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ORIGINAL ARTICLE

Insomnia in patients with acute heart failure: from the KCHF registry

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Abstract

Aims Insomnia is a known risk factor for heart failure (HF) and a predictor of cardiac events in HF patients, but the clinical significance of insomnia in patients with acute HF (AHF) is not adequately evaluated. This study aimed to investigate the association between insomnia and subsequent clinical outcomes in patients with AHF.

Methods From the Kyoto Congestive Heart Failure registry, consecutive 3414 patients hospitalized for HF who were discharged alive were divided into the 2 groups at discharge: insomnia group and non-insomnia group. We compared baseline characteristics and 1 year clinical outcomes according to the presence of insomnia. The primary outcome measure was all-cause death.

Results There were 330 patients (9.7%) and 3084 patients (90.3%) with and without insomnia, respectively. In the multivariable logistic regression analysis, brain-type natriuretic peptide above median value at discharge (OR = 1.50, 95% CI = 1.08–2.10, $P = 0.02$) and the presence of oedema at discharge (OR = 4.23, 95% CI = 2.95–6.07, $P < 0.001$) were positively associated with insomnia at discharge, whereas diuretics at discharge (OR = 0.60, 95% CI = 0.39–0.90, $P = 0.01$) were negatively associated with insomnia at discharge. The cumulative 1 year incidence of all-cause death was significantly higher in the insomnia group than in the non-insomnia group (25.1% vs. 16.2%, $P < 0.001$). Even after adjusting the confounders, the higher mortality risk of patients with insomnia relative to those without insomnia remained significant (HR = 1.55, 95% CI = 1.24–1.94; $P < 0.001$).

Conclusions Patients with insomnia at discharge were associated with a higher risk of mortality than those without insomnia at discharge.

Keywords Acute heart failure; Insomnia; Outcome

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Introduction

Heart failure (HF) is one of the major causes of death and hospitalization in elderly patients. Despite significant progress in treatment strategies of HF, mortality and morbidity remain high.[1,2] Insomnia is the most commonly encountered sleep disorder. Insomnia leads to an unhealthy vicious cycle and abnormal autonomic nervous systems and neuroendocrine systems,[3] and these changes increase the risk of incident HF.[4] Patients with HF who have insomnia are more likely to develop depression, fatigue and worsening physical function[5] and associated with poor medical adherence.[6] A recent single-centre study demonstrated that patients with insomnia in patients hospitalized HF was associated with a higher risk for a composite of cardiovascular death or HF hospitalization, in which approximately half of the patients were diagnosed as having insomnia.[7] When HF worsens, there is an increase in the prevalence of insomnia.[8] However, there is a paucity of data on the incidence and risk factors of insomnia in patients with acute HF (AHF) along with the prognostic implication of insomnia. Therefore, we investigated the incidence and risk factors of insomnia and association of insomnia with clinical outcomes in patients hospitalized for AHF using data from a large Japanese registry.

