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Impact of Controlling Nutritional Status score on short-term outcomes after carotid endarterectomy: a retrospective cohort study

Hee Won Son, Gyeongseok Yu, Seung Jun Lee, Jimi Oh

Department of Anesthesiology and Pain Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

Background: Malnutrition and impaired immune responses significantly affect the clinical outcomes of patients with atherosclerotic stenosis. The Controlling Nutritional Status (CONUT) score has recently been utilized to evaluate perioperative immunonutritional status. This study aimed to evaluate the relationship between immunonutritional status, indexed by CONUT score, and postoperative complications in patients undergoing carotid endarterectomy (CEA).
Methods: We retrospectively evaluated 188 patients who underwent elective CEA between January 2010 and December 2019. The preoperative CONUT score was calculated as the sum of the serum albumin concentration, total cholesterol level, and total lymphocyte count. The primary outcome was postoperative complications within 30 days after CEA, including major adverse cardiovascular events, pulmonary complications, stroke, renal failure, sepsis, wounds, and gastrointestinal complications. Cox proportional hazards regression analysis was used to estimate the factors associated with postoperative complications during the 30-day follow-up period.
Results: Twenty-five patients (13.3%) had at least one major complication. The incidence of postoperative complications was identified more frequently in the high CONUT group (12 of 27, 44.4% vs. 13 of 161, 8.1%; $p<0.001$). Multivariate analyses showed that a high preoperative CONUT score was independently associated with 30-day postoperative complications (hazard ratio, 5.98; 95% confidence interval, 2.56–13.97; $p<0.001$).
Conclusion: Our results showed that the CONUT score, a simple and readily available parameter using only objective laboratory values, is independently associated with early postoperative complications.

Keywords: Carotid endarterectomy; Nutritional status; Postoperative complications; Prognosis

Introduction

Stroke is the second leading cause of mortality and adult disability [1]. Extracranial carotid artery disease accounts for 20% of all stroke cases. Previous studies have shown that carotid endarterectomy (CEA) is significantly effective in preventing cerebrovascular events in patients with high-grade stenosis of the carotid artery and, thus, is regarded as a "gold standard" treatment [2,3]. However, the benefits of CEA shown in previous studies may be limited at any time because of the development of perioperative complications that are influenced by patient-related factors. Indeed, patients undergoing CEA have a residual risk of future stroke or major car-

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Corresponding author: Jimi Oh, MD
Department of Anesthesiology and Pain Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, 877 Bangujinsunhwando-ro, Dong-gu, Ulsan 44033, Korea
Tel: +82-52-250-7248 • Fax: +82-52-250-7249 • E-mail: ohzie82@gmail.com

diovascular events owing to the systemic nature of atherosclerosis [4]. The cause of this increased risk of postoperative complications in patients with CEA is unclear.

Malnutrition and immune responses are involved in the atherosclerotic process; their content is associated with the recurrence of stroke or cardiovascular events and is an important cause of postoperative complications in various surgeries [4,5]. Therefore, malnutrition-immune data may be necessary for categorizing risk and understanding the residual risk in patients undergoing CEA.

The Controlling Nutritional Status (CONUT) score can be determined from one immune marker (total lymphocyte count) and two metabolic parameters (serum albumin concentration and total cholesterol levels), which are representative indicators of immune defense, protein reserves, and lipid metabolism, respectively. A decrease in each parameter is assigned a higher score, with higher scores indicating poorer nutritional status. Compared to traditional screening tools, these CONUT score parameters consider the influence of non-nutritional factors. Although the CONUT score has recently been considered as a scoring system for predicting postoperative morbidity and evaluating nutritional status in various settings, including oncology therapy and cancer surgery, clinical data using the CONUT score to predict unfavorable prognosis in CEA patients are scarce [6,7]. Given that the CONUT score is a marker of nutritional and immune responses, this study aimed to confirm whether the CONUT score can predict postoperative complications independent of other known prognostic factors.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Ulsan University Hospital (IRB No: 2021-05-038), and the requirement for informed consent was waived.

