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Clinical Research

All-cause Mortality Can Be Predicted in Patients with Chronic Total Occlusion with CONUT and PNI Scores

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ABSTRACT

Objective: CTO is defined as 100% occlusion of a coronary artery for more than one month. Nutritional status has been shown to be a prognostic marker in many clinical situations. CONUT and PNI scores are objective indices that can be calculated based on simple blood parameters and can be used to evaluate the nutritional status of patients. The aim of this study was to examine the effect of nutritional status assessed by CONUT and PNI on all-cause mortality in patients with CTO.
Material and Method: The retrospective study included 516 patients who had CTO on coronary angiography. The nutritional status of the patients was evaluated with PNI and CONUT scores, and categorical groups were formed according to these results and compared.
Results: All-cause mortality occurred in 127 (24.6%) patients during median follow-up period of 48 months. At the end of the follow-up period, the patients were divided into two groups as survival and non-survival. In terms of all-cause mortality, mean PNI score (47,87±6,31 vs. 42,41±6,57) and median CONUT score (1(2) vs. 3(3)) differed significantly between the surviving and non-surviving groups (p <0.001). Kaplan-Meier analysis showed a significant difference in survival between the PNI and CONUT scores cathegorical groups (p <0.001).
Conclusion: Higher CONUT scores and lower PNI scores were found to be associated with poor outcomes in CTO patients. Evaluation and monitoring of nutritional status in CTO patients by these nutritional scores may provide additional prognostic information.

Keywords: *CTO, PNI, CONUT, Malnutrition.*

ÖZ

CONUT ve PNI Skorları ile Kronik Total Oklüzyonlu Hastalarda Tüm Nedenlere Bağlı Mortalite Öngörülebilir
Amaç: CTO, bir aydan daha uzun bir süre boyunca bir koroner arterin %100 tıkanması olarak tanımlanır. Beslenme durumunun birçok klinik durumda prognostik bir belirteç olduğu gösterilmiştir. CONUT ve PNI skorları, basit kan parametrelerine dayalı olarak hesaplanabilen ve hastaların beslenme durumunu değerlendirmek için kullanılabilen objektif indekslerdir. Bu çalışmanın amacı, CTO'lu hastalarda CONUT ve PNI tarafından değerlendirilen beslenme durumunun tüm nedenlere bağlı mortalite ve prognoz gelişimi üzerindeki etkisini incelemekti.
Gereç ve Yöntem: Retrospektif çalışmaya Aralık 2012 ile Aralık 2019 tarihleri arasında koroner anjiyografide herhangi bir arterde CTO saptanan 516 hasta dahil edildi. Hastaların beslenme durumları PNI ve CONUT skorları ile değerlendirildi ve bu sonuçlara göre kategorik gruplar oluşturularak karşılaştırıldı.
Bulgular: Ortalama 50 aylık takip süresi içinde 127 (%24.6) hastada tüm sebepli mortalite meydana geldi. Hastalar takip süresi sonunda yaşayan ve yaşamayan olarak iki gruba ayrıldı. Ortalama PNI skoru yaşamayan grupta yaşayan gruba kıyasla daha düşük tespit edildi (42.41'e karşı 47.87; p <0,001). CONUT skoru yaşamayan grupta anlamlı olarak daha yüksek tespit edildi (3.34'e karşı 1.71; p <0,001). Kaplan-Meier analizi, PNI ve CONUT skorlarının kategorik grupları arasında sağkalım açısından anlamlı bir fark gösterdi (p <0,001).
Sonuç: CTO hastalarında yüksek CONUT skoru ve düşük PNI skorunun artmış tüm sebepli mortalite ile ilişkili olduğu bulundu. CTO hastalarında beslenme durumunun bu nutrisyonel skorlarla değerlendirilmesi ve takip edilmesi ek prognostik bilgi sağlayabilir.
Anahtar Sözcükler: *CTO, PNI, CONUT, Malnutrisyon.*

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Chronic total occlusion (CTO) is defined as 0 or 1 flow of Thrombolysis in Myocardial Infarction (TIMI) for more than one month as a result of complete occlusion of a coronary artery based on angiographic recordings. (1). CTO in at least one coronary artery is commonly detected in routine coronary angiography. Clinically, CTO can develop insidiously with minimal symptoms or may manifest as acute coronary syndrome (1).

