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Original Study

The Impact of Prognostic Nutritional Index on Coronary Flow Reserve in Patients with Inflammatory Bowel Disease

İnflamatuvar Bağırsak Hastalarında Prognostik Nütrisyonel Indeksin Koroner Akım Rezervi Üzerine Etkisi

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ABSTRACT

Objective: *The recurring inflammation of mucosal layer of intestines is known as inflammatory bowel disease (IBD), which can be accompanied by nutritional deficiencies. The association between inflammation and coronary artery disease has been established. Coronary flow reserve (CFR), which is an established method to evaluate combined microvascular and epicardial flow of coronary arteries, can be assessed by using transthoracic echocardiography. The aim of this study was to evaluate the association of Prognostic Nutritional Index (PNI) with CFR in IBD patients.*
Method: *This prospective study included 101 patients with IBD. These patients were compared to control group (n=32). PNI was calculated by using serum albumin level and lymphocyte count. CFR was assessed by using Doppler echocardiography.*
Results: *Multivariate regression analysis indicated that the presence of IBD, age (>40 years) and decreased PNI (<53.8) independently predict impairment of CFR. The area under the curve (AUC) was 75.1% (95% CI:0.664-0.838), and PNI levels were significant predictor of low CFR (p<0.001).*
Conclusion: *This study showed that PNI, which is calculated using the serum level of albumin and lymphocyte count, is a strong predictor of decreased CFR in IBD patients in remission. Our findings support previous studies showing the relationship between PNI and coronary artery disease. This immunonutritional index has only two components and is easy to calculate, and inexpensive.*

Keywords: *Coronary flow reserve, inflammatory bowel disease, prognostic nutritional index*

ÖZ

Amaç: *Nutrisyonel yetersizliklerin eşlik edebildiği bağırsak mukoza katmanının tekrarlayıcı inflamasyonu, inflamatuvar bağırsak hastalığı (İBH) olarak bilinmektedir. İnflamasyon ve koroner arter hastalığının ilişkisi ortaya konulmuştur. Mikrovasküler ve epikardiyal akımı kombine bir şekilde değerlendirebilen koroner akım rezervi (KAR), transtorasik ekokardiyografi ile değerlendirilebilir. Bu çalışmanın amacı, İBH hastalarında prognostik nutrisyonel indeks (PNI) ile KAR arasındaki ilişkiyi değerlendirmekti.*
Yöntem: *Bu çalışma, prospektif olarak dahil edilen 101 İBH hastasını içermektedir. Bu hastalar kontrol grubu (n=32) ile karşılaştırılmıştır. PNI, serum albümin düzeyi, lenfosit sayısı kullanılarak hesaplanmıştır. KAR, doppler ekokardiyografi ile değerlendirilmiştir.*
Bulgular: *Çok değişkenli regresyon analizi İBH varlığı, yaş (>40) ve azalmış PNI'nın (<53,8) KAR'daki bozulmayı bağımsız bir şekilde predikte ettiğini ortaya çıkarmıştır. Eğri altında kalan alan (AUC) %75'di (95% CI: 0,664-0,838) ve PNI seviyesi düşük KAR için anlamlı bir prediktördü (p<0,001).*
Sonuç: *Bu çalışma göstermiştir ki serum albümin seviyesi, lenfosit sayısı ile hesaplanan PNI, remisyondaki İBH hastalarında azalmış KAR için güçlü bir prediktördür. Çalışmamız PNI ile koroner arter hastalığı ilişkisini gösteren önceki çalışmaları desteklemektedir. Bu immunonutrisyonel indeks sadece iki komponente sahiptir, kolayca hesaplanabilir ve ucuzdur.*

Anahtar kelimeler: *Koroner akım rezervi, inflamatuvar bağırsak hastalığı, prognostik nutrisyonel indeks*

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INTRODUCTION

Ischemic heart disease still remains as the leading cause of death for both men and women and accounted for 9.4 million deaths worldwide in 2016[1]. Hence, the early diagnosis and treatment of cardiovascular diseases plays a crucial role in the prevention of cardiovascular diseases. Prognostic nutritional index (PNI), which is a new combined inflammatory score calculated by using plasma albumin levels and lymphocyte count, has been studied as a mortality predictor in ST-segment elevation myocardial infarction (STEMI) and stable angina pectoris[2,3]. Malnutrition has been shown to be associated with poor prognosis in patients with cancer, acute heart failure, and patients with chronic kidney disease on dialysis[4-6], and has been established as a predictor of mortality and morbidity after gastrointestinal surgery[7].

