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Research Article

A combination of depression and decreased physical function further worsens the prognosis of patients with chronic cardiovascular disease

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Abstract

Background: Patients with Cardiovascular Disease (CVD) have high rates of depression and decreased physical function. In addition, the physical function has been reported to decline in patients with depression. However, there is no clear relationship between depression and physical function in patients with CVD. Moreover, the effects of the combination of depression and decreased physical function on prognosis are unclear. This study was performed to clarify the relationship between depression and physical function, in the prognosis of patients with CVD.

Methods: The study population consisted of 472 patients with chronic CVD. We investigated depression by Hospital Anxiety and Depression Scale (HADS), and physical function by grip strength, quadriceps isometric strength, gait speed, and 6-Minute Walking Distance (6MWD). The prognosis was investigated in patients divided into three groups according to HADS and physical function.

Results: Among the 472 patients, 109 (23.1%) had depressive tendency according to HADS. An analysis of covariance, all physical function showed significantly low values in combination with depressive tendency. Kaplan–Meier analysis followed by Bonferroni's multiple comparison test revealed that the incidences of all-cause mortality and readmission due to heart failure were significantly higher in patients with depressive and decreased 6MWD than in those with only one feature. In cox proportional hazards analysis, only the combination of depressive tendency and decreased 6MWD further increased the risk of all-cause mortality and readmission due to heart failure.

Conclusions: Depressive tendency is associated with decreased physical function, and their combination is associated with poor prognosis in patients with chronic CVD.

Introduction

The aging of the population in Japan is accompanied by increases in the number of elderly patients with heart disease. It has been reported that the rate of depression is high in patients with Cardiovascular Disease (CVD) [1-3] for several reasons. However, the treatment of depression is difficult in patients with CVD. This is because cardiologists who are

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not specialists in depression oversee the treatment of these patients, so depression may be overlooked or appropriate treatment may not be provided. The American College of Cardiology has recommended regular screening for depression in patients with CVD since 2008 [4]. According to the World Health Organization, the main causes of disease burden related to morbidity and mortality are expected to be unipolar depressive disorder followed by ischemic heart disease by 2030 [5]. Therefore, it is important to prevent and treat depression and cardiovascular disease. Depressed CVD patients have been reported to have increased cardiovascular events and mortality [6-8]. Besides, increasing the severity of symptoms of depression has been reported to further increase the risk of cardiovascular events. [9] Elderly community-dwelling people with depression have also been reported to have increased cardiovascular events and mortality [10-12] and they have been reported to be associated with decreased physical function [13] and physical activity [14]. The decreased physical function has been reported to be an independent determinant of prognosis in patients with CVD and community-dwelling elderly people [15-17]. However, there have been few investigations regarding the relationship between depression and physical function in patients with CVD, and few studies of the effects of the combination of depression and decreased physical function on prognosis.

Clarification of the relationship between depression and physical function in patients with CVD will be useful for screening patients who are prone to a decrease in physical function, leading to improved prognosis and reduction of medical costs. This study was performed to clarify the relationship between depression and physical function in patients with CVD, and the effects of the combination of depression and decreased physical function on prognosis.

Materials & methods

Study population

The study population consisted of 472 chronic CVD patients over the age of 40 whose HADS [18,19] and physical function could be measured simultaneously during outpatient visits between April 2011 and December 2018. The definition of patients with chronic cardiovascular disease was 6 months or more after the diagnosis of heart disease, and patients with any heart disease such as ischemic heart disease and heart valve disease who have prescribed an outpatient heart disease secondary prevention program. This was a retrospective study in a cohort with prescriptions for cardiac rehabilitation at the Kitasato University Cardiovascular Prevention Center. Those who re-hospitalized for heart failure within six months from the measurement, those who had a diagnosis of depression, were excluded. This study was performed by the Declaration of Helsinki and approved by the Ethics Committee of Kitasato University Hospital.

Data collection

Data on all variables were collected from the patients' electronic medical records. We recorded the clinical details for patients, including diagnosis, comorbidities, echocardiography, blood biochemical test results, medication use, and demographic characteristics. The Body Mass Index (BMI) was calculated as body weight (kg) divided by height (m) squared. The estimated Glomerular Filtration rate (eGFR) was defined according to the formula of the Japanese Society of Nephrology [20]. B-type Natriuretic Peptide (BNP) concentration was determined using a commercial immunoradiometric assay (Shionogi, Osaka, Japan). Simpson's method was used to estimate the Left Ventricular Ejection Fraction (LVEF) from 2D echocardiograms.

