Impact of Nutritional Assessment on Long-Term Outcomes in Patients with Carotid Artery Stenting

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Abstract

Objective: Malnutrition is associated with poor clinical outcomes in many diseases. The Controlling Nutritional Status (CONUT) is an objective index used for evaluating nutritional status of hospitalized patients. The aim of this study was to investigate the relationship between malnutrition assessed by CONUT score and the prognosis in patients undergoing carotid artery stenting (CAS). Methods: The study included 170 patients who underwent CAS due to symptomatic or asymptomatic severe carotid artery stenosis. Median follow-up period was 50 (interquartile range [IQR], 41-60) months. Patients were divided into two groups according to the CONUT score: (i) normal nutrition (<2) and (ii) malnutrition ([?]2). Primary endpoint was accepted as MACE (major adverse cardiac events) including all-cause death and ischemic stroke. Results:The prevalence of MACE was significantly higher in the malnutrition group (p=0.001). Kaplan Meier analysis showed lower survival rates in the malnutrition group (log rank = 9.36, p=0.002; Figure 4). In multivariate logistic regression analysis, age and CONUT score were independent predictors of all-cause death and stroke after adjustment for confounding factors, respectively, (OR: 1.058, 95% CI: 1.013-1.105, p=0.011, OR: 1.318, 95% CI: 1.017-1.881, p=0.039). Conclusion: Higher CONUT scores were associated with adverse outcomes in patients with CAS. Malnutrition assessed by the CONUT score may provide valuable prognostic information in patients with CAS.

Introduction

Stroke is a leading cause of disability and death worldwide. Atherosclerotic narrowing of the extracranial carotid arteries is responsible for approximately one-fifth of all strokes (1). There are two main interventional treatment methods in symptomatic or asymptomatic high-grade carotid artery stenosis: carotid artery stenting (CAS) and carotid endarterectomy (2,3). Although there is sufficient evidence on the long-term outcomes of patients after CAS, potential risk factors affecting the long-term course of the disease have not yet been studied sufficiently (4,5).

Comorbid diseases accompanying severe CAS affect the long-term outcomes of the disease. Although risk factors showing long-term consequences such as diffuse proliferative hyperplasia after CAS, low high-density lipoprotein cholesterol level, diabetes mellitus, low body mass index (BMI), and contralateral carotid artery occlusion have so far been identified, a detailed risk assessment has not yet been performed (6-10).

Malnutrition is associated with adverse outcomes in many diseases (11-12). The Controlling Nutritional Status (CONUT) score is an objective index widely used for evaluating nutritional status of individuals. The CONUT score is calculated based on serum albumin level, total cholesterol level, and total lymphocyte count and it can assess protein reserves, calorie deficit, and immune response (13). Clinical significance of malnutrition as assessed by the CONUT score has been demonstrated in patients with hypertension, acute coronary syndrome (ACS), and heart failure (14-16).

Although the CONUT score is a practical, applicable, scoring system with a prognostic value, its clinical significance has not yet been elucidated in CAS patients. The aim of this study was to investigate the

relationship between malnutrition assessed by CONUT score and prognosis in patients undergoing CAS.

Methods

Study Population

The study was designed as a single-center, retrospective study and included 170 patients who underwent CAS due to symptomatic or asymptomatic severe carotid artery stenosis in Dicle University Medical School Hospital between December 2011 and December 2020. Patients with hematological diseases, systemic inflammatory diseases, malignancies, active infectious diseases, end-stage kidney and liver diseases, and a history of thrombolytic therapy within the last 24 hours were excluded from the study. The study was conducted in accordance with the Helsinki Declaration and the study protocol was approved by the local ethics committee. The experimental protocols and the process for obtaining informed consent were approved by the appropriate institutional review committee.

Definitions

A detailed medical history was obtained from all patients at the time of admission. Hypertension was defined as a systolic blood pressure (SBP) of [?]140 mmHg or a diastolic blood pressure (DBP) of [?]90 mmHg or using antihypertensive medication. Diabetes mellitus (DM) was defined as a fasting glucose level of [?]126 mg/dl or use of antidiabetic agents or HbA1c >7%. Dyslipidemia was defined as a total cholesterol level of >200 mg/dl or low-density lipoprotein level (LDL) of >130 mg/dL. Smoking was defined as current cigarette smoking. Coronary artery disease (CAD) was defined as >50% narrowing in at least one coronary artery. Peripheral artery disease (PAD) was defined as >50% stenosis in peripheral arteries. Transient ischemic attack (TIA) was defined based on the 2009 American Heart Association/American Stroke Association (AHA/ASA) guidelines as a transient episode of neurological dysfunction in the spinal cord, retina, and focal brain without acute infarction. Ischemic stroke was defined as an infarction causing neurological dysfunction in the focal brain, spinal cord, and retina lasting more than 24 hours.

