



Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrn1.com

Applied nutritional investigation

10-year survival in coronary artery bypass grafting surgery patients in Tehran heart center, coronary outcome measurement study: Predictive power of dietary inflammatory index and dietary antioxidant quality

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ARTICLE INFO

Article History:

Received 25 October 2018

Accepted 17 January 2019

Keywords:

Survival

Mortality

CABG

DII

DAQ

MEDQI

ABSTRACT

Objectives: There is a higher rate of mortality from cardiovascular disease (CVD) in Iran and the mortality rate increases even after coronary artery bypass grafting (CABG). The aim of this study was to evaluate the association between mortality and survival in patients 10 y after CABG, using the dietary inflammatory index (DII) and dietary antioxidant indices.

Methods: In the current prospective cohort study, 450 patients with CVD who were referred to the Tehran Heart Center and who underwent an isolated CABG during the 6-mo period between April and September 2006 were enrolled. Anthropometric measurements and clinical assessments were performed. Biochemical assay, including hemoglobin A1c, serum lipids, creatinine, blood urea nitrogen, lipoprotein(a), albumin, and C-reactive protein, were also measured. DII, dietary antioxidant quality (DAQ) scores, and dietary Mediterranean quality index (MEDQI) were measured using the data obtained from a semi-quantitative food frequency questionnaire. Survival analysis was performed using the Kaplan–Meir method followed by log-rank test. The association between all-cause mortality and study parameters was performed with Cox proportional hazard model.

Results: According to the present results, older ages, male sex, lower educational attainment, opium use, previous history of diabetes and myocardial infarction, and higher hematocrit and creatinine concentrations were associated with higher mortality rates. Among nutritional indices, a high inflammatory diet was a positive predictor of mortality, whereas a higher DAQ score was a negative predictor ($P < 0.05$). No association was found between the MEDQI score and mortality rate among patients.

Conclusion: According to the present findings, a diet high in inflammatory foods and low in antioxidant content is a potent predictor of mortality 10 y post-CABG. Therefore, reducing the inflammatory potential of the diet and improving its antioxidant content will be a preventive strategy for reducing mortality after CABG.

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MAF designed the idea of the project, wrote the manuscript, and performed the statistical analysis. FM was involved in writing the draft. MN was the main supervisor of the project and was also involved in data interpretation. MAJ was involved in statistical analysis. MAF affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. All authors have read and approved the manuscript. The reporting of this work is compliant with COREQ guidelines. MN affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Introduction

Cardiovascular disease (CVD), stroke, and specifically coronary heart disease (CHD) are the leading causes of mortality and disability worldwide [1]. In 2015, there was a reported 17.92 million deaths from CVD and 422.7 million cases of CVD globally, which accounted for nearly one-third of total deaths [1]. Currently, nearly 80% of CVD deaths occurs in middle- and low-income countries [1], where access to treatment and health care infrastructures are