1. Study design and patient population

A total of 198 patients who underwent CEA between January 2010 and December 2019 were retrospectively evaluated. Patients who underwent an emergency CEA procedure (n = 4), underwent other surgeries concurrently (n = 3), or had incomplete or missing data (n = 3) were excluded from this analysis. Thus, 188 patients were enrolled in the present study (Fig. 1). Clinical data, including demographic characteristics, comorbidities, postoperative complications, surgery side, degree of stenosis, and shunting, were reviewed using a computerized patient record system (Ulsan University Hospital Information of Clinical Ecosystem).

2. Markers of nutritional status

Blood samples were routinely collected within 1 week preceding CEA in all patients. The detection indices included white blood cells, lymphocyte counts, platelets, hemoglobin, C-reactive protein, albumin, blood urea nitrogen, serum creatinine, total cholesterol, total bilirubin, and uric acid. The immunonutritional status of each patient was evaluated based on the CONUT score. A score of > 2 indicated malnutrition (Fig. 2) [8]. The CONUT score was calculated as the sum of three laboratory parameters: serum albumin level (g/dL), total lymphocyte count (cells/μL), and total cholesterol level (mg/dL), as summarized in Fig. 2.

3. Outcomes

The primary endpoint in our analysis was a composite of the main complications throughout the 30 days following CEA. The 30-day postoperative complications were selected according to the European Perioperative Clinical Outcome definitions [9] as follows: (1) major adverse cardiovascular events (e.g., malignant ventricular arrhythmia, myocardial infarction, and heart failure); (2) pulmonary complications; (3) stroke; (4) renal complications; (5) sepsis; (6) wound complications; (7) gastrointestinal complications; and (8) death. As secondary clinical outcomes, the duration of intensive care and hospitalization and readmission within 30 days after CEA were confirmed.

4. Statistical analysis

Descriptive variables are expressed as numbers (proportions), mean ± standard deviation (SD), or medians (interquartile ranges [IQR]). Continuous variables were compared using the Student *t*-test, whereas the chi-square or Fisher exact test was used for categorical variables.

Cox proportional hazards regression analysis was used to estimate the factors associated with postoperative complications during the 30-day follow-up period. Unadjusted relationships between risk factors and 30-day postoperative complications were es-

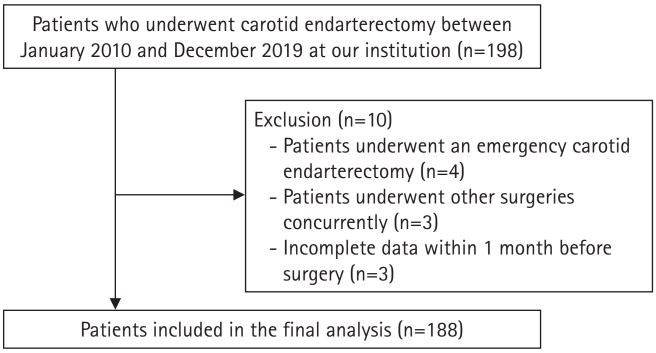
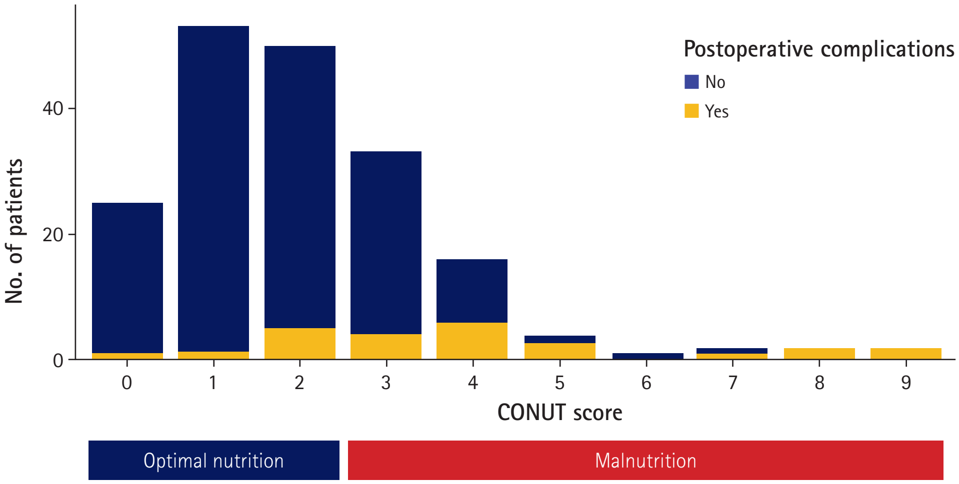


Fig. 1. Flow chart of patient selection and classification.



