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Relationship between the neutrophil to HDL-C ratio and anatomical significance of coronary artery stenosis in patients with documented myocardial ischemia

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Abstract. – OBJECTIVE: Diagnostic work-up of coronary artery disease (CAD) requires a stepwise approach, starting with detailed history-taking and ending with invasive coronary angiography (ICA) in some cases. The neutrophil to high-density lipoprotein cholesterol (HDL-C) ratio (NHR) is related to CAD. We assessed the association between the NHR and anatomical significance of coronary artery stenosis (CAS) in patients with documented ischemia.

PATIENTS AND METHODS: The study enrolled 306 consecutive patients with documented myocardial ischemia on myocardial perfusion imaging (MPI). All patients underwent ICA. Patients with no visible stenosis (NVS) or minimal or mild CAS were compared with those with moderate or severe CAS.

RESULTS: The study compared 85 patients with NVS or minimal or mild CAS (46.51% female) and 221 patients with moderate or severe CAS (31.58% female). In the latter group, hypertension and diabetes mellitus (DM) were more prevalent than in the former group (83.73% *vs.* 60.47%, $p<0.001$; 47.37% *vs.* 30.23%, $p=0.005$, respectively). A higher NHR (cut-off point of 103.2) was associated with moderate or severe CAS.

CONCLUSIONS: Even when myocardial ischemia is demonstrated by MPI, NVS or minimal or mild CAS is still frequently diagnosed based on ICA. A lower NHR could be an inexpensive, non-invasive marker of the need for ICA.

Key Words:
Coronary artery disease, Myocardial perfusion imaging, Neutrophils, High-density lipoprotein cholesterol.

Introduction

Coronary artery disease (CAD) is a pathological process involving atherosclerotic plaque formation in the epicardial arteries and causes adverse cardiac events in severe cases. Although there have been advances in the treatment of CAD, it still has the highest mortality rate of any disease worldwide[1]. The diagnostic workup of CAD requires a stepwise approach, starting with a detailed history and ending with invasive coronary angiography (ICA) in some cases. Recent guidelines suggest that either non-invasive functional imaging of ischemia or anatomical imaging using coronary computed tomography angiography (CCTA) should be performed if patients do not have symptoms refractory to guideline-based medical treatment.

Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is the most commonly used non-invasive functional imaging modality for diagnosing CAD, and also provides information on the extent of ischemia and viability of myocardial tissue. MPI SPECT has an acceptable sensitivity (85%) but a relatively low specificity (60%) for detecting obstructive CAD[2-4].

Lipid metabolism and the inflammation process play crucial roles in atherosclerosis pathophysiology. Recently, a new biomarker called the neutrophil to high-density lipoprotein cholesterol (HDL-C) ratio (NHR), which uses the neutrophil count as a marker of inflammation and the HDL-C level as an anti-atherosclerotic lipid marker, was found to be related to CAD and an independent predictor of severe coronary stenosis[5]. We assessed the association between NHR and anatomical significance of coronary artery stenosis (CAS) in patients with ischemia demonstrated by MPI SPECT imaging. The value of using the NHR before MPI SPECT imaging to improve specificity was also evaluated.

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Patients and Methods

Study Population

This single-center retrospective study enrolled 306 consecutive patients with myocardial ischemia revealed by MPI SPECT. All patients were referred for ICA between February 2019 and September 2019. The study protocol was conformed to the tenets of the 1975 Declaration of Helsinki. Ankara City Hospital Ethics Committee approved the study (Trial No.:2130, Decision No.: E1-21-2139).

MPI SPECT was performed in all patients using technetium 99 m, with either exercise or dipyridamole. Only patients at high risk (i.e., ischemic area in the left ventricular myocardium ≥ 10% on MPI SPECT) were referred for ICA.

Patients with acute coronary syndrome, severe congestive heart failure, atrial fibrillation, severe valvular disease, hypertrophic cardiomyopathy, or severe renal or liver failure were excluded.

