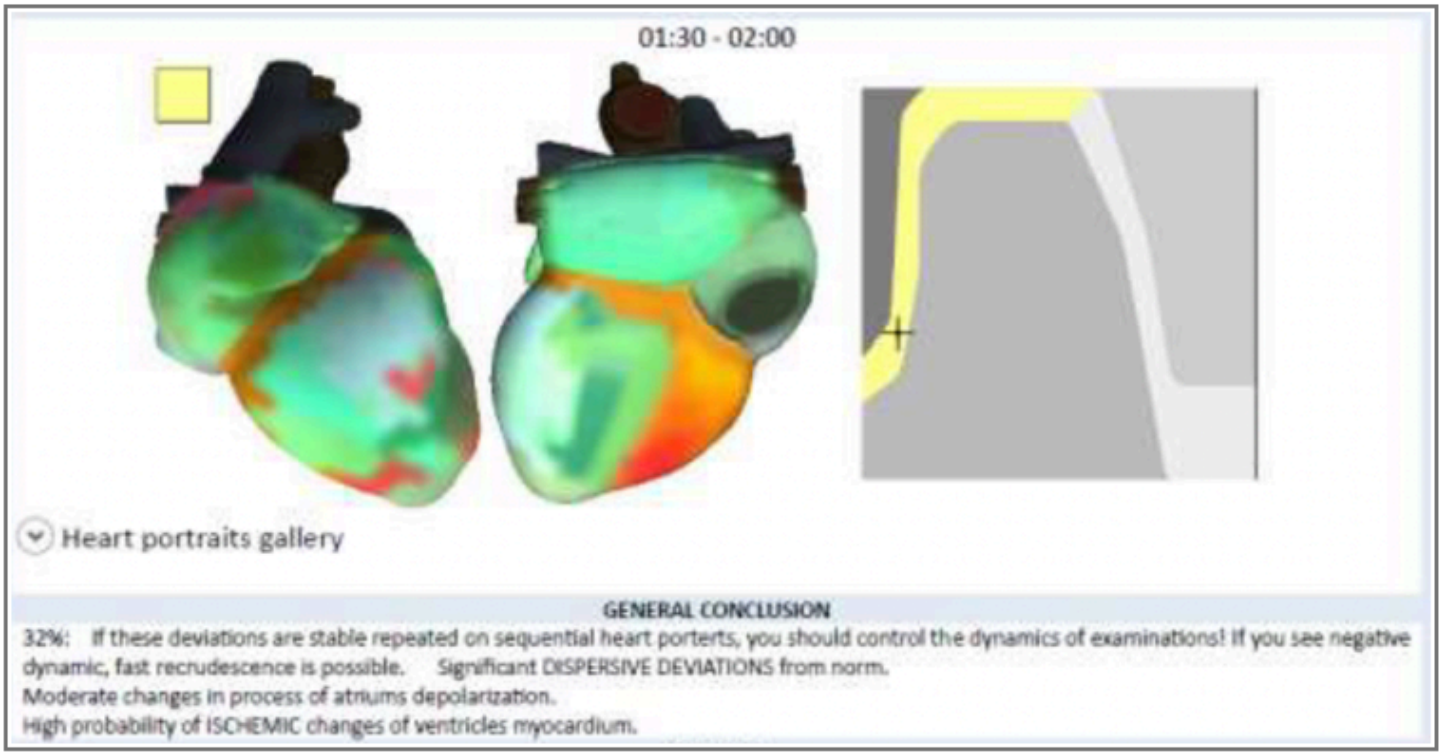


Figure 1

Example of MMI result reflecting MMI 32% with colour coded heart potraits (adapted from the HealthEXPRESS™ sytem manual book)