Parameter	Normal	Mild	Moderate	Severe
Albumin (g/dL)	≥3.5	3.00–3.49	2.50–2.99	<2.50
Total lymphocyte count (cells/μL)	>1,600	1,200–1,599	800–1,199	<800
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3

Fig. 2. Distribution and classification of the Controlling Nutritional Status (CONUT) scores.

timated using univariate Cox proportional hazards regression analysis and Kaplan-Meier curves. Only variables with a *p*-value of < 0.05 on univariate analysis were incorporated into the backward multivariate analysis. Therefore, we adjusted for preoperative heart failure, clamping time, and serum albumin levels as potential confounders in the multivariate analysis. Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) and R software ver. 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

1. Baseline characteristics of patients

The overall patient cohort had an average age of 67.14 ± 8.04 years, and 79.3% were men. In total, 112 patients (59.6%) were symptomatic (Table 1). In our study, 32.4% of the patients were malnourished. Systolic blood pressure and diastolic blood pressure were 139.07 ± 20.24 and 79.49 ± 13.19 mmHg (mean ± SD). Shunting was performed in 131 CEA procedures. All procedures were performed under general anesthesia. Detailed patient information is presented in Table 1.

2. Clinical outcomes

The postoperative outcomes of the study are summarized in Table 2. At least 13.3% of the patients had one acute postoperative complication, and it was confirmed that the high CONUT group had a higher incidence of complications (12 of 27, 44.4% vs. 13 of 161, 8.1%; $p < 0.001$) (Table 2). The CONUT score of the patients who underwent CEA and the distribution of postoperative complications based on the CONUT score are presented in Fig. 1. Concerning secondary clinical outcomes, it was confirmed that hospital stay was also extended in the group with a high CONUT score (median, 7 days [IQR, 6–17 days] vs. 6 days [IQR, 6–8 days], $p = 0.022$) (Table 2).

3. Prognostic factors for postoperative complications

Univariate and multivariate analyses were performed to identify prognostic factors for acute complications after surgery. The presence of heart failure (hazard ratio [HR], 8.43; 95% confidence interval [CI], 2.87–24.74; $p < 0.001$), clamping time (HR, 0.97; 95% CI, 0.93–1.00; $p = 0.04$), albumin (HR, 0.27; 95% CI, 0.14–0.53; $p < 0.001$), and CONUT score (HR, 6.47; 95% CI, 2.95–14.20; $p < 0.001$) were prognostic markers for postoperative complications. After adjusting for confounders, the CONUT score (HR, 5.98; 95% CI, 2.56–13.97; $p < 0.001$) was an independent prognostic marker of acute postoperative complications (Table 3). Kaplan-Meier curves showed that the possibility of complications after CEA was significantly higher for patients with higher CONUT scores than for those with lower CONUT scores ($p < 0.001$) (Fig. 3).

