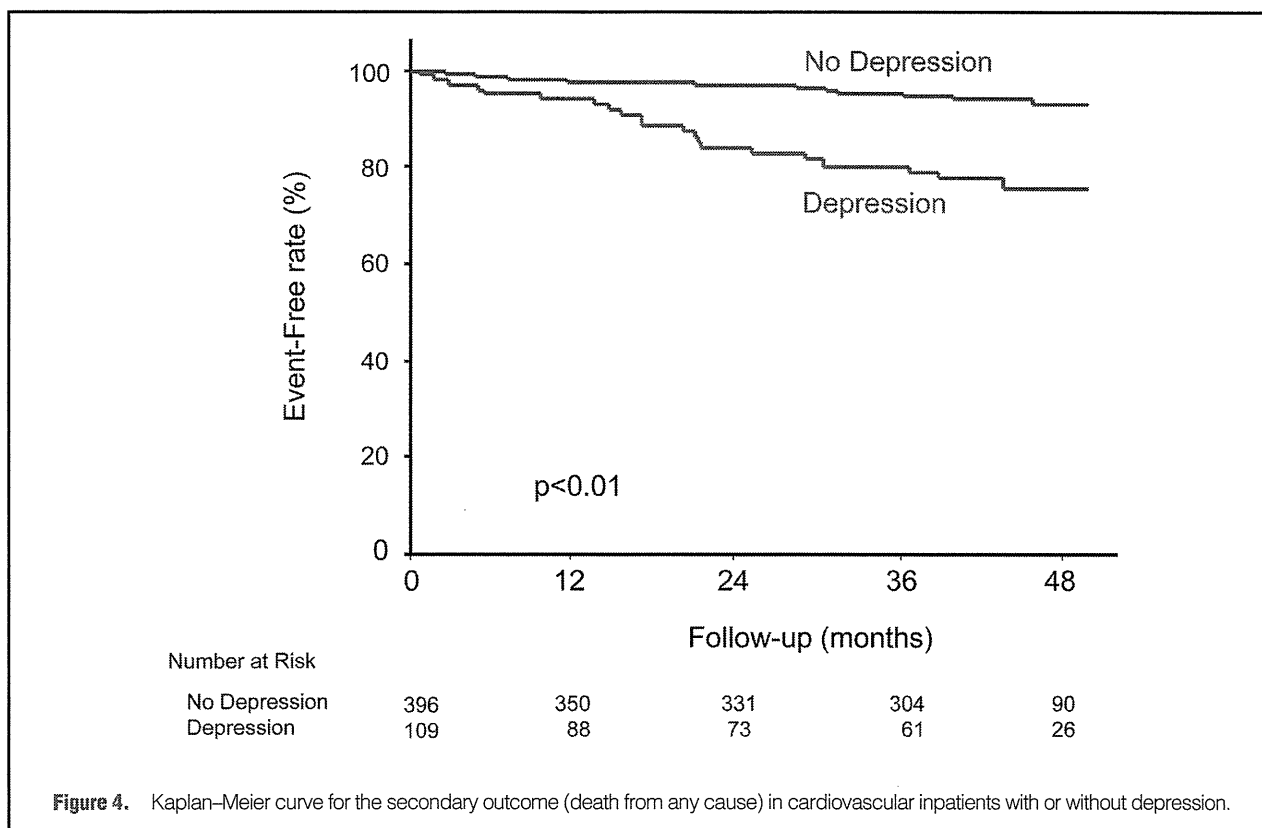


Table 2. Cause of Death and Rate of Cardiovascular Events			
	Depression (n=109)	No depression (n=396)	P value
Death from any cause	21	20	<0.01
Cardiovascular death	18	17	<0.01
Sudden death	1	8	0.42
Heart failure	17	5	<0.01
Myocardial infarction	0	2	0.45
Cerebral infarction	0	1	0.59
Peripheral artery disease	0	1	0.59
Non-cardiovascular death	3	3	0.08
Infection-related death	1	1	0.32
Surgery-related death	1	0	0.06
Hepatocellular carcinoma	0	1	0.59
Hepatic failure	1	0	0.06
Pulmonary hemorrhage	0	1	0.59
Hospitalization for heart failure	22	30	<0.01
Hospitalization for unstable angina	2	3	0.31
Hospitalization for revascularization	5	5	0.02
Hospitalization for stroke	0	1	0.59
Hospitalization for refractory arrhythmia	1	3	0.86
Ventricular tachyarrhythmia requiring ICD therapy	3	9	0.77
Hospitalization for other cardiovascular events	1	2	0.61

Abbreviation see in Table 1.



patients (18%) reached the primary outcome. Kaplan–Meier curves for the primary outcome are shown in **Figure 3**. There was a significantly higher incidence of the primary outcome in patients with depression than in those without depression. Causes of death and each cardiovascular event are listed in

Table 2. Kaplan–Meier curves for death from any cause are shown in **Figure 4**. There was a significantly higher mortality in patients with depression than in those who were not depressed.

