ORIGINAL ARTICLE

Noninvasive Detection of Functional Myocardial Ischemia: Multifunction Cardiogram Evaluation in Diagnosis of Functional Coronary Ischemia Study (MED-FIT)

Tetsuma Kawaji, M.D.,* Hiroki Shiomi, M.D.,* Takeshi Morimoto, M.D., Ph.D.,† Ryusuke Nishikawa, M.D.,* Mariko Yano, M.D.,* Hirooki Higami, M.D.,* Junichi Tazaki, M.D.,* Masao Imai, M.D.,* Naritatsu Saito, M.D.,* Takeru Makiyama, M.D.,* Satoshi Shizuta, M.D.,* Koh Ono, M.D.,* and Takeshi Kimura, M.D.*

*From the *Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan and †Division of General Medicine, Department of Internal Medicine, Hyogo College of Medicine, Japan*

Background: Multifunction cardiogram (MCG) is a computer-enhanced, resting electrocardiogram analysis developed to detect hemodynamically relevant coronary artery disease (CAD). Based on data from previous studies suggesting excellent diagnostic accuracy in detecting CAD, MCG (approved by the Food and Drugs Administration) received a Current Procedure Terminology (CPT) code in 2010 in United States. However, there is no previous study validating MCG by using fractional flow reserve (FFR) as the reference standard.

Methods: Multifunction cardiogram Evaluation in Diagnosis of Functional coronary Ischemia sTudy (MED-FIT) was designed as a single-center, prospective study enrolling 100 stable patients with suspected CAD scheduled for coronary angiography. The primary and secondary analyses evaluated the diagnostic performance of the MCG severity score to detect functional myocardial ischemia by FFR ≤0.80, and angiographically significant coronary stenosis (percent diameter stenosis ≥50%) by quantitative coronary angiography.

Results: The current analysis set consisted of 91 patients in whom MCG data with adequate quality was obtained. The prevalence of positive functional myocardial ischemia and angiographically significant stenosis in the current study was 42.7% and 41.8%, respectively. Area under the receiver operating characteristics curve (AUC) of the MCG severity score for functional myocardial ischemia and angiographically significant stenosis was low (AUC 0.51, 95% confidence interval [CI] 0.38–0.63, and AUC 0.58, 95%CI 0.46–0.70, respectively). Sensitivity, and specificity of the MCG severity score for functional myocardial ischemia and angiographically significant stenosis was also low (32%/67%, and 37%/72%) using a cutoff value of 4.0.

Conclusions: Diagnostic performance of the MCG severity score was poor for both functional myocardial ischemia, and angiographically significant stenosis.

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MCG; coronary artery disease; noninvasive diagnosis; myocardial ischemia

Current guidelines for the management of stable coronary artery disease (CAD) recommend documenting myocardial ischemia with a noninvasive functional test (e.g., single photon emission

Address for correspondence: Takeshi Kimura, M.D., Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Tel: +81-75-751-4254; Fax: +81-75-751-3289; E-mail: taketaka@kuhp.kyoto-u.ac.jp

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Table 1. Baseline Characteristics

Clinical Characteristics	N = 91
Age (years)	71.2 ± 10.6
Age ≥ 75	44 (48.3%)
Male	67 (73.6%)
Height (cm)	161.2 ± 9.3
Body weight (kg)	60.9 ± 11.4
BMI ≥25 (kg/m^2)	15 (16.5%)
Hypertension	63 (6.9%)
Calcium channel blocker use	40 (44.0%)
Dyslipidemia	64 (70.3%)
Diabetes mellitus	24 (26.4%)
Current smoking	21 (23.1%)
Family history	5 (5.5%)
Typical angina	24 (26.3%)
Updated Diamond–Forrester risk score	55.3 ± 21.0
Intermediate (20–80%) pretest risk	70 (76.9%)
Atrial fibrillation	6 (6.6%)
Previous PCI	28 (30.8%)
Previous CHF	6 (6.6%)
Hemoglobin ≤ 11 (g/dL)	9 (9.9%)
eGFR ≤ 30 (mL/min/1.73 m^2)	2 (2.2%)
Ejection fraction (%)	67.2 ± 9.7
Ejection fraction ≤ 55%	7 (7.7%)
LVDd ≥ 55 (mm)	2 (2.2%)

