

Assessment of Non-Invasive Diagnostic Imaging Modalities Efficiency for Detecting Myocardial Ischemia in Patients Suspected of Having Stable Angina

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Abstract

Purpose: This study aimed to assess and compare the detection efficiency of non-invasive diagnostic imaging modalities as easy-to-understand indices for patients with myocardial ischemia.

Methods: We included 1,000 patients with chest pain and possible coronary artery disease (CAD), based on their clinical condition. The modalities to be assessed were as follows: cardiac magnetic resonance imaging (CMRI), single-photon emission computed tomography, positron emission computed tomography (PET), stress echocardiography (SE), and fractional flow reserve derived from coronary computed tomography angiography (FFRCT). We used the decision tree simulation analysis to assess and compare the following: (1) the number of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) test results per 1,000 patients, (2) positive predictive value (PPV), (3) negative predictive value (NPV), (4) post-test probability (post-TP), (5) diagnostic accuracy (DA), and (6) the number needed to diagnose (NND).

Results: In the basic settings (pre-test probability: 50%), PET generated the highest TP (450), NPV (89%, 95% confidence interval [CI]: 86%-92%), DA (87%, 95% CI: 85%-89%), and NND (1.35, 95% CI: 1.26-1.48). In contrast, CMRI produced the highest TN (435), PPV (87%, 95% CI: 84%-90%), DA (87%, 95% CI: 85%-89%), and NND (1.35, 95% CI: 1.26-1.48). In addition, FFRCT generated the highest FP (120). SE produced the highest FN (155) and post-TP (29%, 95% CI: 25%-33%).

Conclusion: PET and CMRI were considered more efficient than other modalities. The results of our study will be useful for both physicians who order the examination and patients who undergo it.

Introduction

Numerous cardiac imaging methods are currently available for detecting myocardial ischemia associated with ischemia-causing coronary artery disease (CAD), including coronary computed tomography angiography (CCTA), cardiac magnetic resonance imaging (CMRI), single-photon emission computed tomography (SPECT), positron emission computed tomography (PET), stress echocardiography (SE), and fractional flow reserve derived from CCTA (FFRCT) [1, 2]. Moreover, they are widely performed as a non-invasive diagnostic imaging modality, and several researchers have reported on their diagnostic ability [3–6]. Recent guidelines recommend using CCTA for workup in patients with suspected stable angina, based on their initial test results [7, 8]. However, CCTA generates exclusively morphological information about coronary arteries. To diagnose the presence of myocardial ischemia irrespective of the presence coronary artery stenosis, it is recommended that myocardial perfusion should be assessed with another modality [8–10]. Studies that have detected myocardial ischemia by diagnostic imaging on stable angina primarily use sensitivity and specificity as indices, thus indicating their ability. However, patients without prior knowledge might find it difficult to understand the meaning of the examination contents, despite being directly informed about the numerical values described in the literature. Therefore, it is desirable to clarify these indices not only as values obtained from the literature, but also as indices that are easy to understand. Additionally, this practice might be beneficial not just the patient but also the medical experts associated with their examination. Therefore, we aimed to assess and compare the efficiency of detecting myocardial ischemia using non-invasive diagnostic imaging modalities as easy-to-understand indices by simulation.

Methods

Study design

We included 1,000 patients with chest pain and any of the following clinical conditions:

High clinical likelihood of obstructive CAD expected from basic testing [11];

Requirement for myocardial perfusion evaluation;

Suspected CAD on CCTA.