Blood Samples and Nutritional Indexes

Hematological and biochemical tests were conducted on the venous blood samples obtained from each patient immediately before routine carotid angiography. Determination of the counts and types of shaped elements of blood was performed for each patient using an automated hematological analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois, USA). Biochemical measurements were performed using the standard methods. The CONUT score is calculated based on three parameters: serum albumin level, total cholesterol level, and total lymphocyte count (Table 1). Patients were divided into two groups according to the CONUT score: (i) normal nutrition (<2) and (ii) malnutrition ([?]2). Prognostic nutritional index (PNI) was calculated using the following formula: 10 x serum albumin value (g/dL) + 0.005 x total lymphocyte count in the peripheral blood (per mm^3). Patients were divided into two groups based on a PNI cutoff value of 40: (i) low PNI ([?]40) and (ii) high PNI (>40).

MACE and follow-up

Primary endpoint was accepted as MACE (major adverse cardiac events) including all-cause death and ischemic stroke. The follow-up period was defined as the time from the moment of admission to our clinic for angiography to death due to any cause or to the last clinical visit. Data on patients' death were accessed by telephone interviews or were retrieved from the civil registration records.

Statistical analysis

Data were analyzed using SPSS for Windows version 25.0 (Armonk, NY: IBM Corp.). Normal distribution of data was analyzed using Kolmogorov-Smirnov test. Categorical variables were expressed as percentages (%) and were compared using Chi-square test. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and were compared using Student's t-test. Continuous variables with nonnormal distribution were expressed as median (25^{th}-75^{th} percentile) and were compared using Mann-Whitney U test. Independent predictors of mortality were determined using univariate and multivariate

logistic regression analysis and the results were expressed with odds ratio (OR) and 95% confidence interval (CI). The optimum PNI and CONUT score cutoff values for the prediction of mortality were determined using receiver operating characteristic (ROC) curve analysis. Correlations were analyzed using Spearman's correlation coefficient. Survival analysis was performed using Kaplan-Meier analysis. A p value of <0.05 was considered significant.

Results

The study included 170 patients, comprising 105 (61.8%) men and 65 women (38.2%) with a mean age of 68.27±10.23 years. Median follow-up period was 50 (interquartile range [IQR]: 41-60.25) months. Patients were divided into two groups according to the CONUT score: (i) normal nutrition (<2) and (ii) malnutrition ([?]2). Clinical characteristics of both groups are shown in Table 2. The mortality rate and the neutrophil-to-lymphocyte ratio (NLR) were significantly higher and the PNI scores were significantly lower in the malnutrition group compared to the normal nutrition group (p =0.001,p <0.001, and p <0.001, respectively). Table 3 presents a comparison of baseline hematological and biochemical parameters of both groups. Significant differences were found between the two groups with regard to serum hemoglobin, hematocrit, lymphocyte, glucose, creatinine, albumin, total cholesterol, LDL, high-density lipoprotein (HDL), thyroid stimulating hormone (TSH), and C-reactive protein (CRP) levels.

In univariate logistic regression analysis, age, PNI, and CONUT score were found to be independent predictors of all-cause death and stroke (Odds Ratio [OR]: 1.061, 95% CI: 1.020-1.103, p =0.003, OR: 0.915, 95% CI: 0.864-0.970, p =0.003, OR: 1.134, 95% CI: 1.130-1.590, p =0.001). In multivariate logistic regression analysis, age and CONUT score were independent predictors of all-cause death and stroke, respectively (OR: 1.058, 95% CI: 1.013-1.105,p =0.011, OR: 1.318, 95% CI: 1.017-1.881, p =0.039) (Table 4).

