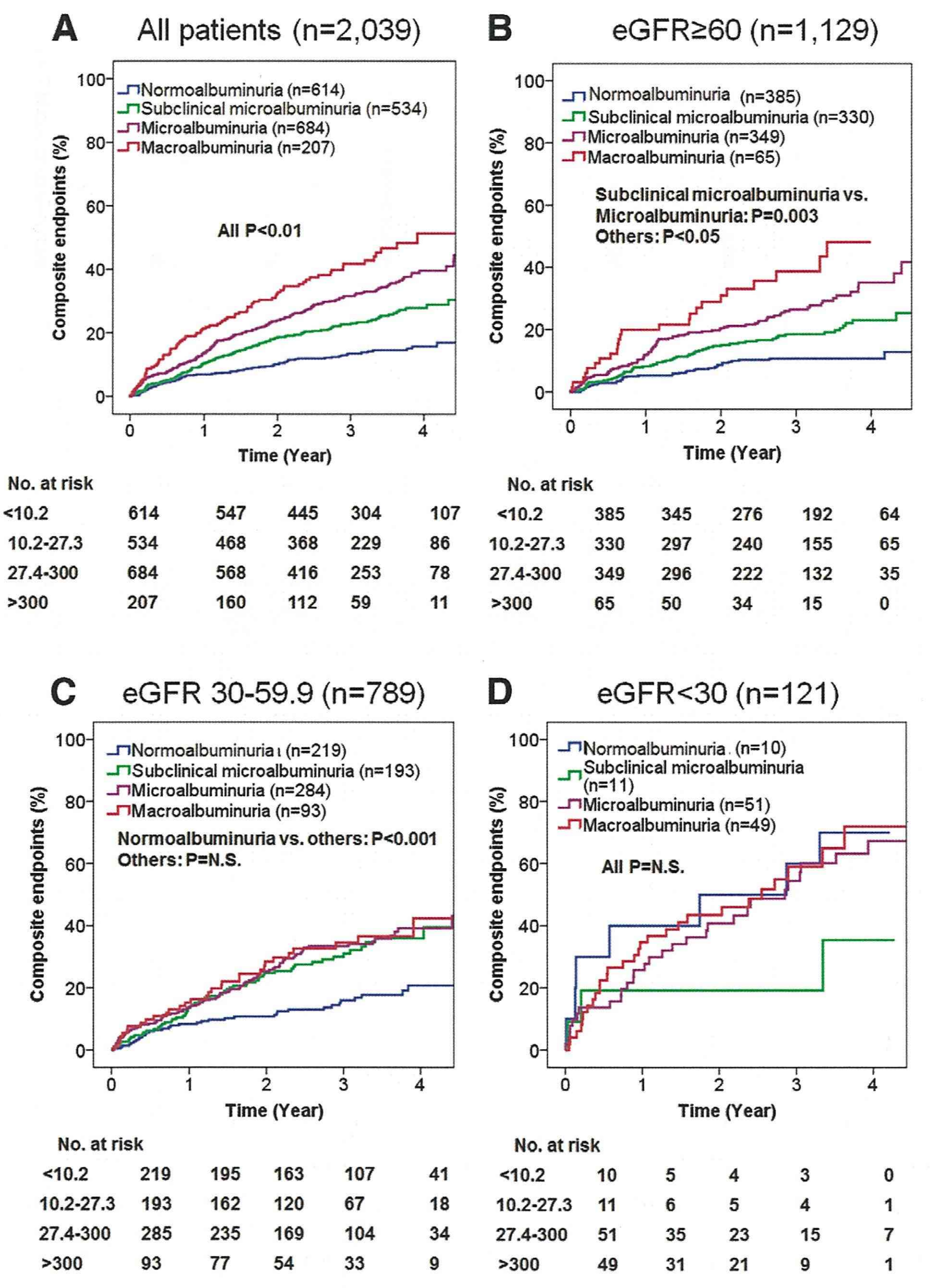

Figure 3. Kaplan-Meier curves for composite endpoints. (**A**) All patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min^{-1}·1.73 m^{-2}; (**C**) eGFR 30–59.9 ml·min^{-1}·1.73 m^{-2}; (**D**) eGFR <30 ml·min^{-1}·1.73 m^{-2}.