Methods

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

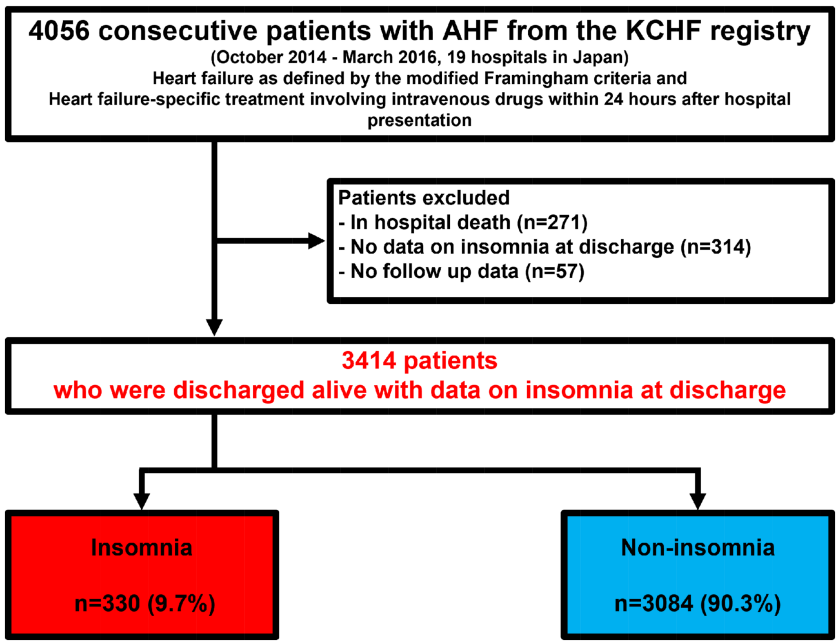
Study design

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled consecutive patients hospitalized for AHF for the first time between 1 October 2014 and 31 March 2016, across 19 secondary and tertiary hospitals throughout Japan. The overall design of the study has been previously described in detail.[9,10] Briefly, we enrolled consecutive patients with AHF, as defined by the modified Framingham criteria, who were admitted to the participating centres and who received HF-specific treatment involving intravenous drugs administered within 24 hours of hospital presentation. Among the 4056 patients who were enrolled in the KCHF registry, we excluded 271 patients who died during the index hospitalization, 314 patients without data on insomnia at discharge, and 57 patients who were lost to follow-up. The final study population consisted of 3414 patients who were discharged alive with data on insomnia (*Figure 1*).

Ethics

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethical committee in Kyoto University Hospital (local identifier: E2311) and each participating hospital. A waiver of written informed consent was granted by the institutional review boards of Kyoto University and each participating centre, as the study met the conditions outlined in the

Figure 1 Study flowchartAHF, acute heart failure; KCHF, Kyoto Congestive Heart Failure.



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Japanese ethical guidelines for medical and health research involving human subjects.[11] We disclosed the details of the present study to the public as an opt-out method and informed the patients of their right to refuse enrolment.

Definitions

Insomnia was defined in a patient-oriented fashion by questionnaires regarding the sleep status asked by the attending physician ('Are you sleeping well?' with the response option 'Yes/No'. If patient's answer was 'No', the next question was 'For how many days have you had trouble with your sleep?' with the response option '1, Seldom; 2, Frequent; 3, Continuous'). We defined the patients as having insomnia if the patient's answer was 'No'. Anaemia was defined using the World Health Organization criteria (haemoglobin $<$12.0 g/dL in women and $<$13.0 g/dL in men). Chronic lung disease was defined as asthma or chronic obstructive pulmonary disease. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2 at admission.[12]

Data collections

The attending physicians or research assistants at each participating hospital collected data on patient demographics, medical histories, underlying heart disease, signs, symptoms, medications, laboratory tests, chest radiographs on admission and at discharge, electrocardiography, and echocardiography during the index hospitalization. One-year clinical follow-up data with an allowance of 1 month were collected in October 2017. The attending physicians or research assistants at each participating hospital collected data on clinical events that occurred during follow-up from the hospital charts or by contacting patients, their relatives, or their referring physicians with their consent.

Outcomes

The primary outcome measure in the present study was all-cause death. The secondary outcome measures were cardiovascular death, HF death, non-cardiovascular death, and HF hospitalization. Detailed definitions of clinical outcome measures were described previously.[10] A clinical event committee adjudicated all the endpoint events.[9,10]

Statistical analysis

Categorical variables were presented as numbers and percentages and were compared using the χ^2 test. Continuous variables were expressed as means and standard deviations or medians with interquartile ranges (IQRs) and were compared using Student's *t*-test or Wilcoxon rank sum test based on their distributions. To determine the factors associated with insomnia at discharge, we created a multivariable logistic regression model. We examined all clinical characteristics, and laboratory categorical variables at discharge and medications at discharge using univariate analysis. We subsequently included all factors with $P < 0.05$ using a multivariate model. The results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We compared baseline characteristics and 1 year clinical outcomes according to the presence or absence of insomnia. We regarded the date of discharge from the index hospitalization as 'time zero' for clinical follow-up. The cumulative incidences of all-cause death, cardiovascular death, HF death, non-cardiovascular death and HF hospitalization after discharge were estimated using the Kaplan–Meier method with intergroup differences assessed by the log-rank test. Multivariable Cox proportional hazard models were developed for the primary and secondary outcome measures by adjusting the potential confounders. The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We included the following 24 clinically relevant risk-adjusting variables according to the clinical relevance and relations to the clinical outcomes consistent with previous studies[13]: age $\geq$80 years, sex, body mass index (BMI) $\leq$ 22 kg/m^2, aetiology of HF hospitalization associated with acute coronary syndrome, prior HF hospitalization, left ventricular ejection fraction (LVEF) $<$ 40%, hypertension, diabetes, atrial fibrillation or flutter, prior myocardial infarction, prior stroke, chronic lung disease, New York Heart Association (NYHA) functional class III or IV, ambulatory status, systolic blood pressure $<$90 mmHg, heart rate $<$60 b.p.m., eGFR $<$30 mL/min/1.73m^2, serum albumin $<$3.0 g/dL, serum sodium $<$135 mEq/L, anaemia, and prescription of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) at discharge, prescription of beta-blockers at discharge, prescription of mineralocorticoid receptor antagonist (MRA) at discharge and prescription of diuretics at discharge. Continuous variables were dichotomized using clinically meaningful reference values or median values. We also evaluated the interactions between the subgroup factors such as age, sex, BMI, LVEF, prior HF hospitalization, eGFR, serum sodium, prescription of diuretics at discharge, and prescription of beta-blockers at discharge and the effects of insomnia relative to non-insomnia on all-cause death after discharge. All the statistical analyses were conducted by two physicians (Y. S. and T. K.) and a statistician (T. M.) using JMP version 15 (SAS Institute Inc., Cary, NC, USA). All the reported *P*-values were two-tailed, and the level of statistical significance was set at $P < 0.05$.