Depressive tendency index

HADS was used as an indicator of depressive tendency [18,19]. HADS is a self-administered scale developed to assess depression and anxiety in outpatients, which consists of seven items related to depression and seven items related to anxiety. In this study, we investigated seven items related to depression. Each item consists of 4 levels, 0-3 points, suggesting that a higher score is associated with stronger depressive tendencies.

Physical function measurement

Grip strength, Quadriceps Isometric Strength (QIS), 10-m usual gait speed, and 6-Minute Walking Distance (6MWD) were measured as parameters of physical function. Grip strength was measured using a grip strength meter (Handgrip Meter 6103, Tanita, Tokyo, Japan). The upper limb was measured at the shoulder position in the middle position of the shoulder joint, with the elbow joint at 90° flexion, and the middle position of the forearm. The measurement was performed with isometric contraction for 3 s each on the left and right sides, and the average of the left and right maximum values was used in the analysis. The QIS was measured using a handheld dynamometer (μ-Tas; ANIMA, Tokyo, Japan). The patient was seated so that the hip and knee joints were at 90° with the dynamometer fixed to the front of the lower leg so that the lower end of the pressure sensor was two finger-widths above the lateral malleolus. The measurement of QIS was performed twice in 5 s, and the value obtained by dividing the average of the left and right maximum values by body weight (% BW) was used in the analysis. Gait speed was determined as the sped of walking in a straight line over a distance of 16 m including a 6-m runway. The time required to cover a distance of 10 m at usual gait was measured with a stopwatch, and the usual gait speed (m/s) was calculated. The measurement was performed once, and the value was used in the analysis. 6MWD was measured according to the report of the American Thoracic Society [21]. Briefly, the subject walked as far as possible in 6 minutes, and the distance (m) was used in the analysis.

Definition of decreased physical function

The cut-off values for decreased physical function in this study were based on previous reports. The values for grip strength were < 26 kg for males and < 18 kg for females [22], QIS was 40% BW [23], gait speed over 10 m was < 1.0 m/s [24], and 6MWD was < 400 m [25].

Outcome measure

The primary outcome measures of this study were all-

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cause mortality and readmission due to heart failure. The time to the events was calculated as the number of days from the date of HADS and physical function measurement to the date of the event.

Statistical analysis

Regarding previous research, the HADS cut-off value was set to 8 points; subjects with ≥ 8 points were classified as the depressive tendency group, and those with ≤ 7 points were classified as the non-depressive tendency group in this study [26]. We compared clinical background factors according to the presence of depressive tendencies. For continuous variables, the Mann–Whitney U test was used. For nominal measures, the $\chi 2$ test or Fisher's exact test was used. The results are shown as the median (interquartile range) for non-normally distributed indices. To examine the relationship between depressive tendency and physical function, we conducted multiple regression analysis with the dependent variable as the physical function index. In Model 1, independent variables were age, gender, BMI, and HADS. Model 2 added hemoglobin A1c (HbA1c), Albumin (Alb), eGFR, C-Reactive Protein (CRP), BNP, LVEF, and the presence or absence of chronic heart failure to Model 1. Model 3 added the presence or absence of hypertension, dyslipidemia, diabetes, and smoking, which are coronary risk factors, to Model 2. We also performed covariance analysis with age, gender, BMI, HbA1c, Alb, eGFR, CRP, BNP, LVEF and the presence or absence of chronic heart failure as covariates, and compared the physical function according to the presence or absence of depressive tendency. The associations between depressive tendency, physical function, and prognosis were classified into three groups: Non-D and High-P group, with neither depressive tendency nor decreased physical function; D or Low-P group, with a depressive tendency or decreased physical function; D and Low-P group, with depressive tendency and decreased physical function. Kaplan-Meier survival analysis, Bonferroni's multiple comparison test, and Cox proportional hazards analysis were used. The dependent variables were all-cause mortality and readmission for heart failure, and the dependent variables were HADS and physical function. In multivariate analysis, all-cause mortality was adjusted by age, BMI, and BNP, and readmission due to heart failure was adjusted by age, sex, BMI, BNP, Alb and the presence or absence of chronic heart failure. JMP (ver. 13.1) was used for statistical analysis. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Study population

The baseline characteristics for all patients and for groups classified according to HADS are shown in Table 1. The study population had a median age of 72 (67-78) years, consisted of 70.8% males, and had a median HADS of 4 (2-7). Among 472 patients, 109 (23.1%) were positive for depressive tendency according to HADS. CVD patients with depressive tendencies had significantly higher rates of chronic heart failure and higher circulating BNP levels than non-depressive patients.