Table 1. Preoperative clinical characteristics of study participants

Variable	Total	Composite = 0	Composite = 1	*p*-value
No. of patiens	188	163	25	
Baseline characteristics				
Age (yr)	67.14 ± 8.04	66.94 ± 7.99	68.44 ± 8.41	0.39
Male sex	149 (79.3)	129 (79.1)	20 (80.0)	0.92
Body mass index (kg/m^2)	24.34 ± 3.14	24.56 ± 3.02	23.95 ± 3.56	0.05
Heart rate (beats/min)	75.78 ± 13.94	75.56 ± 14.18	77.20 ± 12.46	0.59
Systolic blood pressure (mmHg)	139.07 ± 20.24	138.10 ± 19.60	145.40 ± 23.48	0.09
Diastolic blood pressure (mmHg)	79.49 ± 13.19	78.96 ± 13.09	82.96 ± 13.58	0.16
Symptomatic lesion	112 (59.6)	93 (57.1)	19 (76.0)	0.27
Ipsilateral stenosis, > 70%	169 (89.9)	147 (90.2)	22 (88.0)	0.55
ASA PS classification	3.18 ± 0.82	3.14 ± 0.82	3.40 ± 0.82	0.34
Comorbidity				
Diabetes mellitus	75 (39.9)	67 (41.1)	8 (32.0)	0.39
Hypertension	128 (68.1)	114 (69.9)	14 (56.0)	0.16
Dyslipidemia	24 (12.8)	24 (14.7)	0 (0)	0.05
Heart failure	6 (3.2)	2 (1.2)	4 (16.0)	0.003
Previous MI	29 (15.4)	25 (15.3)	4 (16.0)	0.76
Previous CABG	2 (1.1)	2 (1.2)	0 (0)	0.78
Atrial fibrillation history	18 (9.6)	14 (8.6)	4 (16.0)	0.27
Previous arterial disease	48 (25.5)	41 (25.2)	7 (28.0)	0.76
Medication				
Antiplatelet use	179 (95.2)	155 (95.1)	24 (96.0)	0.78
> 1 Antiplatelet	116 (61.7)	100 (61.4)	16 (64.0)	0.80
Statin use	163 (86.7)	142 (87.1)	21 (84.0)	0.91
Hematologic biomarker				
Hematocrit (%)	39.49 ± 4.97	39.66 ± 4.88	38.34 ± 5.46	0.22
Lymphocyte (cells/µL)	1,896.4 ± 644.7	1,881.3 ± 637.1	2,010.3 ± 704.7	0.38
Albumin (g/dL)	4.12 ± 0.46	4.17 ± 0.40	3.80 ± 0.66	0.01
Total bilirubin (mg/dL)	0.54 ± 0.34	0.52 ± 0.30	0.64 ± 0.50	0.27
Creatinine (mg/dL)	1.04 ± 0.84	1.05 ± 0.88	0.96 ± 0.53	0.51
Uric acid (mg/dL)	5.41 ± 1.63	5.43 ± 1.60	5.30 ± 1.85	0.71
Total cholesterol (mg/dL)	146.88 ± 42.07	148.99 ± 40.83	133.12 ± 48.06	0.08
Triglyceride (mg/dL)	136.2 ± 104.4	135.5 ± 106.3	142.3 ± 90.5	0.79
High-density lipoprotein (mg/dL)	40.32 ± 10.91	40.53 ± 10.20	38.99 ± 14.94	0.62
Low-density lipoprotein (mg/dL)	98.51 ± 38.40	99.11 ± 38.58	94.60 ± 37.72	0.59
Intraoperative variable				
Shunt use	131 (69.7)	116 (71.2)	15 (60.0)	0.26
Operation time (min)	202.69 ± 47.53	203.56 ± 46.75	197 ± 53.05	0.32
Clamping time (min)	56.63 ± 13.97	57.36 ± 14.02	51.08 ± 12.52	0.04
Operation side				
Left	88 (46.8)	76 (46.6)	12 (48.0)	0.90
Right	100 (53.2)	87 (53.4)	13 (52.0)	0.82
Nutrition index				
CONUT score	2.05 ± 1.68	1.85 ± 1.31	3.40 ± 2.87	0.01

Values are presented as number only, mean ± standard deviation, or number (%).

ASA, American Society of Anesthesiologists; PS, physical status; MI, myocardial infarction; CABG, coronary artery bypass grafting; CONUT, Controlling Nutritional Status.

Table 2. Postoperative outcomes for CONUT groups

Variable	Total (n = 188)	Low CONUT (n = 161)	High CONUT (n = 27)
Primary outcome			
Postoperative complication	25 (13.3)	13 (8.1)	12 (44.4)[a]
Major adverse cardiovascular events	7	2	5
Pulmonary complications	4	2	2
Stroke	9	6	3
Renal complications	1	1	0
Sepsis	1	0	1
Wound complications	1	1	0
Gastrointestinal complications	1	1	0
Death	1	0	1
Secondary outcome			
Intensive care unit stay (hr)	33.7 ± 84.3	34.2 ± 90.8	30.9 ± 20.9
Hospital stay (day)	7 (6–8)	6 (6–8)	7 (6–17)[a]
30-Day readmission	2 (1.1)	1 (0.6)	1 (3.7)

Values are presented as number (%), number only, mean ± standard deviation, or median (interquartile range).
CONUT, Controlling Nutritional Status.
[a] $p < 0.05$ vs. the low CONUT group.