Assessment of nutritional status is highly important in cardiac conditions, as in all diseases. The development or presence of cachexia is corraleted with a worse prognosis as in most diseases. To date, various methods and indices have been proposed for the assessment of nutritional situation and have been used to predict

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poor prognosis in various clinical conditions (2, 3).
Serum parameters such as albumin level and lymphocyte count are commonly used in nutritional indices. Moreover, admission hypoalbuminemia has been shown to be an independent predictor of long-term mortality and the development of advanced heart failure in patients who undergoing primary percutaneous coronary intervention (PCI) with ST segment elevation myocardial infarction (STEMI) (4). In a recent study, serum albumin levels at admission were found to be statistically lower in the massive pulmonary embolism group than in the submassive and nonmassive groups (5). On the other hand, a relationship has been reported among a single nutritional parameter, such as albumin, and coronary collateral circulation (CCC), which is a predictor of mortality in patients with CTO (6). Prognostic Nutritional Index (PNI) is calculated by total lymphocyte count and serum albumin and reflects immunonutritional status and the risk of developing postoperative complications (7). Controlling Nutritional Status (CONUT) is an effective instrument for early finding and continuous check of hospital malnutrition, calculated based on serum albumin level, lymphocyte count and total cholesterol level (8).
The aim of this study was to examine the effect of nutritional situation determined by objective nutritional indices on the development of all-cause mortality and prognosis in patients with CTO.

MATERIAL AND METHOD

Study setting and population

This retrospective, single-center, and observational study included patients that were detected with CTO in any artery on coronary angiography in our university Cardiology Department from December 2012 and December 2019. The study was planned in accordance with the Declaration of Helsinki and was approved by the ethics committee of our university. Data on clinical characteristics including presence of chronic heart failure, hypertension, diabetes, chronic kidney disease, dyslipidemia, stroke and smoking status were retrieved from electronic medical records. Patients' medical histories were obtained via telephone interviews. Patients that did not provide a consent to the study and those who were aged under 18 years, had a CTO artery diameter <2 mm and those with a history of bypass surgery were excluded from the study. The endpoint of the study was all-cause mortality.

Laboratory parameters and nutritional indices

Blood samples were routinely obtained from venous blood during hospital admission. Complete blood count (CBC) was performed using an Abbott Analyzer system and hematological indices were calculated for each patient. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and other biochemical levels were measured using an Abbott system. Left ventricular ejection fraction (LVEF) was measured using transthoracic 2D echocardiography during hospitalization. Table 1 presents the calculation methods of PNI and CONUT scores and the risk classifications performed according to total scores (9).

Table1. *Methods for calculating nutritional indexes and the formation of nutritional status groups.*

CONUT Score		
Total Conut Score= Albumin Score+ Total lymphocyte score+ Total cholesterol score		
Dysnutritional state (Total Conut Score) Normal (0-1), Mild (2-4), Moderate (5-8), Severe (9-12)		
Albumin Score;	**Total lymphocyte Score;**	**Total cholesterol Score;**
≥3.5 g/dL **0 point**,	≥1600 count/mL **0 point**,	≥180 mg/dL **0 point**,
3.0–3.4 g/dL **2 point**,	1200–1599 count/mL **1 point**,	140–179 mg/dL **1 point**,
2.5–2.9 g/dL **4 point**,	800–1199 count/mL **2 point**,	100–139 mg/dL **2 point**,
<2.5 g/dL **6 point**	<800 count/mL **3 point**	<100 mg/dL **3 point**
PNI Score		
PNI = 10 × serum albumin in g/dL + 0.005 × total lymphocyte count in mm3		
Dysnutritional state (PNI score) Normal (>38), Moderate (35–38), Severe (<35)		

Based on PNI scores, patients were categorized as follows: (i) <35; severe malnutrition, (ii) 35-38; moderate malnutrition, and (iii) >38; no malnutrition. Based on CONUT scores, patients were categorized as follows: (I) <2; no malnutrition, (II) 2-4; mild malnutrition, (III) 5-8; moderate malnutrition, and (IV) >8; severe malnutrition. Since the number of patients in the severe malnutrition group was remarkably low, the moderate and severe malnutrition groups were grouped together as a single group.