A simulation analysis was performed to assess the efficiency. As a basic setting, we set the pre-test probability (PTP) of CAD to 50% by referring to past reports [8,11]. We used decision analysis [12] to calculate the efficiency, assuming the aforementioned group of patients would undergo the following five types of examinations:

- 1) CMRI (perfusion magnetic resonance imaging)
- 2) SPECT
- 3) SE
- 4) FFRCT
- 5) PET

Literature search

We performed a literature search for the data analysis. We searched for meta-analysis articles on non-invasive diagnostic imaging modalities that used invasive FFR as a reference standard and investigated the diagnostic ability (sensitivity and specificity) of CAD on a patient basis. This literature search was performed using the PubMed database to identify articles published between January 2015 and October 2018. The search items were as follows: (i) diagnostic accuracy of coronary artery disease and (ii) diagnostic performance of coronary artery disease. In case of multiple results, we extracted the top two articles with the highest number of target studies described in the meta-analysis. In contrast, we selected the relatively new article if the number of target studies included was similar. Subsequently, we conducted a qualitative evaluation of the literature. Referring to the method reported by Chong *et al.*[13], the contents of each literature were evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Diagnostic Test Accuracy (PRISMA DTA) checklist [14]. The PRISMA DTA Checklist contains 27 items that assess the quality of meta-analyses. We categorized each checklist item of the candidate literature as follows: “sufficiently described”, “insufficiently described”, and “not described”. While one point was assigned to each checklist item with “sufficiently described”, zero points were assigned to other items. Moreover, we calculated the total score of each candidate literature. We eventually selected the literature with the highest total score for the analysis. In case of same scores, the relatively newer literature was selected. We eventually extracted the sensitivity and specificity from the selected literature and used them for the data analysis.

Definition of efficiencies for detecting myocardial ischemia

We defined the efficiencies for detecting myocardial ischemia as follows:

- a) The number of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results per 1,000 patients
- b) Positive Predictive Value (PPV) = post-test probability (for positive result)
- c) Negative Predictive Value (NPV)
- d) Post-test probability (post-TP [for negative results]) [15]
- e) Diagnostic accuracy (DA)
- f) The number needed to diagnose (NND) [16]

Calculation of efficiencies

In the aforementioned patient group, we assumed that a work-up examination had been performed to assess the presence of myocardial ischemia. Based on the sensitivity and specificity, we conducted a decision analysis using the Bayes' theorem. We calculated the PPV, NPV, and the probability of a positive or negative result from the PTP, sensitivity, and specificity. Moreover, we calculated the probabilities of finally arriving at the endpoint of each branch of the decision tree (Fig. 1). Each probability was used to calculate the TP, FP, FN, and TN per 1,000 patients. The NND was calculated simultaneously. It indicates the number of patients to be tested to correctly detect the disease in one of them [16]. For calculation of efficiencies, we used the method published by Hsu *et al.*[17] to calculate the number of people. Efficiencies were calculated and compared for each imaging modality. Table 1 summarizes the method used to calculate each efficiency. We simultaneously calculated the 95% confidence interval (95% CI) as the value of the point estimates from b)-f). We eventually compared the efficiencies of the estimated five imaging modalities. The absence of an overlap between each 95% CI indicated a statistically significant difference while comparing the aforementioned efficiencies ($p < 0.05$).

Sensitivity analyses

The PTP was set at 50% in the basic analysis settings. However, the PTP of CAD depends on the background factors of patients, such as sex, age, and the presence or absence of risk factors in individual patients [8,11]. Therefore, we conducted sensitivity analyses to assess the efficiencies, considering the uncertainties associated with the hypothesis-based analysis. The PTP was changed from 10% to 90%, centering on the intermediate PTP [8], which reportedly requires imaging tests to detect myocardial ischemia. The change in efficiencies in each imaging modality were evaluated and compared. The efficiencies targeted for the sensitivity analysis were limited to one, which varied with changes in the PTP. Their post-test probabilities were calculated using various PTPs and each efficiency.

We calculated each efficiency and 95% CI using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, package: epiR) and Microsoft Excel for Mac 2016 Ver.16.16.27.

Results

Selected literature

We extracted five, three, two, three, and seven articles for CMR [3,4,18-20], SPECT [4,19,20], PET [4,20], SE [4,19,20], and FFRCT, respectively [4-6,19,21-23], for the initial selection (Table 2). Among them, the contents reported by Jiang (2016) [3]: CMRI; Dai (2016) [4]: SPECT, PET, and SE; and Wu (2016) [5]: FFRCT met the aforementioned conditions. Therefore, the sensitivity and specificity published in these articles were used for the analysis.