Discussion

We evaluated the short-term prognostic value of the immunonutrition state using the CONUT score in patients who underwent CEA. Our findings showed a higher prevalence of postoperative complications in patients experiencing malnourishment than in those with normal nutrition.

Various nutritional screening tools are currently used to assess patient prognosis, as several studies have shown that malnutrition can lead to unfavorable outcomes [10]. Subjective Global Assessment and Mini Nutritional Assessment (MNA) are based on subjective data assessed by trained healthcare practitioners [11,12], whereas Prognostic Nutritional Index (PNI), Nutritional Risk Index (NRI), and CONUT scores are based on clinical or objective biochemical data [13,14]. To properly reflect the nutritional status of a patient, it would be more accurate to confirm both subjective and objective information. However, in a clinical setting, an objective, practical, and simple measurement method for primary nutritional screening may be more important. Several scoring systems, such as the PNI, NRI, and CONUT scores, have been proposed as reliable tools. Among the malnutrition scores, the CONUT score revealed the highest predictive ability for major adverse events in patients who underwent carotid artery stenting (CAS) [15]. The CONUT score was initially proposed by Ignacio de Ulíbarri et al. [16] as an easy and efficient nutritional screening tool for identifying malnutrition in hospitalized patients. A recent meta-analysis found that malnutrition calculated by the CONUT score was related to poor prognosis in surgical patients with hepatopancreatobiliary and gastrointestinal cancers [17]. Another study demonstrated an association between CONUT score and unfavorable clinical prognosis in hospitalized patients with various cardiovascular diseases [18]. Despite substantial evidence demonstrating the effectiveness of the CONUT score as an indicator of malnutrition for clinically unfavorable outcomes in various diseases, only one study has used the CONUT score as a prognostic indicator in patients undergoing CAS [15]. The results revealed that higher CONUT scores were associated with a clinically unfavorable prognosis in patients with CAS. In our study, CONUT score was positively associated with acute postoperative complications. However, more research is needed to assess which nutritional-immunological screening tools are the most practical and accurate in predicting clinically unfavorable prognosis after CEA.

Malnutrition accounts for a significant proportion of patients with stroke and neurological impairment, ranging from 6.1% to 62% [19]. According to the CONUT guidelines of our study, 32.4% of patients undergoing CEA were classified as malnourished. Thus, it is essential to elucidate how nutritional status affects acute postoperative complications in patients undergoing CEA. However, the exact pathophysiological mechanism underlying the association between CONUT score and increased postoperative morbidity remains unknown. Indeed, the mechanism of the relationship between CONUT score and increased risk of postoperative complications is considered multifactorial. Other investigators have hypothesized that malnutrition increases major postoperative complications owing to alterations in protein metabolism or decreased physiological reserves to cope with acute surgical stress

Table 3. Predictors associated with acute postoperative complications in patients undergoing carotid endarterectomy