Table 1:

		HADS		
		≦7	≧8	
	Overall	Non-depressive tendency	Depressive tendency	
	(n = 472)	(n = 363)	(n = 109)	P value
Age, years	72 [67 - 78]	72 [67 - 78]	74 [69 - 77]	0.384
Male, n (%)	334 (70.8)	257 (70.8)	77 (70.6)	1.000
BMI, kg/m²	23.8 [21.3 - 26.5]	23.7 [21.3 - 26.4]	24.2 [21.2 - 27.0]	0.619
Chronic heart failure , n (%)	211 (44.7)	148 (40.8)	63 (57.8)	0.002
Ischemic heart disease, n (%)	300 (63.6)	229 (63.1)	71 (65.1)	0.734
Arrhythmia, n (%)	129 (27.3)	99 (27.3)	30 (27.3)	1.000
Valvular heart disease, n (%)	72 (15.3)	60 (16.5)	12 (11.0)	0.175
Cardoimyopathy, n (%)	27 (5.7)	23 (6.3)	4 (3.7)	0.356
Chronic kidney disease, n (%)	139 (29.5)	105 (28.9)	34 (31.2)	0.634
Coronary risk factors, n (%)				
Hypertension	354 (75.0)	273 (75.2)	81 (74.3)	0.900
Diabetes	177 (37.5)	138 (38.0)	39 (35.8)	0.735
Dyslipidemia	374 (79.2)	289 (79.6)	85 (80.0)	0.689
Past smoker	288 (61.0)	71 (65.1)	217 (59.8)	0.370
Internal medicine, n (%)				
ACE-I or ARB	299 (63.4)	233 (64.2)	66 (60.6)	0.498
Calcium chaneel blocker	161 (34.1)	119 (32.8)	42 (38.5)	0.300
Beta-blocker	275 (58.3)	214 (59.0)	61 (56.0)	0.582
Diuretic agents	131 (27.8)	98 (27.0)	33 (30.3)	0.542
Statin	304 (64.4)	236 (65.0)	68 (62.4)	0.649
Oral diabetes	87 (18.4)	64 (17.6)	23 (21.1)	0.402
Laboratory data				
HbA1c, %	6.1 [5.8 - 6.5]	6.1 [5.7 - 6.5]	6.0 [5.8 - 6.7]	0.699
Alb, g/dL	4.3 [4.1 - 4.5]	4.3 [4.1 - 4.5]	4.2 [4.0 - 4.5]	0.065
eGFR, mL/min/1.73m²	59.3 [49.0 - 69.9]	59.8 [49.8 - 69.0]	57.5 [46.3 - 72.2]	0.639
HDL-C, mg/dL	53 [43 - 62]	53 [44 - 62]	50 [42 - 59]	0.053
LDL-C, mg/dL	92 [77 - 110]	92 [77 - 109]	91 [76 - 115]	0.659
CRP, mg/dL	0.1 [0.1 - 0.2]	0.1 [0.1 - 0.3]	0.1 [0.1 - 0.3]	0.637
BNP, pg/mL	57.7 [27.9 - 135.1]	52.5 [26.5 - 123.9]	69.3[33.8 - 168.0]	0.030
LVEF (%)	62.0 [53.2 - 67.0]	62.0 [52.0 - 66.1]	63.0 [57.0 - 68.0]	0.052
LVEF ≧ 50, n (%)	388 (82.2)	293 (80.7)	95 (87.2)	0.153
HADS	4 [2 - 7]	3 [1 - 5]	9 [8 - 11]	<.001

Values are expressed median [interquartile range], or n (%). HADS, hospital anxiety and depression scale; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HbA1c, HemoglobinA1c; Alb, Albumin; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

Relationship between depressive tendency and physical function

Table 2 presents the results of multivariate linear regression analyses for predicting physical function. HADS was an independent determinant of physical function index in all models. In particular, gait speed and 6MWD with the high absolute value of the standardized regression coefficient were more closely related to depressive tendency. Next, the results of the comparison of physical function by covariance analysis, classified according to the presence or absence of depressive tendency, are shown in Figure 1. Patients with CVD and depressive tendencies showed significantly lower values of all parameters of physical function.

Relationships between prognosis, depressive tendency, and physical function: The median observation periods were 46 (27-78) months for all-cause mortality and 43.5 (25-72) months for readmission due to heart failure until the end of the observation period at 84 months. The total numbers of events were 32 all-cause mortalities and 50 readmissions due to heart failure. Kaplan–Meier survival curves are shown in Figures 2 and 3. The rate of all-cause mortality was significantly higher in the D and Low-P group than in groups Non-D and High-P and D or Low-P in 6MWD. The rate of readmission due to heart failure was significantly higher in groups D or Low-P and D and Low-P than group Non-D and High-P in grip strength, QIS, and gait speed. 6MWD showed differences between all groups.