Efficiencies at the basic settings

Table 3 summarizes the efficiencies at the basic settings. The order of the calculated number of TP, FP, FN, and TN was PET (450) > FFRCT > CMRI > SPECT > SE (345), FFRCT (120) > SE > SPECT > PET > CMRI (65), SE (155) > SPECT > CMRI > FFRCT > PET (50), and CMRI (435) > PET > SPECT > SE > FFRCT (380), respectively. While CMRI had the highest PPV, SE was the lowest. In contrast, PET had the highest NPV and lowest SE. While the post-test probability (negative result) of SE was the highest, that of PET was the lowest. CMR and PET had the highest DA and the lowest SE. NND ranged from 1.35 (CMRI and PET) to 2.17 (SE). We observed significant differences between the following modalities in PPV: CMRI-SPECT, CMRI-SE, CMRI-FFRCT, and PET-SE. There were significant differences in NPV between the following modalities: CMRI-SPECT, CMRI-SE, PET-SPECT, PET-SE, FFRCT-SPECT, and FFRCT-SE. In post-TP (negative results), there were significant differences between the following modalities: CMRI-SPECT, CMRI-SE, PET-SPECT, PET-SE, FFRCT-SPECT, and FFRCT-SE. In contrast, there were significant differences in DA between the following modalities: CMRI-SPECT, CMRI-SE, PET-SPECT, PET-SE, and FFRCT-SE. There were significant differences in NND between the following modalities: CMRI-SPECT, CMRI-SE, PET-SPECT, PET-SE, and FFRCT-SE.

Changes of efficiencies in sensitivity analysis

Figs. 2-3 depict the change in efficiencies at the various PTPs in the sensitivity analysis. In all PTPs, the estimates of TPs for PET were highest with no change in the order of the five modalities (PET > FFRCT > CMRI > SPECT > SE). In addition, FPs, FNs, and TNs were highest for FFRCT, SE, and CMRI, respectively, with no change in the order of the five modalities (FP: FFRCT > SE > SPECT > PET > CMRI, FN: SE > SPECT > CMRI > FFRCT > PET, and TN: CMRI > PET > SPECT > SE > FFRCT). The estimates in CMRI in PPV were highest in all PTPs with no change in the order of the modalities (CMRI > PET > SPECT = FFRCT > SE). Moreover, PET was highest in NPV in all PTPs with no change in the order of the modalities (PET > FFRCT > CMRI > SPECT > SE). In the post-TP (negative results), SE was highest in all PTPs, with no change in the order of the modalities (SE > SPECT > CMRI > FFRCT > PET). Furthermore, estimates in CMRI and SPECT were almost constant in DA. With an increase in PTP, estimates in DA for PET and FFRCT were increased (up to 4% and 11%, respectively), and SE was decreased (up to 6%).

Discussion

We evaluated and compared efficiencies of five non-invasive diagnostic imaging modalities for the detection of myocardial ischemia in patients with stable angina. In addition, we conducted a sensitivity analysis to

account for the variation in PTP due to differences in patient background factors. Our study findings that may be useful to patients were as follows:

Among the five types of modality in basic settings (PTP: 50%),

- The maximum and minimum probability of a positive result and ischemia was 87% (CMRI) and 75% (SE), respectively.
- The maximum and minimum probability of a negative result and no ischemia was 89% (PET) and 71% (SE), respectively.
- Despite a negative result, the minimum and maximum probability of ischemia, i.e., the probability of missing detection was 11% (PET) and 29% (SE), respectively.
- PET generated the best TP, NPV, and least FN among the five imaging modalities.
- CMR generated the best DA, PPV, TN, and least FP among the five imaging modalities.
- FFRCT produced more false-positive cases than PET, CMR, and SPECT.
- SE was inferior to all modalities.

In addition, the following information may be useful to physicians who order the examinations:

In the sensitivity analysis,

- PET generated the highest TP, NPV, and lowest FN in all PTPs.
- The TPs and FNs of FFRCT were almost similar to those of PET.
- The NPVs of FFRCT were almost similar to those of CMR.