Diabetes mellitus (DM) was defined as a fasting plasma glucose level > 126 mg/dL or currently on antidiabetic treatment. Hyperlipidemia (HL) was defined as a fasting serum low-density lipoprotein (LDL) cholesterol level > 130 mg/dL or currently being treated with lipid-lowering drugs. Patients with resting blood pressure ≥ 140/90 mmHg on at least two measurements or currently taking antihypertensive medication were deemed to have hypertension (HT).

Data Collection

Patient gender, age, medical history, comorbidities, routine biochemistry results, 12-lead electrocardiography, transthoracic echocardiography, and MPI SPECT data were collected from the medical records of our hospital.

Coronary Angiography

Selective coronary angiography was performed using the Judkins technique via radial or femoral access. Two experienced invasive cardiologists blinded to the MPI SPECT results interpreted the coronary angiography recordings. We defined ≥ 50% CAS in at least one of the left anterior descending, left circumflex, left main coronary, and right coronary arteries as moderate or severe CAS, according to the Society of Cardiovascular Computed Tomography (SCCT) grading scale for CAS[6]. Group 1 comprised patients with no visible stenosis (NVS) or minimal or mild CAS, and Group 2 included those with moderate or severe CAS (Figure 1).

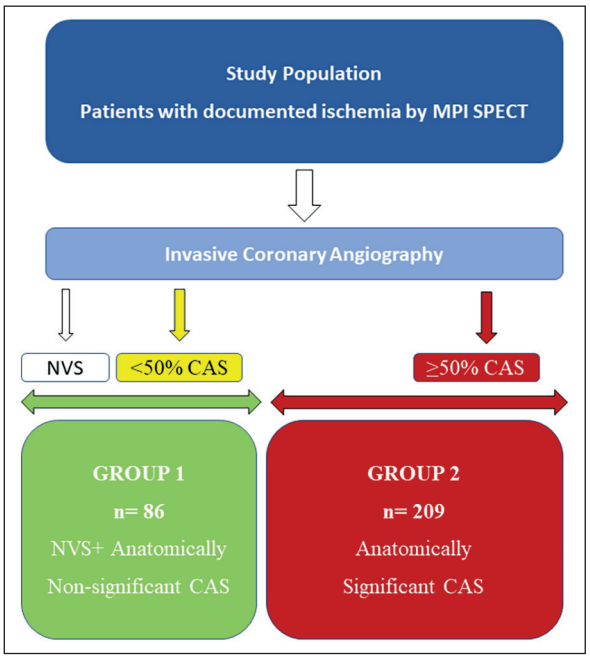

Figure 1. Flow chart of study design. CAS, coronary artery stenosis; MPI: myocardial perfusion imaging, NVS: no visible stenosis, SPECT: single photon emission computed tomography.

Statistical Analysis

All data were analyzed using SPSS software (ver. 22.0; SPSS Inc., IBM, Armonk, NY, USA). Continuous data are presented as the mean ± standard deviation (SD) and were analyzed with the *t*-test. Pearson's chi-square was used to analyze categorical data. The area under the receiver operating characteristic curve (AUC) was used to determine the cut-off point of NHR for anatomically significant CAS. Uni- and multivariate logistic regression was used to identify predictors of anatomically significant CAS in patients with documented ischemia on MPI SPECT. All tests were two-tailed and a p-value < 0.05 was considered statistically significant.

Results

We analyzed 306 patients with myocardial ischemia (according to MPI SPECT) who had undergone ICA and separated them into Groups 1 (n = 85, 46.51% female, mean age = 57 ± 9 years) and 2 (n = 221, 31.58% female, mean age = 61.0 ± 9.1 years). Table I summarizes their demograph-

Table I. Demographic, clinical and laboratory data of study population according to coronary artery stenosis.