Tables 3 and 4 show the results of univariate and multivariate Cox proportional hazard analyses. In multivariate analysis, all-cause mortality was adjusted by age, BMI and

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Table 2:

	Model 1				Model 2				Model3			
Physical function	B	95% CI	β	P value	B	95% CI	β	P value	B	95% CI	β	P value
Grip strength	-0.23	-0.40 - -0.06	-0.09	0.009	-0.19	-0.36 - -0.01	-0.07	0.036	-0.19	-0.37 - -0.02	-0.07	0.029
QIS	-0.59	-0.89 - -0.29	-0.15	< 0.001	-0.59	-0.89 - -0.28	-0.15	< 0.001	-0.61	-0.92 - -0.30	-0.16	< 0.001
Gait speed	-0.02	-0.02 - -0.01	-0.21	< 0.001	-0.01	-0.02 - -0.01	-0.18	< 0.001	-0.01	-0.02 - -0.01	-0.19	< 0.001
6MWD	-6.62	-8.94 - -4.30	-0.21	< 0.001	-5.44	-7.70 - -3.18	-0.17	< 0.001	-5.44	-7.71 - -3.18	-0.17	< 0.001

Model 1: adjusted for age, gender, body mass index (BMI), hospital anxiety and depression scale (HADS). Model 2: adjusted for model 1 + HemoglobinA1c (HbA1c), Albumin (Alb), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), the presence or absence of chronic heart failure. Model 3: adjusted for model 2 + the presence or absence of hypertension, dyslipidemia, diabetes, and smoking, which are coronary risk factors.

B, regression coeffidencent; CI, confidence interval; β, standardized regression coefficient; QIS, quadriceps isometric strength; 6MWD, 6-minute walking distance.

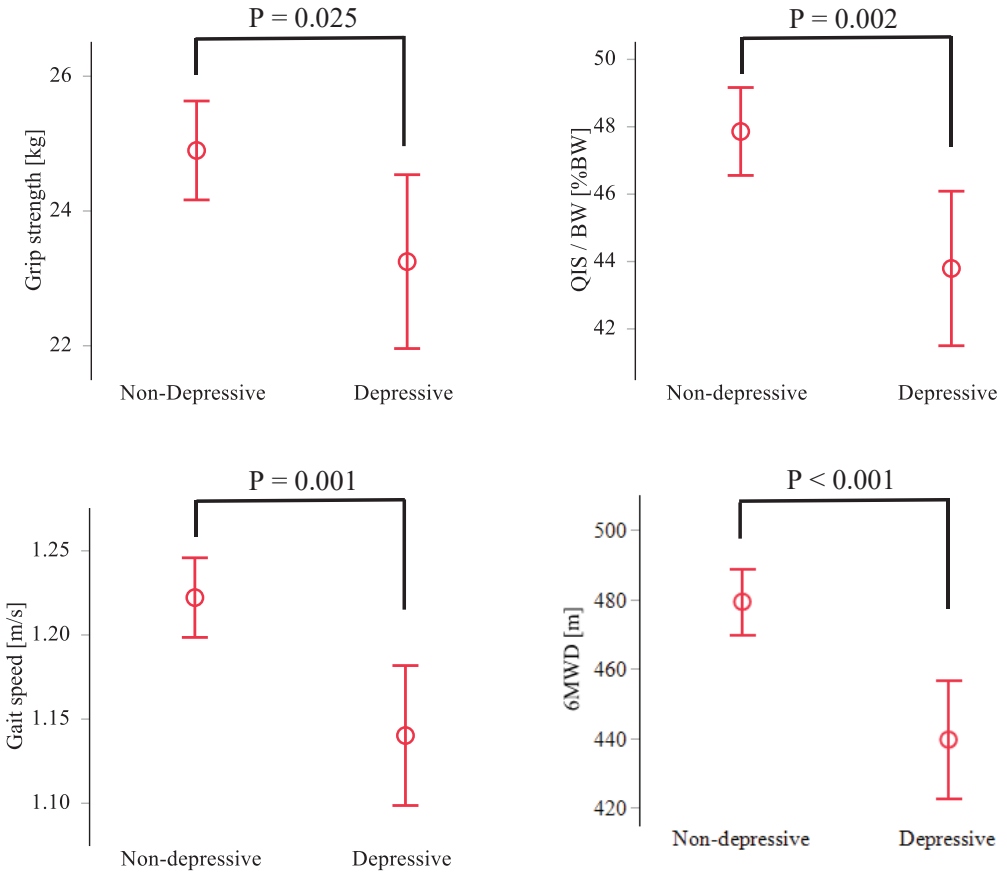

Figure 1: Relationship between depressive tendency and physical function.
Comparison of physical function between the depressive group and non-depressive group by analysis of covariance (ANCOVA) adjusted for age, gender, BMI, HbA1c, Alb, eGFR, CRP, BNP, LVEF and the presence or absence of chronic heart failure as covariates. Red dots indicate adjusted mean values, with error bars representing 95% confidence intervals. QIS, quadriceps isometric strength; BW, body weight; 6MWD, 6-minute walking distance.

