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Title

The prognostic impact of the controlling nutritional status (CONUT) score in patients undergoing cardiovascular surgery

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All authors have no conflict of interest.

Consent

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Ethical approval

Use of the clinical data in this study was approved by the human ethics review committee of Misato Central General Hospital.

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Abstract

Background

Various postoperative predictive markers following cardiovascular surgery have been examined for use in the current aging population. The Controlling Nutritional Status (CONUT) score, which is advocated not only as a screening tool for poor nutritional status, but also as an immunonutritional assessment, has started to attract attention in several clinical settings, such as in cancer and heart failure patients. The aim of this study was to evaluate the value of the CONUT score as a postoperative prognostic marker in patients who underwent cardiovascular surgery.

Methods

A total of 75 patients who underwent elective cardiovascular surgery between January 2015 and October 2017 were retrospectively analyzed. The patients were divided into two groups according to their preoperative CONUT score (i.e., $\text{CONUT} < 2$ or $\text{CONUT} \geq 2$), and their clinicopathological characteristics, surgical outcomes, and overall survival were compared. The median follow-up period was 23 months (range 0-43 months) after surgery.

Results

The high CONUT group ($\text{CONUT} \geq 2$), which consisted of 30 (40.0%) patients, had a significantly worse prognosis than the low CONUT group with regard to overall survival ($p=0.0007$). On multivariate analyses, the CONUT score was identified as the only independent prognostic factor for overall survival (hazard ratio 1.47 per 1 CONUT score increase, 95% confidence interval 1.05-2.06, $p < 0.026$).

Conclusions

The CONUT score is a reliable and independent preoperative predictor of overall survival after cardiovascular surgery.

Text

Introduction

In step with the acceleration of global population ageing, cardiovascular surgery is being performed for increasing numbers of elderly patients each year. Many elderly patients tend to have frailty and sarcopenia, which reflect a state of reduced physiological reserve and vulnerability to stressors [1]. Recent research indicates that frailty status, assessed by mobility, disability, and nutritional status, affects clinical outcomes following major cardiac surgery [2-4]. Nutrition is closely linked with frailty and sarcopenia, and, therefore, preoperative nutritional status is thought to affect postoperative outcomes. If a nutritional indicator could predict morbidity, mortality, functional status, and quality of life, such information would be important to make informed decisions before surgery.

Various nutritional indices have been examined, and the Controlling Nutritional Status (CONUT) score, which is calculated from the serum albumin concentration, the total peripheral lymphocyte count, and the total cholesterol concentration, is advocated as a screening tool for early detection of poor nutritional status [5]. Recently, the CONUT score has received attention as a predictive biomarker of survival following operations for several cancers, rather than simply as a nutritional assessment [6-9]. The significance of the CONUT score in cardiovascular surgery is still unknown. This retrospective study, therefore, investigated the usefulness of the CONUT score for evaluating the prognosis of patients undergoing cardiovascular surgery.

Materials and methods

Patients

Between January 2015 and October 2017, 75 patients underwent elective cardiovascular surgery at the Department of Cardiovascular Surgery, Misato Central General Hospital. Their clinical data were reviewed retrospectively. The median follow-up period was 23 months (range 0-43

months) after surgery. The endpoint of the study was all-cause death. This study was approved by the ethics committee of Misato Central General Hospital (the approval number: 2018006), and informed consent was obtained from all patients.

CONUT score

The CONUT score is known as a method of nutritional status assessment, and it is calculated based on serum albumin levels, total lymphocyte counts, and total cholesterol levels. The range of the CONUT score is 0 to 12, and the scores are categorized as normal nutrition (0-1), light malnutrition (2-4), moderate malnutrition (5-8), or severe malnutrition (9-12) (Table 1) [5]. In this study, preoperative blood samples were obtained within a week before surgery.

The CONUT score as a continuous variable was used as the test variable, and all-cause death was the state variable. As a preliminary analysis for the cut-off value of the CONUT score, the receiver operating characteristic (ROC) curve analysis was performed in the patient group. The most appropriate cut-off value was 2 (area under the curve 0.804, 95% CI 0.694–0.915, $p < 0.001$, with sensitivity of 1.000 and specificity of 0.652). Therefore, 2 was set as the cut-off value for the CONUT score in this study, and the patients were divided into a low CONUT (0-1) group and a high CONUT (≥ 2) group.