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Results

Patient characteristics of the study population

From the 3414 patients included in this study, 330 patients (9.7%) had insomnia (*Figure 1*). Characteristics of the patients with or without insomnia are different in several aspects (*Table 1*). Patients with insomnia more often had prior hospitalization for HF and were less often ambulatory than in patients without insomnia. LVEF was not significantly different between the two groups. Serum creatinine at admission was significantly higher, whereas serum sodium level was significantly lower in the insomnia group than in the non-insomnia group. Diuretics were less frequently prescribed at discharge in the insomnia group than in the non-insomnia group. Brain-type natriuretic peptide (BNP) at discharge was significantly higher, whereas eGFR, haemoglobin level and serum albumin level at discharge were significantly lower in the insomnia group than in the non-insomnia group. C-reactive protein (CRP) $>$ 1.0 mg/dL at discharge was more frequent in patients with insomnia. Residual oedema was more often observed in the insomnia group than in the non-insomnia group (*Table 1*).

Factors associated with insomnia at discharge

In the multivariable logistic regression analysis, BNP above median value at discharge (adjusted OR = 1.50, 95% CI = 1.08–2.10, P = 0.02), the presence of oedema at discharge (adjusted OR = 4.23, 95% CI = 2.95–6.07, $P < 0.001$) were positively associated with insomnia at discharge, whereas diuretics at discharge (adjusted OR = 0.60, 95% CI = 0.39–0.90, P = 0.01) were negatively associated with insomnia (*Table 2*).

Clinical outcomes: Insomnia versus non-insomnia at discharge

The median follow-up duration was 475 (IQR: 358–652) days with 94.9% follow-up rate during 1 year period. The cumulative 1 year incidence of the primary outcome measure (all-cause death) was significantly higher in patients with insomnia than in those without insomnia (25.1% vs. 16.2%, $P < 0.001$) (*Figure 2A*). The cumulative 1 year incidences of cardiovascular death, HF death and non-cardiovascular death were also significantly higher in patients with insomnia than in those without insomnia (15.8% vs. 10.0%, P = 0.002, 10.5% vs. 6.6%, P = 0.01 and 11.0% vs. 6.9%, P = 0.02) (*Figure 2B–D*). The cumulative 1 year incidence of HF hospitalization was not significantly different between the 2 groups of patients with and without insomnia (24.2% vs. 24.4%, P = 0.37) (*Figure 2E*). After adjusting for confounders, the excess risk of patients with insomnia relative to those without insomnia remained significant for all-cause death (adjusted HR = 1.55, 95% CI = 1.24–1.94, $P < 0.001$), cardiovascular death (adjusted HR = 1.51, 95% CI = 1.13–2.02, P = 0.006), HF death (adjusted HR = 1.46, 95% CI = 1.02–2.11, P = 0.04) and non-cardiovascular death (adjusted HR = 1.63, 95% CI = 1.15–2.30, P = 0.006), but was not significant for HF hospitalization (adjusted HR = 1.09, 95% CI = 0.86–1.38, P = 0.48) (*Table 3* and *Figure 2A–E*).

In the subgroup analysis, there was no significant interaction between the effect of insomnia relative to non-insomnia on the primary outcome measure and the subgroup factors except for those related to eGFR (*Figure 3*).

Discussion

The main findings of the present study are as follows: (i) insomnia was present in 9.7% of AHF patients at hospital discharge; (ii) the factors independently associated with insomnia were BNP above median value at discharge, no prescription of diuretics at discharge and the presence of residual oedema at discharge; (iii) insomnia compared with non-insomnia was associated with a significant excess adjusted risk for all-cause death, cardiovascular death, HF death, and non-cardiovascular death, but not for HF hospitalization.

In the current study, 9.7% of patients with AHF complained insomnia at discharge. A previous study reported the presence of insomnia in 31.3% of the chronic HF patients,[14] while another study in a single centre in Japan reported 48.7% incidence of insomnia at discharge among the AHF patients.[7] These studies included patients with insomnia who were prescribed hypnotics in the insomnia group. Nevertheless, the prevalence of insomnia in their study was much different from ours. The difference between Kanno's study[7] and ours may be derived from the regional difference with younger ages of enrolled patients in their study than in ours, and the difference in the inclusion criteria in which we defined insomnia only by the patient-reported fashion.