BNP, and readmission due to heart failure was adjusted by age, sex, BMI, BNP,

Alb and the presence or absence of chronic heart failure. In univariate and multivariate analysis, the D and Low-P group had a higher risk of all-cause mortality than group Non-D and High-P in 6MWD. Also, the risk of readmission due to heart failure was higher in groups D and Low-P and D or Low-P than group Non-D and High-P in all physical functions.

Discussion & conclusion

In this study, the proportion of patients with depressive tendencies as determined by HADS was 23.1%. The proportions of patients with chronic heart failure and circulating levels of BNP were significantly higher in the group of CVD patients with depressive tendencies than in the non-depressive tendency group. HADS is an independent determinant of physical function taking into consideration confounding factors, and the

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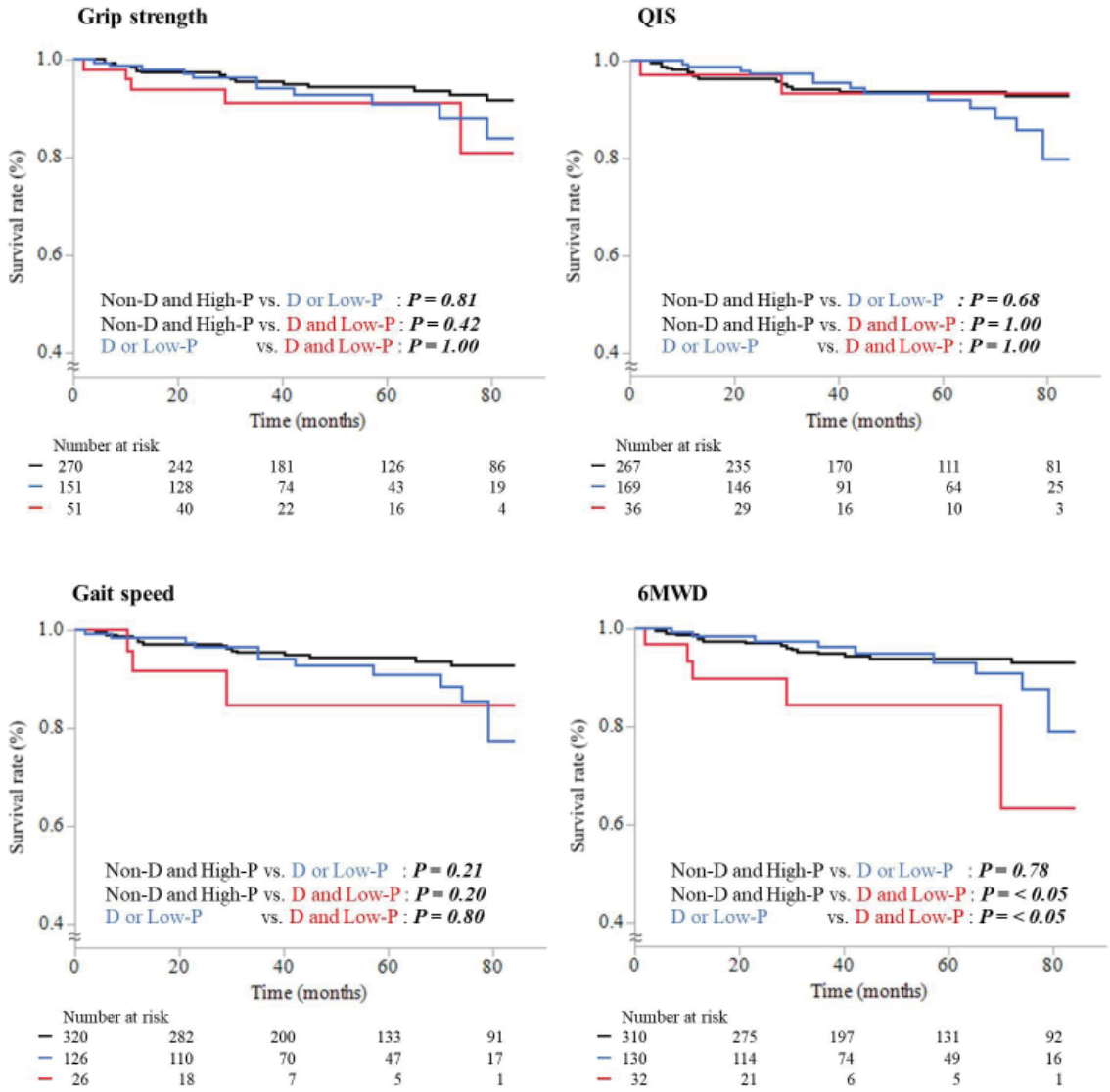