	Group 1 (NVS and CAS < 50%) n = 85	Group 2 (CAS ≥ 50%) n = 221	*p*-value
Age, year	57 ± 9.0	61 ± 9.1	.001
LVEF (%)	60 ± 8.7	56 ± 10.8	.006
Female n, (%)	40 (46.51)	66 (31.58)	.011
Hypertension n, (%)	52 (60.47)	175 (83.73)	.000
Diabetes Mellitus n, (%)	26 (30.23)	99 (47.37)	.005
Hyperlipidemia n, (%)	37 (43.02)	154 (73.68)	.000
PCI History	19 (22.09)	84 (40.19)	.002
Laboratory parameters			
Hemoglobin, g/dL	13.86 ± 1.53	14.05 ± 1.66	.369
WBC, 10^3/μL	7.43 ± 1.89	7.91 ± 2.12	.069
Neutrophils, 10^3/μL	4.43 ± 1,38	4.81 ± 1.72	.070
Lymphocytes, 10^3/μL	2.24 ± 0.65	2.96 ± 10.45	.521
Monocytes, 10^3/μL	0.75 ± 2.63	0.45 ± 0.14	.102
Platelets, 10^3/μL	264.76 ± 69.48	264.41 ± 76.34	.971
Creatine, mg/dL	0.84 ± 0.19	0.93 ± 0.51	.084
TC, mg/dL	183.01 ± 37.56	184.72 ± 43.47	.750
Triglyceride, mg/dL	174.33 ± 85.7	196.48 ± 112.45	.102
HDL-C, mg/dL	45.47 ± 11.63	41.59 ± 9.13	.002
LDL-C, mg/dL	103.58 ± 31.77	106.16 ± 37.06	.572
NHR	105 ± 46.6	121.1 ± 50.8	.012
MHR	17.2 ± 60.7	11.4 ± 4.4	.171
LHR	2.4 ± 0.8	2.6 ± 0.9	.043
Echocardiographic parameters			
LVEF	60 ± 8.7	56 ± 10.8	.006
SWMA	24 (27.91%)	84 (40.19%)	.031
Drugs, n (%)			
Statin	27 (31.8)	41 (18.6)	.013

CAS: coronary artery stenosis; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LHR: Lymphocyte/High-density lipoprotein cholesterol LVEF: left ventricular ejection fraction; MHR: Monocyte/High-density lipoprotein cholesterol; NVS: no visible stenosis; NHR: Neutrophil/ High density lipoprotein cholesterol; PCI: percutaneous coronary intervention TC: total cholesterol; WBC: White blood cell.

ic, clinical, and laboratory data. HT (83.73% *vs.* 60.47%, $p<0.001$), DM (47.37% *vs.* 30.23%, $p=0.005$), and HL (73.68% *vs.* 43.02%, $p<0.001$) were more prevalent in Group 2 than Group 1. The NHR (121.1 ± 50.8 *vs.* 105.0 ± 46.6, $p=0.012$) and lymphocyte to HDL-C ratio (LHR; 2.6 ± 0.9 *vs.* 2.4 ± 0.8, $p=0.043$) were higher in Group 2 than Group 1, while HDL-C (41.59 ±9.13 *vs.* 45.47 ± 11.63, $p=0.002$) was lower.

The cut-off value of NHR for anatomically significant CAD was 103.2. An NHR higher than 103.2 predicted the presence of anatomically significant CAD with a sensitivity of 61.2% and specificity of 58.1% (AUC, 0.607, 95% CI: 0.535-0.678; $p=0.004$) (Figure 2).

In the univariate logistic regression analyses, age, male gender, HT, DM, left ventricular ejection fraction (LVEF), creatinine, and NHR ≥ 103.2 predicted moderate or severe CAS, while older age, male gender, HT, lower LVEF, and NHR ≥ 103.2 remained independent predictors

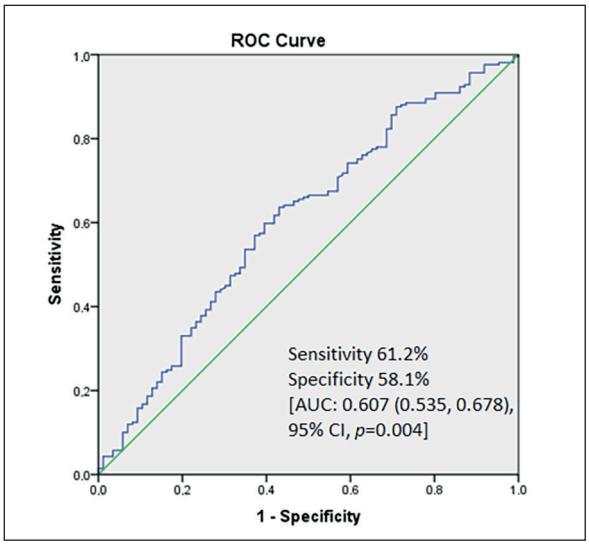

Figure 2. Receiver operating characteristic (ROC) curves for neutrophil to high density lipoprotein ratio (NHR) associated with anatomically significant coronary artery stenosis (CAS).