We found that BNP above median value, no prescription of diuretics and residual oedema at discharge were associated with insomnia in the multivariable analysis. These factors are linked to residual congestion. Diuretics are used as clinically needed for decongestion. The use of diuretics may be negatively associated with insomnia, probably because the intolerance of loop diuretics was due to a poor baseline status in patients with insomnia. Moreover, HF symptoms such as orthopnoea, and nocturnal dyspnoea may interfere with a good quality of sleep.[8] In managing older patients with HF, it is important to pay attention to insomnia in relation to residual congestion.

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Table 1 Patient characteristics

Variables	Insomnia (n = 330, 9.7%)	Non-insomnia (n = 3084, 90.3%)	P-value	No. of patients analysed
Demographics				
Age, years	81 (72–86)	80 (72–86)	0.26	3414
Age ≥80 years*	183 (55.5)	1592 (51.6)	0.19	3414
Men*	168 (50.9)	1718 (55.7)	0.096	3414
BMI, kg/m^2	22.6 ± 4.8	22.9 ± 4.5	0.18	3248
BMI ≤ 22 kg/m^2*	160 (51.3)	1338 (45.6)	0.054	3248
Aetiology			0.26	3414
Coronary artery disease	94 (28.5)	1001 (32.5)		
Acute coronary syndrome*	26 (7.9)	158 (5.1)		
Cardiomyopathy	51 (15.5)	467 (15.1)		
Valvular heart disease	67 (20.3)	588 (19.1)		
Hypertensive heart disease	82 (24.8)	787 (25.5)		
Other heart disease	36 (10.9)	241 (7.8)		
Medical history				
Prior hospitalization due to HF*	137 (41.5)	1077 (34.9)	0.02	3414
Atrial fibrillation or flutter*	127 (38.5)	1321 (42.8)	0.13	3414
Hypertension*	237 (71.8)	2243 (72.7)	0.72	3414
Diabetes*	114 (34.5)	1152 (37.4)	0.32	3414
Dyslipidaemia	122 (37.0)	1193 (38.7)	0.54	3414
Prior myocardial infarction*	63 (19.1)	710 (23.0)	0.10	3414
Prior stroke*	45 (13.6)	500 (16.2)	0.22	3414
Current smoking	33 (10.2)	386 (12.7)	0.20	3372
Chronic kidney disease	160 (48.5)	1343 (43.5)	0.09	3414
Chronic lung disease*	54 (16.4)	405 (13.1)	0.10	3414
Malignancy	52 (15.8)	443 (14.4)	0.49	3414
Cognitive dysfunction	68 (20.6)	533 (17.3)	0.13	3414
Social backgrounds and activities				
Living alone	72 (21.8)	650 (21.1)	0.75	3414
Ambulatory*	242 (74.5)	2449 (80.2)	0.01	3379
Vital signs at presentation				
Systolic BP, mmHg	145.1 ± 35.9	148.6 ± 34.7	0.09	3403
Systolic BP < 90 mmHg*	11 (3.4)	76 (2.5)	0.33	3407
Heart rate, b.p.m.	97.1 ± 26.0	95.7 ± 28.0	0.36	3391
Heart rate <60 b.p.m.*	18 (5.6)	221 (7.2)	0.28	3391
NYHA Class III or IV*	295 (89.7)	2683 (87.4)	0.23	3400
Tests at admission				
LVEF	46.2 ± 16.1	46.5 ± 16.3	0.71	3340
LVEF classification			0.77	3403
HFrEF (LVEF <40%)*	118 (35.9)	1130 (36.8)		
HFmrEF (LVEF 40–49%)	59 (17.9)	585 (19.0)		
HFpEF (LVEF ≥50%)	152 (46.2)	1359 (44.2)		
BNP, pg/mL	765 (415–1506)	707 (389–1238)	0.08	2998
NT-proBNP, pg/mL	6974 (3653–16 358)	5456 (2642–12 149)	0.23	641
Creatinine, mg/dL	1.19 (0.84–1.80)	1.10 (0.82–1.59)	0.049	3408
eGFR, mL/min/1.73m^2	44.0 ± 24.5	46.5 ± 23.2	0.06	3408
eGFR <30 mL/min/1.73m^2*	108 (32.7)	784 (25.5)	0.004	3408
Serum sodium, mEq/L	138.7 ± 4.2	139.3 ± 4.2	0.02	3401
Sodium <135 mEq/L*	45 (13.7)	346 (11.3)	0.19	3401
Haemoglobin, g/dL	11.4 ± 2.3	11.6 ± 2.3	0.35	3409
Anaemia*	221 (67.0)	2033 (66.0)	0.73	3409
Albumin, g/dL	3.47 ± 0.51	3.49 ± 0.48	0.45	3308
Albumin <3.0 g/dL*	44 (13.9)	395 (13.2)	0.74	3308
CRP, mg/dL	0.54 (0.19–2.46)	0.60 (0.20–1.90)	1.00	3328
Medication at discharge				
Number of prescribed drugs	9 (7–11)	8 (6–11)	0.11	3252
ACE-Is/ARBs*	181 (54.8)	1800 (58.4)	0.22	3414
MRAs*	150 (45.5)	1384 (44.9)	0.84	3414
Beta-blockers*	222 (67.2)	2071 (67.2)	0.96	3414
Diuretics*	262 (79.4)	2605 (84.5)	0.02	3414
Tests at discharge				
BNP, pg/mL	338 (157–604)	263 (134–504)	0.001	2150
BNP > median value	126 (60.3)	949 (48.9)	0.002	2150
NT-proBNP, pg/mL	2937 (1338–8248)	1876 (763–4262)	0.04	417
Creatinine, mg/dL	1.20 (0.86–1.89)	1.12 (0.86–1.56)	0.047	3370

