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Highlights

- We showed an association between n-6 PUFAs and cognitive function in CAD patients.
- Serum levels of DGLA were significantly lower in the MCI patients with CAD.
- Serum levels of DGLA were positively associated with MoCA-J score.
- Serum levels of DGLA were significantly associated with MCI.
- DGLA might be useful in identifying early cognitive decline in CAD patients.

**Serum concentration of dihomo- γ -linolenic acid is associated with cognitive function
and mild cognitive impairment in coronary artery disease patients**

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Keywords: Dihomo- γ -linolenic acid; Mild cognitive impairment; Coronary artery disease.

Abstract

Background: The relation between levels of n-6 polyunsaturated fatty acids (PUFAs) and cognitive function and mild cognitive impairment (MCI) in patients with coronary artery disease (CAD) is unclear. The purpose of the present study was to examine the associations between levels of n-6 PUFAs and cognitive function and MCI in patients with CAD.

Methods: We conducted a cross-sectional study of 129 patients with CAD but without probable dementia. MCI was estimated with the Japanese version of the Montreal Cognitive Assessment (MoCA-J). We classified patients into the normal cognitive group and MCI group and compared their clinical characteristics and serum levels of PUFAs. The relation between these levels and cognitive function and MCI was clarified with Pearson correlation analysis and logistic regression analysis.

Results: The serum levels of dihomo- γ -linolenic acid (DGLA) in the CAD patients with MCI were significantly lower than those in the patients with normal cognitive function ($p = 0.04$). The serum levels of DGLA were positively associated with the MoCA-J score ($r = 0.24$, $p = 0.005$) and significantly associated with MCI in the univariate logistic regression analysis (odds ratio, 0.97; $p = 0.035$). However, in the multivariate logistic regression analysis, only age was significantly associated with MCI (odds ratio, 1.11; $p < 0.001$).

Conclusions: The serum levels of DGLA were associated with cognitive function and MCI

in patients with CAD. Although not an independent predictor, DGLA might be one useful marker with which to identify early cognitive decline in these patients.

1. Introduction

Elderly patients with cardiovascular disease and patients with dementia in Japan are increasing and are becoming public health problems [1,2]. Accordingly, prevention of and therapeutic intervention for these problems are demanded. Cardiovascular disease and dementia have similar risk factors, one of which is essential fatty acids. Essential fatty acids, n-3 polyunsaturated fatty acids (PUFAs) and n-6 PUFAs are needed by the human body, and intake of these essential fatty acids can help in treating cardiovascular diseases and even improve body composition and mental and physical performance [3]. In particular, it is widely accepted that the intake of n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce the incidence of major coronary events and cognitive impairment [4,5].

By contrast, little attention has been paid to the relation between n-6 PUFAs, dihomo- γ -linolenic acid (DGLA) and arachidonic acid (ARA), and cognitive impairment. It was found that ARA was associated with a decrease of age-related cerebral function. When the quantity of ARA in the brain was compared between early-age rats and old-age rats, it was decreased in old-age rats, and the decrease in the long-term potentiation of the brain hippocampus was improved by the intake of ARA [6]. Moreover, it was reported that

dietary supplementation with ARA and DHA improves cognitive dysfunction in patients with mild cognitive impairment (MCI) according to the modified criteria of Petersen et al. and organic brain lesions such as cerebral infarction, hemorrhage, or traumatic brain injuries more than 5 years after onset [7].

From these findings, we hypothesized that reduced serum levels of n-6 PUFAs would be associated with cognitive function and cognitive impairment in patients with coronary artery disease (CAD). However, to our knowledge, little research has been conducted into the relation between levels of n-6 PUFAs and cognitive function and MCI in these patients. Thus, the purpose of the present study was to examine the associations between levels of n-6 PUFAs and cognitive function and MCI in patients with CAD.

2. Methods

2.1. Study population

This cross-sectional study comprised 1532 consecutive patients with CAD, including those with acute myocardial infarction, acute coronary syndrome, and stable and unstable angina, who were admitted to the Sakakibara Heart Institute in Okayama, Japan from May

2018 to June 2019.

