MCBU SBED
MANİSA CELAL BAYAR ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ DERGİSİ
MANISA CELAL BAYAR UNIVERSITY JOURNAL OF INSTITUTE OF HEALTH SCIENCE
ISSN: 2147-9607

ARAŞTIRMA MAKALESİ
RESEARCH ARTICLE
CBU-SBED, 2021, 8(1): 129-134

Karotis Arter Hastalığı Tanısı Almış Hastalarda Prognostik Beslenme İndeksi ile Karotis Arter Darlığı Arasındaki İlişki

The Relationship Between Prognostic Nutritional Index and Carotid Artery Stenosis in Patients with Diagnosed Carotid Artery Disease

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Gönderim Tarihi / Received: 17.12.2020
Kabul Tarihi / Accepted: 18.01.2021
DOI: 10.34087/cbusbed. 842454

Öz

Giriş ve Amaç: Prognostik beslenme indeksi (PNI) ile karotis arter stenozu (KAS) arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışma, karotis endarterektomi (CEA) geçiren hastaları ve tıbbi tedavi gören kritik olmayan KAS'lu hastaları içermektedir. Tüm veriler geriye dönük olarak hastanemizin tıbbi dosya kayıtlarından alındı. Hastaneye kabul sırasında hastalardan elde edilen değerler PNI hesaplamasında kullanıldı.
Bulgular: Cerrahi grupta 82 hasta (% 68,3 erkek, ortalama yaş: 70,5 ± 8,9 yıl), medikal grupta 79 hasta (% 72,2 erkek, ortalama yaş: 62,0 ± 9,1 yıl) kaydedildi. Cerrahi grupta anlamlı düzeyde daha yüksek BUN (p <0,001), daha yüksek CRP (p = 0,037), daha düşük lenfosit sayısı (p <0,001), daha düşük PNI (p = 0,008) ve daha düşük LDL-C (p = 0,045) değerleri tespit ettik . Karotis stenoz gelişimini tahmin etmek için, 47,25'lik bir Cut-Off seviyesinde, PNI için% 73,4 duyarlılık ve% 46,3 özgüllük vardı (Eğri altındaki alan (EAA): 0,619, % 95 CI: 0,533-0,706, Log rank p = 0.009).
Sonuç: Çalışmamızda PNI'nın KAS progresyonunu öngören bağımsız bir değişken olmadığını bulmamıza rağmen, PNI değerleri cerrahi grupta istatistiksel olarak anlamlı derecede düşüktü. PNI, hastalarda olası bir KAS belirteci olabilir. Bunun için sağlıklı bireyleri içeren geniş çaplı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ateroskleroz, Karotis Arter Stenozu, Prognostik Beslenme İndeksi.

Abstract

Objective: To investigate the relationship between prognostic nutritional index (PNI) and carotid artery stenosis (CAS).
Material and Methods: This retrospective observational study included patients undergoing carotid endarterectomy (CEA) and patients with non-critical CAS who received medical treatment. All data retrieved retrospectively from the hospital medical files. The values acquired from the patients during acceptance to the hospital were used in the calculation of PNI.
Results: There were 82 patients (68.3 % male, mean age: 70.5±8.9 years) in surgical group, and 79 patients (72.2% male, mean age: 62.0±9.1 years) were recorded in medical group. We detected statistically difference in surgical group in terms of higher BUN (p <0.001), higher CRP (p = 0.037), lower lymphocyte (p <0.001), lower PNI (p = 0.008) and lower LDL-C (p = 0.045). For predicting development of carotid stenosis, in a cut-off level of 47.25 there were 73.4% sensitivity and 46.3% % specificity for PNI (Area under the curve (AUC): 0.619, 95% CI: 0.533-0.706, Log rank p = 0.009).
Conclusion: Although we found that PNI was not an independent variable predicting CAS progression in our study, PNI values were statistically significantly lower in the surgical group. PNI may be a potential marker of CAS in patients. For this, large-scale studies involving healthy individuals are needed.