At a cutoff value of 1.5, the CONUT score predicted long-term all-cause death and stroke with a sensitivity of 66% and a specificity of 62% (ROC area under curve [AUC]: 0.644, 95% CI: 0.541-0.747; Figure 1). At a cutoff value of 46, PNI predicted long-term all-cause death and stroke with a sensitivity of 65% and a specificity of 57% (AUC: 0.655, 95% CI: 0.560-0.749; Figure 2). A negative correlation was observed between the CONUT score and PNI (r = -0.716, p <0.001; Figure 3). Kaplan Meier analysis showed lower survival rates in the malnutrition group (log rank = 9.36, p =0.002; Figure 4) and in the group with a low PNI score ([?]40) (log rank = 14.98,p <0.001; Figure 5).

Discussion

The present study investigated the long-term prognostic value of malnutrition assessed by the CONUT score in CAS patients and the results indicated a higher prevalence of all-cause death and stroke in malnourished patients compared to patients with normal nutrition.

The CONUT score was first described by Ignacio de Ulı´barri et al as an objective parameter reflecting malnutrition in hospitalized patients (13). In recent studies, the association of the CONUT score with clinical poor outcomes has been demonstrated in various cardiovascular diseases. Takahashi et al. reported that high CONUT score was associated with adverse outcomes in patients with ACS and also showed its prognostic value in ACS patients (15). Nochioka et al. showed that malnutrition assessed by the CONUT score was associated with adverse cardiac events in patients with chronic heart failure (17). Kunimura et al. demonstrated that the combined use of BMI and CONUT score in stable CAD was associated with MACE (18). In some other studies, the CONUT score was shown to be an independent strong predictor of adverse cardiovascular events and foot events in PAD patients (19). Additionally, it was also reported to be associated with increased prevalence of all-cause death in patients with ST elevation myocardial infarction (STEMI) (20).

To date, numerous nutritional indicators such as serum albumin, total cholesterol, Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), and Geriatric Nutritional Risk Index (GNRI) have been reported (21-23). Of these, MNA and SGA are dependent on the physician's subjective observations. Nevertheless, an evaluation performed with only one nutritional indicator may be affected by various factors

and may not provide sufficient information. Therefore, in this study, we used PNI in addition to the CONUT score. PNI, which is calculated on serum albumin level and total lymphocyte count, is an objective nutritional indicator reflecting the immune-nutritional status of individuals. Decreased albumin and lymphocyte response in acute diseases reflect poor immune-nutritional status. On the other hand, PNI is mainly used as a parameter reflecting the immune-nutritional status of patients planned for gastrointestinal surgery to assess the risk of perioperative surgery (24,25). In our study, a PNI score of [?]40 was associated with a shorter survival time.

In the literature, CAS patients have been evaluated with biochemical parameters as well. Of these, NLR has been shown to be associated with in-stent restenosis in CAS patients (26). Additionally, CRP and B-type natriuretic peptide (BNP) have been demonstrated to have a prognostic value in CAS patients undergoing carotid surgery (27).

Both the studies in the literature and our study indicated that malnutrition is associated with mortality. Accordingly, the CONUT score, which is an objective and easily applicable scoring system, can be a useful nutritional indicator in predicting adverse events in CAS patients and, as a novel indicator, can contribute to the prediction of adverse events such as long-term mortality and stroke in the CAS patients, in addition to traditional parameters.

The study had several limitations. First, it was a single-center retrospective study and had a relatively small sample size. Second, the CONUT scores were not assessed after hospital discharge and thus the effect of changes in post-discharge CONUT scores on clinical outcomes could not be evaluated. Third, malnutrition was assessed only by using the CONUT score and PNI, and other nutritional indicators such as MNA, SGA, and GNRI were not used.

In conclusion, malnutrition assessed by the CONUT score was associated with poor prognosis in patients with CAS. The CONUT score is a useful tool for risk stratification of patients with CAS.

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Table 1. Severity of malnutrition assessed by CONUT score

Parameter	**Severity**	**Severity**	**Severity**	**Severity**
	Normal	Mild	Moderate	Severe
Serum albumin (g/dl)	[?]3.5	3-3.49	2.5-2.99	<2.5
Score	0	2	4	6
Total lymphocytes (/μL)	[?]1600	1200-1599	800-1199	<800
Score	0	1	2	3
Total cholesterol (mg/dl)	[?]180	140-179	100-139	<100
Score	0	1	2	3
Total CONUT score	0-1	2-4	5-8	9-12