The cause of ischemic heart disease is not only due to stenosis of the epicardial arteries but also can be due to microvascular endothelial dysfunction. The microvascular function of coronary arteries and atherosclerotic burden of epicardial coronary artery can be assessed by using Doppler echocardiography derived coronary flow reserve (CFR) measurement[8]. The association of inflammation with coronary endothelial function has been well-established[9,10].

The recurring inflammation of mucosal layer of intestines is known as inflammatory bowel disease (IBD), which is accompanied by systemic inflammation. The systemic inflammation, which has been accepted as a cardiovascular risk factor[11], affects many organs including coronary vessels. Due to the nature of inflammatory disease, its relationship with atherosclerosis has been studied and an association between IBD and atherosclerosis has been shown[12,13]. We hypothesized that the combination of chronic systemic inflammation and malnutrition might compromise the coronary artery flow. Hence, the aim of this study was to evaluate the relationship between Prognostic Nutritional Index (PNI) and CFR in IBD patients.

MATERIAL and METHODS

This study approved by the Istanbul Medeniyet University, Clinical Studies Ethic Committee of Goztepe Training and Research Hospital (7 May 2017, 2017/0117). Informed consent was taken from the parents of the patients enrolled in this study.

Patients and study design

We enrolled patients with IBD between the ages of 18 and 60. The diagnosis of IBD was established based on histopathological analysis of colonic biopsy materials, clinical manifestations, laboratory studies, and medical history. The exclusion criteria included high alcohol intake (>120 g/day) and presence of hypertension, any cardiac disease (ischemic, congenital, valvular) and arrhythmias, electrocardiographic abnormality, pulmonary disease (chronic obstructive or interstitial pulmonary disease, asthma), thyroid disease, hepatic and/or renal dysfunction, and diabetes mellitus. The patients with high triglyceride levels (>400 mg/dL), high body-mass indices (>35 kg/m^2), and increased left ventricular wall thickness (>1.0 cm) were also excluded from the study. We assessed 110 patients with IBD (CD and UC) fulfilling the inclusion criteria for the study, and applied to the gastroenterology outpatient clinic. 12 of CD patients had ileal, while 28 of them had ileocolic, 14 of them colic involvement. The mean duration of the disease in patients with CD was 3.5±1.9 years. 8 patients with UC had proctocolitis, 21 of them had left-sided colitis, 6 of them had extensive disease, and 17 of them had pancolitis. The mean duration of the disease in patients with UC was 6.5±2.9 years. A total of 9 (CD=4, UC=5) subjects were not on any treatment for IBD. The rest of IBD patients were on mesalamine (CD=49, UC=46), azathioprine (CD=36, UC=9), methotrexate (CD=3, UC=0), TNF-alfa inhibitors (CD=4, UC=0) therapy. None of them were on steroid therapy. Subjects were evaluated after a mini-

mum 15-day attack-free period (Crohn's Disease Activity Index [CDAI] <150 and Truelove-Witts Index [TWAS] <4)[14,15]. Control group consisted of 36 healthy, age and sex-matched volunteers. Data on demographic characteristics (age, gender) and BMI was recorded for each subject.

PNI was calculated by the following equation: 10 x [serum level of albumin (g/dL) plus lymphocyte count (per mm^3)]. A receiver operating characteristic (ROC) curve analysis was applied to all possible cut-off values that would predict the in-hospital survival so as to calculate the optimal optimal cut-off value for the continuous PNI. A receiver operating characteristic (ROC) curve analysis revealed that the PNI levels were able to predict the decreased CFR (AUC: 0.75; 95% CI:0.664-0.838; p<0.001) with an optimal cut-off value of 53.8 (Fig 1).

The study participants underwent transthoracic echocardiography and all basic parameters were obtained after 24-h restriction of beverages containing methylxanthine and its derivatives. The distal left anterior descending artery (LAD) was used to evaluate CFR. To visualize the LAD, the modified 2-chamber view was used and the average of three Doppler velocities of the LAD was obtained at baseline and after peak infusion of intravenous dipyridamole (0.56 mg/kg over 4 minutes)[16]. Due to the suboptimal visualization of the distal LAD, a total of 4 subjects in the IBD and 4 subjects in the control group were excluded from the study.