(*Continues*)

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Table 1 (continued)

Variables	Insomnia (n = 330, 9.7%)	Non-insomnia (n = 3084, 90.3%)	P-value	No. of patients analysed
eGFR, mL/min/1.73m^2	42.5 ± 24.4	45.2 ± 22.2	0.04	3370
eGFR <30 mL/min/1.73 m^2	115 (35.3)	754 (24.8)	<0.001	3370
Serum sodium, mEq/L	138.4 ± 4.1	138.6 ± 3.7	0.38	3355
Sodium <135 mEq/L	48 (14.7)	362 (12.0)	0.15	3355
Haemoglobin, g/dL	11.2 ± 2.1	11.5 ± 2.2	0.01	3349
Anaemia	244 (74.6)	2094 (69.3)	0.046	3349
Albumin, g/dL	3.26 ± 0.52	3.37 ± 0.49	<0.001	2994
Albumin <3.0 g/dL	73 (26.1)	522 (19.2)	0.006	2994
CRP, mg/dL	0.50 (0.14–1.25)	0.40 (0.17–1.02)	0.11	3097
CRP > 1.0 mg/dL	99 (31.8)	704 (25.3)	0.01	3097
Residual oedema	120 (36.6)	323 (10.5)	<0.001	3407

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro BNP, N-terminal-pro brain-type natriuretic peptide; NYHA, New York Heart Association.
Values are number (%) or mean ± SD, or median (interquartile range). P-values were calculated using the chi square test for categorical variables, and the Student's t-test or Wilcoxon rank sum test for continuous variables.
*Risk-adjusting variables selected for the Cox proportional hazard models.

Table 2 Logistic regression analysis for the factors associated with insomnia at discharge

	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Prior hospitalization due to HF	1.32	1.05–1.67	0.02	1.20	0.85–1.69	0.30
Ambulatory	0.72	0.55–0.94	0.02	1.03	0.70–1.50	0.89
BNP > median value at discharge	1.59	1.19–2.12	0.002	1.50	1.08–2.10	0.02
eGFR <30 mL/min/1.73 m^2 at discharge	1.66	1.30–2.11	<0.001	1.18	0.82–1.71	0.38
Anaemia at discharge	1.30	1.00–1.69	0.047	0.88	0.60–1.28	0.50
Albumin <3.0 mg/dL at discharge	1.48	1.12–1.97	0.007	1.10	0.73–1.65	0.65
CRP > 1.0 mg/dL at discharge	1.38	1.07–1.78	0.01	1.16	0.80–1.67	0.44
Prescription of diuretics at discharge	0.71	0.53–0.94	0.02	0.60	0.39–0.90	0.01
Presence of oedema at discharge	4.92	3.82–6.34	<0.001	4.23	2.95–6.07	<0.001

BNP, brain-type natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; OR, odds ratio.