CONUT: Controlling Nutritional Status

Table 2. Clinical characteristics

	Total N=170	**CONUT <2 N=93**	**CONUT [?]2 N=77**	p
Age (Years)	68.27±10.23	66.17±10.23	70.81±9.70	0.003
Male	105 (61.8%)	55 (59.1%)	50 (64.9%)	0.439
Follow-up period (Months)	50 (41-60.25)	52 (42.5-59)	48 (37-64.5)	0.306
Mortality	40 (23.5%)	13 (14%)	27 (35.1%)	0.001
New-onset stroke (Follow-up period)	4 (2.4%)	1 (1.1%)	3 (3.9%)	0.330*
MACE	44 (25.9%)	15 (16.1%)	29 (37.7%)	0.001
Hypertension	126 (74.1%)	67 (72%)	59 (76.6%)	0.497
Diabetes mellitus	63 (37.1%)	33 (35.5%)	30 (39%)	0.640
Dyslipidemia	130 (76.5%)	76 (81.7%)	54 (70.1%)	0.076
Active smoking	82 (48.2%)	48 (51.6%)	34 (44.2%)	0.333
CAD	104 (61.2%)	61 (65.6%)	43 (55.8%)	0.194
PAD	7 (4.1%)	4 (4.3%)	3 (3.9%)	0.652
Stroke	66 (38.8%)	31 (33.3%)	35 (45.5%)	0.106
Transient ischemic attack	73 (42.9%)	39 (41.9%)	34 (44.2%)	0.771
Amaurosis fugax	13 (7.6%)	8 (8.6%)	5 (6.5%)	0.607
Rhythm Sinus rhythm Atrium fibrillation	161 (94.7%) 9 (5.3%)	87 (93.5%) 6 (6.5%)	74 (96.1%) 3 (3.9%)	0.459
Stented vessel Right Carotid Artery	78 (45.9%)	49 (52.7%)	29 (37.7%)	0.050
Left Carotid Artery	102 (60%)	50 (53.8%)	52 (67.5%)	0.068
Left carotid stenosis 0-50% 50-69% 70-89% 90-100%	55 (32.4%) 5 (2.9%) 43 (25.3%) 67 (39.4%)	36 (38.7%) 2 (2.2%) 23 (24.7%) 32 (34.4%)	19 (24.7%) 3 (3.9%) 20 (26%) 35 (45.5%)	0.218*
Right carotid stenosis 0-50% 50-69% 70-89% 90-100%	89 (52.4%) 3 (1.8%) 42 (24.7%) 36 (21.2%)	42 (45.2.7%) 3 (3.2%) 29 (31.2%) 19 (20.4%)	47 (61%) 0 (0%) 13 (16.9%) 17 (22.1%)	0.040*
ASA/clopidogrel	170 (100%)	93 (100%)	77 (100%)	**
ACEI/ARB	112 (65.9%)	61 (65.6%)	51 (66.2%)	0.930
Beta-blocker	118 (69.4%)	61 (65.6%)	57 (74%)	0.235
Statins	162 (95.3%)	89 (95.7%)	73 (94.8%)	0.784
Body mass index, kg/m^2	25.22 (24.08-27.2)	25 (24.03-26.94)	25.40 (24.21-27.45)	0.398
Ejection fraction (%)	60 (60-60)	60 (55-60)	60(60-60)	0.231
SBP mmHg DBP mmHg	130 (120-137) 76.5 (70-80)	130(120-136) 76(70-80)	130(120-138) 78(70-80)	0.539 0.752
Prognostic nutritional index	46.35±6.59	50.12±4.57	41.81±5.76	<0.001
Neutrophil to lymphocyte ratio	2.53(1.93-3.46)	2.25(1.81-2.83)	2.96(2.25-4.9)	<0.001

Data are expressed as mean ± standard deviation (SD), frequencies (percentages) or as median (interquartile range) as appropriate. *Fisher's Exact Test. **No statistics were computed because ASA and clopidogrel are constant. MACE: Major adverse cardiac events, CAD: Coronary artery disease, PAD: Peripheral artery disease, ASA: Acetylsalicylic acid, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3. Baseline hematological and biochemical parameters