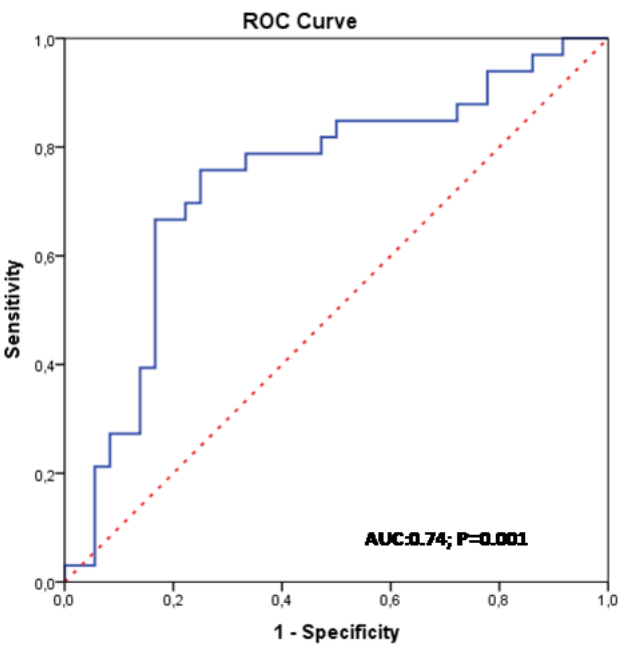

Figure 1.

Statistical analyses

Since the variables we studied have non-normal distributions, for descriptive analyses we used median and interquartile range The Mann-Whitney U test was applied for comparison of continuous and ordinal variables. Fisher's exact test was used to compare the proportions in different groups. The capacity of PNI values in predicting low CFR was analyzed by using ROC curve analysis. Age and CFR values were divided into two groups according to their median values. The univariate logistic regression analysis was performed to determine variables associated with decreased CFR. The multivariate logistic regression was applied to identify the independent predictors for decreased CFR.

RESULTS

A total of 138 subjects were included in the study. The baseline clinical, demographic, and biochemical characteristics of the participants are summarized in Table 1. Thirty-two patients were in the control group, while 106 patients had IBD (52 UC, 54 CD); and the mean age of the groups was 40±4 and 41±12 years, respectively. IBD patients had significantly lower serum albumin levels (4.2±0.4 vs 4.5±0.3 mg/dL; p=0.01) than the control group, whereas there was no significant difference between the groups in terms of BMI, age, HDL cholesterol, and fasting glucose levels. The levels of high-sensitive C-reactive protein (hs-CRP) and the prognostic nutritional index were not significantly different between the two groups (Table 1).

Table 1. Demographic and biochemical characteristics in patients with IBD disease and control subject.

	IBD	Control	P value
Age (years) Mean±SD	41±12	40±4	0.52
Gender (famale/male)	56/45	13/19	0.14
BMI (kg/m^2) Mean±SD	25.2±4.4	26.3±1.7	0.17
Systolic BP (mmHg) Mean±SD	122±15	120±8	0.29
Diastolic BP (mmHg) Mean±SD	75±8	77±5	0.43
Heart rate (beat/minute) Mean±SD	73±4	74±10	0.43
HDL cholesterol (mg/dL) Median (IQR)	45 (39-50)	43 (36-51)	0.30
LDL cholesterol (mg/dL) Mean±SD	114±30	114±21	0.98
Total cholesterol (mg/dL) Median (IQR)	183 (170-200)	181 (164-202)	0.70
Triglyceride (mg/dL) Mean±SD	121±50	118±45	0.82
Hs-CRP (mg/dL) Median (IQR)	1.45 (0.33-3.45)	1.29 (1.00-1.95)	0.42
Albumin, g/dL Mean±SD	4.2±0.4	4.5±0.3	0.01
Hs-CRP/Albumin ratio Median (IQR)	0.25 (0.06-0.73)	0.28 (0.23-0.46)	0.28
PNI Mean±SD	52.6±6.0	53.7±5.3	0.39
CDAI score Mean±SD	61±20	-	-
TWAS score Median (IQR)	4 (3-4)	-	-

BMI: Body mass index; BP: blood pressure, BUN: blood urea nitrogen; HDL: high density lipoprotein; LDL: low density lipoprotein; hsCRP: high sensitivity C-reactive protein; PNI: prognostic nutritional index; CDAI: Crohn's disease activity index, TWAS: Truelove Witts index

Table 2. Echocardiographic findings and Standard and tissue Doppler coronary flow reserve parameters of left ventricle.