Multivariate analysis showed that patients with depression had an increased risk of the primary outcome: death from any

cause and cardiovascular events (HR, 1.98; 95%CI: 1.32–2.98, $P < 0.001$; Table 3). This risk was independent of whether patients met the criteria of NYHA functional class III/IV, $LVEF \leq 35\%$ and $eGFR < 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$.

Discussion

The present study has shown that the prevalence of depression was 22% in hospitalized patients with cardiovascular disease. ICD/CRT-D implantation, NYHA functional class III/IV at baseline, unmarried status, and unemployment were associated with depression. Furthermore, higher mortality and death from any cause and cardiovascular events were more prevalent in patients with depression than in those who were not depressed. Finally, depression was shown to be an independent factor for worsening clinical outcome.

Depression is often comorbid with chronic physical disease. The World Health Organization World Health Survey reported that an average of 9.3–23.0% of subjects with one or more physical diseases, such as angina, arthritis, asthma and diabetes, also suffer from depression.⁴⁴ A large study based on National Health Interview Survey data of 30,801 US adults reported that the 12-month prevalence of major depression was 9.3% in subjects with coronary artery disease, 9.3% in subjects with diabetes, 8.0% in subjects with hypertension and 7.9% in subjects with congestive heart failure, compared with 4.8% in those with no chronic medical disorder.⁴⁵ Recently, the American Heart Association recommended routine depression screening in patients with coronary artery disease using the 2- and 9-item tests from the Patient Health Questionnaires (PHQ-2 and PHQ-9).⁴⁶ Sowden et al reported that approximately 9% of 3,504 screened inpatients in cardiac care units had positive PHQ-2 scores (≥ 3). Of these patients, 74.1% had a PHQ-9 score ≥ 10 , but the details of the patients' clinical backgrounds are unknown.⁴⁷ Previous studies have used several methods to measure depression, including the Beck Depression Inventory, SDS, the Hospital Anxiety and Depression Scale, and the Centre for Epidemiologic Studies Depression Scale (CES-D).^{5,8} The Sowden et al PHQ-2 cut-off score was higher than that in general use (≥ 2)⁴⁸ to avoid false-negative results. The prevalence of patients with a PHQ-2 ≥ 2 was at least 15% in the Sowden et al study.⁴⁷ In the present study, 22% of all cardiovascular disease inpatients met the criteria for depression (Zung SDS index score ≥ 60).

The prevalence of depression in the present inpatients was comparable to the prevalence reported previously in Western countries, but the methods for measuring depression varied. In the present patients, ICD/CRT-D implantation and NYHA functional class III/IV as baseline were associated with depression. Previous studies have indicated that ICD implantation improves quality of life (QOL) in most ICD patients,^{49,50} but an underlying disease or comorbidity, poor social support, or ICD-specific problems, such as frequent shocks and poor understanding of ICD therapy, increase depressive symptoms and reduce the QOL for ICD patients.^{10,50–52} This is an important problem in clinical practice because the number of ICD implantations being carried out to prevent sudden cardiac death is increasing. A meta-analysis showed that depression is common among patients with heart failure, and substantially higher rates of clinically significant depression are present among patients with more severe heart failure.⁵³ In the present study, concomitant use of amiodarone/nifekalant, i.v. inotropics and i.v. vasodilators at the time of the questionnaire was higher in patients with depression. These findings might be due to a higher proportion of moderate to severe heart failure

Table 3. Multivariate Analysis for the Primary Outcome

	HR (95%CI)	P value
NYHA class III/IV	2.07 (1.14–3.72)	0.01
Implantation of ICD/CRT-D	4.04 (2.15–7.06)	<0.01
$eGFR < 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$	3.26 (1.84–5.76)	<0.01
$LVEF \leq 35\%$	2.06 (1.03–4.13)	0.04
Depression	2.25 (1.30–3.92)	<0.01
Female gender	1.02 (0.55–1.87)	0.94
Age ≥ 65 years	0.83 (0.48–1.44)	0.83
Diabetes	1.47 (0.74–2.94)	0.26
Hypertension	0.97 (0.53–1.74)	0.91

HR, heart rate; CI, confidence interval. Other abbreviations see in Table 1.

patients among patients with depression. More than half of the heart failure patients in Japan have non-ischemic etiologies, unlike in Western countries, where the majority of heart failure patient have ischemic etiologies.^{54–56} From the present results, regardless of the etiology, severe heart failure, higher plasma BNP and higher NYHA functional class were associated with depression and are risk factors for cardiovascular events and mortality. The prevalence of heart failure increases with age, and depression will be expected to rise in coming years because of the growing elderly population.

