Relationship between hematologic parameters and left ventricular systolic dysfunction in stable patients with multi-vessel coronary artery disease

Yaygın koroner arter hastalığı ve kronik kararlı anjinası olan hastalarda sol ventrikül sistolik işlev bozukluğu ile hematolojik parametreler arasındaki ilişki

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ABSTRACT

Objectives: Multi-vessel coronary artery disease (MVCAD) has long been recognized as an important predictor of adverse outcomes in patients with chronic stable angina. The aim of this study is to investigate the relationship between hematologic parameters and impairment of left ventricular systolic functions in patients with stable MVCAD.

Study design: Patients (n=202) with stable angina and MVCAD were included in this study. According to the left ventricle ejection fraction (LVEF) determined by echocardiography, patients were divided into two groups as the preserved group (LVEF >50%) and the impaired group (LVEF <50%). The preserved group consisted of 106 patients and the impaired group consisted of 96 patients.

Results: The frequency of diabetes mellitus was significantly higher in the impaired group compared to the preserved group (respectively, 50% *vs.* 33%, p=0.01). High sensitivity C-reactive protein (hs-CRP) levels and, neutrophil/lymphocyte ratio (N/L ratio) were significantly higher in the impaired group than in the preserved group (3.9±2.4 *vs.* 7.9±3.8, p<0.001; 2.7±0.7 *vs.* 3.9±1.2, p<0.001, respectively). There was a significant correlation between LVEF, N/L ratio and hs-CRP; hs-CRP and N/L ratio were positively correlated (r=0.584; p<0.001), and LVEF was negatively correlated with both hs-CRP and N/L ratio (r=-0.48, p<0.001 and r=-0.43, p<0.001, respectively). A N/L ratio >3.0 had 77% sensitivity and 68% specificity in predicting left ventricular dysfunction in patients with stable MVCAD. In multivariate analysis, N/L ratio (OR: 2.456, <95% CI 2.056–4.166; p<0.001) was an independent predictor of left ventricular dysfunction in stable patients with MVCAD.

Conclusion: N/L ratio and hs-CRP, which is inexpensive and easily measurable in the laboratory, is independently associated with impaired LV systolic functions in patients with stable MVCAD.

ÖZET

Amaç: Yaygın koroner arter hastalığı (YKAH) kronik kararlı anjinalı hastalarda gelişecek klinik olayların öngördürücüsü olarak bilinmektedir. Bu çalışmanın amacı, YKAH olanlarda sol ventrikül sistolik fonksiyonları ile hematolojik parametreler arasındaki ilişkiyi araştırmaktır.

Çalışma planı: Yaygın KAH olan kararlı anjinalı 202 hasta çalışmaya alındı. Hastalar ekokardiyografiyle belirlenen sol ventrikül ejeksiyon fraksiyonuna (LVEF) göre, bozulmuş ventrikül grubu (LVEF <%50) ve korunmuş ventrikül grubu (LVEF >%50) olarak ikiye ayrıldı. Korunmuş ventrikül grubunda 106 ve bozulmuş ventrikül grubunda 96 hasta bulunmaktaydı.

Bulgular: Diabetes mellitus sıklığı, bozulmuş ventrikül grubunda daha fazla olarak bulundu (sırasıyla, %50 ve %33, p=0.01). Bozulmamış ve bozulmuş ventrikül gruplarının ortalama yüksek duyarlıklı C-reaktif protein (hs-CRP) düzeyi (sırasıyla, 3.9±2.4 ve 7.9±3.8, p<0.001) ve nötrofil/lenfosit oranı (N/L oranı) (sırasıyla 2.7±0.7 ve 3.9±1.2, p<0.001) bozulmuş ventrikül grubunda anlamlı olarak daha yüksekti. LVEF, N/L oranı ve hs-CRP arasında anlamlı korelasyon vardı. N/L oranı ve hs-CRP arasında pozitif (r=0.584, p<0,001) korelasyon vardı. LVEF hem hs-CRP, hem de N/L oranıyla negatif bir korelasyon gösterdi (sırasıyla, r=-0.48, p<0.001 ve r=-0.43, p<0.001). N/L oranının >3 olması, %77 duyarlılık ve %68 özgüllük ile YKAH'ı olan kararlı anjinalı hastalarda sol ventrikül sistolik işlev bozukluğunu öngördü. Çok değişkenli analizde N/L oranı (OO: 2.456, <%95 GA 2.056-4.166, p<0.001) kararlı KAH hastalarda sol ventrikül işlev bozukluğunun bağımsız bir öngördürücü faktörüydü.