Data are presented as number of patients (prevalence). Continuous variables are presented as mean ± SD.
BMI = body mass index; ECG = electrocardiogram; PCI = percutaneous coronary intervention; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; and LVDd = left ventricular diameter at end diastolic phase.

computed tomography [SPECT], stress echocardiography, or cardiac magnetic resonance imaging) before considering invasive coronary angiography.[1] However, these noninvasive imaging technologies have been validated by using the angiographically significant stenosis as the reference standard, although they are regarded as functional tests to detect myocardial ischemia.[2–4] Fractional flow reserve (FFR) measured by using intracoronary pressure wire, which assesses the ratio of flow across a stenosis to putative flow in the absence of a stenosis, has been regarded as the accepted reference standard for detecting myocardial ischemia. Several prospective randomized trials demonstrated that FFR-guided percutaneous coronary intervention (PCI) successfully distinguished patients and coronary lesions that will benefit from coronary revascularization from those that will not.[5–7] Diagnostic accuracy of both SPECT and stress echocardiography for functional myocardial ischemia was reported to be relatively poor when FFR was used as the reference standard.[8,9]

Multifunction cardiogram (MCG: Multifunction Cardiogram version 2.1.1; Premier Heart, LLC, Port Washington, NY, USA) is a computer-enhanced, resting electrocardiogram (ECG) analysis developed to detect hemodynamically relevant CAD noninvasively. Based on data from previous studies suggesting excellent diagnostic performance in detecting CAD, MCG (approved by the Food and Drugs Administration [FDA] received a Current Procedure Terminology (CPT) code in 2010 in United States.[10–14] However, there is no previous study validating MCG by using FFR as the reference standard for functional myocardial ischemia. Therefore, we designed a prospective single-center study (Multifunction cardiogram Evaluation in Diagnosis of Functional coronary Ischemia sTudy [MED-FIT]) to evaluate the utility of noninvasive MCG in detecting functional myocardial ischemia by using FFR as the reference standard.

METHODS

Study Design

MED-FIT was designed as a single-center, prospective study under physicians' leadership enrolling 100 stable patients with suspected CAD scheduled for invasive coronary angiography in Kyoto University Hospital from April to October 2013. We excluded those patients who could not tolerate bed rest in the supine position for 20 minutes during measurement of MCG. Exclusion criteria included acute coronary syndrome, prior coronary artery bypass grafting, severe valvular heart disease, electrocardiographic evidence of prior myocardial infarction, and patients taking medications known to affect the MCG score such as nitrates and beta-blockers. Patients with prior PCI were included if PCI had been performed at least 3 months before MCG measurement.

The primary purpose of this study was to assess diagnostic performance of the MCG severity score to detect functional myocardial ischemia by FFR as well as angiographically significant coronary artery lesion by quantitative coronary angiography (QCA).

The study protocol was approved by the ethics committee in Kyoto University Hospital and written informed consent was obtained from all the patients before MCG measurement. The study

Table 2. FFR and QCA Results

FFR	Target Vessels N = 89
Positive for functional ischemia	38 (42.7%)
Qualified by FFR ≤ 0.8	15 (16.9%)
Qualified by angiography only	23 (23.8%)
Location of the Culprit Lesion	
LAD	28 (31.5%)
LCX	6 (6.7%)
RCA	4 (4.5%)
Negative for functional ischemia	51 (57.3%)
Qualified by FFR >0.8	24 (27.0%)
Qualified by angiography only	27 (30.3%)
QCA	**Target Lesions N = 91**
Minimum lumen diameter (mm)	1.3 ± 0.7
Reference diameter (mm)	2.6 ± 0.5
Lesion length (mm)	13.8 ± 8.8
%DS (%)	51.6 ± 24.1
Angiographic stenosis %DS ≥ 50%	38 (41.8%)

Data are presented as number of patients (prevalence). Continuous variables are presented as mean ± SD.
FFR = fractional flow reserve; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; QCA = quantitative coronary angiography; and %DS = percent diameter stenosis.

sponsor, the distributor of the MCG device in Japan (TORAY Medical Co., Ltd., Tokyo, Japan), was not involved in the design of the study protocol, data collection, analysis, and writing of the manuscript. The manuscript was submitted after giving a notice to the sponsor.