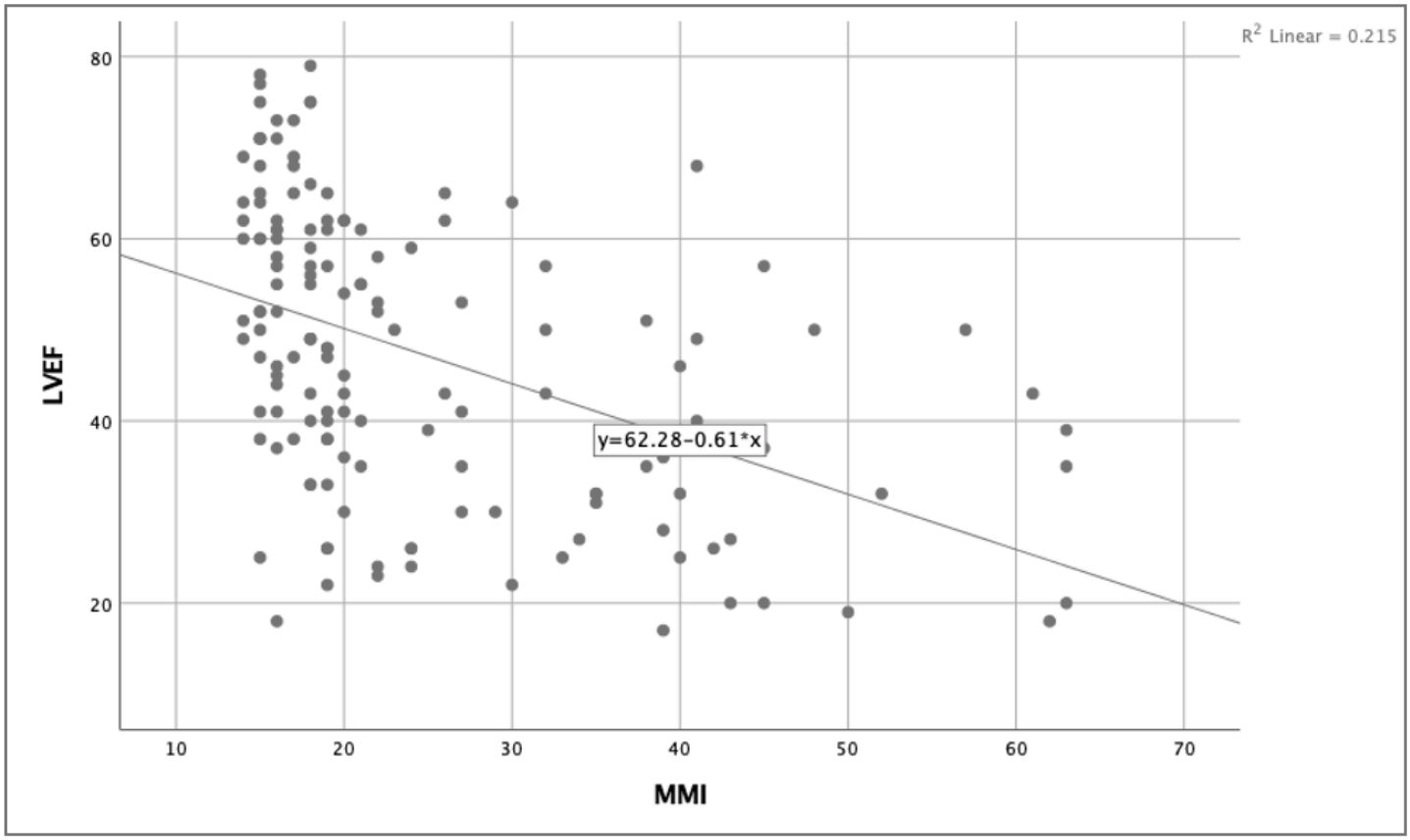


Figure 2

Scatter plot of MMI vs. EF with fitted linear regression line ($R^2 = 0.215$). A significant negative monotonic correlation was found (Spearman's $\rho = -0.524$, $p < 0.001$).

