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A novel and simply calculated nutritional index serves as a useful prognostic indicator in patients with coronary artery disease

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ABSTRACT

Objective: No nutritional index has been firmly established yet in patients with coronary artery disease (CAD). In this study, we propose a simple to calculate nutritional indicator in patients who underwent percutaneous coronary intervention (PCI) by using parameters routinely measured in CAD and evaluated its prognostic implication.
Methods: This study is a retrospective observational analysis of a prospective database. The subjects were consecutive 3567 patients underwent their first PCI between 2000 and 2013 at Juntendo University Hospital in Tokyo. The median of the follow-up period was 6.3 years (range: 0–13.6 years). The novel nutritional index was calculated by the formula; Triglycerides (TG) × Total Cholesterol (TC) × Body Weight (BW) Index (TCBI) = TG × TC × BW / 1000 (TG and TC: mg/dl, and BW: kg).
Results: The Spearman non-parametric correlation coefficient between TCBI and the most often used conventional nutritional index, Geriatric Nutritional Risk Index (GNRI), was 0.355, indicating modest correlation. Moreover, Unadjusted Kaplan-Meier analysis showed higher all-cause mortality, cardiovascular mortality, and cancer mortality in patients with low TCBI. Consistently, elevation of TCBI was associated with reduced all-cause (hazard ratio: 0.86, 95%CI: 0.77–0.96, $p < 0.001$), cardiovascular (0.78, 0.66–0.92, $p = 0.003$), and cancer mortality (0.76, 0.58–0.99, $p = 0.041$) in patients after PCI by multivariate Cox proportional hazard analyses.
Conclusion: TCBI, a novel and easy to calculate nutrition index, is a useful prognostic indicator in patients with CAD.

1. Introduction

The association between malnutrition and an increased risk of adverse outcomes in patients with various cardiovascular diseases, such as heart failure [1], peripheral artery disease [2,3] and coronary artery disease (CAD) [4,5] has been recognized. While the underlying mechanisms of this association have yet to be determined due to the complex pathophysiology of cardiovascular diseases, frailty may be one of the critical elements in the link between malnutrition and a poor prognosis in cardiovascular disease [6].

Although the simplest and most frequently used indicator of nutritional status in cardiovascular disease in clinical settings is body mass index (BMI), its prognostic implication is still a subject of intense debate in terms of the controversy regarding the "obesity paradox" [7–9]. A number of other questionnaires, scoring systems, and indices for the assessment of nutritional status have been proposed. However, in clinical settings, there are currently no established nutritional indicators that are used in a majority of assessments. Among these indicators, we and others recently reported that the Geriatric Nutritional Risk Index (GNRI) and the Controlling Nutritional Status (CONUT) are useful prognostic indicators for patients with CAD [4,5]. Nonetheless, despite their usefulness as prognostic indicators of cardiovascular disease, GNRI and other indicators are still not commonly calculated, most likely due to the requirement of complex calculations of parameters which are not commonly used in cardiovascular clinical practice.

High levels of serum total cholesterol (TC) and triglycerides (TG) and a high body weight (BW)/body mass index (BMI) are known risk factors for the progression of atherosclerosis [10–12]. However, total cholesterol has been paradoxically used in the nutritional indicator CONUT and its reduced level was shown to be associated with higher mortality in patients with stable angina [13], ST segment elevation myocardial infarction [14,15], and chronic heart failure [16]. Moreover, triglycerides have been recently recognized as a candidate for an objective nutritional indicator [17]. The controversy regarding the prognostic effects of low levels of serum TC and TG in assessing cardiovascular risk is similar to that of BW/BMI in the "obesity paradox".

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In this study, we tested our hypothesis that the simple multiplication of commonly measured objective parameters in patients with CAD; serum TG, serum TC, and body weight, may be a useful indicator of nutritional status, and whether its low level may be associated with adverse outcomes in a patient population with atherosclerosis and CAD.