Sonuç: Ucuz ve laboratuvarda kolaylıkla belirlenebilen N/L oranı ve hs-CRP YKAH olan kararlı anjinalı hastalarda sol ventrikül sistolik işlev bozukluğunun belirleyicileri olarak bulunmuştur.

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The clinical presentation, involvement of coronary arteries, and left ventricular systolic function are the important predictors of adverse outcomes and mortality in patients with coronary artery disease (CAD).[1] Multi-vessel coronary artery disease (MVCAD) has long been recognized as an important predictor of long-term survival in patients with chronic stable angina.[2] Some patients with stable MVCAD have normal ejection fraction (EF) in echocardiographic examination, while others have impaired EF in spite of the absence of coronary event history. The main pathophysiological mechanisms of impairment of left ventricular systolic functions are not clearly understood.

There is an established relationship between inflammatory status and adverse outcomes in CAD.[3,4] With the growing understanding of the role of inflammation in the atherosclerotic process, studies have focused on high sensitivity C-reactive protein (hs-CRP) and other inflammatory markers. hs-CRP is an acute phase protein and several studies have shown that CRP may have prognostic value in patients with CAD who are undergoing percutaneous coronary intervention (PCI).[5-7] N/L ratio is the sign of balance between neutrophil and lymphocyte levels in the body and is an indicator of systemic inflammation.[8,9] High N/L ratio is known to be an independent prognostic predictor of mortality in patients with CAD and a predictor of long-term mortality in patients with ST-elevation myocardial infarction.[10,11] In the present study, we aimed to investigate the relationship between inflammatory parameters and impairment of left ventricular systolic functions in patients with stable MVCAD.

PATIENTS AND METHODS

In this prospective and cross-sectional study, 202 (124 male, mean age 66.7±10.1) consecutive patients with stable angina and MVCAD as determined by coronary angiography were included. According to LV function in echocardiography, the patients were divided into two groups as the preserved group [left ventricle ejection fraction (LVEF) ≥50%] and the impaired group (LVEF <50%).

The exclusion criteria were known previous myocardial infarction or any revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), unstable angina pectoris, congenital heart disease, severe valvular heart disease, chronic renal failure, known malignancy, known inflammatory disease, infectious disease, hematological disease, autoimmune disease, and anticoagulant agent use. Age, gender, current therapy, lipid profile, risk factors for CAD, body mass index, hematological parameters, and biochemical measurements were recorded in all patients. This study complied with the Declaration of Helsinki and the protocol was approved by our local ethics committee. Informed consent was obtained from each patient.

Abbreviations:

CAD	*Coronary artery disease*
DM	*Diabetes mellitus*
EF	*Ejection fraction*
hs-CRP	*High sensitivity C-reactive protein*
LVEF	*Left ventricle ejection fraction*
MVCAD	*Multi-vessel coronary artery disease*
PCI	*Percutaneous coronary intervention*

A conventional coronary angiography was performed using Philips Integris 5000 equipment (Philips Medical Systems, Best, The Netherlands) in all patients after admission. Two independent cardiologists interpreted each angiogram. Severity of CAD was assessed by using the Gensini scoring system, which grades narrowing of the lumens of the coronary arteries.[12] In addition, each coronary lesion was separately scored and added for each coronary vessel to provide the vessel Syntax score and then summed to provide the overall patient Syntax score as previously described using dedicated software (Syntax score V1.0.003, Cardialysis B.V., Rotterdam, The Netherlands).[13] According to the results of coronary angiography, significant stenosis was defined as ≥70% of the major coronary arteries. Intra- and inter-observer variability were obtained from random samples of 60 patients. The intra- and inter-observer variability for significant stenosis were 3% and 5%, respectively.