There are multiple mechanisms underlying the pathogenesis of insomnia in cardiovascular disease, including dysregulation of the hypothalamic–pituitary axis, abnormal modulation of the autonomic nervous system, and increased sympathetic nervous system activity, and increased systemic inflammation.[15] Increased sympathetic nervous system activity, increased systemic inflammation and hypothalamic–pituitary–adrenal axis dysregulation due to insomnia lead to increased risk of cardiovascular disease, and mortality through increased heart rate and blood pressure, increased atherogenesis, and increased lipids levels and insulin resistance.[15] Patients with sleep disturbances are often unaware of their sleep abnormalities.[16]

Kanno *et al*. reported insomnia was associated with composite of cardiovascular death or HF hospitalization.[7] In the current study, insomnia was associated with higher risk of all-cause, cardiovascular, HF death and non-cardiovascular death, while not associated with higher risk of HF hospitalization. The exact reason of no increase in HF re-hospitalization in the insomnia group are unknown; one of the proposed reasons was that substantial numbers of patients in the insomnia group died without hospitalization due to sudden death or were hospitalized for other non-cardiovascular disease but eventually died due to HF. The proportion of patients with high severity of HF may be high in the insomnia group because they had a higher risk for HF death. Similarly, the patients with insomnia had a higher risk for non-cardiovascular death. These suggested that insomnia may be a general marker of poor health condition. As using the self-reported definition of insomnia, some of patients with sleep disturbances may be included in the non-insomnia group. This may also partly address that the excess risk of patients with insomnia relative to those without insomnia was not apparent for HF hospitalization.

The cause-effect relationship between insomnia and poor clinical outcomes could not be determined because this is

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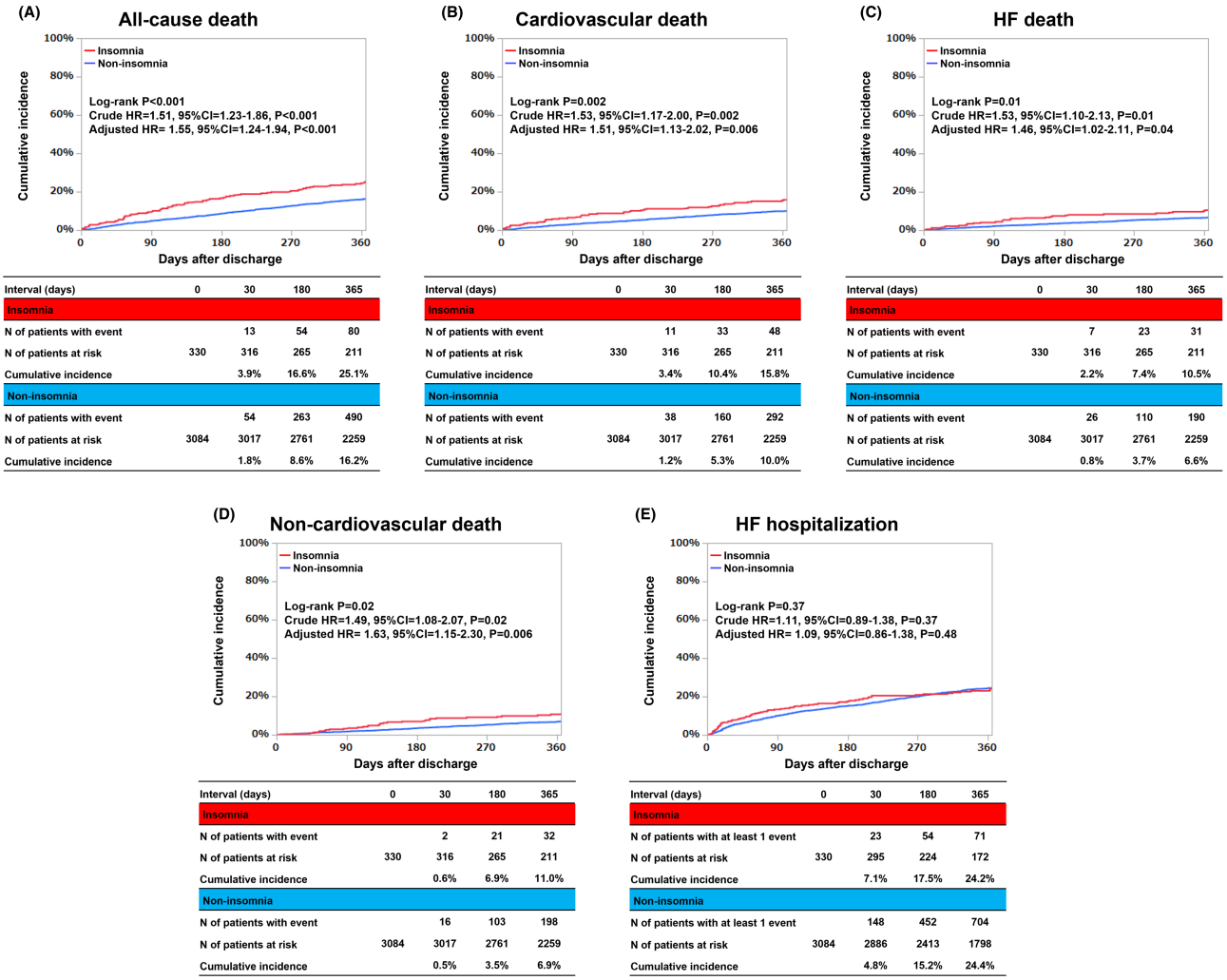
Figure 2 Kaplan–Meier curves for the primary and secondary outcome measures*(A)* All-cause death, *(B)* Cardiovascular death, *(C)* HF death, *(D)* Non-cardiovascular death and *(E)* HF hospitalization. The primary outcome measure was all-cause death. CI, confidence interval; HF, heart failure; HR, hazard ratio.