Inclusion criteria included patients who underwent rehabilitation and were admitted for more than 2 days, except those admitted for only one night and two days, for percutaneous coronary intervention. Exclusion criteria included patients who did not give informed consent, underwent coronary artery bypass surgery, had mental disease, experienced a cerebral vascular accident, could not walk without total assistance, had probable dementia as indicated by a Mini-Mental State Examination (MMSE) score below 24 [8,9], died in hospital, and had missing data.

This study was approved by the Okayama Ethics Committee of Sakakibara Heart Institute (approval no. A2018-0401), and informed consent was obtained from each patient. The present study complied with the principles of the 1975 Declaration of Helsinki regarding investigations in human subjects.

2.2. Clinical characteristics of the patients

Clinical characteristics of the patients were retrospectively evaluated from their medical records. Baseline characteristics assessed included age, sex, body mass index (BMI), educational background (categorized as >13 years of schooling), diagnosis, number

of significant stenoses of the coronary arteries ($\geq 75\%$; especially left main trunk, $\geq 50\%$), treatments, left ventricular ejection fraction (LVEF) as calculated with the Simpson method for cardiac echocardiography, maximum creatine kinase-myocardial band, serum hemoglobin levels, estimated glomerular filtration rate (eGFR), serum albumin levels, HbA1c, triglycerides, total cholesterol levels, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, comorbidities, and medications. Laboratory and cardiac echocardiographic data were evaluated just prior to patient discharge.

2.3. Measurement of cognitive function

The Japanese version of the Montreal Cognitive Assessment (MoCA-J) [10] and the MMSE were used to measure cognitive function in the patients [8,9]. The MoCA-J is used to screen persons with MCI and was reported to have a sensitivity of 93% and specificity of 87% in identifying MCI [10]. The multiple cognitive domains measured by the MoCA-J are visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation. A MoCA-J cutoff point value of 26 was previously used to define MCI [10], and thus we also defined patients with MCI as having a MoCA-J score < 26 and those with normal cognitive function as having a MoCA-J score ≥ 26 .

Although the MMSE is used globally as a screening tool for dementia [9], it is not sensitive enough to discover early cognitive decline associated with MCI [11]. Thus, we used the MMSE only as a means to select the patients with probable dementia for exclusion. A MMSE cutoff score of <24 was used to define probable dementia [9]. Assessments of cognitive function were measured by a physical therapist at the time of discharge.

2.4. Measurement of PUFAs

We measured serum levels of PUFAs, including levels of EPA, DHA, DGLA and ARA, by using gas-liquid chromatography at a commercially available laboratory (SRL, Tokyo, Japan). The EPA/ARA ratio and DHA/ARA ratio were also calculated because the EPA/ARA ratio is associated with the incidence of major adverse cardiac events or mortality in Japanese elderly people [12,13] and the DHA/ARA ratio is associated with cognitive and behavioral development in infancy [14]. The serum levels of PUFAs were evaluated as close to patient discharge as possible.

2.5. Statistical analysis

Patient characteristics and measured outcomes are shown as percentages for the categorical variables and as the mean $\pm$ standard deviation for the continuous variables. The unpaired *t*-test, Mann-Whitney U test and χ^2 test were used as appropriate to evaluate differences in patients' characteristics and in measured outcomes between the MCI and normal cognitive function groups. Pearson correlation analysis was used to test the relations between the MoCA-J scores and serum levels of PUFAs. Logistic regression analysis was used to clarify the relation between MCI and serum levels of PUFAs, with the dependent variable being MCI and the independent variables being patient characteristics and serum levels of PUFAs. The overall level of statistical significance was set at 0.05. Statistical analyses were performed with R ver. 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics

A flowchart of the patients included in this study is shown in Figure 1. Of the 1532

consecutive patients with CAD, 540 met the inclusion criteria, but 411 patients were subsequently excluded due to the reasons shown in Figure 1. Therefore, 129 patients were ultimately included in our final analysis and were divided into the normal cognitive function group ($n = 85$, 65.9%) and MCI group ($n = 44$, 34.1%).