Keywords: Atherosclerosis, Carotid Artery Stenosis, Prognostic Nutritional Index.

1. Introduction

Ischemic stroke is an important reason of long-term loss of workforce in developed countries. One of the most important causes of ischemic stroke is carotid artery stenosis (CAS). Many studies have shown that carotid endarterectomy reduces the risk of stroke and death (1). Additionally, in patients with asymptomatic CAS, the incidence of stroke increases by 0.35-5%, meantime the incidence and mortality of acute cardiovascular disease also increases significantly (2). As the main cause of CAS, it is well known that atherosclerosis is associated with inflammation and immunity (3). In this context, the importance of albumin originates from its anti-inflammatory, antioxidant, anticoagulant features and its effects on osmotic pressure. Similarly, lymphopenia is associated with important adverse events in atherosclerotic cardiovascular diseases. The relationship between inflammatory biomarkers and coronary artery disease (CAD) has been demonstrated in many studies (4). In previous study, they found that a relationship between low serum albumin levels and increased cardiovascular morbidity and mortality (5). Malnutrition has been reported to be associated with worse clinical outcomes in patients with heart failure (6). The prognostic nutritional index (PNI), which is a parameter that calculated using albumin and lymphocyte count, can be used in the evaluation of atherosclerosis. However, the prognostic significance of the PNI in patients with CAS has not been fully investigated. Therefore, the aim of the present study was to evaluate the prognostic value of nutritional status using the PNI in patients who underwent carotid endarterectomy (CEA) and unoperated patients who have less than 50% CAS.

2. Materials and Methods

2.1. Patients

In this retrospective observational study, we included patients who underwent CEA and patients with noncritical CAS who were followed up with medical therapy. This study was carried out between 2017 - 2019 in Bursa Yüksek İhtisas Training and Research Hospital Cardiovascular Surgery Department. The study was approved by the local institutional Ethical Committee of Health Sciences University Bursa Higher Specialization Training and Research Hospital (Ethical Committee number: 2011-KAEK-25 2020/06-15).

Carotid artery stenosis was diagnosed by history and physical examination followed by Doppler ultrasonography and carotid digital subtraction angiography or CT angiography. All evaluated data were taken from the hospital's medical records retrospectively. In our center, carotid endarterectomy was performed to symptomatic patients with more than 50% carotid stenosis and to asymptomatic patients in low and moderate risk groups with more than 80% carotid stenosis. Similarly, surgery was performed in asymptomatic patients at risk of embolism and with 60-80% ulcerated carotid artery stenosis.

Patients who underwent coronary artery bypass and CEA surgery simultaneously, patients with malignancy, inflammatory disease and chronic renal failure were excluded from the study. After exclusion, 82 patients who underwent CEA included in the surgical group and 79 patients with less than 50% CAS who were followed up with medical treatment were included in the medical group. All data were recorded as age, gender, comorbidities (hypertension, diabetes mellitus), the presence of CAD, statin usage, and previous cerebrovascular event (CVE). Patients with undergoing CEA were operated under local anaesthesia.

2.2. Laboratory measurements

Fasting venous blood samples were taken from the antecubital vein of each patient. Hematologic parameters were measured by using an automated haematological analyser (Coulter LH 780 Analyzer, CA, USA). Levels of biochemical parameters were measured using the chemistry analyser (Beckman Coulter AU5800, CA, USA).

Prognostic Nutrition Index (PNI) Calculation

The values obtained from the blood tests taken from the patients during admission to the hospital were used in the calculation of PNI with the following formula:

PNI= Serum albumin level (g/L) + total lymphocyte count (103/μL) x 5

2.3. Statistical Analysis

Continuous and ordinal variables were expressed as mean ± standard deviation and median (minimum-maximum). Nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test of normality were used to identify distribution of variables. Student's t test was used to compare two groups for continuous variables with normal distribution. Chi Square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. Predictors of disease progression were identified by using binary logistic regression analysis. Receiver-operating characteristic (ROC) curve was applied for the prediction of disease progression and the area under the curve (AUC) was calculated for PNI. For all tests, a p value of < 0.05 was considered statistically significant.