Transthoracic echocardiography was performed in the cardiology department's echocardiography laboratory by two independent echocardiographer cardiologists using Vivid 7 instruments (GE Medical Systems, Milwaukee, WI, USA), with a 2.5-MHz transducer and harmonic imaging. According to the recommendations of the American Society of Echocardiography,[14] left ventricular systolic and diastolic diameters were measured by M-mode echocardiography. The LVEF was assessed using the modified biplane Simpson's method.[15]

In all patients, antecubital venous blood samples for laboratory analysis were drawn on admission to the emergency room. hs-CRP was measured using a

BN2 model nephlometer (Dade-Behring). Common blood count parameters were measured by Sysmex K-1000 auto analyzer within 5 minutes of sampling using citrate based anticoagulant tubes. Glucose, creatinine, blood urea nitrogen, lipid profile (total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, triglyceride were determined by standard methods.

Table 1. Baseline characteristics of patients in groups

	Preserved group (n=106)			Impaired group (n=96)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			65.8±9.9			67.6±10.3	0.21
Gender							
Female	41	39		37	39		0.98
Male	65	61		59	61		
Body mass index (kg/m^2)			25.5±2.8			25.9±2.9	0.30
Smoking	37	5		28	29		0.38
Hypertension	71	67		62	65		0.72
Hypercholesterolemia	40	38		29	30		0.21
Diabetes mellitus	35	33		48	50		0.01
Blood pressure (mmHg)							
Systolic			135.7±17.4			137.7±16.7	0.40
Diastolic			77.1±14.8			79.5±15.7	0.25
Heart rate (beats/min)			81.5±13.5			79.5±16.4	0.33
Biochemical parameters							
Total cholesterol (mg/dl)			173.1±37.5			181.4±40.6	0.13
HDL-cholesterol (mg/dl)			35.6±6.7			35.5±5.7	0.90
LDL-cholesterol (mg/dl)			120.5±28.8			126.5±30.8	0.15
Plasma triglycerides (mg/dl)			125.7±59.3			118.8±39.1	0.33
Fasting glucose (mg/dl)			129.6±36.3			134.3±35.8	0.35
Blood urea nitrogen (mg/dl)			23.2±8.3			22.3±6.2	0.37
Creatinine (mg/dl)			1.23±0.32			1.24±0.31	0.88
Uric acid (mg/dl)			4.0±1.8			3.9±1.7	0.76
hs-CRP (mg/l)			3.9±2.4			7.9±3.8	**<0.001**
Current therapy							
Aspirin	33	35		29	30		0.47
Beta-blockers	21	20		22	23		0.59
ACE-inhibitors/ARB	53	50		45	47		0.65
Nitrates	9	9		11	12		0.48
Statins	45	43		40	42		0.91
Ca-antagonists	33	31		26	28		0.52
Angiographic properties							
Gensini score			85.5±29.1			88.1±22	0.47
Syntax score			27.7±5.2			28.3±4.9	0.40

LDL-cholesterol: Low-density lipoprotein cholesterol; HDL-cholesterol: High-density lipoprotein cholesterol; hs-CRP: High sensitivity C-reactive protein; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker.

Table 2. Echocardiographic parameters of all patients in groups

	Preserved group (n=106)	Impaired group (n=96)	*p*
Left ventricular end-diastolic diameter (mm)	51.0±4.3	63.0±6.8	**<0.01**
Left ventricular end-systolic diameter (mm)	33.2±4.0	48.7±7.8	**<0.01**
Interventricular septum thickness (mm)	11.9 ±1.9	10.9±1.4	**<0.01**
Posterior wall thickness (mm)	11.2±1.4	10.6±1.0	**<0.01**
Left ventricular ejection fraction (%)	58.4±6.7	28.9±5.3	**<0.01**
Left ventricular mass (gr)	160.1±33.9	155.1±34.2	0.29
Left atrial size (mm)	34.7±4.8	41.4±3.3	**<0.01**
Right ventricular end diastolic diameter (mm)	35.9±4.0	39.5±2.8	**<0.01**
Systolic pulmonary artery pressure (mmHg)	32.6±10.6	38.5±13.2	**<0.01**