MCG Analysis

MCG records a two-lead resting ECG from leads II and V_5 for 82 seconds in each session using proprietary hardware and software with patients quietly lying supine following 20 minutes of bed rest. ECG data are analyzed with frequency analysis of ECG without electrical noise filters and the digitized ECG data are encrypted and securely transmitted over the Internet to the central server in New York.

At the server, a series of Discrete Fourier Transformations are performed on the data from the two ECG leads followed by signal averaging. The final averaged digital data segment is then subjected to six mathematical transformations (power spectrum, coherence, phase angle shift, impulse response, cross-correlation, and transfer function) in addition to an amplitude histogram, all of which is used to generate indexes of abnormality. The resulting patterns of the indexes are then compared for abnormality to the patterns in the reference database to reach a final diagnostic output. In addition to the automatic differential diagnosis based on the database comparison, a severity score from 0 to 20 is calculated that indicates the level of myocardial ischemia (if present) resulting from CAD.

We measured MCG within 48 hours before coronary angiography. The quality of MCG data ("good," "marginal," or "poor") was indicated for each session. We excluded those patients whose quality of MCG was "poor" in all the sessions evaluated. We sent the ECG data with "good" or "marginal" quality to the server via the Internet. Data were analyzed by the Premier Heart with clinical and angiographic information of the patients blinded to the analysts. We received the report indicating the automatic differential diagnosis, and the MCG severity score for each session. We used the average value of MCG severity score in two or three sessions for analysis. As a sensitivity analysis, we also used the maximum MCG severity score.

Coronary Angiography and FFR Measurement

Coronary angiography was performed by using 5 or 6 French diagnostic catheter with either transradial or transfemoral approach by the certified interventional cardiologists who were blinded to the results of MCG results. To assess FFR, we used a 0.014-inch pressure wire (CertusG7, CertusG8 or AerisG8, St. Jude Medical Inc., St Paul, Minesota, USA and PrimeWire PRESTIGE PLUS, Volcano Inc., San Diego, CA, USA). Aortic pressure was measured by a guiding catheter ≥6 French. Maximum hyperemia was induced by intravenous adenosine 150 μg/kg/min after crossing of the pressure wire through the target vessel. Functional myocardial ischemia in this study was evaluated by using minimum FFR value within 3 minutes after adenosine infusion.

Actual FFR measurement was to be performed in patients with coronary artery lesion with percent diameter stenosis (%DS) of 30–99% and vessel size >2 mm by visual estimation. FFR value ≤0.8 in any vessel was considered to be positive for functional ischemia. When functional ischemia was positive in one vessel, further FFR measurement for the remaining vessels in the same patient was