PET is considered best for patients or physicians who focus on an accurate detection and less missed diagnoses of CAD. However, it has slightly higher FPs than CMR. This can be attributed to the relatively lower specificity, compared to that of CMR. The DA and NND of PET and CMR were almost similar in basic settings. However, the number of FP in PET was about 20 cases more than that in CMR. PET may be slightly inferior to CMR, in terms of its role as a gatekeeper for CAG or revascularization. In contrast, CMR is considered best if it focuses on higher DA, PPV, and less FP. The TPs and FNs of FFRCT are almost similar to PET. Thus, FFRCT should be added to CCTA when the results of CCTA are equivocal. However, the number of FPs in FFRCT was the highest among the five modalities due to the lowest specificity of FFRCT (Fig. 2-b and Table 2). The FP and FN results can lead to an inaccurate diagnosis. In addition to unnecessary psychological distress, FP test results in patients with no disease can increase their medical risk due to additional examinations [24]. Moreover, FN test results can cause late diagnosis or misdiagnosis [24].

Among non-invasive diagnostic imaging modalities, researchers have primarily conducted studies to evaluate the efficiency of detecting myocardial ischemia in stable angina by economic analysis, such as cost-effectiveness analysis, cost-benefit analysis, and cost-benefit analysis [25-27]. However, an interpretation of

the indicators of efficiency obtained from the results, such as cost-effectiveness ratio and cost-utility ratio requires a certain degree of specialized knowledge. Therefore, patients might find it difficult to understand these indicators, despite being presented directly with the information. This is the first study that used currently available evidences to assess the efficiency of each modality to detect myocardial ischemia by simulation. Therefore, we could elucidate the number of TP, FN, FP, and TN per 1,000 patients as efficiencies. In addition, by comparing them, we could elucidate the difference in efficiency as a specific index. Similarly, the efficiency of indices, such as PPV, NPV, DA, and post-test probability were also elucidated and compared with each other. The aforementioned calculations require setting the PTP. However, we were able to assess efficiencies at different PTPs using sensitivity analyses. Besides, physicians might easily understand the indicators using NND than standard diagnostic accuracy expressions, such as sensitivity and specificity [16]. Thus, it is conceivable that our results would help patients to understand the ability of each examination and undergo the appropriate one. Apart from sensitivity and specificity, the aforementioned indices would be needed not only by patients but also by physicians who order the examinations during busy practices. Furthermore, physicians can determine the degree of an inaccurate CAD diagnosis by the percentage and number of people. Therefore, our findings might contribute to reviewing diagnostic strategies and improving the workflow for diagnosis in patients with suspected CAD. The primary purpose of using non-invasive imaging modalities was to select patients who were likely to benefit from invasive coronary angiography and revascularization [1,28,29]. Therefore, the importance of non-invasive imaging is increasing [1]. Each imaging modality has a good ability to detect CAD. Moreover, they contribute to the reduction of unnecessary revascularization and optimization of the diagnosis and treatment costs. However, physicians should refer to the various economic evaluations while considering the efficiencies of each examination, based on diagnostic costs.

Limitations

Our study has several limitations. First, each index calculated as the efficiency was a value calculated by simulation. Therefore, our results may not be appropriate in alternative situations. Hence, we considered citing the results of meta-analyses for determining the diagnostic ability. Moreover, we performed a sensitivity analysis to enable the application of the aforementioned method in different cases. Second, the diagnostic abilities of each modality used to calculate efficiencies were cited from the meta-analyses. We failed to obtain any literature data from the same patient population. In addition, we could not consider the difference in the diagnostic ability, depending on sex. Thus, it might have introduced bias. Third, we defined the efficiency as “indices that are easily understood by patients”. However, our results have not yet been used to explain to actual patients. Therefore, we failed to verify whether patients could understand the calculated efficiencies. This necessitates further verification by taking measures, such as hearing patient opinions.