Figure 2: Kaplan–Meier analysis of all-cause mortality according to depressive tendency and physical function.
Kaplan–Meier survival analysis of all-cause mortality in patients classified into three groups according to presence or absence of depressive tendency and/or decreased physical function: Non-D and High-P group, with neither depressive tendency nor decreased physical function; D or Low-P group, depressive tendency or decreased physical function; and D and Low-P group, depressive tendency and decreased physical function. The black line represents Non-D and High-P group, the blue line represents D or Low-P group, and the red line represents D and Low-P group. QIS, quadriceps isometric strength; 6MWD, 6-minute walking distance.

depressive tendency group showed significantly lower values in all measures of physical function than the non-depressive tendency group. The combinations of depressive tendency and only decreased 6MWD group significantly increased the incidences of all-cause mortality and readmission due to heart failure compared to the D or Low-P group and the Non-D and High-P group. In Cox proportional hazards analysis, the combination of depressive tendency and decreased 6MWD further increased the risks of all-cause mortality and readmission due to heart failure. In patients with CVD, the depressive tendency was associated with decreased physical function, and their combination was associated with poor prognosis. The prevalence of depression in CVD patients has been reported to be 17.5% to 46.3% [1-3]. The population in this study did not consist of acute CVD patients, but in outpatients with chronic CVD. The prevalence of depression in the present study was 23.1%, which was consistent with previous reports.

The combination of depression with CVD and in community-dwelling elderly people has been reported to be poor prognostic factors [7,11]. In addition, it has been reported that among community-dwelling elderly people, the depressive tendency is associated with chronic inflammation [27] and decreased physical activity [14], possibly resulting in decreased physical function. However, the relationship between depressive tendency and physical function in patients with CVD and the effects of the combination of both on prognosis is not clear. To our knowledge, this is the first report regarding the relationship between depressive tendency and physical function in patients with CVD and the effects of their combination on prognosis.

The depressive tendency is caused by chest pain [1] fatigue [3] and autonomic abnormalities [28] due to decreased cardiac function. On the other hand, the cardiac function has been reported to decline as a result of decreased heart rate variability