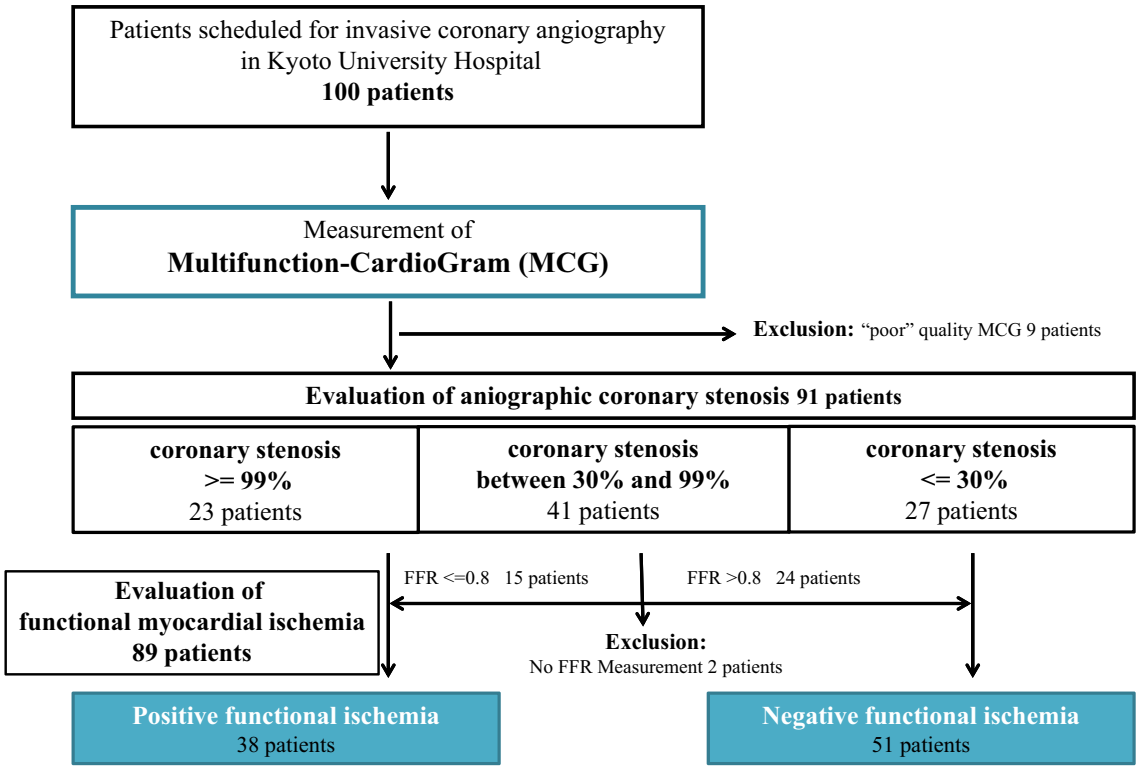

Figure 1. Study flow chart.
FFR = fractional flow reserve.

not mandated. Patients not having any coronary lesion with %DS ≥30% in vessels >2 mm in diameter by visual estimation were regarded as negative for functional ischemia without actual FFR measurement. Likewise, patients having at least one coronary lesion with %DS ≥99% in a vessel >2 mm in diameter by visual estimation were regarded as positive for functional ischemia without actual FFR measurement.

QCA Analysis

QCA analysis was performed by the standard technique with automated edge-detection algorithms (CAAS Quantitative Coronary Angiography-Research 5.4.1/2D Bifurcation option Pie Medical Imaging BV, Maastricht, The Netherlands), using the outer diameter of the catheter filled with contrast as the calibration standard. Target lesion for QCA in a given patient was defined as the most severely looking lesion in a vessel >2 mm in diameter. We measured minimal lumen diameter, reference diameter, and %DS. Angiographically significant stenosis was defined as %DS ≥ 50% by QCA.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) or range, and were compared using the Student's *t*-test or Wilcoxon rank-sum test based on their distributions. Categorical variables were presented as number and percentage and were compared with the chi-square test. The target population of 100 patients was determined by the investigators based on the feasibility of enrollment. Diagnostic performance was assessed by the area under the receiver operating characteristics curve (AUC) of the MCG severity score for the diagnosis of functional ischemia and angiographically significant coronary stenosis. We also calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the MCG severity score for the presence of functional myocardial ischemia

and angiographically significant coronary stenosis. Statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC, USA) software. A P value <0.05 was considered statistically significant.

RESULTS

Study Population and Baseline Patients Characteristics

We enrolled 100 patients in the current study and performed MCG measurement and invasive coronary angiography in all patients. The current analysis set consisted of 91 patients, excluding nine patients in whom MCG data with adequate quality fulfilling the criteria described above was not obtained (Fig. 1).

The current study population was characterized by the high prevalence of patients with coronary risk factors, such as male, hypertension, and dyslipidemia (Table 1). The prevalence of patients who received calcium channel blocker was 44.0%. A history of previous PCI was observed in 30.8%. The prevalence of atrial fibrillation was 6.6% and the majority patients have normal cardiac function by echocardiography. Mean updated Diamond–Forrester risk score was 55.3 ± 21.0% with intermediate (20–80%) pretest risk in 70 patients (76.9%).