Other clinical data

Clinical data, including age, sex, body mass index (BMI), diabetes mellitus (DM), hemodialysis (HD), left ventricular ejection fraction (LVEF), type of surgery, JapanSCORE, European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, Clinical frailty scale (CFS), 5-meter gait speed (5MGS), and grip strength, were also evaluated. BMI was calculated from the preoperative heights and weights of the patients, which were measured within a week before surgery. DM was defined by patient self-report of a history of DM, current use of insulin or

hypoglycemic agents, or serum HbA1c level $\geq 6.5\%$. The JapanSCORE and EuroSCORE II as predictors of mortality were calculated for each patient. The CFS was used to assess each patient's frailty status according to the Canadian Study of Health and Aging grading criteria, ranging from 1 to 9, with higher scores reflecting greater frailty. For the 5MGS, participants were instructed to walk at a comfortable pace for a distance of 5 m, and, if necessary, they were permitted to use assistive devices such as walkers and canes. Patients repeated the walk 3 times, and their mean speed was calculated.

Short-Term Outcomes

Postoperative mortality (death within 30 days after surgery and in-hospital mortality), morbidity, duration of hospital stay, and rehospitalization within 30 days were reviewed as short-term outcomes. In the present study, morbidity was defined as prolonged ventilation (> 24 hours), reoperation for any reason, stroke, and infection. Postoperative infection included infection of any organ, such as surgical site infection, pneumonia, sepsis, and prosthetic valve endocarditis.

Statistical analysis

Continuous variables are presented as means \pm standard deviation (SD) or medians (interquartile range, IQR), and categorical variables are presented as numbers and percentages. Differences between groups were assessed using the Mann-Whitney U test for continuous variables and Fisher's exact test or the Chi-squared test for categorical variables. Overall survival (OS) rates were calculated using the Kaplan-Meier method, and differences between curves were analyzed using the log-rank test. To investigate prognostic factors associated with OS, a Cox proportional hazard model was used for univariate and multivariate analyses, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A p value < 0.05 was considered significant. These statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA).

Results

Figure 1 shows the distribution of the CONUT scores. For these 75 patients, the mean CONUT score was 1.6 ± 1.7 ; 30 (40.0%) patients were classified into the high CONUT (≥ 2) group, and 45 (60.0%) patients were classified into the low CONUT (0-1) group.

The clinical characteristics and short-term surgical results of the patients are shown in Table 2.

The patients in the high CONUT group were significantly older, had lower BMI, had higher risk based on both risk scores, had higher frailty on the CFS, were slower in the 5MGS, and had longer hospitalization after surgery.

In total, 6 cases of all-cause death were identified during follow-up, and all cases were in the high CONUT group. Three were in-hospital deaths within 30 days after surgery, with one having intraoperative rupture of a descending aortic aneurysm and two having pneumonia.

There were another 3 cases of non-cardiac death occurring 4, 11, and 26 months after surgery.

Figure 2 shows the Kaplan-Meier curves for OS for the two groups. OS was clearly lower in the high CONUT group (log-rank $p = 0.0007$).

Table 3 shows the results of the Cox proportional hazard model for OS. On univariate analyses, the CONUT score as a continuous variable was significantly associated with poor OS (HR 1.47 per 1 CONUT score increase, 95% CI 1.05-2.06, $p < 0.026$). On multivariate analysis using backward stepwise elimination, the CONUT score as a continuous variable was the only independent prognostic factor for OS (HR 1.47 per 1 CONUT score increase, 95% CI 1.05-2.06, $p < 0.026$).

Discussion

The present study demonstrates that the preoperative CONUT score is an independent prognostic factor for OS in patients undergoing cardiovascular surgery. This is the first report to identify the prognostic significance of the CONUT score after cardiovascular surgery. The

CONUT score, which is derived from three parameters, serum albumin and total cholesterol concentrations and the total lymphocyte count, is an efficient tool for the early detection and ongoing control of undernutrition in hospitalized patients [5]. Individually, hypoalbuminemia [10], hypocholesterolemia [11], and lymphopenia [12] are each independent prognostic factors in patients with heart failure. In addition, the CONUT score as an aggregate of these markers is an independent predictor in heart failure patients [13,14]. Recently, the CONUT score has been reported to be a predictive biomarker of survival in patients undergoing operations for several types of cancers [6-9].