Table II. Univariate and multivariate logistic regression analysis showing the independent predictors of anatomically significant coronary artery stenosis in patients with documented ischemia.

	Univariate		Multivariatel	
	Odds ratio 95% CI	*p*-value	Odds ratio 95% CI	*p*-value
Age, year	1.058 (1.028-1.089)	< **0.001**	1.073 (1.038-1.110)	< **0.001**
Gender, male	1.969 (1.181-3.280)	**0.009**	2.222 (1.131-4.368)	**0.021**
Hypertension	3.131 (1.814-5.405)	< **0.001**	4.024 (2.103-7.702)	< **0.001**
DM	1.945 (1.143-3.310)	**0.014**	1.433 (0.789-2.602)	0.237
LVEF	0.963 (0.937-0.990)	**0.007**	0.967 (0.937-0.999)	**0.041**
Creatinine	8.407 (2.113-33.452)	**0.003**	2.039 (0.404-10.296)	0.388
NHR ≥ 103.2	2.041 (1.222-3.408)	**0.006**	2.084 (1.147-3.786)	**0.016**

DM: diabetes mellitus; LVEF: left ventricular ejection fraction; NHR: neutrophil/high-density lipoprotein cholesterol ratio.

of moderate or severe CAS in patients with documented ischemia (Table II).

Discussion

This study had two main findings: NHR was independently associated with moderate or severe CAS, and the NHR cut-off point for moderate or severe CAS in patients with ischemia (according to MPI SPECT) was ≥ 103.2.

Angina pectoris is the most typical symptom of CAD, affecting approximately 112 million people worldwide[7]. ICA remains the gold standard for diagnosing obstructive CAD. Nevertheless, it has crucial limitations, such as access site bleeding, contrast nephropathy, and procedural complications, including death[8]. Consequently, recent guidelines suggest that ICA be performed only in patients with symptoms refractory to guideline-based medical treatment or considered at high risk based on non-invasive tests[9].

High risk is defined as an estimated area of myocardial ischemia covering ≥ 10% of the left myocardium on MPI. However, Neglia et al[3] reported 56% specificity for MPI SPECT for diagnosing hemodynamically significant CAS. We calculated a positive predictive value (PPV) of MPI SPECT for anatomically significant CAD of 72.2%. Similarly, Takt et al[4] reported a PPV of 71% for SPECT for hemodynamically significant CAS. These results indicate that many patients are still being referred for ICA unnecessarily. In this trial, we evaluated the utility of baseline characteristics and NHR for detecting patients for whom ICA would be unnecessary.

CCTA can be used if MPI yields nonsignificant results before ICA. Therefore, we used the SCCT grading scale to assess the degree of coronary luminal diameter stenosis, which ranged from 0 (NVS) to 5 (at least one total occlusion) in both settings[6]. We grouped our patients (according to coronary stenosis grade) into NVS or minimal/mild coronary stenosis and moderate/high coronary stenosis groups, because it has been suggested that patients with moderate or severe CAS on CCTA should undergo ICA for a definitive diagnosis.

Up to 70% of patients undergoing ICA because of angina or documented myocardial ischemia do not have obstructed coronary arteries; this is more common in women than in men[10]. We also observed a higher proportion of females with NVS, or minimal or mild CAS (Group 1) compared with moderate or severe CAS (Group 2). The NHR was higher in moderate or severe CAS cases, although all the patients had documented ischemia.