The patients' clinical characteristics can be compared between the two groups in Table 1. Compared to the patients in the normal cognitive function group, those in the MCI group were significantly older and had lower ratios of male sex, lower educational background, lower MoCA-J score, lower serum levels of hemoglobin and albumin, and lower eGFR ($p < 0.05$).

3.2. Correlation between n-6 PUFAs and MoCA-J scores, and MCI

The serum levels of PUFAs can be compared between the two groups in Table 1. The serum levels of DGLA in the CAD patients with MCI were significantly lower than those in the patients with normal cognitive function ($p < 0.05$). There were no significant differences in the serum levels of EPA, DHA and ARA and in the ratios of EPA/ARA and DHA/ARA between the two groups.

The Pearson correlation analysis showed that serum levels of DGLA were positively

associated with the MoCA-J score ($r = 0.24$, $p = 0.005$). There were no significant relations between the MoCA-J score and serum levels of EPA, DHA and ARA and the ratios of EPA/ARA and DHA/ARA (Figure 2).

Univariate and multivariate logistic regression analyses are shown in Table 2. In the univariate logistic regression analysis, age (odds ratio [OR], 1.11; 95% confidence interval [CI], 1.06–1.16; $p < 0.001$), male sex (OR, 0.40; 95% CI, 0.16–0.99; $p = 0.048$), eGFR (OR, 0.98; 95% CI, 0.96–0.99; $p = 0.009$), serum levels of hemoglobin (OR, 0.68; 95% CI, 0.54–0.86; $p = 0.002$) and albumin (OR, 0.33; 95% CI, 0.15–0.77; $p = 0.010$) and serum levels of DGLA (OR, 0.97; 95% CI, 0.93–0.998; $p = 0.035$) were significantly associated with MCI. However, in the multivariate logistic regression analysis, only age was significantly associated with MCI (OR, 1.11; 95% CI, 1.06–1.16; $p < 0.001$).

4. Discussion

To our knowledge, this is the first study to show a relationship between levels of n-6 PUFAs and cognitive function and MCI in patients with CAD. In this study, the serum levels of DGLA in the CAD patients with MCI were significantly lower than those in the patients with normal cognitive function, and DGLA was found to be significantly

associated with cognitive function and MCI in the patients with CAD. However, it was not an independent predictor in the multivariate logistic regression analysis.

Recently, it was reported that lower levels of n-6 PUFAs, but not n-3 PUFAs, are associated with clinical outcomes (all-cause death, cardiovascular death and worsening heart failure) in patients with acute decompensated heart failure [15]. Moreover, decreased serum DGLA levels are associated with long-term mortality in patients with acute cardiovascular disease and acute decompensated heart failure [16]. Thus, in recent years, re-attention has been paid to the role of n-6 PUFAs in patients with cardiovascular disease and heart failure.

However, little research has been conducted to show the relation between levels of n-6 PUFAs and cognitive function and cognitive impairment in these patients. Furthermore, in a meta-analytic review of PUFAs and cognitive impairment, DGLA was not included as a target for analysis although EPA, DHA and ARA were included [17]. Thus, the relation between DGLA levels and cognitive impairment is unknown. In the present study, we showed for the first time, to our knowledge, the relation between serum DGLA levels and cognitive function and MCI in patients with CAD. This finding may indicate the important role of DGLA in preventing and improving cognitive decline in patients with CAD.

The potential mechanism underlying the association between DGLA and cognitive

function in patients with CAD has not been determined. Previous studies have shown that DGLA is converted to series 1 prostaglandins and has positive effects on the agglomeration of platelets, reduction of inflammation and the maintenance of homeostasis [18–20]. Moreover, DGLA forms precursors to prostaglandin E1 via the cyclooxygenase pathway, which contains potent vasodilators and platelet anti-aggregators and thus are expected to have an anti-atherosclerotic effect [21,22]. Because of the roles played by DGLA in a variety of aspects, it may have an effect on reducing cognitive decline.