limited. The significant health and economic burdens related to CVD death has been shown to be a major cause of a large part of premature death (death before 75 y of age) [2]. Iran is overburdened with CVD, and it is one of the major causes of mortality, morbidity, and disability, accounting for nearly 50% of all deaths per year [3]. Coronary artery bypass grafting (CABG) surgery is a common type of open heart surgery used to restore normal blood flow to an obstructed coronary artery. CABG aims at improving quality of life and reducing mortality in the later stages of coronary artery disease (CAD) [3]. CABG is often chosen when coronary arteries have a 50% to 99% obstruction. The obstruction being bypassed is typically owing to atherosclerosis, arteriosclerosis, or both [4]. Oxidative stress and chronic inflammation are potential triggering factors of CVD in the region, which is frequently argued in the literature [5]. In general, oxidative stress and vascular inflammation are closely related to vascular damage, endothelial dysfunction, and thus atherosclerosis. Oxidative stress and inflammation are closely interconnected because oxidative stress can induce inflammation, which in turn can cause oxidative stress. The adverse effects of oxidative stress on the cardiovascular system are the outcome of endothelial dysfunction through decrease in nitric oxide availability, lipid peroxidation, and inflammatory response [6]. The excessive reactive oxygen species (ROS) (molecules that contain one or more unpaired electrons and singlet oxygen activate nuclear factor (NF)- κ B and result in transcriptional stimulation of >100 genes involved in inflammatory responses such as interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , IL-6, IL-8, and IL-12 [7]. These inflammatory responses are a major driving force in patients with CAD, underlying the beginning of coronary plaques, their unbalanced progression, and ultimate disruption [8]. Multiple factors contribute to this oxidative and inflammatory process, including sex, age, physical activity, smoking, and diet [9]. Among the many determining risk factors for CVD, diet plays the main role [10]. Diet is one of the key lifestyle-related factors reducing the oxidative and inflammatory processes. Different dietary patterns and individual foods can have beneficial health effects related to their antioxidative and anti-inflammatory properties. Currently, there is an increasing interest in the antioxidative and anti-inflammatory properties of food patterns in preventing CVD and increasing survival [11]. However, to our knowledge, there is no study evaluating the inflammatory and oxidative potential of the overall diet in survival of patients who previously underwent CABG. The dietary inflammatory index (DII) and dietary antioxidant quality (DAQ) score [12] were developed to estimate the inflammatory potential and the antioxidant-nutrient intake of food, respectively. The DII is based on 1943 articles published from 1950 to 2010 that report the effect of 45 nutritional parameters on six inflammatory biomarkers [13]. These nutritional parameters received a positive score (+1) if its effect was pro-inflammatory (significantly enhanced TNF- α , IL-1 β , IL-6, or C-reactive protein [CRP], or reduced IL-4 or IL-10), a negative score (–1) if its effect was anti-inflammatory, and 0 if no significant alteration in biomarkers associated to nutritional parameter was found. Antioxidant systems such as free radical scavengers keep the organism against ROS [14]. Among non-enzymatic system, zinc, β -carotene, manganese, selenium, and vitamins C, A, and E are several nutrients with major antioxidant properties [15]. The DAQ score refers to the consumption of vitamins C, A, E, zinc, and selenium, which are confirmed to act as antioxidant nutrients, and it has a calculated cutoff at two-thirds of the Recommended Daily Intake (RDI) of these nutrients, established according to Aranceta et al. suggested protocol [16]. A value of 0 is dedicated when the consumption of nutrient is less than two-thirds of RDI. When this intake is equal or above the RDI, it is dedicated a value of 1.

Several studies investigated an association between DII and CVD mortality [17,18] or its incidence [19–22]. Moreover, several studies investigated the association between several particular dietary antioxidants and CVD [23–25]. Higher risk for all-cause mortality in most studies was seen among participants with the highest proinflammatory values of the DII score. However, the potential predictability of DII and DAQ score for long-term survival in patients who underwent CABG has not been evaluated yet. Therefore, the aim of the current study was to evaluate this hypothesis.

Methods

Participants

In the current cross-sectional study, participants were patients who underwent isolated CABG with cardiopulmonary bypass. Participants were recruited for the THC-COM (Tehran Heart Center–Coronary Outcome Measurement) study. The study was performed between May and September 2006. In this study, contributors were patients accepted to the cardiothoracic ward for CABG surgery at the Tehran Heart Center during this time period. The sample size calculation was described previously [26]. The formula for comparing two proportions:

$$N = \frac{[(Z\alpha/2 + Z\beta)2 \times \{(p1(1-p1) + (p2(1-p2)))\}]}{(p1-p2)^2}$$

was used for sample size calculation where p_2 is the proportion of the men with low-quality Mediterranean regimen (0.25), p_1 is the proportion of the women with low quality Mediterranean regimen (0.3), power = 80% ($1-\beta$), and α -error = 0.05. Therefore, 125 participants in each group was determined for the study. We also supposed 20% loss (125 + 25), and because there are twice as many men with CAD as women (150 + 300), it was determined that 450 participants would be considered for the study [26–28]. Reasons for exclusion or drop out were incomplete demographic questionnaires ($n = 5$) and incomplete dietary questionnaires ($n = 1$). In this study, the final analytical sample consisted of 454 participants ages 35 to 80 y who completed both the medical examination and the questionnaire. More details of study's biochemical assays and procedures were presented elsewhere [26]. Written informed consent was acquired from each participant. The study was confirmed by the Ethics Committee of Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.