In cardiac surgery, although the associations of the CONUT score and postoperative outcomes have not yet been identified, patients with a poor nutritional status have been demonstrated to have worse outcomes, including higher morbidity and mortality [15,16]. The surgical stress leads to the activation of neutrophils, endothelial cells, and platelets and the release of inflammatory mediators, such as tumor necrosis factor α (TNF α) and various interleukins (IL) [17,18]. Cardiac surgery in particular, with foreign surface contact and hemodilution during cardiopulmonary bypass (CPB), activates not only leukocytes and platelets [19,20], but also humoral mediators [21], including the complement system [22,23]. The ischemia-and-reperfusion (I/R)-injury that happens after cross-clamping of the aorta further induces the inflammatory reaction [17,24,25]. Gut ischemia due to hemodynamic instability and prolonged CPB time during cardiac surgery induce increased permeability of the intestinal mucosa and the translocation of intestinal bacteria into the bloodstream, which results in multiple organ damage through the spread of the inflammatory response [25,26].

Serum albumin plays a pivotal role in the maintenance of homeostasis. Albumin has vital roles in serving as a plasma buffer to maintain physiological pH levels and in transporting drugs and endogenous compounds. Albumin provides a balance between hydrostatic and colloid-osmotic pressure within vessels, and it prevents the development of tissue edema. Albumin also has antioxidant properties that scavenge oxygen free radicals related to the pathogenesis of

inflammatory diseases [27].

Lymphocytopenia is considered to reflect a poorly regulated immune response. In patients with physiological stress, systemic cortisol production is increased, and increased cortisol levels result in a decrease in the relative concentration of lymphocytes and an increased percentage of granulocytes. Because the adrenal system has a sensitive feedback function for adverse physiologic conditions, changes in the relative lymphocyte count may be an early marker [28]. Cholesterol is a key component of the plasma membrane and affects membrane structure and function. Hypocholesterolemia has a negative effect on cell membrane fluidity and signal transduction. In addition, cholesterol is a vital material for sex hormones, steroid hormones, bile acids, and vitamin D. Cholesterol has roles in the inflammatory and immune responses [29,30]. The CONUT score that brings these three important biological markers together summarizes the patients' immunonutritional status from various perspectives and presents an excellent prognostic value. Thus, the CONUT score may evaluate patient durability and resilience against surgical stress. Impressively, the present study showed that the CONUT score was an independent prognostic factor for OS and had value for risk stratification. Considering that preoperative nutritional status affects patient prognosis, identifying patients at high nutritional risk is essential for adequate decision-making about the procedures, especially in elderly and frail patients. There are some widely accepted risk scores including the EuroSCORE II, Society of Thoracic Surgeons Predictive Risk of Mortality (STS) score, and the JapanSCORE in the field of cardiovascular surgery that have valuable prognostic ability. They do not directly evaluate nutritional status or frailty. Although some parameters used in CONUT score are not included, existing risk scores evaluate many items and consequently cover a wide range. However, it is very significant that this study showed the relationship between CONUT score which is a simple nutritional screening and OS. Because, CONUT score as a prognostic indicator have some advantages when compared to existing risk scores. It is simple to use and easy to understand, it includes both the nutritional assessment and therapeutic approach.

The results of the present study imply that the CONUT score could contribute valuable prognostic insights that complement existing risk models and could assist surgeons in providing the optimal treatment for their frail patients.

This study has several limitations. First, it involved only a small cohort using a retrospective, single-center design. Second, the follow up period was short. Longer follow-up was needed to reveal long-term prognosis. Third, several factors that affect inflammation-based and nutritional scores, such as medications, were included. Fourth, the CONUT scores after discharge were not recorded; thus, the effect of the post-discharge CONUT score on clinical outcomes could not be determined. These limitations require further examinations to confirm the present findings, and prospective validation studies in a larger number of patients are required. Whether preoperative nutritional intervention might contribute to improving postoperative prognosis will also need to be further investigated in additional prospective studies.

Conclusions

The results of the present study suggest that the CONUT score is a reliable and independent preoperative predictor of OS after cardiovascular surgery. Assessment of the COUNT score is both convenient and valuable for surgeons to select and perform optimal treatment.

Conflict of interest: The authors have declared that no conflict of interest exists.