Interval (days)	0	30	180	365
Insomnia				
N of patients with event		13	54	80
N of patients at risk	330	316	265	211
Cumulative incidence		3.9%	16.6%	25.1%
Non-insomnia				
N of patients with event		54	263	490
N of patients at risk	3084	3017	2761	2259
Cumulative incidence		1.8%	8.6%	16.2%

Interval (days)	0	30	180	365
Insomnia				
N of patients with event		11	33	48
N of patients at risk	330	316	265	211
Cumulative incidence		3.4%	10.4%	15.8%
Non-insomnia				
N of patients with event		38	160	292
N of patients at risk	3084	3017	2761	2259
Cumulative incidence		1.2%	5.3%	10.0%

Interval (days)	0	30	180	365
Insomnia				
N of patients with event		7	23	31
N of patients at risk	330	316	265	211
Cumulative incidence		2.2%	7.4%	10.5%
Non-insomnia				
N of patients with event		26	110	190
N of patients at risk	3084	3017	2761	2259
Cumulative incidence		0.8%	3.7%	6.6%

Interval (days)	0	30	180	365
Insomnia				
N of patients with event		2	21	32
N of patients at risk	330	316	265	211
Cumulative incidence		0.6%	6.9%	11.0%
Non-insomnia				
N of patients with event		16	103	198
N of patients at risk	3084	3017	2761	2259
Cumulative incidence		0.5%	3.5%	6.9%

Interval (days)	0	30	180	365
Insomnia				
N of patients with at least 1 event		23	54	71
N of patients at risk	330	295	224	172
Cumulative incidence		7.1%	17.5%	24.2%
Non-insomnia				
N of patients with at least 1 event		148	452	704
N of patients at risk	3084	2886	2413	1798
Cumulative incidence		4.8%	15.2%	24.4%

Table 3 Clinical outcomes at 1 year

Outcome	Insomnia		Non-insomnia		Unadjusted			Adjusted		
	No. of patients with event/No. of patients at risk	Cumulative 1 year incidence	No. of patients with event/No. of patients at risk	Cumulative 1 year incidence	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Primary outcome measure										
All-cause death	80/330	25.1%	490/3084	16.2%	1.51	1.23–1.86	<0.001	1.55	1.24–1.94	<0.001
Secondary outcome measures										
Cardiovascular death	48/330	15.8%	292/3084	10.0%	1.53	1.17–2.00	0.002	1.51	1.13–2.02	0.006
HF death	31/330	10.5%	190/3084	6.6%	1.53	1.10–2.13	0.01	1.46	1.02–2.11	0.04
Non-cardiovascular death	32/330	11.0%	198/3084	6.9%	1.49	1.08–2.07	0.02	1.63	1.15–2.30	0.006
HF hospitalization	71/330	24.2%	704/3084	24.4%	1.11	0.89–1.38	0.37	1.09	0.86–1.38	0.48

CI, confidence interval; HF, heart failure; HR, hazard ratio.

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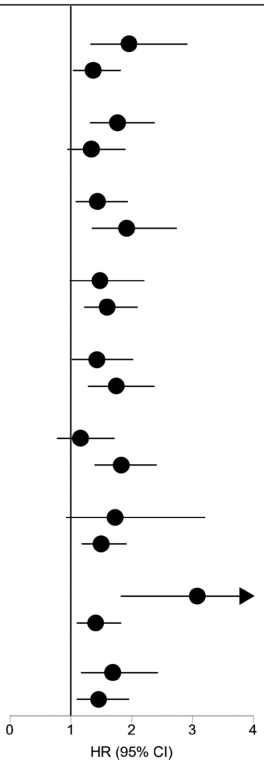
Figure 3 Subgroup analysis for the primary outcome measure The primary outcome measure was all-cause death. BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number.