In this study, the serum levels of ARA were not significantly different between the two groups. However, the levels in the CAD patients with MCI were lower than those in the patients with normal cognitive function. This result might indicate the effect of delta-5 desaturase [23].

Many studies have reported that n-3 PUFAs are associated with cognitive function and cognitive impairment [17,24]. However, in the present study, n-3 PUFAs were not associated with cognitive function and MCI. The reason for this finding different from that of previous studies might be that we targeted patients with CAD with MCI, and we used the MoCA-J score to evaluate cognitive function. Therefore, further studies are needed to clarify the relation between PUFAs and cognitive function and MCI in patients with CAD.

The CAD patients with MCI in the present study were significantly older, fewer were

male, and they had a lower educational background, lower MoCA-J score, lower serum levels of hemoglobin and albumin, and lower eGFR than those with normal cognitive function. Moreover, in the multivariate logistic regression analysis, age was identified as the only independent predictor of the incidence of MCI. These findings largely agreed with the characteristics of MCI patients reported in previous studies [25–27]. Therefore, it may be possible to partly generalize the characteristics of the patients with MCI.

There are several limitations in this study. This is a single-center, cross-sectional study with small sample size, and the findings are based on the results of univariate analysis. Therefore, generalizability of the results may be limited. Assessment of cognitive functions was limited to a single screening tool, and imaging data were not analyzed. We used the MoCA-J to measure cognitive function. However, a ceiling effect might occur with the MoCA-J. Moreover, the influence of changes in factors such as DGLA and cognitive function over time is unknown. Thus, further research is needed in the future to clarify the relation between DGLA and cognitive function and cognitive impairment in patients with CAD.

5. Conclusions

The serum levels of DGLA were found to be significantly associated with cognitive function and MCI in patients with CAD. Although DGLA was not found to be an independent predictor, it might be one useful marker with which to identify early cognitive decline in patients with CAD.

Abbreviations

ACE, angiotensin converting enzyme; ARA, arachidonic acid; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CK-MB, creatine kinase-myocardial band; DGLA, dihomog- γ -linolenic acid; DHA, docosahexaenoic acid; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol levels; LDL-C, low-density lipoprotein cholesterol levels; LVEF, left ventricular ejection fraction; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of the Montreal Cognitive Assessment; OR, odds ratio; PCI, percutaneous coronary intervention; PUFAs, polyunsaturated fatty acids.

Authors' contribution statement

K. Ishihara conceptualized and designed the study, collected data, performed initial analyses and drafted the initial manuscript. K. P. Izawa, M. Kitamura, T. Shimogai, Y. Kanejima, T. Morisawa and I. Shimizu reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of this work.

Data availability statement

All relevant data are present within the paper. Furthermore, if additional data or permission is needed, for example, for use in a meta-analysis, it can be obtained from the Sakakibara Hospital Ethics Committee (E-mail: izawapk@harbor.kobe-u.ac.jp) for researchers who meet the criteria for access to confidential data.

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Figure legend

Fig. 1. Flow chart of patient selection.

CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol levels; PCI, percutaneous coronary intervention; PUFAs, polyunsaturated fatty acids.

Fig. 2. Pearson correlation analysis between polyunsaturated fatty acids and MoCA-J scores.

ARA, arachidonic acid; DGLA, dihomo- γ -linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MoCA-J, Japanese version of the Montreal Cognitive Assessment.