We report continuous data as mean and standard deviation or median. We compared continuous variables using Student's t-test or Mann-Whitney U-test between groups. Categorical variables were summarized as percentages and compared with the chi-square test. Pearson correlation coefficients examined the degree of association between examined variables. A *p* value <0.05 was considered significant. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of neutrophil/lymphocyte (N/L) ratio, optimal cut-off value for predicting left ventricular dysfunction in stable patients with MVCAD. The effects of individual variables on left ventricular dysfunction were each calculated in univariate analysis. The variables for which the unadjusted *p* value was <0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. P value <0.05 was considered significant and confidence interval (CI) was 95%. All statistical analyses were performed using SPSS version 15 (SPSS, Inc., Chicago, Illinois).

RESULTS

The baseline demographic, biochemical characteristics, history of pharmaceutical use, and the angiographic properties of patients in both groups are shown in Table 1. Age, gender, biochemical parameters, and angiographic properties were similar between groups. The presence of diabetes mellitus (DM) was significantly higher in the impaired group compared to the preserved group (respectively; 50% *vs.* 33%, p=0.01), however, hypertension and smoking status were similar between groups. With respect to baseline laboratory status, fasting glucose, cholesterol parameters blood urea nitrogen creatinine levels were not significantly different between groups. However, hs-CRP levels were significantly higher in the impaired group than in the preserved group (3.9±2.4 vs. 7.9±3.8, p<0.001). The Gensini and Syntax scores of patients were also similar in the preserved and impaired groups (Gensini score=85.5±29.1, 88.1±22, p=0.47; Syntax score=27.7±5.2, 28.3±4.9, p=0.40, respectively). The echocardiographic parameters are shown in Table 2. Among the echocardiographic parameters, while the mean LVEF was 58.4±6.7 in the preserved group, it was 28.9±5.3 in the impaired group (p<0.01). CBC parameters are shown in Table 3. Hemoglobin, white blood cells, platelet count, mean platelet volume and red cell distribution width were similar between groups. With respect to white blood cell distribution, there was no significant difference in eosinophil and monocyte counts between groups (p=0.11 and p=0.46, respectively). However, neutrophil levels (64.1±5.2 *vs.* 70.3±6.0) were significantly higher in the impaired group, while lymphocyte levels (24.6±4.1 *vs.* 19.5±4.5) were significantly higher in the preserved group (p<0.001 for each). N/L ratio was also significantly higher in the impaired group (2.7±0.7 *vs.* 3.9±1.2, p<0.001) (Table 3). The ROC curve of N/L ratio for predicting LV function is shown in Fig. 1. A N/L ratio >3.0 mg/dl had 77% sensitivity and 68% specificity in predicting left ventricular dysfunction in stable patients with MVCAD. A significant correlation was also detected between hs-CRP and N/L ratio (r=0.584; p<0.001).

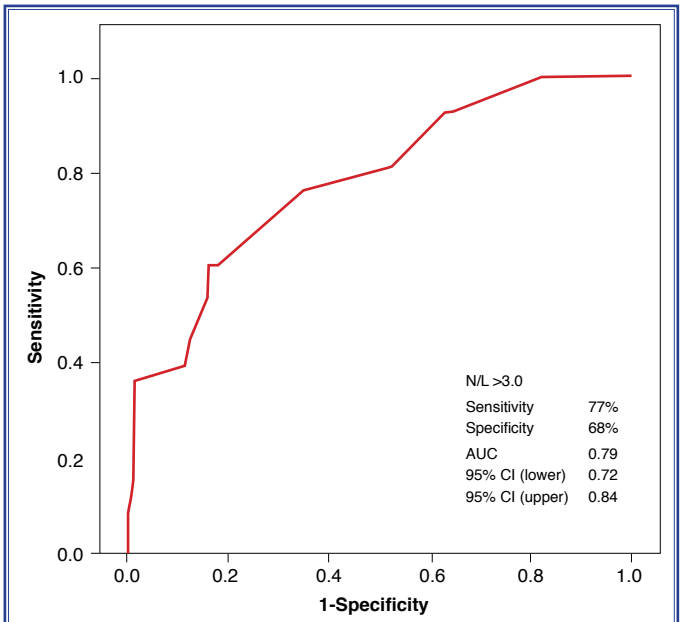

Figure 1. The receiver-operating characteristic curve of neutrophil/lymphocyte ratio for predicting LV function in patients with multi-vessel coronary artery disease.