Clinical assessment of patients

Preoperative cardiac status and clinical assessment was also measured by some variables including number of diseased vessels, left ventricular ejection fraction, the European system for cardiac operative risk evaluation (EuroSCORE), and New York Heart Association (NYHA) functional class (FC) [29]. NYHA functional arrangement provides a simple method of classifying the degree of heart failure. The NYHA FC places patients in one of four classifications based on how much they are limited pending physical activity; what their symptoms or limitations are regarding ordinary breathing and varying degrees in shortness of breath or angina; NYHA FCs are composed of four classes from severe symptoms, marked limitation in activity owing to symptoms, mild symptoms, and no symptoms [30].

The EuroSCORE is an additive risk model of perioperative death and is a beneficial predictor of the long-term risk of cardiovascular events leading to hospital admissions after cardiac surgery or death [31]. It is calculated pursuant to the standard additive methods and was evaluated as a continuous variable [32].

Anthropometric assessments

Anthropometric variables including height and weight were measured. Weight was measured with participants wearing light clothes. Body mass index (BMI) was also calculated [33].

Dietary assessments and DII and DAQ score calculation

DII calculation was done based on a 138-item semiquantitative food frequency questionnaire (FFQ) containing a list of foods with standard serving sizes usually consumed by Iranians. Participants were asked to recall how often they consumed each of the food items with regard to the number of times per year, per month, per week, or per day during the previous year. The stated frequency for each food item was then changed to daily intake. Portion sizes of consumed foods were changed to grams by using household measures [34]. Previously, the FFQ was validated for the healthy Iranian population [35]. The DII is a population-based index representing the anti-inflammatory or proinflammatory potential of a diet based on a scoring algorithm extracted from a wide literature review; it has been described in detailed elsewhere [13]. Briefly, dietary parameters are scored according to

whether they had an anti-inflammatory (−1), proinflammatory (+1), or no effect (0) based on six inflammatory biomarkers: IL-4, IL-1 β, IL-10, IL-6, TNF-α, and CRP. For DII calculation, the dietary data were primarily linked to the world database, which provided a powerful estimate of the mean and SD for each food variable allocated [13]. Then, world means were calculated from the real intakes and divided by its SD, resulting in the z-score. To diminish the effects of right skewing, the z-scores were changed into percentile scores. Individually, the centralized percentile scores of each food variable was attained by doubling the percentiles and subtracting 1 and then was multiplied by the respective effect score of food variable (inflammatory potential for each food variable). In the final step to providing the total DII score, all of the attained values were summed across all food parameters. More negative values indicated the more anti-inflammatory diets and a higher DII score indicated the more proinflammatory the diet. The DII scores in the present study ranged from −19.33 (maximally anti-inflammatory) to 10.62 (maximally proinflammatory). The DII score calculated based on this study's FFQ included data on 28 of the 45 probable food variables creating the DII: energy, carbohydrates, fats, protein, fiber, cholesterol, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), ω-3, ω-6, saturated fats, *trans*-fats, riboflavin, thiamin, niacin, vitamin B₆, folic acid, vitamin B₁₂, zinc, iron, magnesium, selenium, vitamin A, vitamin E, vitamin C, vitamin D, β-carotene, garlic, caffeine, and tea. The food ingredients were selected according to previously published articles regarding the main association of these food components with cardiovascular risk factors [20]. To examine the correlation between outcomes of interest and DII scores, the DII was divided into quartiles with the following cut points: Q1: −29.83 to ≤−15.05; Q2: −15.04 to ≤−5.36; Q3: −5.35 to ≤−0.2; and Q4: −0.19 to ≤7.01. We evaluated the antioxidant-nutrient intake by applying the DAQ score [12]. This score refers to the consumption of vitamin C, vitamin A, vitamin E, zinc, and selenium, which are confirmed to act as antioxidant nutrients, and it supposes a cutoff at two-thirds of the RDI, established according to Aranceta et al. [16]. A value of 1 was assigned when the intake of nutrient was equal to or greater than two-thirds of the RDI, and when this intake was less than two-thirds of the RDI, it was assigned a value of 0. Thus, we calculated the total DAQ score, which ranges from 0 (*very poor quality*) to 5 (*high quality*).