67.4 years and male patients accounted for 68.9%. History of ischemic heart disease was noted in 46.2% and mean LVEF and eGFR were 55.3±15.7% and 62.8±20.9 ml·min^{-1}·1.73 m^{-2}, respectively. The prevalence of eGFR <60 ml·min^{-1}·1.73 m^{-2} was 44.6% (n=910), and median UACR was 21.5 mg/g. On CART analysis UACR=27.4 mg/g and 10.2 mg/g were identified as the first and the second discriminating points to stratify risk for composite endpoints, respectively (**Figure 1**). Thus, normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria were defined as UACR (mg/g) <10.2, 10.2–27.3, 27.4–300, and >300, respectively. The prevalence of normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria was 30.1%, 26.2%, 33.5%, and 10.2%, respectively. As shown in **Figure 2**, the prevalence of normoalbuminuria was decreased along with a decrease in eGFR categories. It was noted that, even in patients with preserved eGFR and mildly reduced eGFR, the prevalence of subclinical microalbuminuria was 29.2% and 24.5%, respectively. The characteristics of the patients with subclinical microalbuminuria or microalbuminuria were generally intermediate between those with normoalbuminuria and those with macroalbuminuria, in terms of age, comorbidity, NYHA class,

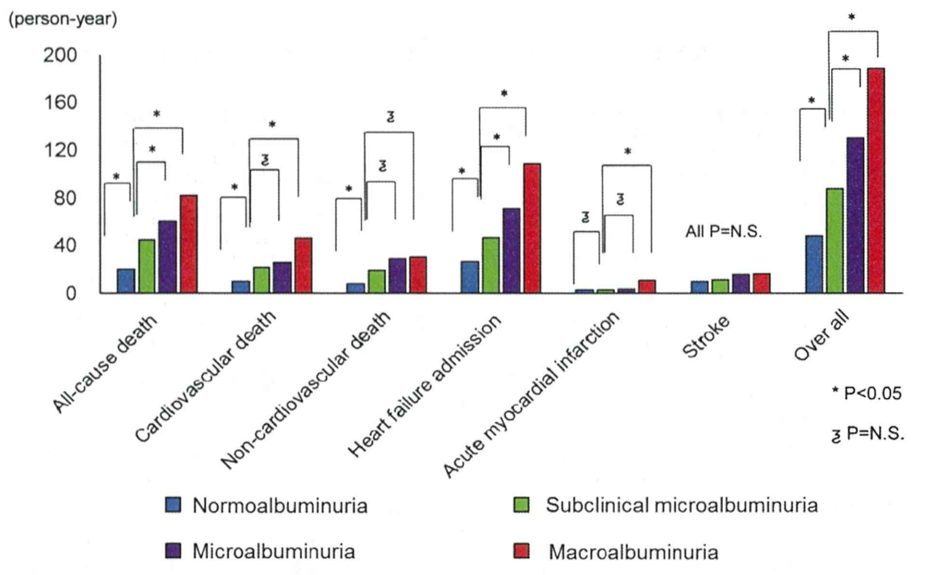

Figure 4. Incidence of composite endpoints. The patients with subclinical microalbuminuria had significantly higher event rates of death, heart failure admission.