3. Results and Discussion

In this study, 82 patients were included in the surgical group and 79 patients in the medical group. The demographic characteristics of the patients are summarized in Table 1. There was statistically significant difference in surgical group in terms of age ($p < 0.001$), presence of hypertension ($p = 0.001$), history of CVE ($p < 0.001$), presence of CAD ($p = 0.001$) and statin therapy ($p = 0.001$) (Table1).

The comparison of laboratory findings is shown in Table 2. We detected statistically difference in surgical group

Table 1. Baseline characteristics of the patients

	Surgical Group (n=82)	Medical Group (n=79)	*p* value
Age(years)	70.5±8.9	61.0±9.1	**< 0.001** *
Male gender, n (%)	56 (68.3)	57 (72.2)	0.593 #
Hypertension, n (%)	49 (59.8)	26 (32.9)	**0.001** #
Diabetes mellitus, n (%)	28 (34.1)	24 (30.4)	0.609 #
CVE, n (%)	43 (52.4)	12 (15.2)	**< 0.001**#
CAD, n (%)	36 (43.9)	16 (20.3)	**0.001** #
Statin therapy, n (%)	46 (56.1)	23 (29.5)	**0.001** #

CVE: Cerebrovascular event, CAD: Coronary artery disease, # Pearson Chi- Square, *Student's-t test

in terms of higher BUN (p <0.001), higher CRP (p = 0.008) and lower LDL-C (p = 0.045) (Table2). 0.037), lower lymphocyte (p <0.001), lower PNI (p =

Table 2. Laboratory variables.

	Surgical Group (n=82)	Medical Group (n=79)	*p value*
Haematocrit (%)	38.1±5.4	39.3±6.9	0.217*
White Blood Cell ($10^3/\mu L$)	9.1±2.0	9.0±1.9	0.691*
Platelet ($10^3/\mu L$)	247.8 (106-477)	261.2 (110-552)	0.638 a
BUN (mg/dL)	18.6 (11-28)	16.8 (8-42)	**0.001**a
Creatinine (mg/dL)	0.9 (0.4-1.5)	0.8 (0.4-1.8)	0.388 a
Na (mEq/L)	138.4 (131.4-151)	137.6 (131-146)	0.193 a
K (mEq/L)	4.3 (3.6-5.3)	4.3 (3.5-5.6)	0.523
Ca (mg/dL)	9.2±0.5	9.1±0.4	0.575*
C Reactive protein (mg/dL)	7.9 (3-67.7)	4.2 (2-18.8)	**0.037** a
Total protein (g /dL)	6.8 (4.9-8)	6.9 (4.6-9)	0.299 a
Albumin (g /dL)	3.9 (2.5-4.8)	3.8 (2-4.7)	0.445 a
Lymphocyte ($10^3/\mu L$)	1.8 (0.3-5.2)	2.4 (1-5.2)	**< 0.001**a
PNI	47.6±6.5	50.2±5.8	**0.008** *
Total Cholesterol (mg/dL)	193.1±47.9	203.5±43.2	0.151*
LDL-C (mg/dL)	114.4 (39-218)	124.7 (39-198)	**0.045** a
HDL-C (mg/dL)	44.2 (25-84)	44.7 (27-76)	0.874 a
TG (mg/dL)	187.9 (55-729)	166.8 (45-598)	0.114 a

PNI: Prognostic nutritional index, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, TG: Triglyceride, a Mann-Whitney U test (Data is expressed as median, interquartile range), *Student's-t test (Data is expressed as mean ± Standard deviation)

Risk factors which may be effective in the development of atherosclerosis and plaque in carotid artery disease and the PNI index that we investigated in this study were included into logistic regression analysis. In univariate logistic regression analysis, the development of CAS was significantly correlated with advanced age, presence of hypertension, history of CVE, PNI and presence of CAD, but was not correlated with diabetes mellitus (Table 3).