	Total N=170	**CONUT <2 N=93**	**CONUT [?]2 N=77**	p
White blood cell count ($\times 10^6$ μL)	8652±2384	8628±2084	8681±2717	0.887
Hemoglobin (g/dl)	13.16±1.77	13.61±1.55	12.61±1.88	<0.001
Hematocrit (%)	40.58±4.94	42.12±4.48	38.71±4.86	<0.001
Lymphocytes ($\times 10^6$ μL)	2128±899	2347±738	1863±1005	<0.001
Neutrophils ($\times 10^6$ μL)	5613±2073	5397±1778	5873±2367	0.136
Uric acid	5.72±1.85	5.65±1.8	5.81±1.93	0.579
Glucose (mg/dl)	151±86	137±73	168±97	0.019
Creatinine (mg/dl)	0.97±0.41	0.9±0.28	1.05±0.52	0.021
Total bilirubin (mg/dl)	0.72±0.39	0.75±0.38	0.69±0.41	0.302
Serum albumin (g/dl)	3.57±0.45	3.83±0.24	3.24±0.43	<0.001
Total cholesterol (mg/dl)	196±46	212±42	177±43	<0.001
Triglycerides (mg/dl)	176±92	188±84	161±99	0.050
LDL (mg/dl)	120±40	132±38	107±37	<0.001
HDL (mg/dl)	41±12	43±12	39±12	0.014
INR	1.06±0.34	1.07±0.36	1.05±0.32	0.770
TSH (μIU/mL)	1.02 (0.83-1.66)	1.26 (0.92-1.94)	0.97 (0.7-1.25)	<0.001
CRP (mg/dl)	0.8 (0.4-1.3)	0.6 (0.3-1)	1 (0.5-2.1)	<0.001

Data are expressed as mean ± SD or median (interquartile range) as appropriate. TSH: Thyroid stimulating hormone, CRP: C-reactive protein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, INR: International normalized ratio

Table 4. Predictors of MACE in univariate and multivariate logistic regression analysis

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.061 (1.020-1.103)	0.003	1.058 (1.013-1.105)	0.011
Hypertension	1.800 (0.763-4.245)	0.179	2.187 (0.783-6.109)	0.135
Diabetes mellitus	0.960 (0.471-1.958)	0.912	1.155 (0.505-2.645)	0.733
Smoker	1.407 (0.706-2.802)	0.332	2.203 (0.992-4.890)	0.052
Statins	2.529 (0.302-21.16)	0.392	2.802 (0.293-27.216)	0.370
Rhythm	0.810 (0.162-4.051)	0.797	0.809 (0.140-4.666)	0.813

Parameter	Univariate analysis		Multivariate analysis	
LDL	1 (0.991-1.008)	0.933	1.007 (0.997-1.018)	0.175
Beta blocker	1.240 (0.579-2.658)	0.580	0.890 (0.376-2.108)	0.791
NLR	1.109 (0.977-1.258)	0.108	1.051 (0.913-1.209)	0.489
PNI	0.915 (0.864-0.970)	0.003	1.001 (0.915-1.095)	0.987
CONUT score	1.134 (1.130-1.590)	0.001	1.383 (1.017-1.881)	0.039

MACE: Major adverse cardiac events, OR: Odds ratio, CI: Confident interval, LDL: Low-density lipoprotein, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

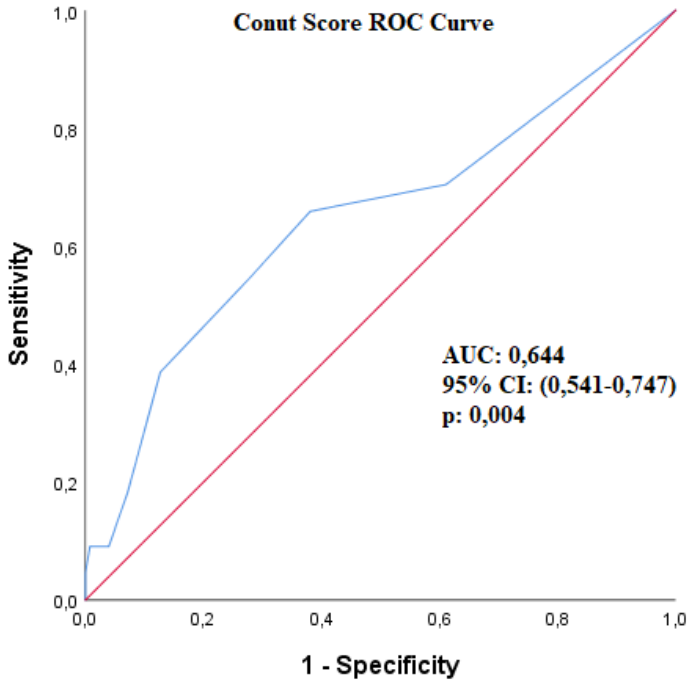


Figure 1. Receiver-operating characteristic (ROC) curve indicating the ability of CONUT score to predict MACE in patients with carotid artery stenting. AUC: Area under the curve, CI: Confident interval