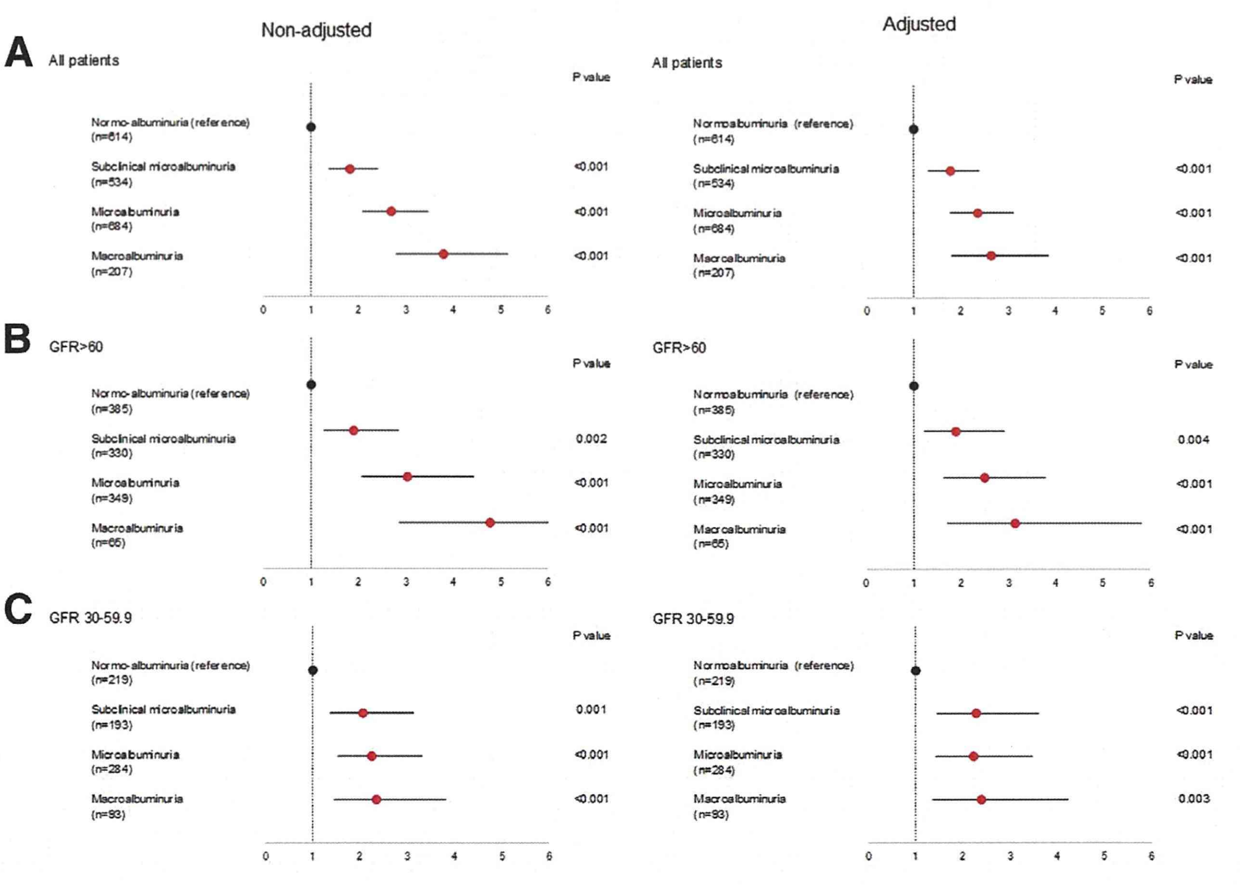

Figure 5. Non-adjusted and adjusted Cox hazard model adjusted for covariates that could potentially influence outcome: (**A**) all patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min^{-1}·1.73 m^{-2}; and (**C**) eGFR 30–59.9 ml·min^{-1}·1.73 m^{-2}.