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Demographics				
Female sex	0.96 (0.36–2.56)	0.94		
Age	1.03 (0.97–1.08)	0.35		
Body mass index	0.85 (0.74–0.98)	0.44		
Diabetes mellitus	0.67 (0.29–1.56)	0.35		
Smoker	0.98 (0.94–1.02)	0.45		
Hypertension	0.56 (0.25–1.23)	0.15		
Dyslipidemia	0.40 (0.00–6.57)	0.22		
Heart failure	8.43 (2.87–24.74)	< 0.001		
Previous ischemic heart disease	1.07 (0.37–3.13)	0.90		
Atrial fibrillation	1.78 (0.61–5.17)	0.29		
Baseline heart rate	1.01 (0.98–1.04)	0.60		
Baseline systolic blood pressure	1.02 (0.99–1.06)	0.15		
Baseline diastolic blood pressure	1.02 (1.00–1.04)	0.09		
Symptomatic lesion	2.29 (0.91–5.73)	0.08		
Antiplatelet use	1.20 (0.16–8.88)	0.86		
Antiplatelet, > 1	1.17 (0.51–2.64)	0.71		
Intraoperative variable				
Shunt use	0.64 (0.29–1.43)	0.28		
Operation time	1.00 (0.99–1.00)	0.54		
Clamping time	0.97 (0.93–1.00)	0.04		
Operation side, left	1.03 (0.47–2.27)	0.93		
Ipsilateral stenosis, > 70%	1.16 (0.35–3.88)	0.81		
Hematologic biomarker and nutrition index				
Hematocrit	0.96 (0.89–1.03)	0.23		
Albumin	0.27 (0.14–0.53)	< 0.001		
Total cholesterol	0.99 (0.98–1.00)	0.09		
Creatinine	0.82 (0.35–1.94)	0.66		
Uric acid	0.96 (0.74–1.23)	0.71		
Triglyceride	1.00 (0.99–1.01)	0.81		
High-density lipoprotein	0.99 (0.95–1.03)	0.53		
Low-density lipoprotein	1.00 (0.99–1.01)	0.60		
CONUT score, > 2	6.47 (2.95–14.20)	< 0.001	5.98 (2.56–13.97)	< 0.001[a]

CI, confidence interval; CONUT, Controlling Nutritional Status.

[a] Adjusted for heart failure, clamping time, and albumin level.

[20]. In other words, malnutrition itself may lead to a poor prognosis after surgery due to multifactorial consequences such as decreased protein synthesis, increased inflammatory response, and changes in immune function. Interestingly, immunonutritional status was readily assessed using the CONUT score based on serum albumin, total cholesterol, and lymphocyte count because a decrease in the response of each variable with acute disease or acute surgical stress may reflect a low immune nutritional status. Of the three CONUT components, serum albumin level was the most critical parameter. It is generally considered a biomarker of nutritional and systemic inflammatory status. Therefore, hypoalbuminemia may contribute to the progression and development of atherosclerosis [21].

Furthermore, hypoalbuminemia is associated with reduced antioxidant and antiplatelet aggregation activities, which result in increased central mediators of cardiovascular stenosis and increased oxidative stress and blood viscosity, leading to cardiovascular complications. In our study, these mechanisms may have influenced the association between malnutrition and cardiovascular complications. Moreover, lymphocytopenia affected the postoperative