Table 3. Logistic regression analysis for progression of carotid artery stenosis

	Univariate analysis			Multivariate analysis		
Variables	**p**	**Odds Ratio**	**95% C.I. Lower Upper**	**p**	**Odds Ratio**	**95% C.I. Lower Upper**
Age	**<0.00 1**	.888	.850 – .928	**<0.00 1**	.894	.852 – .938
HT	**0.001**	.330	.173 – .629	**0.039**	.333	.117 – .945
DM	0.610	.842	.434 – 1.631			
CVE	**<0.00 1**	.162	.077 – .345	**<0.00 0**	.181	.070- .470
PNI	**0.010**	1.072	1.017 – 1.130	0.467	1.025	.959- 1.096
CAD	**0.002**	.780	.161- .654	0.388	1.689	.514 – 5.549

HT: Hypertension, DM: Diabetes mellitus, CVE: Cerebrovascular event, PNI: Prognostic nutritional index, CAD: Coronary artery disease

In multivariate analysis, advanced age, presence of hypertension and history of CVE were identified as an independent predictor of development of CAS, but PNI was not identified as an independent predictor of development of CAS (Table 3).

In the ROC curve analysis, for PNI, a cut-off level of 47.25 was determined to predicting the progression of CAS (AUC: 0.619, 95% CI: 0.533-0.706, log rank p = 0.009) (Figure 1). In the measurements above their cut-off values, there was 73.4% sensitivity and 46.3% specificity for PNI (Figure 1).

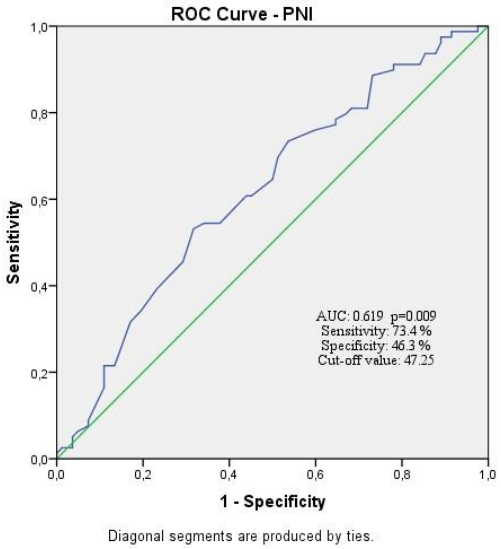

Figure 1. Receiver operation characteristic (ROC) curve and area under the curve (AUC) for prognostic nutritional index (PNI) levels for predicting to progression of carotid artery stenosis.

3. Results and Discussion

3.1. Discussion

In this study, the relationship between PNI and CAS progression was evaluated. We found statistically significantly lower PNI values in the surgical group. In the univariate logistic regression analysis, low PNI values were determined as a possible risk factor for CAS progression, but we found that this was not an independent predictor for CAS progression in multivariate logistic regression analysis. In addition, advanced age, presence of hypertension and history of CVE were seen as independent variables predicting the progression of CAS in logistic regression analysis. Also, in ROC analysis, it was determined cut-off level of 47.25 of PNI for predicting CAS with a sensitivity of 73.4% and a specificity of 46.3%.

A large meta-analysis of four population cohorts showed an impact of age and sex on the incidence of asymptomatic carotid stenosis (7). Similarly, in our study, advanced age was statistically significant in the surgical group, and we identified advanced age was an independent predictor of the progression of CAS in logistic regression analyses.

Yuan et al. stated that the atherosclerotic process in the carotid artery is also associated with hypertension. As a result, they emphasized that the rapid diagnosis and treatment of risk factors such as hypertension has major importance in atherosclerotic processes such as CAS (8). In present study, we determined that hypertension is one of the independent predictors of the progression of CAS.