Some variables that can affect LV function were significantly different between groups. Thus, the effects of multiple variables on the LV function were analyzed with both univariate and multivariate logistic regression analyses. The variables for which the unadjusted *p* value was <0.10 in univariate analysis were identified as potential risk markers for LVEF and were included in the full multivariate model. In multivariate analysis, hs-CRP [Odds ratio (OR)]: 1.347, <95% confidence interval (CI) 1.182-1.534; p<0.001),

Table 3. Common blood counting parameters of patients

	Preserved group (n=106)	Impaired group (n=96)	*p*
Hemoglobin (g/dl)	12.6±1.5	12.4±1.3	0.21
White blood cell count (10^9/L)	7.12±1.9	7.58±2.1	0.12
Platelet count (10^9/L)	244.3±61.5	245.4±64.1	0.90
Hematocrit (%)	41.0±4.6	41.5±4.9	0.48
Red cell distribution width (%)	14.1±1.7	14.4±1.5	0.16
Red blood cell count (10^6/mL)	4.84±0.82	4.78±0.80	0.61
Mean corpuscular volume (fl)	84.3±5.7	83.0±6.0	0.14
Mean corpuscular hemoglobin (pg)	28.6±2.3	28.8±2.4	0.55
Mean platelet volume (fl)	8.7±0.9	8.9±0.9	0.09
Platelet distribution width (%)	15.0±1.8	15.1±1.7	0.47
White cell distribution (%)			
Neutrophil	64.1±5.2	70.3±6.0	**<0.001**
Lymphocyte	24.6±4.1	19.5±4.5	**<0.001**
Eosinophils	2.6±0.5	2.4±0.7	0.11
Monocytes	7.1±0.9	7.0±1.4	0.46
Neutrophil/lymphocyte ratio	2.7±0.7	3.9±1.2	**<0.001**

Table 4. Effects of various variables on LV function in univariate and multivariate logistic regression analyses

	Unadjusted OR	95% CI	*p*	Adjusted OR*	95% CI	*p*
Age	1.018	0.990-1.046	0.214			
Gender	1.006	0.570-1.774	0.984			
Hypertension	0.900	0.510-1.609	0.720			
Diabetes mellitus	2.029	1.148-3.584	0.015	2.207	1.075-4.530	0.031
Smoking	0.768	0.424-1.391	0.384			
LDL-cholesterol	1.007	0.997-1.016	0.154			
Gensini score	1.004	0.993-1.015	0.476			
Syntax score	1.023	0.969-1.081	0.407			
hs-CRP	1.435	1.286-1.608	**<0.001**	1.347	1.182-1.534	**<0.001**
Mean platelet volume	1.293	0.958-1.748	0.082	1.410	0.964-2.063	0.076
Red cell distributed width	1.127	0.953-1.334	0.163			
Neutrophil/lymphocyte ratio	3.072	2.373-5.616	**<0.001**	2.456	2.056-4.166	**<0.001**

OR: Odds ratio; CI: Confidence interval; hs-CRP: High sensitivity C-reactive protein.

* Adjusted for, age, gender, hypertension, diabetes mellitus, smoking, LDL-cholesterol, Gensini score, Syntax score, high sensitive C-reactive protein, red cell distributed width, mean platelet volume and neutrophil/lymphocyte.

N/L ratio (OR: 2.456, <95% Cl 2.056-4.166; p<0.001) and DM (OR: 2.207, <95% Cl 1.075-4.530; p=0.031) were independent predictors of left ventricular dysfunction in stable patients with MVCAD (Table 4).

DISCUSSION

This study includes three major findings for patients with stable MVCAD. There is an independent relationship between N/L ratio, the presence of DM, baseline hs-CRP levels and impaired left ventricular systolic function in patients with stable MVCAD. Baseline N/L ratio is a specific and sensitive predictor of impaired left ventricular systolic function in patients with stable MVCAD. Additionally, these parameters are correlated with each other.