Conclusion

We assessed and compared the efficiency of non-invasive imaging modalities for detecting myocardial ischemia in patients with suspected stable angina. PET and CMRI have a superior efficiency, compared to other methods. Our results shed light on the efficiency of the aforementioned modalities using the “easy-to-understand index”. Hence, they might prove useful for both physicians and patients.

Declarations

Author Contributions

KI contributed to the conception of the study, data collection and analysis, and writing (original draft); KO contributed to the conception and supervision of the study and writing (review and editing). All authors read and approved the manuscript.

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Compliance with ethical standards

Conflict of interest: The authors declare that there are no conflicts of interest.

Ethical approval: This study was conducted exclusively using data from published literature. No patient data were included. Thus, an institutional ethics approval has not been obtained.

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Tables

Table 1. Calculation method for efficiencies per 1,000 patients

		Reference standard (Invasive FFR)	
		Myocardial ischemia (+)	Myocardial ischemia (-)
Index Test	Positive	TP = Sensitivity × PTP × 1000	FP = (1 - Specificity) × (1 - PTP) × 1000
	Negative	FN = (1 - Sensitivity) × PTP × 1000	TN = Specificity × (1 - PTP) × 1000

PPV = Post-test probability (positive test result) = $TP / (TP + FP)$

NPV = $TN / (FN + TN)$

Diagnostic accuracy = $(TP + TN) / (TP + FP + FN + TN)$

Post-test probability (negative test result) = $FN / (FN + TN)$

NND = $1 / (\text{Sensitivity} + \text{Specificity} - 1)$

PTP: Pre-test probability, PPV: Positive Predictive Value, NPV: Negative Predictive Value

FFR: Fractional flow reserve, NND: the number needed to diagnose

Table 2. List of candidate literature and their characteristics

Author (Reference)	Year	Modality	FFR threshold	No. of Studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	PRISMA Score
Kiaos ¹⁸	2018	CMRI	0.75-0.8	6	516	0.90 (0.85- 0.93)	0.85 (0.80- 0.89)	-
Danad ¹⁹	2017	CMRI	0.75-0.8	2	70	0.90 (0.75- 0.97)	0.94 (0.79- 0.99)	-
Jiang ³ □	2016	CMRI	0.75-0.8	12	1041	0.87 (0.83- 0.90)	0.87 (0.84- 0.90)	19
Dai ⁴	2016	CMRI	0.75-0.8	15	1054	0.88 (0.85- 0.91)	0.84 (0.79- 0.87)	17
Takx ²⁰	2015	CMRI	0.75-0.8	10	798	0.89 (0.86- 0.92)	0.87 (0.83- 0.90)	-
Danad ¹⁹	2017	SPECT	0.75-0.8	3	110	0.70 (0.59- 0.80)	0.78 (0.68- 0.87)	-
Dai ⁴ □	2016	SPECT	0.75-0.8	15	1142	0.78 (0.71- 0.84)	0.79 (0.70- 0.87)	17
Takx ²⁰	2015	SPECT	0.75-0.8	8	553	0.74 (0.67- 0.79)	0.79 (0.74- 0.83)	17
Danad ¹⁹	2017	SE	0.75-0.8	2	115	0.77 (0.61- 0.88)	0.75 (0.63- 0.85)	-
Dai ⁴ □	2016	SE	0.75-0.8	6	359	0.69 (0.57- 0.80)	0.77 (0.62- 0.87)	17
Takx ²⁰	2015	SE	0.75	4	177	0.69 (0.56- 0.79)	0.84 (0.75- 0.90)	17
Danad ¹⁹	2017	FFRCT	0.75	3	609	0.90 (0.85- 0.93)	0.71 (0.65- 0.75)	-
Ding ⁶	2016	FFRCT	0.8	4	662	0.90 (0.86- 0.93)	0.73 (0.68- 0.77)	15
Dai ⁴	2016	FFRCT	0.8	4	662	0.90 (0.85- 0.93)	0.75 (0.62- 0.85)	17
Panchal ²¹	2016	FFRCT	0.8	4	662	0.90	0.72	10