2. Patients and methods

2.1. Participants and follow-up duration

This is a retrospective observational cohort analysis of a prospective database and included consecutive 3567 patients who underwent percutaneous coronary intervention for the first time (index PCI) between January 2000 and December 2013 at Juntendo University Hospital, Tokyo, and whose data regarding TG, TC and BW at index PCI were available. PCI includes any type of coronary artery intervention procedure, such as thrombectomy, balloon angioplasty, and deployment of a bare metal stent (BMS) or drug-eluting stent (DES). Patients who underwent index PCI were followed by chart review when followed at our institution and by sending a prognosis survey questionnaire every 5 years if they were transferred to another institution. If no response was received, follow-up was terminated at the latest time point at which his or her survival at the outpatient clinic or an inpatient ward of our institution was confirmed. The median and range of the follow-up period since the index PCI were 6.3 and 0–13.6 years, respectively. This study was approved by the institutional review board at Juntendo University School of Medicine and written informed consent was obtained from all participants.

2.2. Endpoints

The endpoints evaluated were three types of mortality in the follow-up period; all-cause mortality, cardiovascular mortality, and cancer mortality. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, critical arrhythmia, valvular heart disease, an aortic disease, peripheral artery disease, or sudden death for which a non-cardiovascular cause could be excluded. Cancer mortality was defined as death due to any type of malignant disease, including a malignant solid tumor, as well as a hematological malignancy.

During follow-up, all-cause mortality occurred in 501 of the 3567 patients (14.0%). Among these 501 patients, the cause of death was cardiovascular in 212 (42.3%) and cancer in 160 (31.9%). The deaths due to malignancies included gastrointestinal cancer in 50 patients (31.3%), lung cancer in 34 (21.2%), hepatobiliary cancer in 27 (16.9%), and prostate cancer in 14 (8.8%).

2.3. Generation of a novel nutritional and prognostic indicator in patients with coronary artery disease

To generate a useful and versatile nutritional and prognostic indicator in the field of cardiology, we evaluated candidate nutrition-related parameters that met the following requirements, 1) objectively measurable (i.e., not obtained from a subjective questionnaire) 2) measured in the vast majority of atherosclerotic cardiovascular disease cases in clinical practice, and 3) easy to calculate in a clinical setting. The candidate parameters evaluated were BW, body mass index (BMI), TC, and TG. The association between single, double, and triple combinations of these parameters and the 3 types of mortality after PCI were evaluated in comparison with the conventional nutritional index GNRI and serum albumin.

2.4. Calculation of Geriatric Nutritional Risk Index (GNRI) and a novel nutritional risk index, Triglycerides * Total Cholesterol * Body Weight Index (TCBI)

$$\mathrm{GNRI} = 14.89 \times \text{serum Alb (g/dL)} + 41.7 \times (\text{measured body weight (kg)}/\text{ideal body weight (kg)})$$ [18]. Ideal body weight was calculated using the Lorentz-formula. Ideal body weight = (height (cm) − 100) − (height (cm) − 150) / 4 for men and (height (cm) − 100) − (height (cm) − 150) / 2 for women [18].

$$\mathrm{TCBI} = \text{serum triglycerides (TG, mg/dL)} \times \text{serum total cholesterol (TC, mg/dL)} \times \text{body weight (BW, kg)}/1000$$