Multi-vessel disease was associated with worse prognosis compared to single- or two-vessel disease in stable patients with CAD and preserved ventricular function at 5-year follow-up.[16] The presence of MVCAD conferred a 3.1-fold increase in the risk of mortality, regardless treatment.[17] The survival rate of patients with stable CAD and preserved left ventricular function is usually good, but there is a higher risk of mortality in patients with impaired left ventricular function.[18] Additionally, one third of patients with stable angina pectoris have impaired LV function.[19]

In the presence of CAD, DM is a predictor of worsening LV systolic dysfunction independent from other risk factors.[20] Hyperglycemia initially causes metabolic disturbances, endothelial dysfunction, and myocardial microvascular changes. These changes result in myocyte injury, necrosis, myocardial fibrosis, and hypertrophy. Additionally, the diabetic myocardium is susceptible to higher rates of myocyte death by both apoptosis and necrosis.[20] In the present study, the prevalence of DM was significantly higher in the impaired LV systolic function group. Also, the presence of DM was independent predictor of impaired left ventricular systolic functions in patients with stable MVCAD.

Inflammatory processes play a key role at all stages of atherosclerosis. With the growing understanding of the role of inflammation in the atherosclerotic process, studies have focused on hs-CRP and other inflammatory markers for the evaluation of risk.[21] hs-CRP is an acute phase reactant and marker of inflammation with a half-life of 19 hours. It is released approximately six hours after a coronary event.[22] Several studies demonstrated a significant correlation between the vascular occlusion score and baseline hs-CRP levels.[6,7] Inflammation has also been implicated in the development and the progression of CAD.

N/L ratio is a measure of the balance between neutrophil and lymphocyte levels in the body and is an indicator of systemic inflammation.[8,9] N/L ratio was evaluated innumerous studies of CAD and acute

coronary syndromes.[23-25] In our recently published study[23] we demonstrated that N/L ratio is associated with the angiographic progression of the atherosclerotic process in patients with CAD. Papa et al.[24] demonstrated in their study that high N/L ratio was associated with increased cardiac mortality in clinically stable patients with CAD. Duffy et al.[25] evaluated the predictive role of N/L ratio in patients undergoing PCI finding that elevated pre-procedural N/L ratio is associated with an increased risk of long-term mortality.

In the SOLVD study, neutrophil count was shown to be significantly associated with cardiovascular death, while an inverse relationship was demonstrated between the lymphocyte count and mortality in patients with ischemic and non-ischemic left ventricular systolic dysfunction.[26] Some researchers have shown that neutrophils release large amounts of inflammatory mediators and, because of short neutrophil half-life, neutrophilia may be associated with the acute inflammatory response to tissue injury. Increasing attention has been directed toward the role of neutrophils as mediators of tissue destruction in inflammatory conditions. In patients with stable angina, neutrophils secrete the chemotactic agent leukotriene B4.[27] The association between neutrophilia and impaired microvascular perfusion may be a manifestation of neutrophil-mediated microvascular plugging.[27] In addition, Ommen et al.[28] demonstrated a decrease in total and relative number of circulating lymphocytes during acute myocardial infarction and advanced congestive heart failure. In the present study, neutrophils and N/L ratio were higher in the impaired group, while lymphocytes were significantly lower.

In conclusion, complete blood count is the most widely available laboratory data collected on admission to the hospital. In our study, we suggest that N/L ratio, which is an inexpensive and easily measurable laboratory parameter, is independently associated with impaired LV systolic functions in patients with stable MVCAD. In addition, N/L ratio is a sensitive and specific predictor of impaired LV systolic dysfunction. Apart from predictive value, N/L ratio may be a useful biomarker for stratification of risk and provides valuable and timely information about impairment of LV systolic functions in patients with stable MVCAD and may also lead to further therapeutic or interventional implications.

The major limitations of the present study are single center experience and the relatively small number of patients in our two study groups. However, our population contains homogeneous unselected patients with MVCAD and stable angina pectoris, therefore mirroring a real world scenario.

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Key words: C-reactive protein/analysis; coronary artery disease; multivariate analysis.

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