						(0.85-0.93)	(0.67-0.76)	
Wu ⁵ ☐	2016	FFRCT	0.8	5	833	0.89 (0.85-0.93)	0.76 (0.64-0.84)	20
Gonzalez ²²	2015	FFRCT	0.8	4	662	0.90 (0.85-0.93)	0.72 (0.67-0.76)	-
Deng ²³	2015	FFRCT	NA	4	662	0.90 (0.85-0.93)	0.72 (0.67-0.76)	-
Dai ⁴ ☐	2016	PET	0.8	4	609	0.90 (0.80-0.95)	0.84 (0.81-0.90)	17
Takx ²⁰	2015	PET	0.8	2	224	0.84 (0.75-0.91)	0.87 (0.80-0.92)	17

☐ Literature selected for the analysis.

CI: confidence interval

FFR: fractional flow reserve

NA: not available

CMRI: cardiac magnetic resonance imaging

SPECT: single-photon emission computed tomography

SE: stress echocardiography

FFRCT: fractional flow reserve derived from coronary computed tomography angiography

PET: positron emission computed tomography

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 3. A summary of efficiencies at the basic settings (Pre-test probability = 50%).

	CMRI	SPECT	PET	SE	FFR-CT
Number of TP (n)	435	390	450	345	445
Number of FP (n)	65	105	80	115	120
Number of FN (n)	65	110	50	155	55
Number of TN (n)	435	395	420	385	380
Positive predictive value* (%) (95% CI)	87 (84-90)	79 (75-82)	85 (82-88)	75 (71-79)	79 (75-82)
Negative predictive value (%) (95% CI)	87 (84-90)	78 (74-82)	89 (86-92)	71 (67-75)	87 (84-90)
Post-test probability**(%) (95% CI)	13 (10-16)	22 (18-26)	11 (8-14)	29 (25-33)	13 (10-16)
Diagnostic accuracy (%) (95% CI)	87 (85-89)	79 (76-81)	87 (85-89)	73 (70-76)	83 (80-85)
Number needed to diagnose (95% CI)	1.35 (1.26- 1.48)	1.75 (1.56- 2.03)	1.35 (1.26- 1.48)	2.17 (1.86- 2.65)	1.54 (1.40- 1.73)

* Positive Predictive Value (PPV) = Post-test probability (positive result)

** Post-test probability (negative result)

CI: Confidence interval

CMRI: cardiac magnetic resonance imaging, SPECT: single-photon emission computed tomography