Consecutive CAD patients admitted to Sakakibara Heart Institute of Okayama from May 2018 to June 2019 (n=1532)

Inclusion criteria

- Underwent rehabilitation
- Admitted for more than 2 days, except those admitted for only one night and 2 days, for PCI

CAD patients meeting inclusion criteria (n=540)

Exclusion criteria

- Did not give informed consent (n=43)
- Underwent coronary artery bypass surgery (n=211)
- Mental disease (n=7)
- Cerebral vascular accident (n=13)
- Required total assistance to walk (n=29)
- Probable dementia (n=41)
- Hospital death (n=9)
- Missing data: PUFAs and HDL-C (n=58)

CAD patients after exclusion criteria applied (n=129)

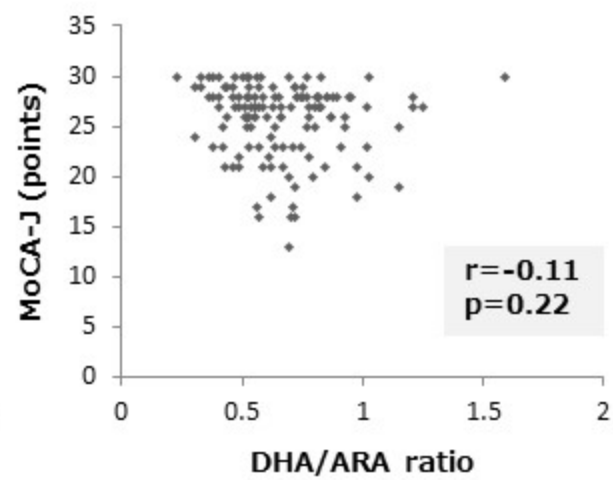
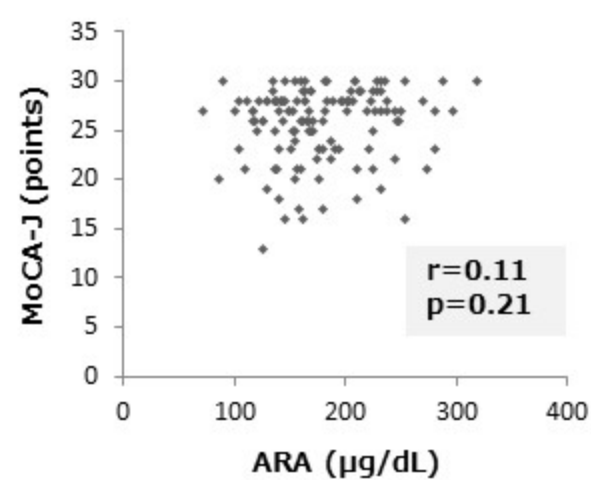
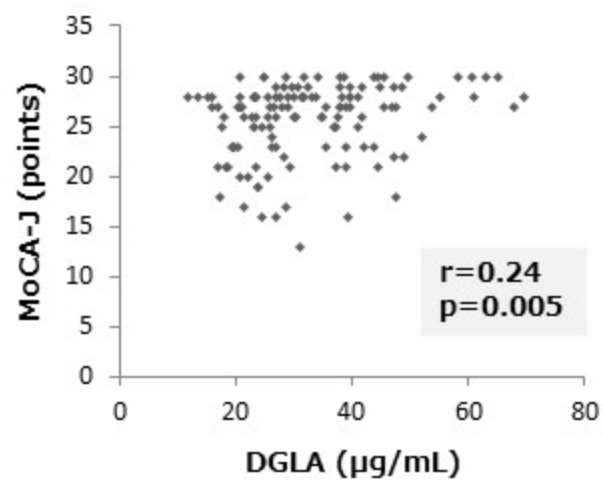
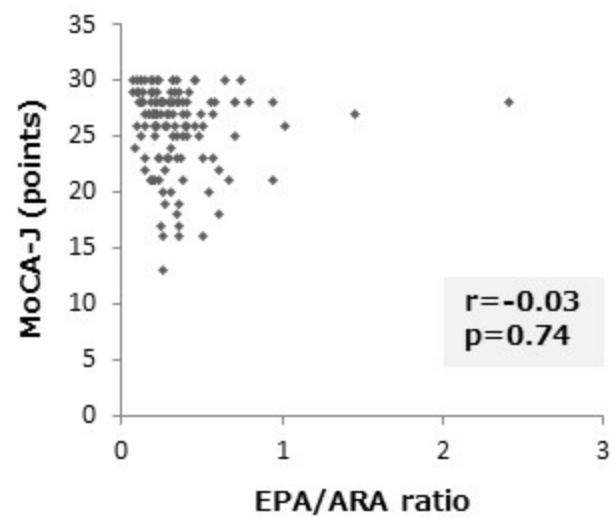
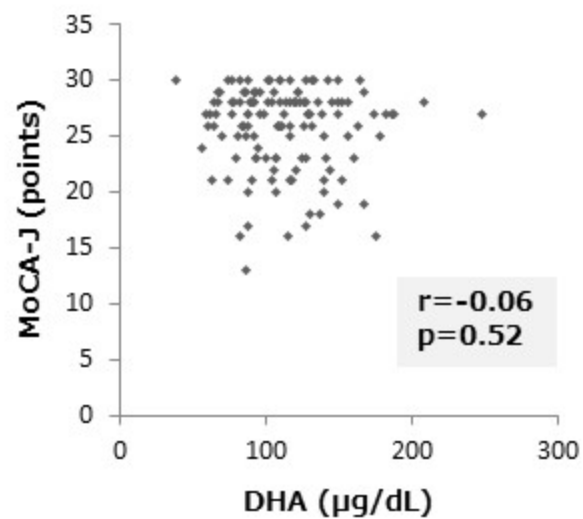
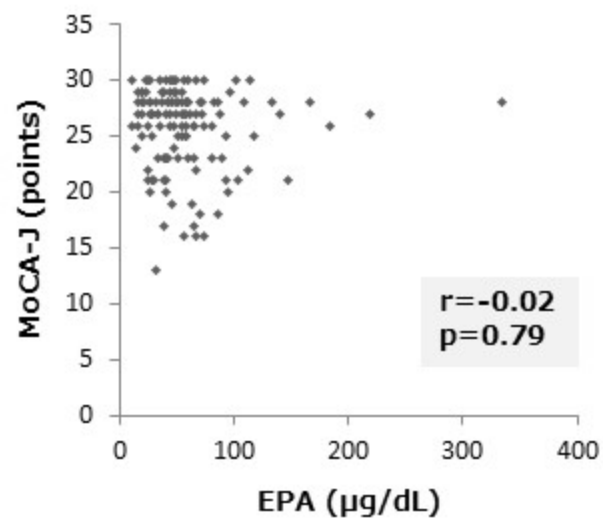