Statistical analysis

Data analyses were conducted with the use of SPSS version 23 (SPSS, Inc. Chicago, IL, USA). Survival analysis was performed using Kaplan–Meir method followed by log-rank. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of all-cause mortality for demographic, clinical, biochemical, and dietary parameters were estimated using Cox proportional hazard regression analysis with time to death by months as the time variable and the other studied parameters as independent variables. In the Cox regression model, study parameters, including age, sex, smoking status, opium use, history of myocardial infarction (MI), history of diabetes, hyperlipidemia, and hypertension, educational level, BMI, serum triacylglycerol, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, high-density lipoprotein cholesterol, lipoprotein(a), CRP, creatinine, hematocrit, albumin, and blood urea nitrogen were used as covariates. Clinical parameters also included NYHA FC, EuroSCORE, number of diseased vessels, and ejection fraction rate. Dietary indices including DII, DAQ, and the dietary Mediterranean quality index (MEDQI) were categorized into quartiles or quintiles and the lowest categories were considered as the reference for analysis of HRs for the other categories. For adjusted models, the parameters with significant values as shown in Table 1 were included as confounders. $P \leq 0.05$ was considered statistically significant.

Results

The general characteristics of study participants have been presented elsewhere [27,28,36]. The association between general demographic and clinical parameters with 10 y mortality among patients is shown in Table 1. Older age ($P < 0.001$), male sex ($P = 0.001$), lower educational attainment ($P = 0.042$), diabetes ($P = 0.008$), MI ($P = 0.049$), opium use ($P = 0.013$), higher EuroSCORE ($P < 0.001$), and lower ejection fraction rates ($P < 0.001$) were significant predictors of mortality among patients who underwent CABG. Among biochemical variables (Table 2), higher hematocrit and creatinine concentrations were significantly associated with mortality. The adjusted Cox regression model for the relationship between dietary indices with 10-y survival in patients is shown in Table 3. Being at second and third quartiles of DII (the more pro-inflammatory scores) compared with first quartile (the more anti-inflammatory scores) made patients 2.11 and 1.99 times more likely to die within 10 y post-CABG, respectively ($P < 0.05$).

Table 1

The adjusted Cox regression model for the relationship between demographic and clinical variables with 10-y survival in patients undergoing coronary artery bypass grafting surgery

Variable	Adjusted HR	95% CI		P-value
		Lower bound	Upper bound	
Age	1.06	1.03	1.09	<0.001
Sex				
Female	Ref.			0.11
Male	2.01	1.09	3.70	0.001
BMI (kg/m ²)	1.03	0.96	1.09	0.37
Education				
<12 y	Ref.			0.12
≥12 y	0.45	0.21	0.973	0.042
Diabetes (yes/ no)	1.96	1.19	3.20	0.008
MI (yes/ no)	1.62	0.99	2.65	0.049
Hyperlipidemia (yes/ no)	0.68	0.39	1.16	0.16
Hypertension (yes/ no)	1.48	0.88	2.50	0.135
Smoking (yes/ no)	0.95	0.52	1.75	0.88
Opium (yes/ no)	2.47	1.21	5.05	0.013
EuroSCORE	1.198	1.09	1.13	<0.001
EF	0.957	0.93	0.98	<0.001
NYHA	0.89	0.63	1.27	0.54
No. diseased vessels	1.35	0.79	2.35	0.26

BMI, body mass index; NYHA, New York Heart Association.

P-values in **bold** indicate statistically significant values.

Table 2

The adjusted Cox regression model for the relationship between biochemical variables with 10-y survival in patients undergoing coronary artery bypass grafting surgery

Variable	Adjusted HR	95% CI		P-value
		Lower bound	Upper Bound	
HbA1c (%)	1.00	0.88	1.14	0.92
TC (mg/dL)	1.1	1.009	1.13	0.08
TG (mg/dL)	1.001	0.99	1.004	0.71
LDL (mg/dL)	0.99	0.98	1.007	0.37
HDL (mg/dL)	0.92	0.96	1.02	0.64
HCT (%)	1.02	1.005	1.044	0.015
Albumin (g/dL)	0.82	0.38	1.73	0.61
Creatinine (mg/dL)	1.92	0.77	4.76	0.157
BUN (mg/dL)	1.02	1.007	1.05	0.01
LP (a) (mg/dL)	1.001	0.99	1.04	0.83
CRP (mg/dL)	1.02	0.99	1.059	0.123

BUN, blood urea nitrogen; CRP, C-reactive protein; Hb, hemoglobin; HCT, hematocrit; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LP, lipoprotein; TC, total cholesterol; TG, triacylglycerol.