SE: stress echocardiography, FFR-CT: fractional flow reserve-computed tomography

TP: true positive, FP: false positive, FN: false negative, TN: true negative

PPV: positive predictive value, NPV: negative predictive value

NND: the number needed to diagnose

Figures

Fig. 1

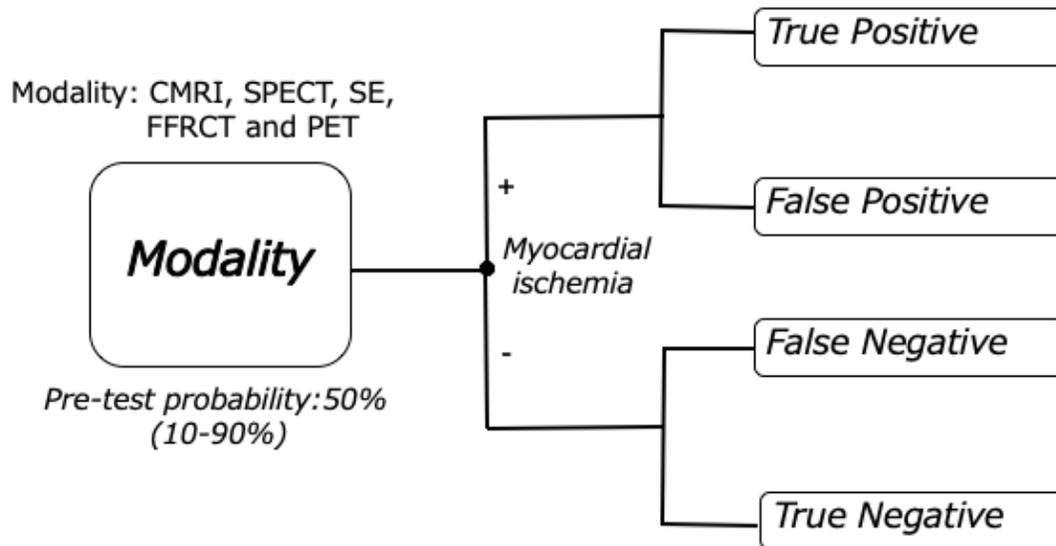


Figure 1

Decision tree model CMRI: Cardiac magnetic resonance imaging SPECT: Single-photon emission computed tomography SE: Stress echocardiography FFRCT: Fractional flow reserve derived from coronary computed tomography angiography PET: Positron emission computed tomography

Fig. 2-a

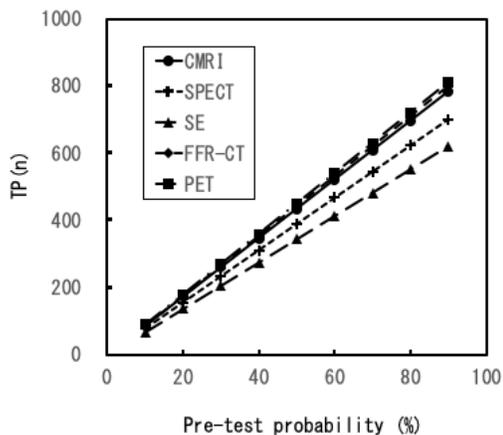


Fig. 2-b

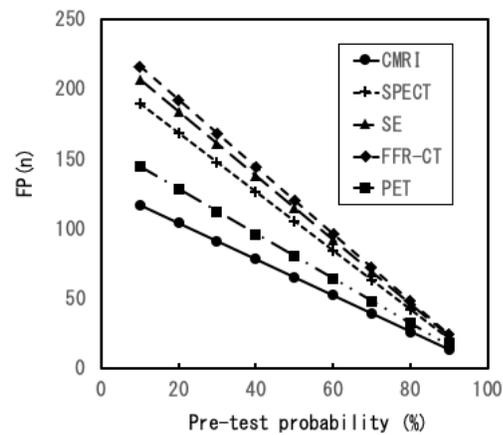


Fig. 2-c

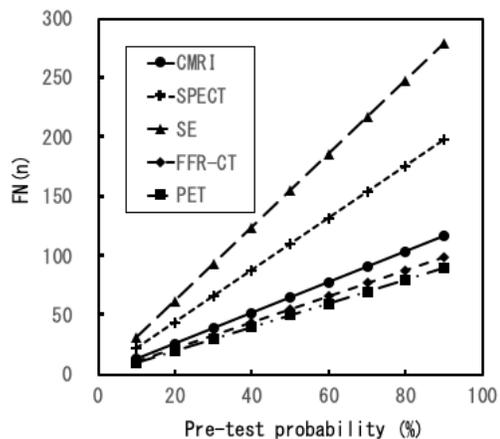


Fig. 2-d

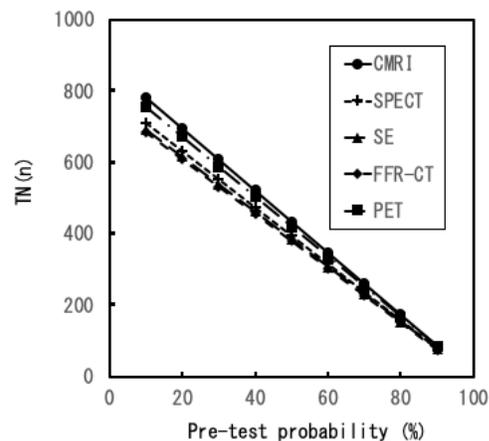


Figure 2

Sensitivity analysis (1) Fig. 2-a: Changes in number of TP with various pre-test probabilities of CAD Fig. 2-b: Changes in number of FP with various pre-test probabilities of CAD Fig. 2-c: Changes in number of FN with various pre-test probabilities of CAD Fig. 2-d: Changes in number of TN with various pre-test probabilities of CAD CMRI: Cardiac magnetic resonance imaging, SPECT: Single-photon emission computed tomography SE: Stress echocardiography FFRCT: Fractional flow reserve derived from coronary computed tomography angiography PET: Positron emission computed tomography TP: True positive FP: False positive FN: False negative TN: True negative