Statistical analysis

We analyzed our data using SPSS for Windows version 25.0. First, we analyzed the normality of the distribution of our data with the Shapiro-Wilk tests or Kolmogorov-Smirnov. We expressed abnormally distributed variables as IQR (interquartile range). Continuous variables were expressed as mean ± standard deviation (SD) or first and third percentiles (Q1-Q3) and median based on the distribution patterns of the data. Continuous variables were compared using Mann-Whitney U test or student t-test as appropriate. We used Chi-square test/Fischer's Exact tests to analyze categorical variables and expressed the variables as percentages (%). In the case of more than one group, we compared groups using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test as appropriate. We used univariate and multivariate analyzes with logistic regression models to identify predictors of all caused mortality. We then performed multivariate logistic regression analyzes to identify independent predictors of all caused mortality. Survival rates in the groups formed based on PNI and CONUT scores were analyzed using the Kaplan-Meier method. A p value of <0.05 was considered significant.

RESULTS

A total of 516 consecutive patients were reviewed in the study.

Baseline demographic characteristics

Median follow-up period was 48 months. Patients comprised 368 (71.3%) men and 148 (28.7%) women with a mean age of 63.2 ± 11.1 years. Total mortality occurred in 127 (24.6%) patients within a median period of 35 months after the procedure (Table 2).

Table 2. *Baseline demographic characteristics and biochemical variables and nutritional indices at admission.*

	All patients (516)	Survivors (389)	Deceased (127)	p values
Age(year)	63,2±11,1	61,4±10,6	68,8±10,7	**<0,001**
Follow up time (month) (IQR)	48(46)	55(48)	30(48)	**<0,001**
Gender (male)(%)	368 (71,3)	279 (71,7)	89 (70,1)	0,722
Smoking (%)	144 (27,9)	108 (27,8)	36 (28,3)	0,899
Comorbidities				
Hypertension (%)	180 (34,9)	120 (30,8)	60 (47,2)	**0,001**
Diabetes mellitus (%)	153 (29,7)	107 (27,5)	46 (36,2)	0,062
Hyperlipidemia(%)	32 (6,2)	27 (6,9)	5 (3,9)	0,314
Chronic Kidney Disease (%)	28 (5,4)	13 (3,3)	15 (11,8)	**0,001**
Congestive Heart Failure (%)	51 (9,9)	24 (6,2)	27 (21,3)	**<0,001**
Previous Stroke (%)	14 (2,7)	4 (1,0)	10 (7,9)	**<0,001**
Symptomatology				
SCAD	237 (45,9)	187 (48,1)	50 (39,4)	0,088
ACS	279 (54,1)	202 (51,9)	77 (60,6)	
Treatment Type				
Medical Therapy	180 (34,9)	116 (29,8)	64 (50,4)	**<0,001**
PCI	262 (50,8)	222 (57,1)	40 (31,5)	
CABGO	74 (14,3)	51 (13,1)	23 (18,1)	
EF(%)	49,13±11,14	50,92±10,21	43,63±12,08	**<0,001**
Leukocyte(K/uL)	9316,3±3000,6	9166,9±2838,7	9773,9±3421,3	**0,048**
RBC(K/uL)	4,85±0,66	4,91±0,65	4,67±0,65	**0,001**
Hemoglobulin(g/dL)	13,58±1,88	13,79±1,81	12,94±1,93	**<0,001**
Hematocrit(%)	40,93±5,43	41,58±5,32	38,94±5,31	**<0,001**
MCV(fL)	84,64±5,92	84,96±5,56	83,68±6,84	0,059
RDW(%)	13,50±2,45	13,02±2,24	14,96±2,50	**<0,001**
Lymphocyte(Null)	2155,2±776,9	2241,8±757,8	1890,1±777,7	**<0,001**
Neutrophil(Null)	6226,5±2928,0	6015,4±2689,3	6873,1±3494,6	**0,012**
Eozonophil(Null) (IQR)	147(179)	152(181)	129(180)	0,560
Glucose(mg/dL) (IQR)	116(74)	112(64)	128(103)	**0,042**
Urea(mg/dL)	43,8±22,1	39,6±16,5	56,7±30,5	**<0,001**
Creatinine(mg/dL)	1,04±0,73	0,97±0,60	1,24±0,99	**0,004**
Albumin(g/dl)	3,57±0,46	3,66±0,42	3,29±0,47	**<0,001**
Total Cholesterol(mg/dL)	176,7±43,5	178,5±43,7	171,4±42,5	0,109
Triglyceride(mg/dL) (IQR)	144(112)	154(115)	120(91)	**0,002**
LDL (mg/dL)	104,0±37,0	103,5±38,1	105,8±33,6	0,547
HDL (mg/dL)	38,5±10,3	39,3±10,3	35,8±10	**0,001**
CONUT score (IQR)	2(2.75)	1(2)	3(3)	**<0,001**
PNI score	46,52±6,79	47,87±6,31	42,41±6,57	**<0,001**