Subgroups	Insomnia N of patients with death/ N of patients at risk (Cumulative 1-year incidence)	Non-insomnia N of patients with death/ N of patients at risk (Cumulative 1-year incidence)	Adjusted HR (95% CI)	P value	P interaction
Age					0.13
<80 years	26/147 (18.2%)	136/1492 (9.3%)	1.96 (1.32-2.92)	<0.001	
≥80 years	54/183 (30.7%)	354/1592 (22.8%)	1.37 (1.04-1.81)	0.02	
Sex					0.19
Men	47/168 (29.1%)	287/1718 (17.1%)	1.77 (1.31-2.38)	<0.001	
Women	33/162 (21.0%)	203/1366 (15.2%)	1.34 (0.95-1.89)	0.10	
BMI					0.22
≤22 kg/m^2	41/160 (26.5%)	294/1338 (22.5%)	1.44 (1.08-1.93)	0.01	
>22 kg/m^2	35/152 (24.0%)	155/1598 (9.9%)	1.92 (1.34-2.74)	<0.001	
LVEF					0.74
<40 %	27/118 (24.1%)	184/1130 (16.7%)	1.48 (0.99-2.20)	0.055	
≥40 %	53/211 (25.8%)	305/1944 (16.0%)	1.60 (1.22-2.10)	<0.001	
Prior HF hospitalization					0.43
No	37/193 (19.8%)	260/2007 (13.2%)	1.43 (1.02-2.02)	0.04	
Yes	43/137 (32.5%)	230/1077 (21.8%)	1.75 (1.29-2.37)	<0.001	
eGFR					0.045
<30 mL/min/1.73m^2	29/108 (28.2%)	191/784 (24.9%)	1.16 (0.78-1.71)	0.47	
≥30 mL/min/1.73m^2	51/222 (23.7%)	297/2294 (13.2%)	1.83 (1.39-2.41)	<0.001	
Sodium					0.55
<135 mEq/L	12/45 (27.6%)	75/346 (22.3%)	1.73 (0.93-3.20)	0.08	
≥135 mEq/L	68/284 (24.8%)	413/2726 (15.5%)	1.50 (1.18-1.91)	0.001	
Diuretics at discharge					0.10
No	21/68 (31.8%)	66/479 (13.9%)	3.08 (1.83-5.16)	<0.001	
Yes	59/262 (23.4%)	424/2605 (16.7%)	1.41 (1.09-1.82)	0.008	
β-blockers at discharge					0.63
No	30/108 (28.5%)	210/1013 (21.3%)	1.69 (1.17-2.44)	0.005	
Yes	50/222 (23.4%)	280/2071 (13.8%)	1.46 (1.09-1.95)	0.01	



an observational study. Therefore, it is not certain that the improvement of insomnia is associated with the improvement of clinical outcomes. There have been no reports on the pharmacological intervention for insomnia in patients with HF. The efficacy of behavioural therapies such as sleep hygiene education, and cognitive therapy remains uncertain.[17,18] Further clinical trials of pharmacological and non-pharmacological treatment are needed to evaluate clinical benefit of the effective management of insomnia in patients with HF.

Limitations

The present study had several limitations. First, cause-effect relationship between insomnia and associated factors was not determined in the present study. It is not possible to clearly distinguish whether insomnia is a cause or a consequence. Second, the observational nature of the study design could have introduced residual confounding factors and selection bias. Because this was an observational study, it was not possible to determine a causal relationship between insomnia and prognosis of HF. Even after adjusting for the confounding factors employed in this study, differences in baseline characteristics may influence outcomes. This would be needed to be confirmed by clinical trials in which the baseline factors would not interfere or explain the final outcome. Third, we do not have data regarding the prescription of hypnotics and types of drugs. Fourth, we diagnosed insomnia based on patient symptoms, and did not use polysomnography or actigraphy, which are objective tests of sleep disorders. Therefore, we could not completely exclude the effect of diseases related to complaints of insomnia such as psychiatric disorders, depression, and cognitive disorders. The definition of patient-reported insomnia might have affected the present results. Fifth, there was a higher rate of prior hospitalization for HF in the patients with insomnia than without insomnia. We did not consider the numbers of prior hospitalization nor the severity of the prior hospitalization. This might have an influence on the results, although we conducted the multivariable

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adjustment using the presence of the prior HF hospitalization. Sixth, we did not have the echocardiographic parameters regarding left ventricular end-diastolic pressure (LVEDP) such as early mitral inflow velocity/peak atrial filling velocity (E/A) and early mitral inflow velocity/early diastolic mitral annular velocity (E/e').

Conclusions

Patients with insomnia at discharge were associated with a higher risk of mortality than those without insomnia at discharge.

Conflict of interest

None declared.

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