Functional Myocardial Ischemia

There were 27 patients who did not have any coronary lesion with %DS ≥ 30% in vessels >2 mm in diameter, with median %DS of 31% (range: 6–45%) by QCA (Fig. 2). There were 23 patients who had at least one coronary lesion with %DS ≥ 99% in a vessel >2 mm in diameter. QCA of the index lesions in these 23 patients demonstrated median %DS of 82% (range: 71–100%) with total occlusion in seven lesions, subtotal occlusion with thrombolysis in myocardial infarction (TIMI) flow grade ≤2 in eight lesions, and nonflow limiting stenosis with TIMI 3 flow in eight lesions (Fig. 2). The minimum lumen diameter (MLD) and %DS in the eight nonflow limiting lesions ranged 0.42–0.6 mm and 72–82%, respectively. Among the remaining 41 patients who had at least one coronary lesion with %DS 30–99% in vessels >2 mm in diameter, FFR measurement was actually performed in 39 patients except for two patients in whom FFR measurement was aborted due to safety concerns. Therefore, we had an analysis set of 89 patients for functional myocardial ischemia (Fig. 1). Among 39 patients with actual FFR measurement, 15 patients (38.5%) had FFR values ≤0.8. Including 23 patients with at least one coronary lesion with %DS ≥99% in a vessel >2 mm in diameter by visual estimation, the prevalence of positive functional myocardial ischemia in the current study was 42.7% (38 patients) (Table 2).

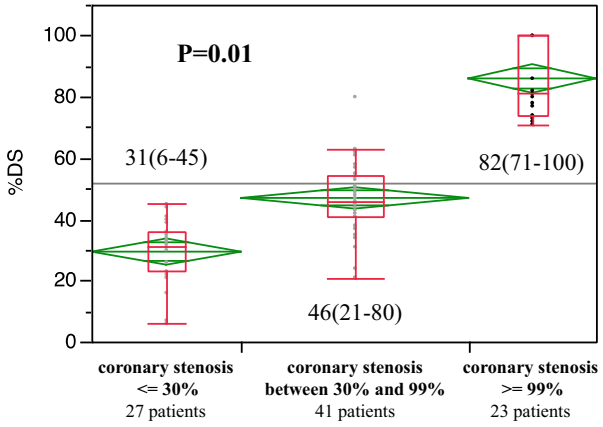

Figure 2. Percent diameter stenosis by quantitative angiographic analysis in the three groups of patients with coronary stenosis ≤ 30%, between 30% and 99%, and ≥ 99% by visual estimation. %DS = percent diameter stenosis.

AUC of the MCG severity score for functional myocardial ischemia was low (0.51, 95% confidence interval [CI]: 0.38–0.63) (Fig. 3A). The MCG severity score was not significantly different with or without functional myocardial ischemia (2.99 ± 0.36 vs 2.86 ± 0.31, P = 0.77) (Fig. 3B). There were only 29 patients (32.6%) who had mean MCG severity score ≥ 4.0, which was the cutoff value used in the previous reports evaluating MCG.[10–14] Sensitivity, specificity, PPV, and NPV of the mean MCG severity score for functional myocardial ischemia was poor (32%, 67%, 41%, and 57%, respectively) using a cutoff value of 4.0 (Table 3A). Diagnostic performance of the maximum MCG severity score for functional myocardial ischemia was also poor (sensitivity: 50%, specificity: 53%, PPV: 44%, and NPV: 59%, respectively).