	IBD	Control	P value
Aortic diameter (cm) Median (IQR)	2.88 (2.66-3.10)	2.70 (2.60-2.95)	0.07
LAD (mm) Mean±SD	31.1±4.5	30.2±2.9	0.30
IVSd (mm) Median (IQR)	9.2 (8.1-10.0)	9.0 (8.5-10.0)	0.55
PWd (cm) Median (IQR)	8.9 (7.9-10.0)	9.5 (8.0-10.0)	0.23
LVSD (mm) Median (IQR)	29.6 (27.1-32.0)	28.0 (27.0-30.0)	0.04
LVDD (mm) Median (IQR)	46.0 (44.3-48.2)	45.0 (42.0-47.0)	0.03
EF (%)	66.5±5.4	67.7±2.3	0.82
LVMI (g/m) Mean±SD	82.5±17.1	79.4±11.8	0.34
Mitral E max (cm/sn) Mean±SD	79.1±17.1	76.0±12.6	0.34
Mitral A max (cm/sn) Median (IQR)	69.0 (60.0-82.0)	58.0 (50.0-67.5)	<0.001
IVRT Median (IQR)	107 (100-127)	87 (80-90)	<0.001
Mitral E deceleration time (sn) Median (IQR)	208 (182-234)	187 (176-198)	0.004
Mit E max/ Lateral Em Median (IQR)	4.57 (3.65-5.54)	3.77 (3.45-4.56)	0.007
Mit E max/ Septal Em Median (IQR)	5.8 (4.8-7.1)	5.0 (4.0-6.1)	0.006
Baseline heart rate (bpm) Median (IQR)	75 (70-80)	75 (66-85)	0.97
Peak heart rate (bpm) Mean±SD	98±9	99±12	0.86
Baseline DPFV (cm/sn) Median (IQR)	24 (22-27)	22 (21-24)	0.005
Hyperemic DPFV (cm/sn) Median (IQR)	55 (48-61)	66 (63-77)	<0.001
Coronary flow reserve Median (IQR)	2.25 (2.08-2.52)	3.09 (2.84-3.33)	<0.001

LAD: indicates atrium diameter; IVSd: interventricular septum thickness at diastole; PWd: posterior wall thickness at diastole; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; EF: ejection fraction; LMVI: left ventricular mass index; Mitral E max: maximum velocity of mitral E wave; Mitral A max: maximum velocity of mitral A wave; IVRT: isovolumic relaxation time; Em: early peak velocity; Am: atrial peak velocity; DPFV: diastolic peak flow velocity of left anterior descending coronary artery.

There were no significant differences between the two groups with regard to the echocardiographic findings, including aortic diameter, left ventricular ejection fraction, left atrial diameter, interventricular septum thickness, posterior wall thickness, and mitral inflow E velocity (Table 2). However, the mitral A velocities [69.0(60.0-82.0) vs 58.0 (50.0-67.5); p<0.001], isovolumetric relaxation time [107 (100-127) vs 87 (80-90); p<0.001], mitral E valve deceleration time [208 (182-234)

Table 3. Correlations between coronary flow reserve and other study variable.

	IBD group		IBD group	
	r value	p value	r value	p value
Age (years)	-0.417	<0.001	-0.087	0.63
Hs-CRP (mg/dL)	-0.120	0.23	-0.194	0.28
Hs-CRP/albumin ratio	0.108	0.31	-0.200	0.27
PNI	0.480	<0.001	0.237	0.19
Mit E max/Lateral Em	-0.101	0.31	-0.108	0.57
Mit E max/Septal Em	-0.168	0.09	-0.108	0.57
Total cholesterol (mg/dL)	-0.154	0.16	0.194	0.28
Triglyceride (mg/dL)	0.006	0.96	0.071	0.69
HDL-cholesterol (mg/dL)	0.018	0.87	0.154	0.39
LDL-cholesterol (mg/dL)	-0.125	0.25	0.069	0.70
Systolic BP (mmHg)	-0.067	0.51	0.132	0.47
Diastolic BP (mmHg)	0.018	0.86	-0.019	0.91
TWAS	0.386	0.01		
CDAI	-0.202	0.02		

hsCRP: high sensitivity C-reactive protein; PNI: prognostic nutritional index; Mitral E max: maximum velocity of mitral E wave; Em: early peak velocity; HDL: high density lipoprotein; LDL: low density lipoprotein; BP: blood pressure; TWAS: Truelove Witts index; CDAI: Crohn's disease activity index.

Table 4. Multivariate logistic regression anaysis for prediction of low coronary flow reserve.

	OR	95% CI Lower-Upper	P value
Constant	0.001		
Age, >40 years	4.586	1.591-13.219	0.005
IBD presence	46.146	5.201-409.415	0.001
Male	2.193	0.749-6.415	0.15
PNI, <53.8	6.732	2.239-20.241	0.001
Mit E vax / Septal Em	1.135	0.816-1.579	0.45

IBD: inflammatory bowel disease; PNI: prognostic nutritional index; Mitral E max: maximum velocity of mitral E wave; Em: early peak velocity.

vs 187 (176-198); p=0.004], mitral Em /lateral Em ratios [4.57 (3.65-5.54)vs 3.77 (3.45-4.56); p=0.007], and mitral Em/septal Em ratios [5.8 (4.8-7.1) vs 5.0 (4.0-6.1); p=0.006] were significantly different in the IBD patients relative to the control group.