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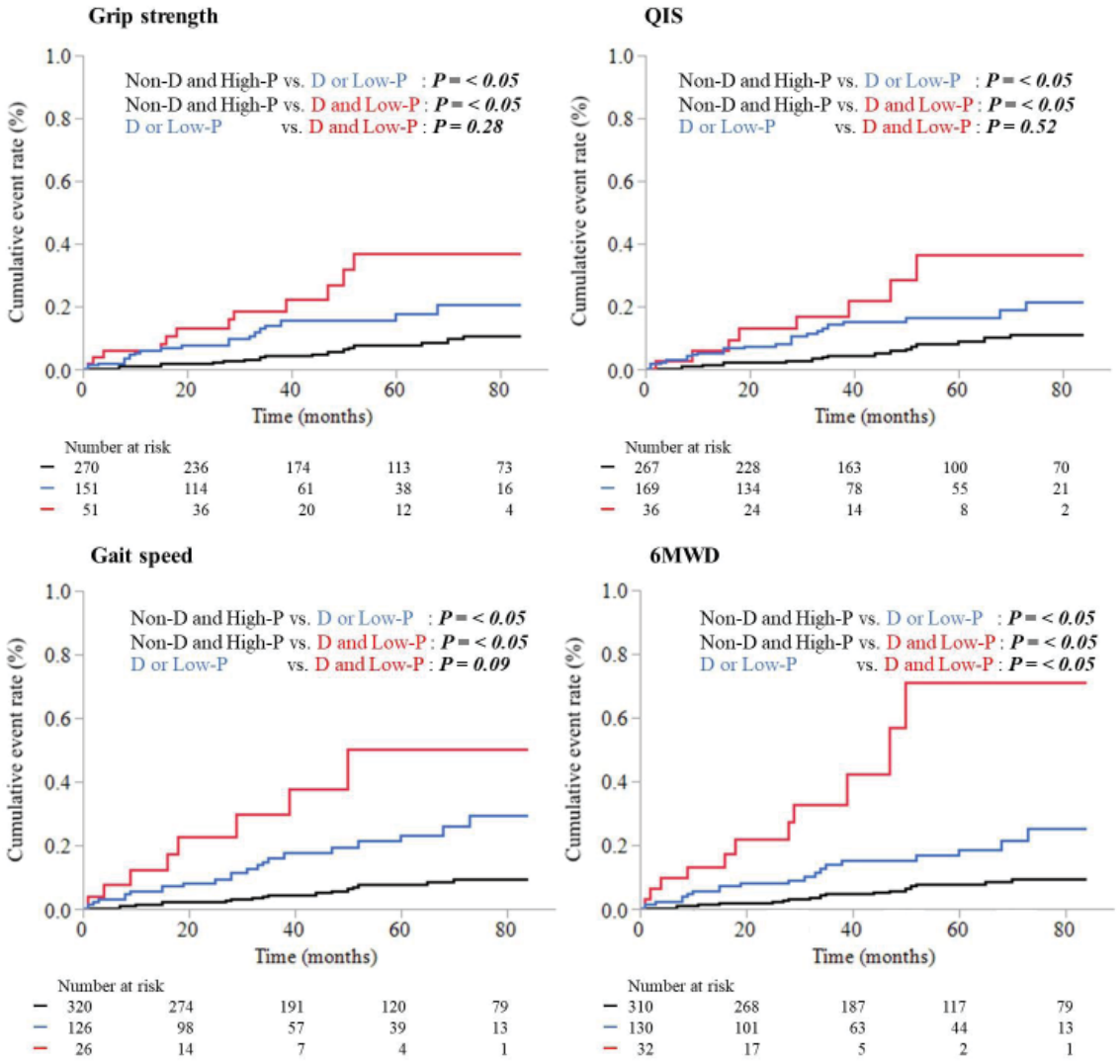

Figure 3: Kaplan–Meier analysis of readmission due to heart failure according to depressive tendency and physical function
Kaplan–Meier survival analysis of readmission due to heart failure in patients classified into three groups according to presence or absence of depressive tendency and/or decreased physical function: Non-D and High-P group, with neither depressive tendency nor decreased physical function; D or Low-P group, depressive tendency or decreased physical function; and D and Low-P group, depressive tendency and decreased physical function. The black line represents Non-D and High-P group, the blue line represents D or Low-P group, and the red line represents D and Low-P group. QIS, quadriceps isometric strength; 6MWD, 6-minute walking distance.

due to depression [29]. Therefore, the study concluded that CVD patients with depressive tendencies due to these causes may have significantly higher rates of chronic heart failure and higher circulating BNP levels than non-depressive patients. However, there were no significant differences in LVEF associated with depressive tendencies. The number of heart failure patients without systolic dysfunction is increasing [30]. This may be due to appropriate disease management in patients with chronic CVD. LVEF was normal in both groups in this study, so there was no significant difference between patients with and without depressive tendencies. It has also been reported that ischemic heart disease [31] and arrhythmia [32] are involved in the development of depression, but there were no significant differences in the percentages of patients with ischemic heart disease and arrhythmia between the two groups in this study.

Various mechanisms have been proposed for the relationship between depressive tendency and physical function in patients with CVD, but the underlying mechanism is still unknown. Patients with CVD develop heart failure symptoms at a high rate, leading to decreased peripheral blood flow, chronic inflammation [27], decreased physical activity [33] and malnutrition [34], which may cause skeletal muscle disorder and decreased physical function [35]. On the other hand, decreased physical function may increase the incidence of cardiovascular events due to decreased balance ability [36] and vascular endothelial Dysfunction [37]. In this study, the depressive tendency determined by HADS was considered to be an independent determinant of physical function, suggesting that physical function declines due to the combination with depressive tendency. However, the subjects of this study are patients with chronic cardiovascular disease who regularly cooperate with doctors, nurses, and physiotherapists to manage the disease as secondary prevention. Therefore, since the state was relatively stable, it is considered that there was no

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Table 3:

		Univariate Cox Analysis			Multivariate Cox analysis		
		HR	95%CI	P value	HR	95%CI	P value
Grip strength	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	1.54	0.71 - 3.33	0.276	1.19	0.54 - 2.64	0.670
	D and Low-P	2.18	0.80 - 5.99	0.129	1.60	0.57 - 4.48	0.370
QIS	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	1.55	0.75 - 3.17	0.236	1.29	0.61 - 2.71	0.499
	D and Low-P	1.16	0.27 - 5.07	0.841	0.83	0.19 - 3.71	0.806
Gait speed	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	1.95	0.93 - 4.08	0.078	1.62	0.76 - 3.45	0.215
	D and Low-P	3.43	0.99 - 11.83	0.051	1.91	0.52 - 7.03	0.329
6MWD	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	1.57	0.72 - 3.44	0.259	1.25	0.55 - 2.81	0.597
	D and Low-P	4.90	1.78 - 13.49	0.002	3.03	1.03 - 8.94	0.045

HR: hazard ratio; CI: confidence interval; QIS: quadriceps isometric strength; 6MWD: 6-minute walking distance; Non-D and High-P: the group without depressive tendency and decreased physical function; D or Low-P: the group with depressive tendency or decreased physical function; D and Low-P: the group with depressive tendency and decreased physical function

Table 4:

		Univariate Cox Analysis			Multivariate Cox analysis		
		HR	95%CI	P value	HR	95%CI	P value
Grip strength	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	2.56	1.35 - 4.86	0.004	2.24	1.14 - 4.37	0.019
	D and Low-P	4.7	2.26 - 9.79	<0.001	3.84	1.73 - 8.52	0.001
QIS	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	2.41	1.30 - 4.44	0.005	2.58	1.36 - 4.92	0.004
	D and Low-P	4.23	1.84 - 9.74	<0.001	3.57	1.39 - 9.15	0.008
Gait speed	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	3.54	1.93 - 6.51	<0.001	3.48	1.83 - 6.62	<0.001
	D and Low-P	8.59	3.74 - 19.8	<0.001	6.05	2.37 - 15.42	<0.001
6MWD	Non-D and High-P	1.00 [Reference]			1.00 [Reference]		
	D or Low-P	2.87	1.53 - 5.38	0.001	2.71	1.40 - 5.25	0.003
	D and Low-P	10.78	5.05 - 23.03	<0.001	7.91	3.23 - 19.36	<0.001

HR: hazard ratio; CI: confidence interval; QIS: quadriceps isometric strength; 6MWD: 6-minute walking distance; Non-D and High-P: the group without depressive tendency and decreased physical function; D or Low-P: the group with depressive tendency or decreased physical function; D and Low-P: the group with depressive tendency and decreased physical function

significant difference in the reference values for the various data such as CRP and Alb. CVD patients with depressive tendencies have been reported to show vascular endothelial dysfunction [38,39] platelet dysfunction [40], left ventricular dysfunction [41-42] reduced adherence to disease management [43] and increased prevalence of lifestyle-related diseases [44], all of which result in poor prognosis. Also, the coronary risk factors, diabetes [45] and smoking [46] and the use of antidepressants

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[46] and beta-blockers [47] have been reported to be associated with depression. However, the rates of these factors and HbA1c, HDL-C, or LDL-C, which are biomarkers of diabetes and dyslipidemia were not significantly different between the two groups in this study. Patients who have been diagnosed with mental illness were excluded from this study, so the cohort did not include patients using antidepressants.

Therefore, the factors in this study that showed lower values in all measures of physical function in the depressive tendency group compared with the non-depressive tendency group are likely due to a decrease in physical activity and vascular endothelial damage due to the depressive tendency. In recent years, there have been many reports that vascular endothelial function and physical activity are related to physical function.

There are several determinants of 6MWD, including cardiopulmonary function, skeletal muscle mass and strength, and mitochondrial function [48]. 6MWD is considered to be a comprehensive measure of physical function that incorporates the elements of grip strength as an index of arm strength, QIS as an index of lower limb strength, and gait speed as a measure of movement ability measured in the present study. 6MWD is considered to be an indicator of muscle strength and cardiopulmonary function, as well as an indicator of functional ability in activities of daily living [49]. It has been reported that 6MWD, which is an indicator of exercise tolerant and comprehensive physical function, is closely related to decreased physical activity and malnutrition, and may further decrease exercise tolerability. It has been reported that depressive tendency causes social isolation and decreased physical activity. In this study, a combination of depressive tendencies and decreased 6MWD triggered a vicious cycle, which may be associated with decreased physical activity, malnutrition, and decreased cardiac function. These factors may be associated with poor prognosis for both all-cause mortality and readmission due to heart failure.

This study had several limitations. First, this study was performed in a single center. Second, the study population consisted only of Japanese patients with CVD, and there were few deaths in the cohort during the observation period. Moreover, many patients were excluded from the analysis as they could not complete baseline physical function and HADS.

In conclusion, the depressive tendency is associated with decreased physical function, and their combination is associated with poor prognosis in patients with CVD.

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