Angiographic Stenosis

In an analysis set of 91 patients for angiographic stenosis, angiographically significant stenosis with %DS ≥50% was present in 38 patients (41.8%) (Table 2). AUC of the MCG severity score for

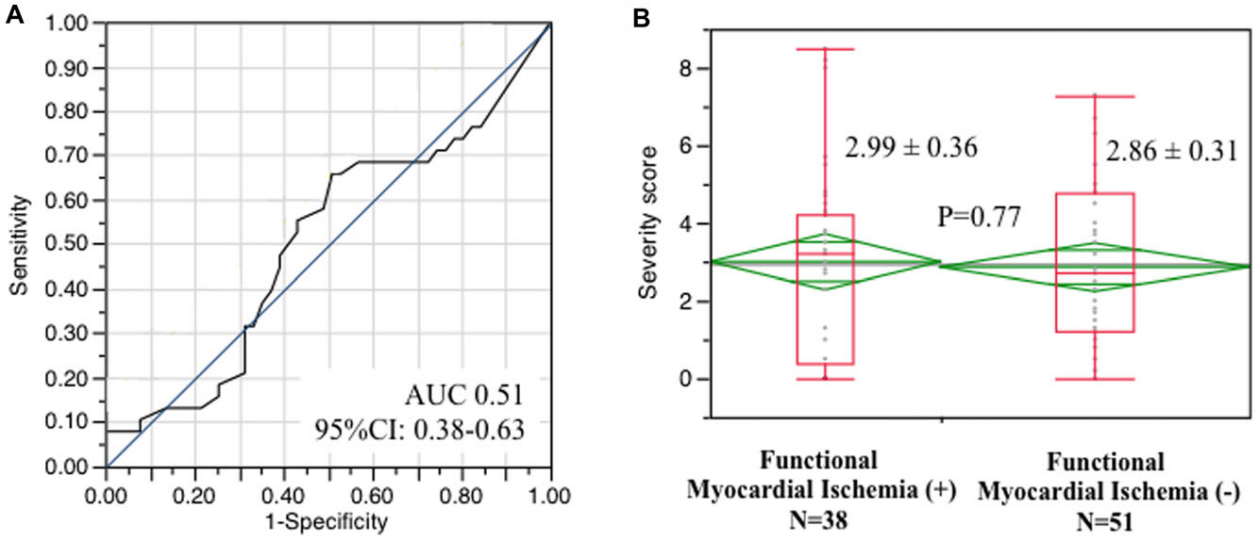

Figure 3. Primary analysis: Diagnostic performance of the MCG severity score in detecting functional myocardial ischemia with FFR ≤0.80. (A) AUC of the MCG severity score for the diagnosis of functional myocardial ischemia. (B) Mean MCG severity score in patients with or without functional myocardial ischemia. AUC = area under the receiver operating characteristics curve; CI = confidence interval; FFR = fractional flow reserve; and MCG = Multifunction CardioGram.