Serum albumin is an important inhibitor of platelet activation and aggregation and has a critical role in inflammation. Endothelial function may be impaired

with increased concentration of free lysophosphatidylcholine, which increases the viscosity in hypoalbuminemia (5). It has also been shown that serum albumin has a protective role by preserving physiological homeostasis, antioxidant activity, anti-inflammatory effects and preventing apoptosis (9). In previous study, they found that a relationship between low serum albumin levels and increased cardiovascular morbidity and mortality (10).

There are several studies indicating the relationship between a single nutritional indicator such as albumin and poor outcomes in cases of chronic heart failure and CAD (11). However, we are in favor of using more complex, objective and well-known indexes such as the PNI to examine the relationship between nutritional status and atherosclerosis. Systematic assessment of immuno-nutritional status can be evaluated more effectively by using PNI, a continuous variable based on serum albumin concentration and total lymphocyte count in peripheral blood. Initially PNI was designed to define the perioperative immuno-nutritional status and surgical risk in patients underwent gastrointestinal surgery. Recently, it has been presented that PNI can indicate systemic inflammation associated with tumour formation and cancer progression (12). There are studies on the correlation between lymphocytopenia and CAD complications and mortality after myocardial infarction (13). Similarly, in their study Açıkel et al indicates that PNI is a remarkable prognostic factor for CAD patients undergoing CABG surgery. They state that there is obvious correlation between PNI with morbidity and mortality after CABG surgery (14). Wada et al. Investigated the relationship between long-term outcomes after percutaneous coronary intervention and PNI in stable coronary artery disease and found that low PNI values were associated with the increase in the incidence of major adverse cardiac events (4). Similarly, in another study, Chen et al. observed more recurrent MI and hospital mortality in the group with low PNI levels after percutaneous coronary intervention in ST-elevation AMI (15). There are not many studies in the literature examining the relationship between carotid artery stenosis and PNI. However, it can be mentioned that there are studies demonstrating that low PNI levels are an indicator of poor prognosis (4,12,13,14,15). Although, we found that lower PNI values was not an independent predictor for CAS progression, low PNI values were statistically significantly in the surgical group. Therefore, we think that low PNI value may be effective in the development of atherosclerosis and thus the progression of the carotid plaque.

Many different studies have indicated that the prevalence and severity of CAS related with the extent of CAD. It has been reported that in patients with CAD the prevalence of CAS (>50%) gradually increased with the number of affected coronary arteries and in the patients with severe CAD scheduled for CABG, the prevalence of CAS is found12-17% (16). Similarly, the incidence of CAD was significantly higher in our surgical group. And as a normal result of present study, the history of CVE was significantly higher in the surgical group.

Although creatine values were similar in the two groups before surgery, BUN values were higher in the surgical group. This result was attributed to the insufficient fluid intake of the patients in the surgical group due to their advanced age. Since statin therapy was used significantly more in the surgical group, preoperative LDL-C values were statistically significantly lower than in the medical group. Among the biomarkers reported to date, one of the promising markers for vascular inflammation is C-reactive protein (CRP). CRP, an acute phase protein, is primarily produced in the liver during acute inflammation or infection processes. CRP is also detected in areas of local inflammation or injury. However, levels of CRP produced in response to vascular inflammation are usually very low (17). On the other hand, in present study, we revealed that CRP levels were high in our surgical group.

Limitations of study

Our study has some limitations. The main limitation of this study is that healthy individuals without carotid artery disease were not included in the study. In addition, the number of patients included in the study is small. Further prospective studies with a larger number of patients are required.

4. Conclusion

In conclusion, many factors contribute to the development of carotid stenosis. There are not enough studies regarding the effect of PNI on CAS. In our study, although PNI was not as an independent variable predicting CAS progression, we found statistically significantly lower PNI values in the surgical group. Therefore, we think that PNI may be effective on CAS. However, a study comparing healthy individuals with those with carotid artery disease would better show the effect of PNI on CAS.

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