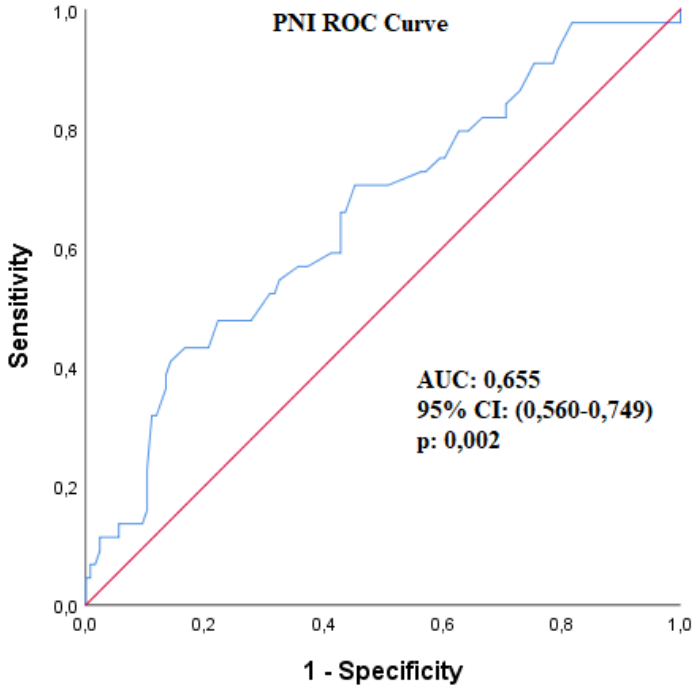


Figure 2. Receiver-operating characteristic (ROC) curve indicating the ability of prognostic nutritional index (PNI) to predict MACE in patients with carotid artery stenting. AUC: Area under the curve, CI: Confident interval