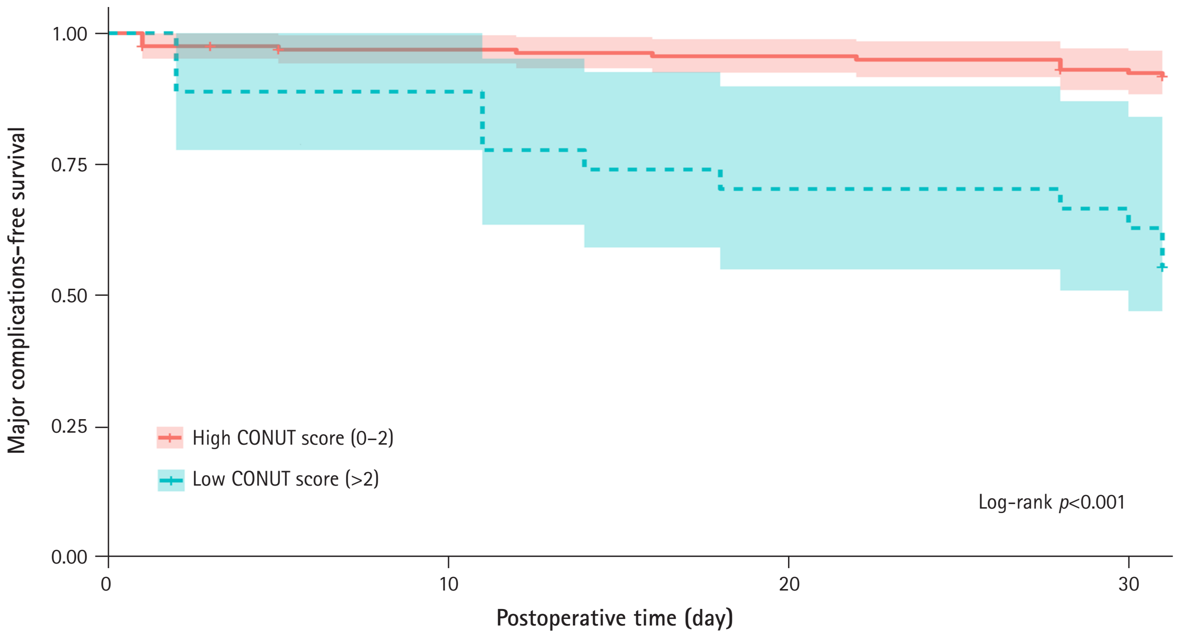


Fig. 3. Kaplan-Meier curves for the development of acute postoperative complications between different Controlling Nutritional Status (CONUT) scores.

complications in patients who underwent CEA in our study. Indeed, low lymphocyte counts may indicate impaired host immunity and poor nutrient intake [22]. Lymphocytopenia has also been studied in association with malnutrition and systemic inflammatory conditions. It has been speculated that specific pathophysiological courses may cause an acute increase in stress-related steroid levels, leading to a decrease in lymphocyte count [23]. In addition, low cholesterol levels may indicate progressive disease and systemic inflammatory activation [24]. Therefore, the CONUT score assesses the immunonutritional status of patients with caloric depletion, reduced protein reserves, and impaired immune defenses, which may serve as incremental values in predicting postoperative complications.

Our results suggest that screening the nutritional status of patients admitted for CEA can identify those at a higher risk of postoperative complications. Additionally, identifying malnutrition in patients undergoing CEA may lead to interventions for secondary prevention such as oral nutritional supplements, dietary counseling, food/fluid enrichment, and educational interventions [25]. There are many malnutrition screening tools, but there are still no standard guidelines for treating patients undergoing CEA. The management of atherosclerotic carotid stenosis is still under development, and the prognostic capabilities of the nutritional index have been found to be valuable and practical in several studies [26]. Therefore, the CONUT score, an easy and objective scoring system, may be selected as a valuable nutritional index for predicting unfavorable clinical outcomes in patients undergoing CEA, in addition to traditional parameters.

Our study has some limitations. First, this was a single-center retrospective observational study with a relatively small patient cohort. Second, our study assessed CONUT scores only on admission and did not evaluate CONUT scores after hospital discharge. Third, we only evaluated CONUT scores as indicators of malnutrition. Due to the retrospective nature of our study, other nutritional indicators, such as the Maastricht Index, MNA Short-Form scale, and NRI, were not used. Fourth, considering the retrospective nature of this study, we verified the *post hoc* power of the sample size. The incidence of acute postoperative complications after CEA in patients enrolled in this study was 13%. For the sample size of 188 people, when an alpha error of 0.05 was considered, only 85% of the post-test power was confirmed. These limitations require further investigation to validate the results. Large multicenter and prospective studies with larger numbers of patients are needed.

In conclusion, this study revealed that malnutrition assessment using the CONUT score can identify patients undergoing CEA who are at elevated risk for postoperative complications. Evaluation of immunonutritional status by CONUT score may help stratify the risk of acute postoperative complications and encourage improvement in nutritional status.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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None.

Author contributions

Conceptualization, Formal analysis: HWS, GY, SJL, JO; Investigation: HWS, GY, SJL; Data curation: HWS, SJL; Methodology: GY, SJL; Project administration, Validation: JO; Visualization, Supervision: HWS, JO; Software: SJL; Writing-original draft: HWS, JO; Writing-review & editing: HWS, JO.

ORCID

Hee Won Son, https://orcid.org/0000-0002-8035-062X
Gyeongseok Yu, https://orcid.org/0000-0003-4326-4674
Seung Jun Lee, https://orcid.org/0000-0001-9278-9923
Jimi Oh, https://orcid.org/0000-0002-2365-0642

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