Continuous variables are presented as mean + SDNominal variables are presented as frequency (%). Abbreviations: ACS- Acute coronary syndrome, CABGO- Coronary artery bypass greft operation, PCI- Percutaneous CONUT- Controlling Nutritional Status, EF- Ejection Fraction, HDL- High Density Lipoprotein, LDL- Low Density Lipoprotein, PNI-Prognostic Nutritional Index, RBC- Red Blood Cell, PCI-Percutan Coronary Intervention, SCAD- Stable coronary artery disease.

Non-surviving group, compared to the surviving group, had a higher prevalence of previous hypertension (47.2% vs. 30.8%), previous chronic kidney disease (11.8% vs. 3.3%), previous heart failure (21.3% vs. 6.2%), and previous cerebrovascular events (7.9 vs. 1.0%).

Three different treatment methods including medical treatment (n= 180; 34.9%), coronary artery bypass graft (CABG) (n= 74; 14.3%) and PCI (n= 262; 50.8%) were used for CTO treatment. Mortality was significantly lower in the PCI group (p <0.001).

Admission Biochemical variables and nutritional indices at admission

Table 2 presents admission biochemical variables and nutritional indices in the surviving and non-surviving groups. Accordingly, LVEF (43.63% vs. 50.92%), hemoglobin (Hgb) (12.94% vs. 13.79%), hematocrit (HCT) (38.94% vs. 41.58%), lymphocyte count (1890.1±777.7 vs. 2241.8±757.8), and albumin level (3.29±0.47 vs. 3.66±0.42 g/dl) were significantly lower in the non-surviving group compared to the surviving group (p <0.001 for all). In terms of all-cause mortality, mean PNI score (47,87±6,31 vs. 42,41±6,57) and median CONUT score (1(2) vs. 3(3)) differed significantly between the surviving and non-surviving groups (p <0.001).

As seen in Figure 1, according to Kaplan-Meier analysis, a significant difference was observed between the categorical groups of PNI and CONUT score in terms of survival time. (p <0.001). However, it is noteworthy that this difference started from the first stages of the follow-up period.

Table 3 presents the results of univariate and multivariate regression analysis that was performed to determine the effect of parameters on mortality.

Table 3. *Predictors of mortality in univariate and multivariate regression analysis.*

	Univariate Cox			Multivariate Cox		
All cause mortality	**OR**	**95% CI**	***p value***	**OR**	**95% CI**	***p value***
Age	1.053	1.036-1.070	***<0.001***	1.033	1.014-1.052	***0.001***
Gender (male)	1.018	0.696-1.489	0.926	1.370	0.862-2.177	0.182
Hypertension	1.662	1.173-2.355	***0.004***	1.234	0.846-1.801	0.275
Previous stroke	2.400	1.257-4.584	***0.008***	1.212	0.542-2.711	*0.640*
Congestive heart failure	3.409	2.217-5.242	***<0.001***	2.638	1.684-4.132	***<0.001***
Chronic Kidney Disease	2.840	1.653-4.878	***<0.001***	1.245	0.530-2.926	*0.615*
Treatment Type (PCI)	0.547	0.356-0.839	***0.006***	0.662	0.425-1.029	*0.067*
Left Venticular EF	0.958	0.944-0.972	***<0.001***			
Hemoglobulin level	0.850	0.779-0.928	***<0.001***	1.000	0.891-1.123	0.998
Urea	1.019	1.014-1.025	***<0.001***			
Glucose level	1.003	1.001-1.004	***0.007***	1.002	1.000-1.004	***0.017***
CONUT score	1.278	1.195-1.366	***<0.001***	1.128	1.030-1.234	***0.009***
PNI score	0.913	0.890-0.936	***<0.001***	0.957	0.926-0.989	***0.008***

The analysis indicated that advanced age, heart failure, high glucose level, low PNI score and high CONUT score at admission were independent predictors of mortality. When the groups with nutritional status indicators are compared among themselves, it is noteworthy that the prognosis worsens as the nutritional group worsens.