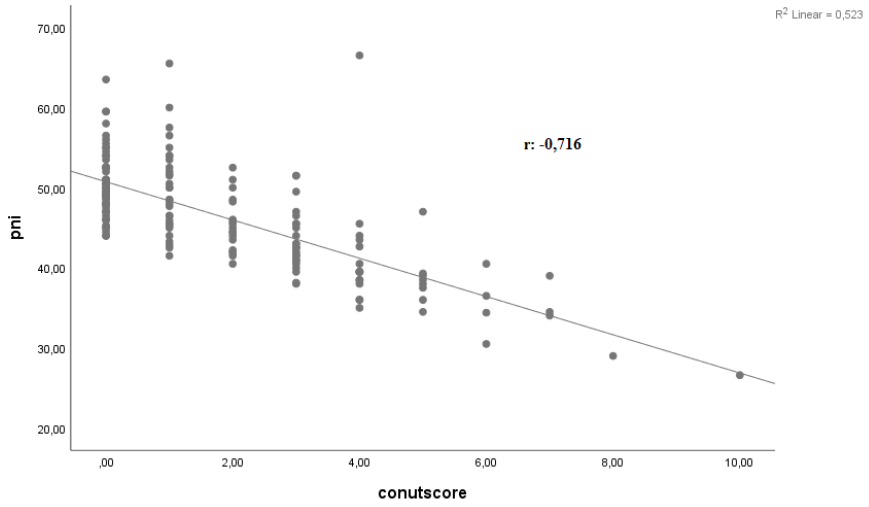


Figure 3. Correlation analysis of CONUT score with PNI

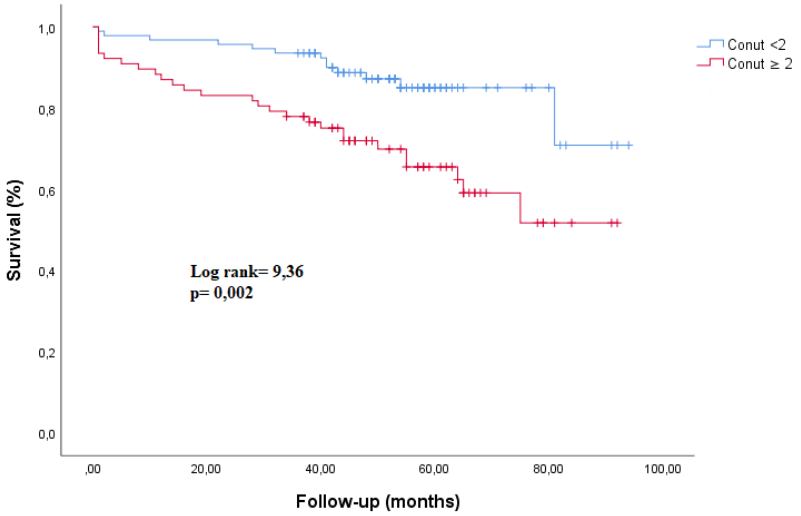


Figure 4. Kaplan-Meier survival analysis for CONUT score. During long-term follow-up period (median, 50 months), patients group with CONUT [?]2 had significantly worse survival than patients group with CONUT <2 (p =0.002). Mean survival period for CONUT <2 and CONUT [?]2 was (83.001±2.946 and 65.965±4.048 months, respectively) (p =0.002).

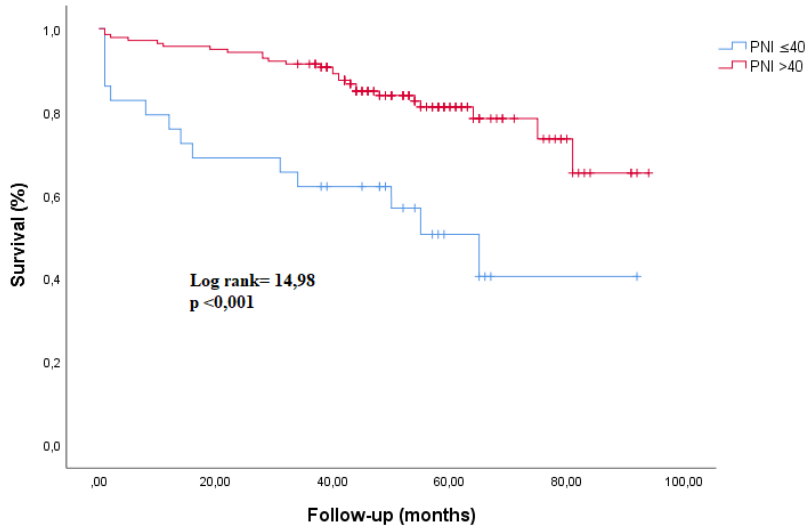
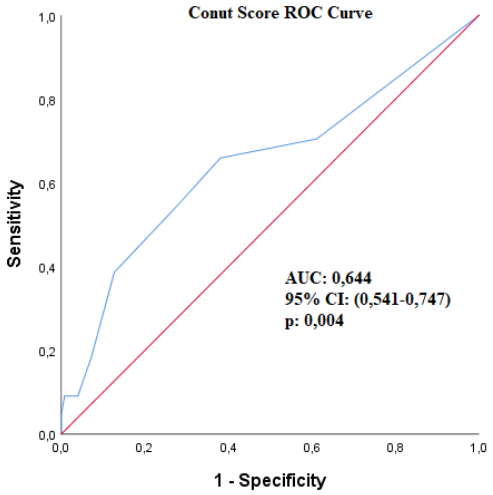
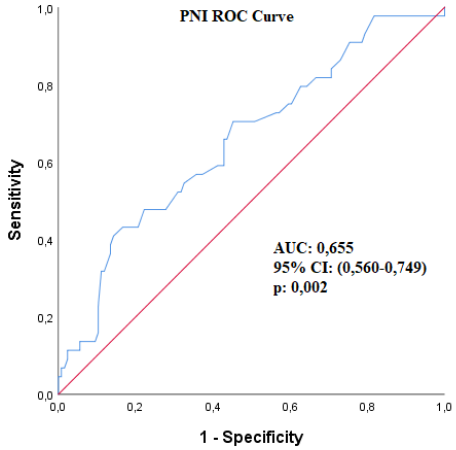
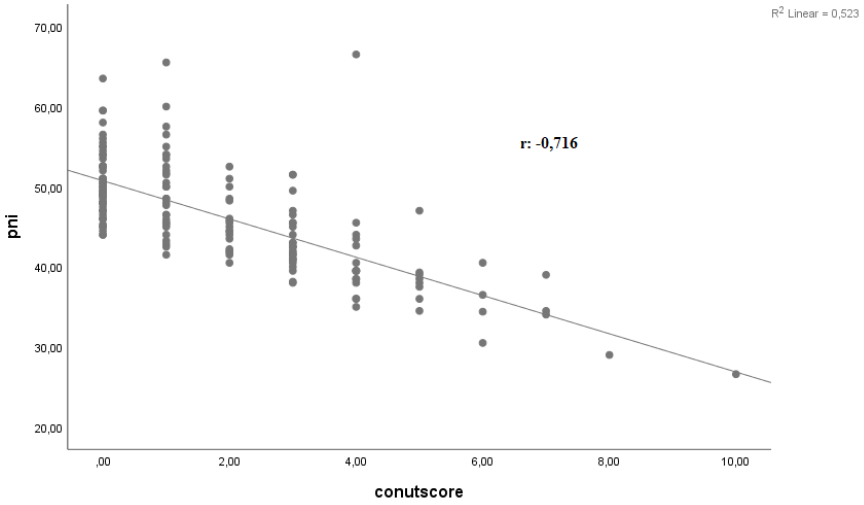
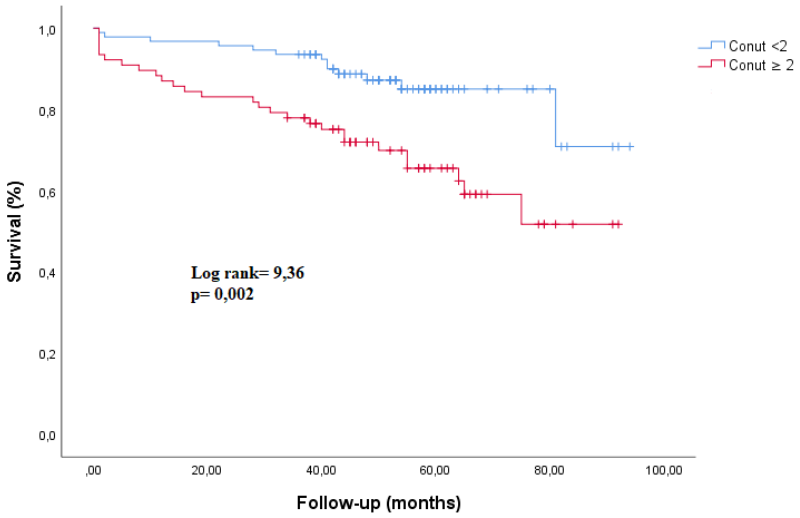