Ischemia due to coronary vascular dysfunction without significant coronary artery obstruction is called ischemia with non-obstructive coronary arteries (INOCA)[10]. To make a diagnosis, most patients with documented ischemia or angina pectoris undergo anatomical imaging with CCTA or ICA (with or without fractional flow reserve). The detection of non-obstructive CAD or a normal coronary artery (NCA) during anatomical evaluation of the coronary arteries leads to patients with INOCA being ignored. However, failure to diagnose obstructive CAS in a patient with documented ischemia should encourage clarification of INOCA endotypes (epicardial and microvascular coronary spasms, impaired vasodilatation, and increased microvascular resistance) before searching for noncardiac causes of chest discomfort. A diagnosis of cardiac microvascular disease underlying INOCA is usually based on functional assessment of the microcirculation, which can be performed using invasive or non-invasive methods, including assessment of delayed contrast flow during angi-

ography, measurement of the coronary flow reserve (CFR) and index of microvascular resistance (IMR), evaluation of angina induced by intracoronary acetylcholine infusion, and assessment of myocardial perfusion by positron emission tomography (PET) and cardiac magnetic resonance (CMR)[11,12]. However, these conditions are rarely diagnosed precisely and customized therapy is not usually prescribed for these patients. Consequently, these patients continue to experience recurrent angina and a poor quality of life, characterized by repeated hospitalizations, unnecessary ICA, and adverse short- and long-term cardiovascular outcomes. Guidelines recommend CCTA as the initial test for low-risk patients, but this approach could bypass INOCA patients. In our study, the NHR was higher in the moderate or severe CAS group compared with the NVS or minimal/mild CAS group with documented ischemia. However, no study has examined the NHR in INOCA patients or patients with noncardiac chest pain. The NHR may have higher predictive value in INOCA patients compared to noncardiac chest pain patients. Further studies of the NHR are needed to understand its clinical significance in patients with chest pain and ischemia.

In a retrospective study of 404 consecutive patients who had undergone coronary angiography for typical angina pectoris, Kou et al[5] compared the NHR in patients classified into CAS $\geq$ 50%, CAS < 50%, and NCA groups, and found that the NHR was highest in the CAS $\geq$ 50% group. Furthermore, they reported that NHR was an independent predictor of severe CAS. They did not document any cases of myocardial ischemia. They also reported that the CAS $\geq$ 50% group had higher neutrophil counts than the other two groups ($p < 0.05$). Similarly, in our study, patients with CAS $\geq$ 50% had a higher NHR, but no group difference was detected in the neutrophil count. Our control group consisted of patients with documented ischemia (mostly INOCA patients). Since increased inflammation is also evident in INOCA patients, higher neutrophil counts might not be seen in the CAS $\geq$ 50% group compared with other groups[13].

It is possible to diagnose CAD with confidence based on detailed history-taking alone. However, recent studies reported that most patients with suspected CAD presented with atypical or nonanginal chest pain as few as 10-15% presented with typical angina[9]. Non-invasive MPI modalities such as MPI SPECT, CMR, and PET are, therefore, increasingly used to detect obstructive CAD, guide treatment, and provide prognostic information. PET and CMR are emerging as powerful tools for evaluating patients with known or suspected CAD. In their meta-analysis, Jaarsma et al[2] reported that both CMR and PET had significantly higher diagnostic accuracy than SPECT. Patients can avoid radiation exposure with CMR, and PET results in substantially lower radiation doses than SPECT[14]. Unfortunately, CMR and PET are less available than SPECT worldwide. Therefore, NHR $\geq$ 103.2 may have added value for evaluating MPI SPECT results.

To our knowledge, this is the first study to investigate the value of baseline characteristics and NHR for diagnosing moderate or severe CAS in patients with documented myocardial ischemia. Female sex, younger age, higher LVEF, and lower NHR were associated with NVS or minimal/mild CAS. Assessment of all these variables is a routine part of angina evaluations and is inexpensive and non-invasive. NHR can guide the clinical decision-making process. We believe that using another non-invasive test in patients who are female, young, and have a normal LVEF and myocardial ischemia on MPI could prevent complications.