When relationship of CFR and others study variables were examined, CFR was significantly and inversely correlated with age (r=-0.417, p<0.001), TWAS score (r=-0,386; p=0.01), CDI (r=-0.202; p=-0.02), and significantly and positively correlated with PNI (r=0.480, p<0.001). CFR was also inversely but not significantly correlated with hsCRP (r=-0.120, p=0.23) and hCRP/albumin (r=-0.108, p=0.31) (Table 3).

Multivariate logistic regression analysis indicated that the presence of IBD, age (>40 years) and decreased PNI (<53.8) independently predicted impaired CFR (Table 4). A ROC curve analysis revealed that the PNI levels was able to predict the decreased CFR (Area under curve: 0.75; 95% CI:0.664-0.838; p<0.001).

DISCUSSION

The PNI, which demonstrates immunonutritional status of the patients, can reflect patients' protein turnover and immune system competence. The PNI was formulated to predict the perioperative outcomes of gastrointestinal surgery[17]. This combined inflammatory score has also been studied for patients with malignancy[18,19]. Kobayashi I et al.[20] studied chronic dialysis patients and they found the risk score to be a significant predictor of mortality. The relationship between immunologic parameters including neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and coronary artery disease has been established in large-scale studies[21,22].

The impact of the nutritional status in cardiovascular diseases has not been well-established although severe weight-loss has been found to be a predictor of mortality in patients with ACS and acute heart failure[4,23]. All of these studies have found that the patients with lower PNI tended to have more than one comorbidity; and after multivariate analysis, the lower PNI remained a significant risk factor of adverse clinical outcomes. Wada H. et al.[3] found the lower PNI as a predictor for adverse outcomes in stable angina pectoris. Some complex mechanisms contribute to the worse outcomes of malnutrition such as protein deficit, and immune system deficiency.

The association between malnutrition and inflammation has been shown in patients with chronic kidney disese and chronic heart failure[24,25]. Based on the current evidence, inflammation can play a crucial role in the development of atherosclerotic plaques in the epicardial coronary arteries and microvascular circulation of the heart[9,10]. The oxidative stress contributes to the arterial wall inflammation, which is due to reduced endothelium-derived nitric oxide. Therefore, the association between inflammation markers such as hs-CRP, white blood cell levels, neutrophil/lymphocyte ratio and acute coronary syndromes has been examined in large-scale studies[26].

The relationship between IBD, which is accompanied by systemic inflammation, and decreased CFR has been shown previously[18]. In this study, the negative correlation between hs-CRP and CFR was found in IBD patients in remission. The association of lower PNI levels with mortality/morbidity in UC patients undergoing surgery has been shown in another novel study[27]. In our study, lower PNI levels were found to be associated with decreased CFR in IBD patients in remission. This relationship persisted even after multivariate analysis (Table 4). Even though IBD patients had normal levels of hs-CRP, they had lower CFR measurements which could be due to the effects of chronic systemic inflammation. This study showed that parameters of diastolic function such as lateral Em, lateral isovolumetric relaxation time were lincreased in the IBD group (Table 2). These results can be explained with decreased CFR that shows compromised myocardial perfusion resulting in left ventricular dysfunction.

Early atherosclerosis is commonly seen in inflammatory immune-mediated disorders and atherosclerotic complications become one of the common causes of death in those patients. Due to the fact that reversible microvascular circulation disturbances[28], precede the epicardial coronary artery stenosis[29], the combined inflammatory score can detect atherosclerosis in early phases and can be used to enable early management of the disease.

CONCLUSIONS

This study showed that PNI, which was derived from the serum level of albumin and lymphocyte count, is a significant predictor of decreased CFR in IBD patients in remission. Our findings support previous studies showing the relationship between PNI and coronary artery disease. This immunonutritional index has only two components and is easy to calculate, and inexpensive.

STUDY LIMITATIONS

This is a single-center prospective study. Due to the suboptimal visualization of the distal LAD, a total of 8 subjects in the IBD and control groups were dropped from the study. Medications used in the treatment of IBD might affect the CFR in patients with IBD despite lack of any evidence of this association. Even though, the multivariate analysis was used; some covariates, which might affect the outcomes could not be measured. The histopathological assessment of biopsy materials could not be used for confirmation of remission and this is another limitation of our study. To confirm our findings, further large-scale studies should be conducted.

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