Single or widow status was associated with depression. Regarding socioeconomic status, the employment rate was lower in patients with depression, although work status was not a statistically independent factor for depression. Education also was not related to depression. Using national survey data, Inaba et al reported that the depression score according to CES-D is higher in women, single people, and people with lower incomes in both Japan and the USA, but there is no association between education and depression in Japan; however, depression is inversely related to education in the USA.⁵⁷ The present findings that higher prevalences of single people and people with low employment status, but not level of education, were seen in patients with depression might be due to certain common features of Japanese patients with depression.

There are several mechanisms to consider concerning the relationships between depression and poor outcomes in patients with cardiovascular disease.⁶ First, behavioral problems decrease patient compliance. Depressive symptoms have been associated with poor adherence to medications, diet, fluid restriction, and exercise as well as poor social support.^{2,6,58,59} In the present subjects, poor social status, such as being unmarried or unemployed, was associated with depression. Poor social support also has been reported to be independently associated with worse cardiovascular outcome.⁶⁰ Second, biological mechanisms are involved in poor cardiovascular outcomes. Several events have been associated with these poor outcomes, including changes in cardiac autonomic tone, activation of the sympathetic nervous system, enhanced activity of the hypothalamic–pituitary–adrenal axis, and elevated inflammatory and pro-inflammatory processes.^{1,2,6,61} Although depression is associated with poorer outcome in patients with cardiovascular disease, its pathophysiologic mechanisms are not completely understood. In the present study, death due to heart failure and hospitalization for heart failure were major adverse cardiovascular events, and the rates of these events were significantly different between patients with and without depression. There was significantly higher use of spironolactone/eplerenone and warfarin at discharge in patients with depression than in those who were not depressed. This difference might be related to a

higher rate of coexisting heart failure in patients with depression. Recently Zuluaga et al suggested that the association between depression and higher long-term mortality in patients hospitalized for heart failure is explained largely by the presence of comorbidities, physical inactivity, and disability.⁶² Moreover, several reports concluded that therapy for depression improved depressive symptoms but not cardiovascular outcomes in patients.^{6,63,64} In the present study, antidepressant use was higher in patients with depression, but the small rate of usage of these drugs did not contribute to patient outcomes. Depression may be merely a surrogate marker of poor prognosis but it may be an important marker, especially in patients with heart failure. The management of depression and cardiovascular disease, including proactive follow-up by nurses or care managers,⁶⁵ intervention with cognitive behavioral therapy, or social support,⁶⁶ is important for improving compliance and therapeutic outcomes in patients with cardiovascular disease and depression.

Study Limitations

There were some limitations in the present study. First, this was a single-center cohort study. The clinical characteristics of the present patients might not reflect those of general cardiovascular patients in Japan because the present institution is a university hospital. The prevalence of coronary heart disease was only 31%, and half of the patients were in NYHA functional class II–IV. In addition, there was a treatment bias. Therefore, the present results have limited generalizability in overall cardiac care. Second, the present patients were not consecutively enrolled, and many patients who received emergent or intensive care were not enrolled because it was not possible for them to complete the questionnaire. Moreover, there was an approximately 50% response rate for the Zung SDS questionnaire in the enrolled patients. This self-report 20-item written questionnaire was used as a convenient screening method but was limited by the document return rate from all subjects and the validity of the responses. From these limited data, we could not determine the contribution of depression to clinical condition in several patients with cardiovascular disease. Third, the questionnaire was not completed before discharge. The primary aim of the present study was to evaluate the prevalence and distribution of depression in hospitalized patients. Moreover, the length of hospital stay ranged from a few days to several months because cardiovascular diseases are heterogeneous. For long-term prognosis, an assessment immediately before discharge might be more appropriate. Previous research has demonstrated, however, that depression at the time of hospitalization, not only before discharge, is associated with poor prognosis in patients with cardiovascular disease.^{66–69} Although this problem exists, the present results demonstrate the importance of assessment at an early stage of management of cardiovascular patients. Four, because the number of subjects in the present study was relatively small, subgroup analysis was not feasible. To clarify these issues, large multicenter clinical investigations that include several regions in Japan are needed.

Conclusion

The present results suggest that depression is not uncommon in Japanese cardiovascular inpatients, especially in those with heart failure or who are on ICD therapy. Depression is associated with subsequent cardiovascular outcomes or mortality and may be an important marker of poor prognosis.

Acknowledgments

We thank Kiyoko Kihara, Atoyo Okuma, Kazue Suga and Chika Sato for their support and assistance.

Disclosures

Competing interests: none declared.

This study was supported by funds from the Japan Research Promotion Society for Cardiovascular Diseases and the Health Labour Sciences Research Grant.

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