P-values in **bold** indicate statistically significant values.

Moreover, having a DAQ score of 5 (the highest dietary antioxidant score) resulted in patients being 50% less likely to die within 10 y after CABG compared with patients with a score of 1 ($P = 0.016$). Figure 1 and 2 present the mean survival rate of patients after CABG according to DII and DAQ categories. The log-rank test (Table 4) revealed no significant difference in the survival rate of patients in different DAQ scores ($P = 0.445$), whereas the survival rate in the higher quartiles of DII was lower than lower quartiles ($P = 0.029$). No association was found between mortality and dietary Mediterranean quality index among study participants.

Discussion

In this large, prospective cohort study, general demographic parameters such as older age, male sex, lower educational attainment, having a previous history of diabetes and MI, opium use, higher EuroSCORE, and lower ejection fraction rates were associated with increased risk for death among patients who underwent CABG.

Table 3

The adjusted Cox regression model for the relationship between dietary indices with 10-y survival in patients undergoing coronary artery bypass grafting surgery

Variable	Adjusted HR	95% CI		P-value
		Lower	Upper	
DII				
Q1	Ref.	1.039	4.32	
Q2	2.11	0.96	4.10	0.039
Q3	1.99	0.98	2.11	0.049
Q4	1.01	1.039	4.32	0.87
DAQ				
Score 1	Ref.			0.21
Score 2	0.56	0.34	0.98	0.67
Score 3	0.678	0.45	1.12	0.981
Score 4	0.876	0.34	0.963	0.783
Score 5	0.54	0.32	0.892	0.016
MEDQI				
Q1	Ref.			
Q2	0.709	0.365	1.37	0.21
Q3	0.507	0.22	1.159	0.11
Q4	1.68	0.51	2.20	0.65

DAQ, dietary antioxidant quality; DII, dietary inflammatory index; MEDQI, Mediterranean quality index; Q, quartile.

P-values in **bold** indicate statistically significant values.

The novel finding of the present study, the positive association between higher DII scores and mortality and its negative association with the dietary antioxidant score, should be further examined. The negative associations between the survival with age, lower educational attainment, diabetes, and MI are not out of expectation. In similar aged patients, the incidence of CVD is reported to be higher in men than in women. This sex difference is more prominent at a younger age [37] and is partly described by defensive effects of sex hormones [38]. The increased CVD

occurrence in women after menopause and the higher cardiovascular risk profile in women with hyperandrogenism [39,40] suggests that sex-related variances in sex steroid hormones might play a prominent role in the pathophysiology of CVD. In the past, it was well demonstrated that the incidence of CVD and the levels of cardiovascular risk factors were found to be higher in individuals with diabetes than in those without [41,42]. Another interesting finding of the recent report was that a higher EuroSCORE was associated with increased risk for deaths among patients who underwent CABG. The EuroSCORE predictive tool is applied in adult patient cardiac surgeries to forecast the cardiovascular mortality with excellent or good predictive ability [32,43]. In a study to investigate the applicability of EuroSCORE in patients undergoing CABG surgery at the Division of Cardiovascular Surgery of Pernambuco Cardiologic Emergency Medical Services—PROCAPE—the EuroSCORE proved to be an objective and simple index, illuminating a satisfactory discriminator of postoperative progression in patients undergoing CABG surgery [44]. In a study by Madeira et al. [45], the EuroSCORE adequately stratified the risk for operative mortality in patients with infective endocarditis undergoing cardiac surgery. Another important finding of this study, increased mortality rate with lower ejection fraction rate, was consistent with findings from Lee et al. [46]. In that study, mortality was increased in patients with reduced ejection fraction, when CHD was the original cause.