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Legends

Table 1 Assessment of the degree of undernutrition by the CONUT score

CONUT, controlling nutritional status [5]

Table 2 Patients' characteristics and short-term surgical results

BMI, body mass index; DM, diabetes mellitus; HD, hemodialysis; LVEF, left ventricular ejection fraction; 5MGS, 5-meter gait speed; CONUT, controlling nutritional status; CABG, coronary artery bypass grafting

Table 3 Univariate and multivariate analyses for overall survival

BMI, body mass index; CFS, Clinical frailty scale; CONUT, controlling nutritional status; LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval

Fig. 1 Distribution of the CONUT scores

CONUT, controlling nutritional status

Fig. 2 Kaplan-Meier curves for overall survival

CONUT, controlling nutritional status

Table 1 Assessment of undernutrition degree by CONUT

<i>Parameter</i>	<i>Undernutrition Degree</i>			
	<i>Normal</i>	<i>Light</i>	<i>Moderate</i>	<i>Severe</i>
Serum Albumin (g/dl)	3.5 - 4.5	3.0 - 3.4	2.5 - 2.9	< 2.5
Score	0	2	4	6
Total Lymphocytes (/ml)	> 1600	1200 - 1600	800 - 1199	< 800
Score	0	1	2	3
Cholesterol (mg/dl)	> 180	140 - 180	100 - 139	< 100
Score	0	1	2	3
Screening Total Score	0 - 1	2 - 4	5 - 8	9 - 12

CONUT controlling nutritional status

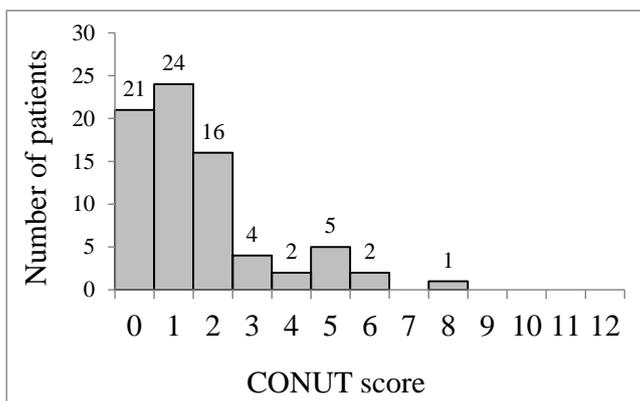


Figure 1 Distribution of the CONUT scores. *CONUT* controlling nutritional status

Table 2 Patient characteristics and short-term surgical results

	Overall (n = 75)	Low CONUT (n = 45)	High CONUT (n = 30)	<i>p</i> value
Demographics				
Age (years)	67.7 ± 10.0	66.0 ± 9.7	70.1 ± 10.1	0.0366
Female	18	9	9	0.4100
Clinical				
BMI (kg/m ²)	23.10 ± 3.35	23.75 ± 3.39	22.12 ± 3.09	0.0393
DM	21	13	8	1.0000
HD	5	1	4	0.1505
LVEF (%)	55.4 ± 12.1	57.4 ± 11.6	52.5 ± 12.4	0.0893
Frailty markers				
Clinical Frailty scale	3.7 ± 0.8	3.5 ± 0.7	3.9 ± 0.8	0.0317
5MGS (s)	5.25 ± 1.86	4.97 ± 1.95	5.67 ± 1.67	0.0259
Grip strength (kg)	27.1 ± 9.2	28.5 ± 9.3	25.6 ± 9.0	0.2490
CONUT score	1.6 ± 1.7	0.5 ± 0.5	3.2 ± 1.7	<0.0001
Type of surgery				
CABG	32	22	10	
Valve	36	19	17	0.5490
Aorta	7	4	3	
Risk score				
JapanSCORE (%)	3.27 ± 3.68	1.87 ± 1.47	5.37 ± 4.87	<0.0001
EuroSCORE II (%)	3.120 ± 3.117	1.832 ± 1.139	5.052 ± 4.049	<0.0001
Mortality or major morbidity				
Mortality	3	0	3	0.0601
Composite mortality & morbidity	20	9	11	0.1207
Prolonged ventilation	15	6	9	0.0876
Reoperation	7	4	3	1.0000
Wound infection	2	0	2	0.1568
Stroke	0	0	0	N/A
Infection	9	3	6	0.1439
Hospital stay (day)	28.6 ± 16.6	25.1 ± 14.8	34.3 ± 18.1	0.0107
Rehospitalization within 30 days	2	0	2	0.1373

CONUT controlling nutritional status, BMI body mass index, DM diabetes mellitus, HD hemodialysis, LVEF left ventricular ejection fraction, 5MGS 5-meter gate speed, CABG coronary artery bypass grafting, N/A not applicable