2.5. Statistical analysis

Continuous valuables are presented as the mean ± standard deviation or median with interquartile range in accordance with the results of the Shapiro-Wilk normality test, and were compared using the non-parametric Mann-Whitney test. Categorical data are shown as numbers and percentages and were compared using the Fisher exact test. Since TCBI was non-normally distributed, the levels of TCBI by quartiles of GNRI, and those of GNRI by quartiles of TCBI were compared by Nonparametric Kruskal-Wallis analysis. Kaplan-Meier curves for evaluation of the time to the three types of mortality were drawn and followed by log-rank test for comparison. Unadjusted univariate Cox proportional hazard analyses for all-cause mortality, cardiovascular mortality, and cancer mortality were performed (Supplementary Table 2). Multivariate Cox proportional hazard analysis using 4 models with variables identified based on univariate unadjusted analysis (Supplementary Table 3) was performed to identify factors associated with the incidence of mortality. Variables used in the models (Models 2–4) of multivariate analysis were selected in accordance with data background demographics and univariate Cox hazard analysis (Table 1 and Supplementary Table 1). All probability values (p-values) were two-tailed and considered as significant if <0.05.

3. Results

3.1. Baseline data of TCBI and its correlation with Geriatric Nutritional Risk Index (GNRI)

The median and interquartile range (IQR) of TCBI were 1309.1 and 857.7–2060.7, respectively. While TCBI was not normally distributed, it was lognormally distributed (Supplementary Fig. 1a). To address the utility of TCBI as a nutritional index, the correlation between TCBI and GNRI was evaluated. The value of GNRI increased with an increase in the quartile of TCBI. Nonparametric Kruskal-Wallis analysis showed significant elevation in GNRI with an increase in quartiles in TCBI ($p < 0.001$). TCBI increased in accordance with the quartile of GNRI ($p < 0.001$) (Supplementary Fig. 1b). Both TCBI and GNRI in the elderly (70 years old or older) and females were significantly lower ($p < 0.001$), while there was no significant difference between patients with diabetes or hypertension (Supplementary Fig. 1c). Spearman's non-parametric correlation coefficient between TCBI and GNRI was 0.355, while those between GNRI and TG or TC were 0.196 and 0.216, respectively (Supplementary Fig. 1d). These findings indicated a moderately positive linear correlation of TCBI with GNRI.

3.2. Baseline patient demographics and lipid parameters by quartiles of TCBI

Baseline patient demographics according to the quartiles of TCBI are shown in Table 1. Patients in the lower quartiles of TCBI were likely to be older, female, and have less dyslipidemia, acute coronary syndrome (ACS), multivessel disease, low left ventricular ejection fraction (LVEF) with higher plasma BNP, and chronic kidney disease (CKD) with lower eGFR. Regarding medications at PCI, fewer patients received beta-blockers and statins in the groups with lower TCBI. Target vessel size was smaller in the lower TCBI groups. Lipid parameters are summarized in Supplementary Table 1. Serum LDL, ApoB100 and ApoE were slightly positively correlated with TCBI, while HDL was inversely correlated with TCBI.

3.3. Unadjusted Kaplan-Meier analyses for evaluating cumulative incidences of all-cause, cardiovascular, and cancer mortality in accordance with quartiles of TCBI

Unadjusted Kaplan-Meier curves showed a significantly higher cumulative incidence of all-cause death in the lowest (Q1) and second lowest (Q2) quartiles of TCBI compared to the third (Q3) and highest quartiles (Q4). Also, the all-cause mortality rate in Q2 was lower than Q1, while those in Q3 and Q4 were similar (Fig. 1a, upper panel). The cardiovascular mortality rate in Q1 was higher than that in the other three quartiles, and the rate in Q2, which was lower than Q1, was also higher than Q3 and Q4 (Fig. 1a, middle panel). Similar to those for all-cause death, the Kaplan-Meier curves of Q3 and Q4 were similar. Regarding cancer mortality, Q1 and Q2 were significantly higher than Q3 and Q4 (Fig. 1a, lower panel).

3.4. Kaplan-Meier analyses in patient subclasses consistently showed lower survival rates in patients with lower quartiles of TCBI

Kaplan-Meier analysis consistently showed higher all-cause mortality rates in patients with the lowest quartile (Q1) or second lowest (Q2) of TCBI compared to the third (Q3) and fourth (highest, Q4) quartiles in various subclasses of patients, such as with preserved and reduced left