In the present study, patients with higher hematocrit concentrations had higher mortality rates. Previous studies of hematocrit values and associated outcomes have yielded contrary results. It has been reported that high hematocrit values ($\geq 33\%$) are associated with reduced cardiac index [47] and higher rates of MI [48] and CHD [49]. However, there are several inconsistencies in this issue among studies, possibly owing to differences in disease stage,

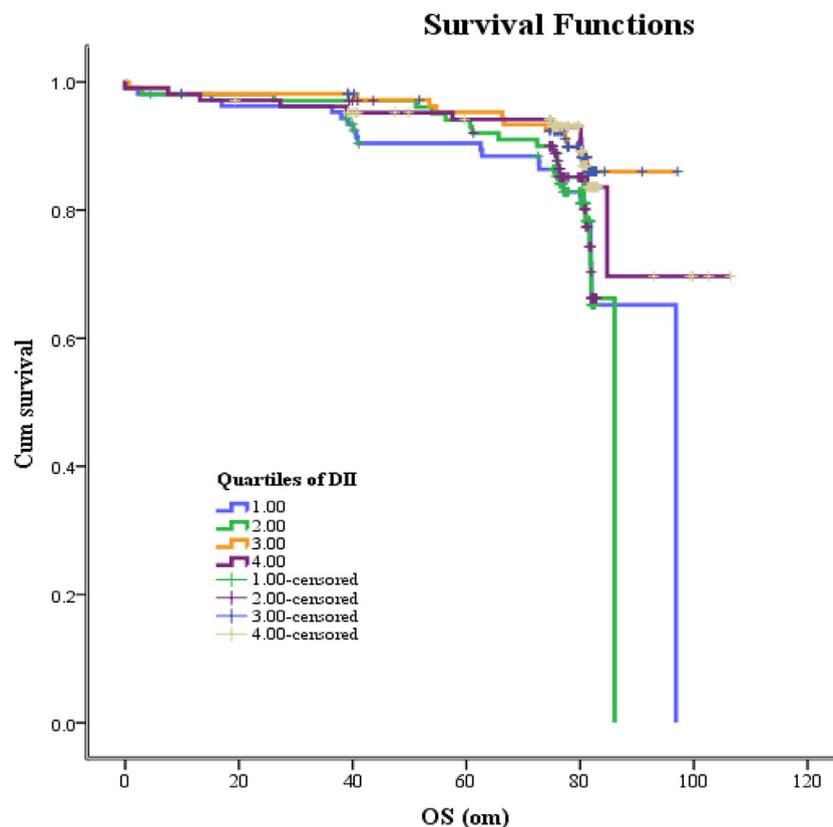


Fig. 1. Quartiles of DII and estimated OS after 10 y in candidates of coronary artery bypass grafting surgery. DII, dietary inflammatory index; OS, operation to survival.