Table 3. Diagnostic Performance of MCG Severity Score with Various Cutoff Values

Cutoff Value	TP	TN	FP	FN	Sens	Spec	PPV	NPV	Correct	OR	95%CI
(A) Functional Myocardial Ischemia											
Score 0.0	29	8	43	9	0.763	0.157	0.403	0.471	0.416	0.60	0.21–1.73
Score 0.5	29	9	42	9	0.763	0.177	0.409	0.500	0.427	0.69	0.24–1.95
Score 1.0	28	11	40	10	0.737	0.216	0.412	0.524	0.438	0.77	0.29–2.06
Score 1.5	26	14	37	12	0.684	0.275	0.413	0.539	0.449	0.82	0.33–2.06
Score 2.0	26	18	33	12	0.684	0.353	0.441	0.600	0.494	1.18	0.48–2.89
Score 2.5	25	24	27	13	0.658	0.471	0.481	0.649	0.551	1.71	0.72–4.07
Score 3.0	21	29	22	17	0.553	0.569	0.488	0.630	0.562	1.63	0.70–3.80
Score 3.5	17	31	20	21	0.447	0.608	0.460	0.596	0.539	1.25	0.54–2.94
Score 4.0	12	34	17	26	0.316	0.667	0.414	0.567	0.517	0.92	0.38–2.27
Score 4.5	8	35	16	30	0.211	0.686	0.333	0.539	0.483	0.58	0.22–1.55
Score 5.0	5	40	11	33	0.132	0.784	0.313	0.548	0.506	0.55	0.17–1.75
(B) Angiographic stenosis %DS ≥ 50%											
Score 0.0	32	11	42	6	0.842	0.208	0.432	0.647	0.473	1.40	0.47–4.18
Score 0.5	32	12	41	6	0.842	0.226	0.438	0.667	0.484	1.56	0.53–4.61
Score 1.0	31	14	39	7	0.816	0.264	0.443	0.667	0.495	1.59	0.57–4.42
Score 1.5	28	17	36	10	0.737	0.321	0.438	0.630	0.495	1.32	0.52–3.33
Score 2.0	28	21	32	10	0.737	0.396	0.467	0.677	0.538	1.84	0.74–4.56
Score 2.5	25	25	28	13	0.658	0.472	0.472	0.658	0.549	1.72	0.73–4.06
Score 3.0	22	31	22	16	0.579	0.585	0.500	0.660	0.582	1.94	0.83–4.51
Score 3.5	18	34	19	20	0.474	0.642	0.487	0.630	0.571	1.61	0.69–3.76
Score 4.0	14	38	15	24	0.368	0.717	0.483	0.613	0.571	1.48	0.61–3.60
Score 4.5	11	40	13	27	0.290	0.755	0.458	0.597	0.560	1.25	0.49–3.21
Score 5.0	7	44	9	31	0.184	0.830	0.438	0.587	0.560	1.10	0.37–3.28

TP = true positive; TN = true negative; FP = false positive; FN = false negative; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; OR = odds ratio; CI = confidence interval; and %DS = percent diameter stenosis.

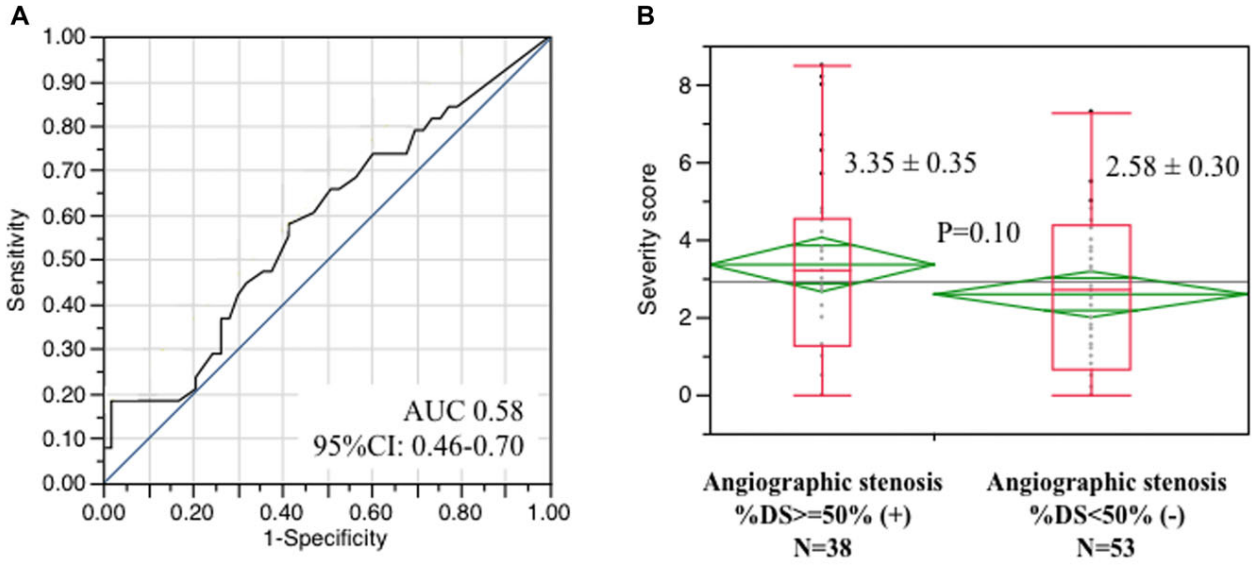

Figure 4. Secondary analysis: Diagnostic performance of the MCG severity score in detecting angiographically significant coronary stenosis (%DS ≥50%) by quantitative coronary angiography. (A) AUC of the MCG severity score for the diagnosis of angiographically significant coronary stenosis. (B) Mean MCG severity score in patients with or without angiographically significant coronary stenosis. AUC = area under the receiver operating characteristics curve; CI = confidence interval; FFR = fractional flow reserve; MCG = Multifunction CardioGram; and %DS = percent diameter stenosis.