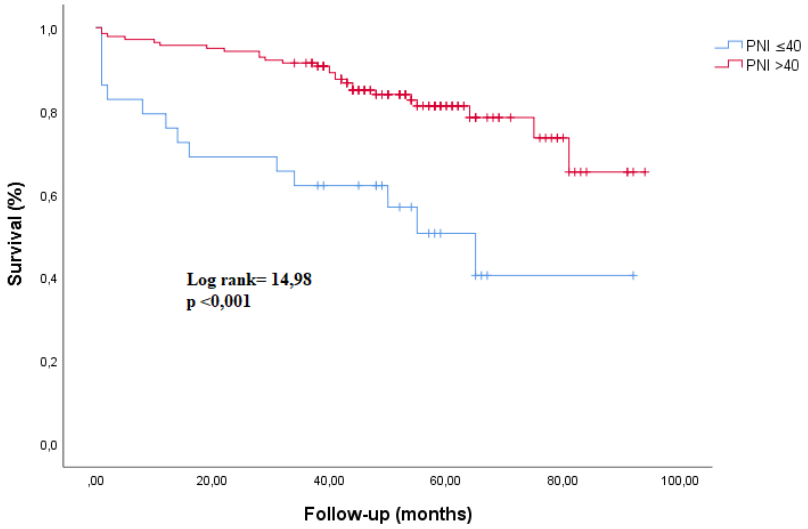
Figure 5. Kaplan-Meier survival analysis for PNI. During long-term follow-up period (median, 50 months), patients group with PNI [?]40 had significantly worse survival than patients with PNI >40 (p <0.001). Mean survival time for PNI [?]40 and PNI >40 was 54.033±7.277 and 79.521±2.607, respectively) (p <0.001).











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