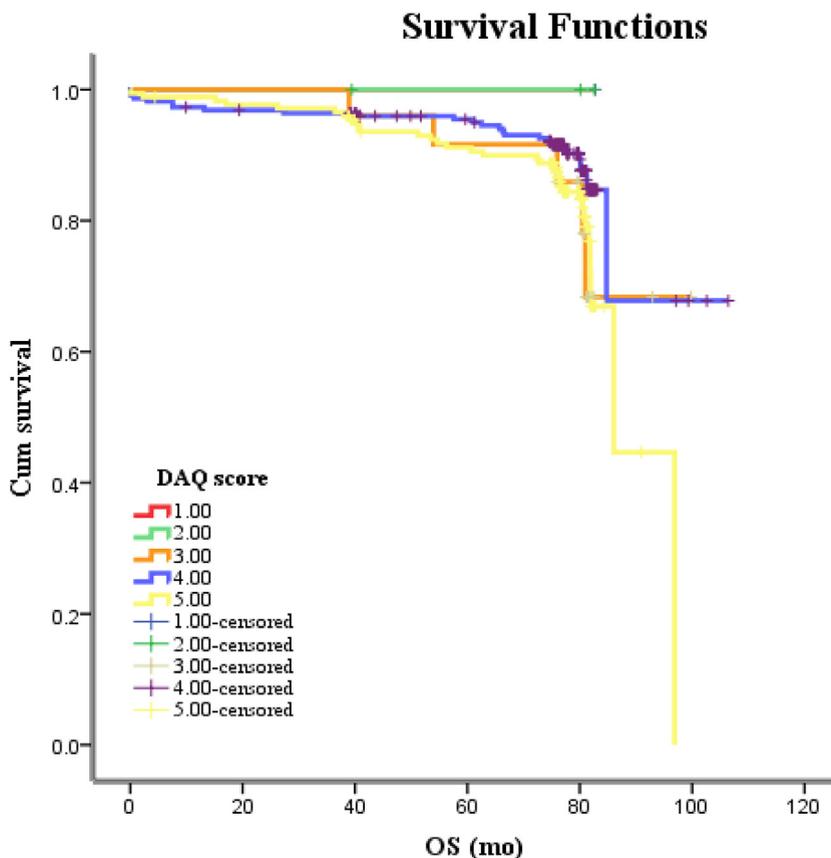


Fig. 2. DAQ score and estimated OS after 10 y in candidates of coronary artery bypass grafting surgery. DAQ, dietary antioxidant quality; OS, operation to survival.

participant characteristics, and the mortality assessment methods used [50,51].

Higher creatinine concentration was associated with increased mortality rate among patients who underwent CABG. Consistently, Irie et al., in a large prospective study of Japanese general populations, reported similar findings [52]. Possible underlying mechanisms are surrogate markers of generalized vascular damage, increased intermediate risk factors of renal dysfunction like hypertension [53], abnormalities of thrombogenic factors [54,55], and hyperhomocysteinemia [56,57].

In the present study, we found that being in quartiles 2 and 3 of DII (the more pro-inflammatory scores) rather than quartile 1 (the more anti-inflammatory scores) resulted in patients being 2.11 and 1.99 times more likely to die within 10 y post-CABG and the survival rate in higher quartiles of DII was lower than lower quartiles. A recent meta-analysis [58] that used results from 14 studies that examined the connection between the DII and CVD showed strong evidence of a relationship between enhancing the inflammatory potential of the diet and CVD risk and related mortality. However, the association between DII and the mortality in patients who underwent CABG has not, to our knowledge, been evaluated before. Increasing dietary intake of anti-inflammatory and healthy dietary components such as

green leafy vegetables and fruits and reducing the intake of pro-inflammatory components such as sugar-sweetened drinks and processed meat may play an essential role in decreasing the risk for CVD and its related mortality. Several studies have demonstrated that anti-inflammatory agents are potent reducers of cardiovascular events [59,60]. Accordingly, a high dietary antioxidant score was associated with a 50% lower risk for mortality after CABG. Growing evidence proposes that antioxidant vitamins, especially vitamin E, metabolize free radicals and decrease the risk for disease outcomes. Free radical impairment has been implicated in the causal pathway of lipid peroxidation, the main factor in atherogenesis and CHD [61–63]. Vitamin E has been associated with a reduction in lipid peroxidation, platelet adhesiveness, and thrombosis [63,64]. Dietary vitamin E was also shown to be significantly and inversely associated with coronary mortality in 5133 women and men ages 30 to 69 y over 14 y [65]. In the previous study, the risk for death from CVD can be increased at low plasma levels of carotene or vitamin C [66]. However, to our knowledge, no study has demonstrated a relationship between mortality and DAQ scores in patients who underwent CABG.

Several limitations of the present study should be addressed. The self-stated dietary information achieved by FFQ could result in potential recall bias. However, the reliability and validity of the questionnaire were confirmed previously. Moreover, the relatively large sample size, inclusion of various covariates in the statistical model, and the use of several clinical indicators of CVD such as the EuroSCORE and NYHA FC scores are strengths of the present study. To our knowledge, this is the first study to evaluate the association of DII and DAQ scores with 10-y survival in patients who underwent CABG. The importance of healthy dietary habits and dietary interventions such as a reduction in the inflammatory potential of the diet and an increase in its antioxidant content, further highlight

Table 4

Test of equality of survival distribution for the different levels of DII quartiles and DAQ scores

Log-rank (Mantel-Cox)	χ^2	df	P-value
DAQ score	6.840	4	0.145
DII quartiles	9.009	3	0.029

DII, dietary inflammatory index; DAQ, dietary antioxidant quality. P-values in bold indicate statistically significant values.

the urgent need for nutrition education in this patient population for inhibition of recurrent cardiac events and reduced mortality. These findings also confirm the clinical applications of the recent findings in translational medicine.

Acknowledgment

The authors acknowledge the study participants. The data sets used and/or analyzed during the present study available from the corresponding author on reasonable request.

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