Our study had several important limitations. First, it was a retrospective, non-randomized study. Further randomized controlled trials will give more precise results. Second, while the cardiologists who evaluated the CAS are experienced, they did not use any software, which could have led to misinterpretation of the data of some patients. Third, while our findings are valuable for guiding decision-making, the complication rates in our study group are unknown. Referring patients with documented ischemia for CCTA before ICA will lead to extra costs for health care systems, and CCTA also has possible complications, such as contrast nephropathy. We believe that a cost-effectiveness analysis should be performed in further large, randomized trials to guide daily practice.

Conclusions

Even when myocardial ischemia is confirmed by MPI, the rate of diagnosis of NVS or minimal/mild CAS is still high in association with ICA. Female sex, younger age, normal LVEF, and lower NHR could be assessed before referring patients for ICA, as they can be measured in an inexpensive and non-invasive manner. A higher NHR is associated with moderate or severe CAS; the cut-off in our study was 103.2.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Authors' Contribution
FB conceived and designed the work; contributed to data acquisition; analyzed and interpreted the data. CÇ drafted the manuscript and revised the manuscript critically for important intellectual content.

Ethical Approval
The study protocol was conformed to the tenets of the 1975 Declaration of Helsinki. Our institutional Ethics Committee approved the study.

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Data Availability Statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1) Zhang CK, Liu L, Wu WJ, Wang YQ, Yan HX, Guo R, Yan Jj. Identifying Coronary Artery Lesions by Feature Analysis of Radial Pulse Wave: A Case-Control Study. Biomed Res Int 2021; 2021: 5047501.
2) Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, Nelemans P, Schalla S. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012; 59: 1719-1728.
3) Neglia D, Rovai D, Caselli C, Pietila M, Teresinska A, Aguadé-Bruix S, Pizzi MN, Todiere G, Gimelli A, Schroeder S, Drosch T, Poddighe R, Casolo G, Anagnostopoulos C, Pugliese F, Rouzet F, Le Guludec D, Cappelli F, Valente S, Gensini GF, Zawaideh C, Capitanio S, Sambuceti G, Marsico F, Perrone Filardi P, Fernández-Golfín C, Rincón LM, Graner FP, de Graaf MA, Fiechter M, Stehli J, Gaemperli O, Reyes E, Nkomo S, Mäki M, Lorenzoni V, Turchetti G, Carpeggiani C, Marinelli M, Puzzuoli S, Mangione M, Marcheschi P, Mariani F, Giannessi D, Nekolla S, Lombardi M, Sicari R, Scholte A J, Zamorano JL, Kaufmann PA, Underwood SR, Knuuti J. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015; 8: e002179.
4) Takx RA, Blomberg BA, El Aidi H, Habets J, de Jong PA, Nagel E, Hoffmann U, Leiner T. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. Circ Cardiovasc Imaging 2015; 8: e002666.
5) Kou T, Luo H, Yin L. Relationship between neutrophils to HDL-C ratio and severity of coronary stenosis. BMC Cardiovasc Disord 2021; 21: 127.
6) Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, Dill KE, Jacobs JE, Maroules CD, Rubin GD, Rybicki FJ, Schoepf UJ, Shaw LJ, Stillman AE, White CS, Woodard PK, Leipsic JA. Coronary Artery Disease - Reporting and Data System (CAD-RADS): An Expert Consensus Document of SCCT, ACR and NASCI: Endorsed by the ACC. JACC Cardiovasc Imaging 2016; 9: 1099-1113.
7) Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1459-1544.
8) Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. Glob J Health Sci 2012; 4: 65-93.
9) Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020; 41: 407-477.
10) Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Karam N, Appelman Y, Fraccaro C, Louise Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D, Baumbach A. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J 2020; 41: 3504-3520.
11) Vancheri F, Longo G, Vancheri S, Henein M. Coronary Microvascular Dysfunction. J Clin Med 2020; 9: 2880.
12) Hombach V, Merkle N, Bernhard P, Rasche V, Rottbauer W. Prognostic significance of cardiac magnetic resonance imaging: Update 2010. Cardiol J 2010; 17: 549-557.
13) Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation 2017; 135: 1075-1092.
14) Stabin MG. Radiopharmaceuticals for nuclear cardiology: radiation dosimetry, uncertainties, and risk. J Nucl Med 2008; 49: 1555-1563.