Table 1

Characteristics of patients in the normal cognitive function group and MCI group.

	Normal cognitive function group (n=85)	MCI group (n=44)	t, χ^2, Z value	p value
Age (years)	65.1 $\pm$ 10.1	74.4 $\pm$ 8.1	-5.27*	<0.001
Male sex, n (%)	74 (87)	32 (73)	4.07 [†]	0.04
BMI (kg/m ²)	24.4 $\pm$ 3.7	23.1 $\pm$ 3.6	0.16	0.08
Diagnosis, n (%)			0.50 [†]	0.78
Acute myocardial infarction	59 (69)	32 (73)		
Acute coronary syndrome	4 (5)	1 (2)		
Angina	22 (26)	11 (25)		
Significant coronary artery stenosis, n (%)			0.15 [†]	0.93
1-vessel disease	39 (46)	19 (43)		
2-vessel disease	28 (33)	16 (36)		

3-vessel disease	18 (21)	9 (21)		
Treatment, n (%)			0.46 [†]	0.50
PCI	81 (95)	43 (98)		
Medication	4 (5)	1 (2)		
LVEF (%)	52.3 ± 9.8	53.4 ± 12.7	0.10	0.26
Laboratory data				
Maximum CK-MB (IU/L)	181.7 ± 211.7	150.9 ± 170.6	0.02	0.83
Hemoglobin (g/dL)	13.0 ± 1.5	11.9 ± 1.9	3.41*	<0.001
eGFR (mL/min/1.73 m ²)	54.8 ± 18.7	45.0 ± 20.4	0.23	0.01
Albumin (g/dL)	3.7 ± 0.5	3.4 ± 0.4	2.70*	0.008
HbA1c (%)	6.7 ± 1.7	6.7 ± 1.3	0.04	0.65
Triglycerides (mg/dL)	128.5 ± 71.8	120.6 ± 75.7	0.07	0.41
Total cholesterol (mg/dL)	165.8 ± 42.3	179.4 ± 55.5	0.10	0.26
HDL-C (mg/dL)	42.4 ± 12.5	47.3 ± 14.9	0.16	0.07
LDL-C (mg/dL)	101.7 ± 34.4	110.1 ± 42.9	0.08	0.40
Comorbidities, n (%)				
Hypertension	42 (49)	26 (59)	1.09 [†]	0.30
Dyslipidemia	48 (57)	23 (52)	0.21 [†]	0.65

Diabetes	37 (44)	21 (48)	0.21 [†]	0.65
Medications, n (%)				
ACE inhibitor	46 (54)	24 (55)	0.002 [†]	0.96
ARB	25 (29)	10 (23)	0.66 [†]	0.42
β-blocker	74 (87)	36 (82)	0.63 [†]	0.43
Nitrates	14 (17)	3 (7)	2.36 [†]	0.12
Calcium antagonist	17 (20)	13 (30)	1.48 [†]	0.22
Statin	77 (91)	39 (89)	0.12 [†]	0.73
N-3 fatty acid -containing drugs	3 (4)	0 (0)	1.59 [†]	0.21
Anticholinergics	0 (0)	0 (0)		
Benzodiazepines	6 (7)	4 (9)	0.17 [†]	0.68
Analgesics	6 (7)	4 (9)	0.17 [†]	0.68
Educational background				
>13 years (%)	36 (42)	6 (14)	10.89 [†]	<0.001
MoCA-J (points)	28.0 ± 1.3	21.4 ± 3.0	0.82	<0.001
PUFAs				
EPA (μg/mL)	58.5 ± 47.7	58.3 ± 29.0	0.08	0.34

DHA (μg/mL)	112.9 ± 36.7	114.5 ± 30.8	0.05	0.59
DGLA (μg/mL)	34.6 ± 13.0	29.7 ± 10.0	0.19	0.04
ARA (μg/mL)	180.5 ± 50.8	173.3 ± 43.6	0.81*	0.42
EPA/ARA ratio	0.4 ± 0.3	0.4 ± 0.2	0.13	0.14
DHA/ARA ratio	0.7 ± 0.2	0.7 ± 0.2	0.09	0.33

Data are presented as mean ± standard deviation or number (%).

Abbreviations: ACE, angiotensin converting enzyme; ARA, arachidonic acid; ARB, angiotensin receptor blocker; BMI, body mass index; CK-MB, creatine kinase-myocardial band; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MCI, mild cognitive impairment; MoCA-J, Japanese version of the Montreal Cognitive Assessment; PCI, percutaneous coronary intervention; PUFAs, polyunsaturated fatty acids.

* t value, † χ^2 value.

Table 2

Univariate and multivariate logistic regression analysis of MCI.

Variable	Univariate model		Multivariate model	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.11 (1.06-1.16)	<0.001	1.11 (1.06-1.16)	<0.001
Male sex	0.40 (0.16-0.99)	0.048		
Hemoglobin	0.68 (0.54-0.86)	0.002		
eGFR	0.98 (0.96-0.99)	0.009		
Albumin	0.33 (0.15-0.77)	0.010	0.42 (0.17-1.04)	0.060
DGLA	0.97 (0.93-0.998)	0.035		

Abbreviations: CI, confidence interval; DGLA, dihomono- γ -linolenic acid; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; OR, odds ratio.

Logistic regression analyses were conducted with MCI present/MCI absent as the dependent variable. Clinical characteristics and DGLA were included as independent variables. The multivariate model was developed by forward stepwise variable selection.