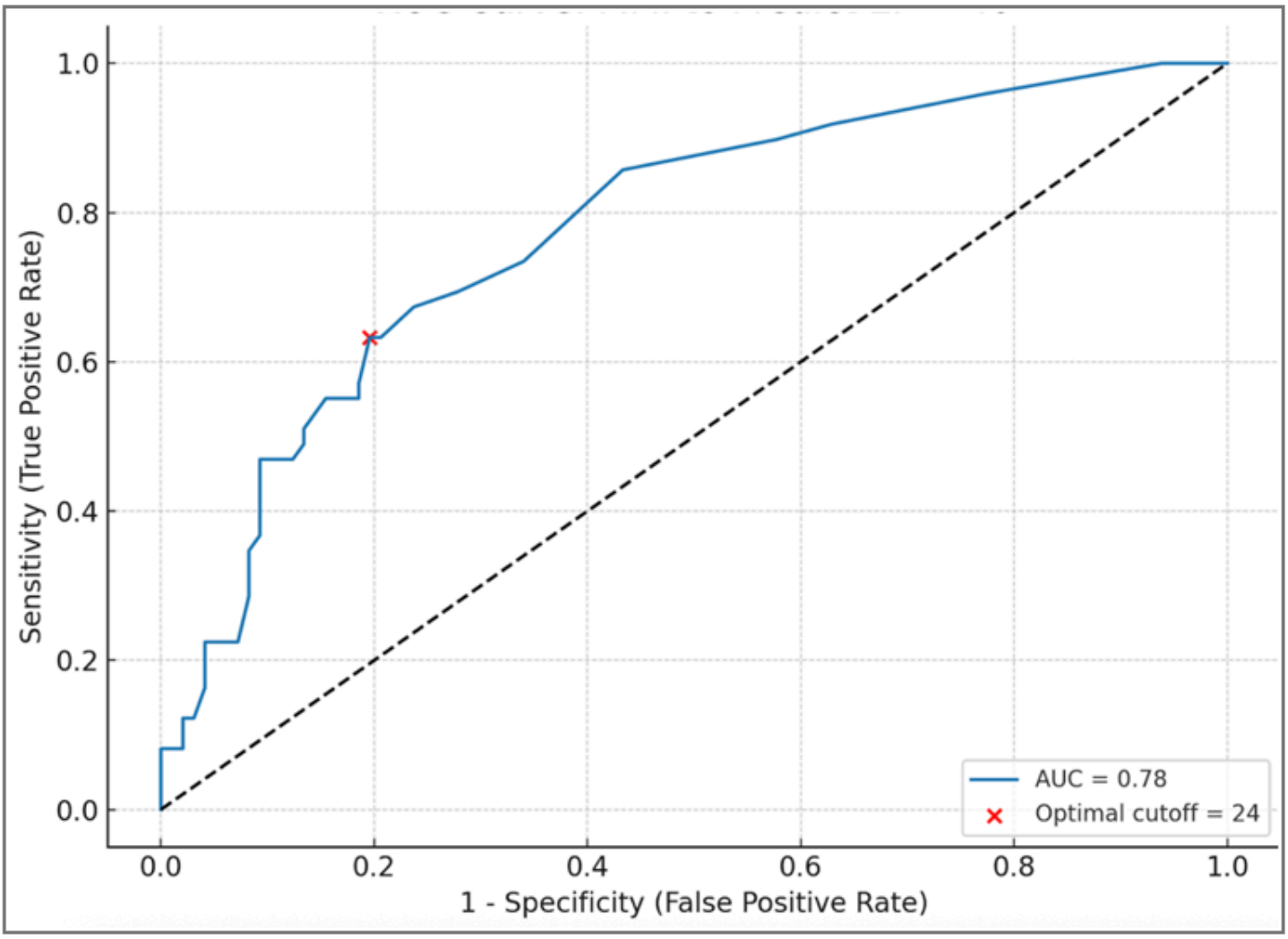


Figure 3

ROC curve of MMI for predicting EF < 40. The AUC was 0.78, and the optimal cutoff was MMI ≥ 24 (sensitivity 63.3%, specificity 80.4%).