DISCUSSION

Correction of reversible factors that have been shown to have an effect on mortality in CTO patients is likely to have a positive effect on the quality of life and life expectancy of patients. Moreover, the use of indices calculated by simple blood markers in the follow-up of patients can be highly beneficial. CONUT and PNI are objective indices used for assessing nutritional status and have been shown to be independently associated with cardiovascular events (10). A recent study reported that in STEMI patients, the nutritional status evaluated by the CONUT score, in addition to other comorbidities, may affect the prognosis particularly in elderly patients (11). In our study, a relationship was found between high CONUT and low PNI scores and all-cause mortality over the median follow-up period of 48 months. Additionally, Kaplan-Meier analysis showed a significant differentiation over time between groups that were divided according to scores. In CTO, patients can continue their lives without being affected by the disease despite having at least one fully occluded artery for a long period of time, which shows that such patients have a good nutritional status. In our study, it was noteworthy that there were very few patients with severe malnutrition. In addition, the effect of nutrition on mortality was remarkably high in our patient group, whose nutritional status was evaluated to be sufficiently good. This finding indicates that these scoring systems may be more valuable than their value reported in the literature.

Successful recanalization of CTO has been shown to result in improved LVEF and regional wall motion (9). In our study, a significant relationship was found between low LVEF and the mortality risk and heart failure was found to be an independent predictor of mortality. These findings suggest that LVEF should be monitored closely since it may be useful in the prediction of the prognosis.

Studies investigating CTO and stable coronary artery disease (SCAD) have shown that successful interventional therapy has a positive effect on survival in patients with increased myocardial ischemia (12). This benefit is often considered to result from a reduction in ischemic burden with successful PCI in patients with greater ischemic burden (13). The present study evaluated 516 CTO patients and revealed that successful PCI reduced the risk of all-cause mortality over a median follow-up period of 48 months. Nonetheless, the criteria used in the selection of the intervention methods administered in our patients were not clearly examined, and thus it may be inappropriate to consider that PCI is superior to CABG in intervention therapy.

A previous study followed up 1092 CTO patients for medium period of 39 months and reported that the presence of chronic kidney disease increased the frequency of events and all-cause death. The authors also noted that all the patients, regardless of the presence of chronic kidney disease, benefited from revascularization, although this benefit was lower in patients with chronic kidney disease (14). Similarly, in our study, a significant relationship was found between the presence of chronic kidney disease and mortality in favor of poor prognosis.

In the presence of severe coronary artery stenosis, good CCC may improve myocardial ischemia, preserve myocardial contractility, improve clinical symptoms, reduce the incidence of myocardial infarction, and reduce myocardial infarct size, thereby leading to reduced mortality from ischemic events (15, 16). A recent study evaluated 128 CTO patients and found a positive correlation between increased serum albumin level and good CCC development and also found a negative correlation between diabetes and CCC development (17). In our study, low serum albumin level and high blood glucose level were found to have a significant relationship with all-cause mortality. Based on these findings, we consider that the close relationship between these parameter changes and CCC development is a clear indication of the importance of CCC development in coronary artery diseases.

Limitations

Our study was limited since it had a retrospective design and thus did not evaluate the changes in laboratory parameters during the follow-up period. Additionally, it also could not assess other parameters associated with malnutrition during blood sampling, such as body mass index (BMI), and thus could not evaluate malnutrition thoroughly.

Conclusion

Both CONUT and PNI, which are objective indices commonly used for assessing nutritional status, were found to be associated with poor outcomes in CTO patients. Evaluation and monitoring of nutritional status in CTO patients by these nutritional scores may provide additional prognostic information. Accordingly, evaluation and monitoring of nutritional status in CTO patients may provide additional prognostic information.

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