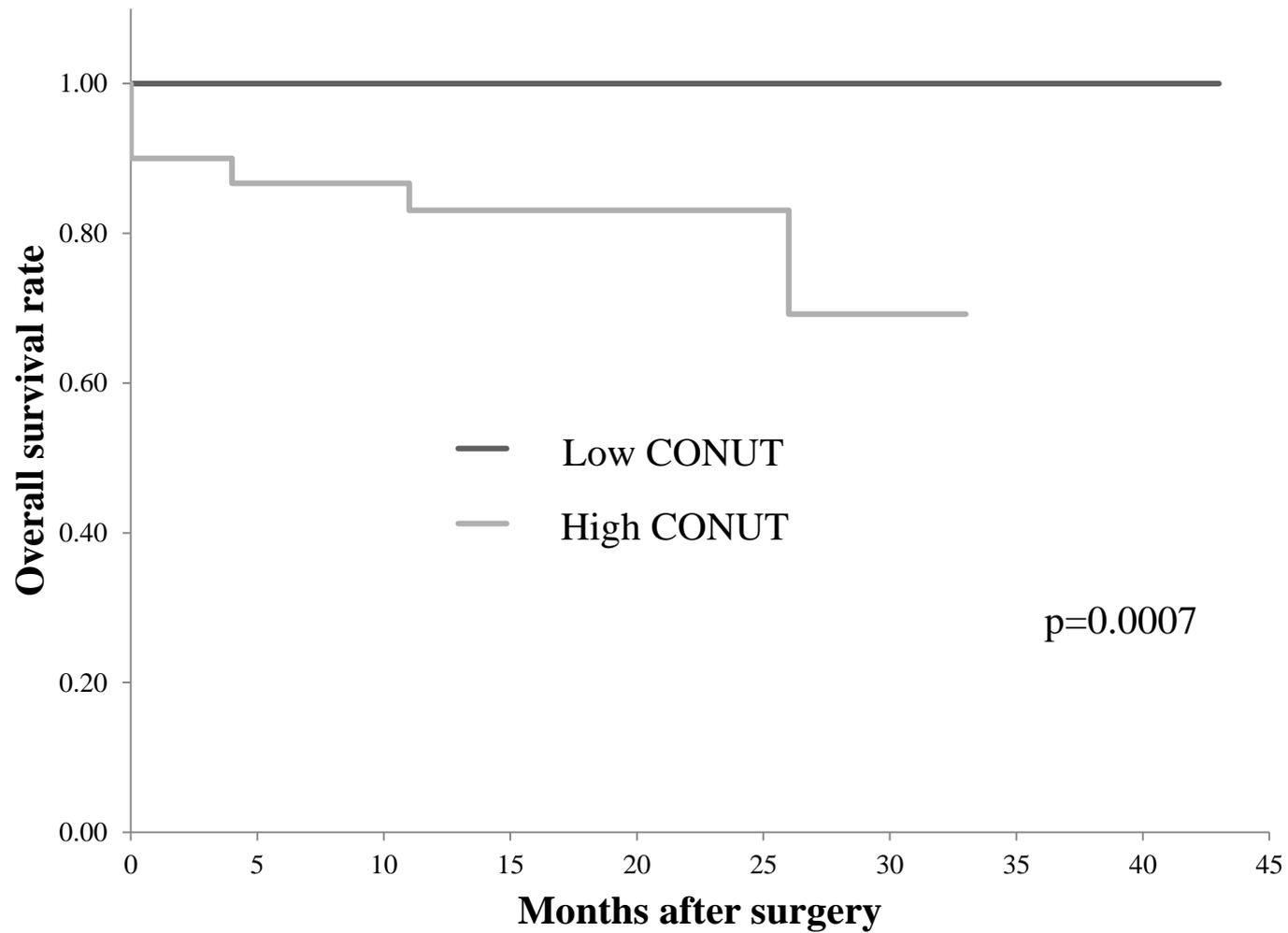


Figure 2 Kaplan–Meier analysis of a overall survival. *CONUT* controlling nutritional status

Table 3 Univariate and multivariate analyses for overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age (≥ 70 years)	4.1661	0.4866-35.6678	0.1927			
Sex (male)	1.6031	0.2935-8.7563	0.5859			
BMI (< 18.5 kg/m ²)	2.0009	0.2337-17.1321	0.5267			
CFS (≥ 4)	1.6414	0.2962-9.0964	0.5706			
CONUT score	1.4703	1.0475-2.0638	0.0258	1.4703	1.0475-2.0638	0.0258
LVEF (< 50 %)	2.5422	0.5075-12.7358	0.2564			
Valve	2.1881	0.4007-11.9473	0.3659			

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *CFS* clinical frailty scale, *CONUT* controlling nutritional status, *LVEF* left ventricular ejection fraction