angiographic stenosis was also low (0.58, 95%CI: 0.46–0.70) (Fig. 4A). The MCG severity score tended to be higher in patients with than in patients without angiographically significant stenosis (3.35 ± 0.35 vs 2.58 ± 0.30, P = 0.10) (Fig. 4B). However, sensitivity, specificity, PPV, and NPV of the MCG severity score for angiographically significant stenosis was poor (37%, 72%, 48%, and 61%, respectively) using a cutoff value of 4.0 (Table 3B). Diagnostic performance of the maximum MCG severity score for angiographically significant stenosis was also poor (sensitivity: 53%, specificity: 57%, PPV: 47%, and NPV: 63%, respectively).

DISCUSSION

The main finding of the current study was that diagnostic performance of the MCG severity score was poor for both functional myocardial ischemia, and angiographically significant stenosis.

In a previous meta-analysis of three published studies of the use of MCG including 1076 patients with variable ethnicities from seven hospitals, diagnostic performance of MCG for the identification of relevant coronary stenosis was reported to be excellent using a cutoff value of 4.0 (AUC: 0.88, Sensitivity: 91%, Specificity: 85%, PPV: 82%, and NPV: 93%).[10–14] The current study, which was meticulously conducted under physicians' leadership independent of the company manufacturing the MCG device, was planned mainly to evaluate the utility of MCG in detecting functional myocardial ischemia by using FFR as the reference standard. In discordant with the previous reports, the MCG severity score in this study had poor diagnostic performance in detecting not only functional myocardial ischemia, but also angiographically significant stenosis. AUC of the MCG severity score in this study in detecting angiographically significant stenosis was markedly lower than that in the previous meta-analysis (0.58 vs 0.88, respectively). AUC in detecting functional myocardial ischemia was even lower (0.51), although the previous reports claimed that MCG assesses functional changes of electromyocardial function secondary to changes in coronary blood flow including both local and global forms of ischemia.

Furthermore, only 33% of patients in this study as compared with 48% in the previous meta-analysis had MCG severity score ≥4.0, which was the cutoff value used in the previous reports,

although the prevalence of angiographically significant CAD in this study was not different from that in the previous meta-analysis (42% and 43%, respectively). However, diagnostic performance of MCG in terms of sensitivity, specificity, PPV, and NPV was poor in detecting functional myocardial ischemia as well as angiographically significant stenosis with all cutoff values evaluated (Table 3).

MCG has already been approved by FDA and received a CPT code in United States. However, we could not find clinical utility of MCG as a noninvasive test for detecting functional myocardial ischemia in patients with suspected CAD. We could not provide good explanations for the discordant between the current study and the previous studies. Nevertheless, approval and reimbursement of a new diagnostic modality for functional myocardial ischemia should be based on more rigorously designed clinical studies.

Study Limitations

There are a few limitations in this study. First, the number of patients enrolled in the current study was relatively small compared with the previous studies. Second, the actual FFR measurement was performed in patients with coronary artery lesion with diameter stenosis of 30–99% and vessel size >2 mm by visual estimation. In the remaining patients, functional myocardial ischemia was actually defined by angiographic stenosis by visual estimation. However, this approach is the standard practice in using FFR as a diagnostic tool and QCA clearly demonstrated the presence of real high-grade stenosis in these lesions with suspected functional myocardial ischemia defined by angiographic stenosis by visual estimation. Finally, we did not evaluate the diagnostic performance of the automatic differential diagnosis derived from MCG session analysis.

CONCLUSIONS

Diagnostic performance of the MCG severity score was poor for both functional myocardial ischemia, and angiographically significant stenosis.

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