Fig. 3-a

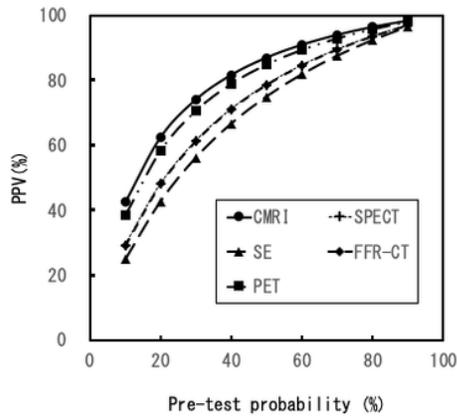


Fig. 3-b

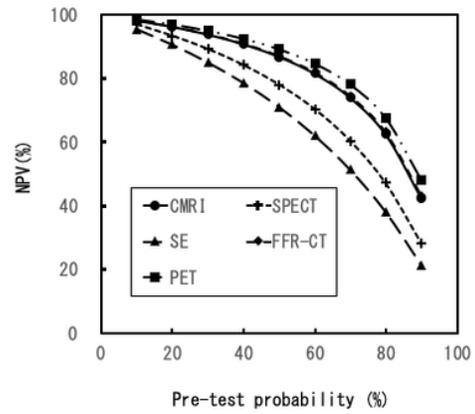


Fig. 3-c

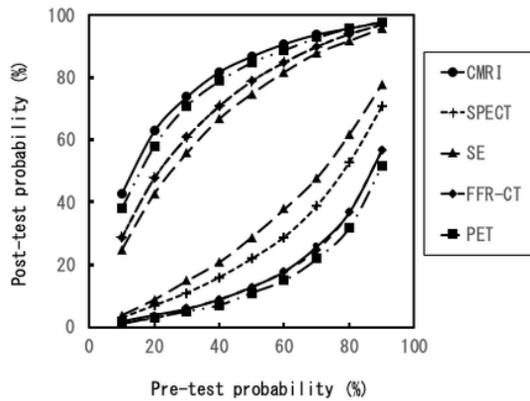


Fig. 3-d

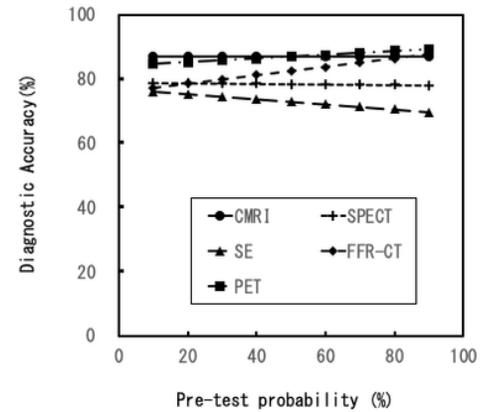


Figure 3

Sensitivity analysis (2) Fig. 3-a: Changes in PPV with various pre-test probabilities of CAD Fig. 3-b: Changes in NPV with various pre-test probabilities of CAD Fig. 3-c: Changes in post-test probability with various pre-test probabilities of CAD Upper: Post-test probability (for positive result) Under: Post-test probability (for negative result) Fig. 3-d: Changes in the diagnostic accuracy with various pre-test probabilities of CAD CMRI: Cardiac magnetic resonance imaging, SPECT: Single-photon emission computed tomography SE: Stress echocardiography FFRCT: Fractional flow reserve derived from coronary computed tomography angiography PET: Positron emission computed tomography PPV: Positive predictive value NPV: Negative predictive value