Table 2. Subgroup Analysis for Composite Endpoints

	HR	95% CI	P-value	HR	95% CI	P-value	P for interaction
	Male			Female			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.96	1.37–2.79	<0.001	1.35	0.75–2.43	0.320	0.40
Microalbuminuria	2.27	1.61–3.19	<0.001	2.25	1.32–3.85	0.003	0.45
Macroalbuminuria	2.71	1.73–4.23	<0.001	3.10	1.50–6.41	0.002	0.33
	Age ≥69 years			Age <69 years			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	2.04	1.37–3.05	<0.001	1.66	1.02–2.68	0.040	0.35
Microalbuminuria	2.56	1.76–3.73	<0.001	1.95	1.24–3.08	0.004	0.70
Macroalbuminuria	2.75	1.65–4.57	<0.001	3.31	1.83–6.00	<0.001	0.26
	LVEF ≥50%			LVEF <50%			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.87	1.19–2.94	0.007	1.71	1.13–2.58	0.010	0.14
Microalbuminuria	2.31	1.51–3.55	<0.001	2.31	1.57–3.41	<0.001	0.33
Macroalbuminuria	2.57	1.48–4.47	0.001	2.66	1.55–4.56	<0.001	0.04
	(+) Hypertension			(–) Hypertension			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.69	1.20–2.38	0.003	1.97	1.01–3.85	0.040	0.66
Microalbuminuria	2.37	1.72–3.26	<0.001	1.70	0.86–3.36	0.140	0.47
Macroalbuminuria	2.52	1.65–3.86	<0.001	5.41	2.30–12.69	<0.001	0.22
	(+) Diabetes			(–) Diabetes			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.81	1.07–3.07	0.030	1.70	1.17–2.47	0.005	0.78
Microalbuminuria	2.30	1.42–3.73	0.001	2.13	1.48–3.07	<0.001	0.78
Macroalbuminuria	2.26	1.26–4.06	0.006	3.09	1.82–5.23	<0.001	0.17
	(+) *β*-blocker			(–) *β*-blocker			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.98	1.31–2.97	0.001	1.57	0.98–2.50	0.120	0.61
Microalbuminuria	2.39	1.63–3.49	<0.001	1.98	1.28–3.07	0.002	0.87
Macroalbuminuria	2.78	1.66–4.64	<0.001	2.50	1.41–4.43	0.002	0.93
	(+) RAS inhibitor			(–) RAS inhibitor			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.90	1.32–2.71	0.006	1.49	0.83–2.69	0.180	0.45
Microalbuminuria	2.57	1.83–3.59	<0.001	1.40	0.78–2.54	0.260	0.32
Macroalbuminuria	2.96	1.90–4.62	<0.001	1.62	0.75–3.50	0.220	0.18
	(+) Statin			(–) Statin			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.77	1.04–3.01	0.030	1.78	1.23–2.58	0.002	0.76
Microalbuminuria	2.25	1.37–3.70	0.001	2.29	1.61–3.25	<0.001	0.46
Macroalbuminuria	2.52	1.37–4.64	0.003	2.85	1.74–4.68	<0.001	0.56

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

hemodynamics, and hemoglobin, BUN, eGFR and BNP. The patients with subclinical microalbuminuria and microalbuminuria, however, were characterized by lower prevalence of male gender, whereas LV function was similar among the 4 groups (**Table 1**).

Prognostic Impact of Clinical and Subclinical Microalbuminuria

During the median follow-up period of 2.69 years (IQR, 1.63–3.63 years), composite endpoints occurred in 506 patients (24.8%). **Figure 3A** shows the estimated curves for composite endpoints. As compared with the patients with normoalbuminuria, those with macroalbuminuria, microalbuminuria and subclinical microalbuminuria had poorer prognosis. As compared with the patients with normoalbuminuria, those with subclinical microalbuminuria had significantly increased incidence of cardiovascular death, non-cardiovascular death, and HF admission, but had similar incidence of acute myocardial infarction and stroke (**Figure 4**). Importantly, the patients with subclinical microalbuminuria and preserved eGFR or mildly reduced eGFR had significantly poorer prognosis compared with those with normoalbuminuria (**Figures 3B,C**). Furthermore, in patients with mildly reduced eGFR, there was no difference in the occurrence of the composite endpoints regard-

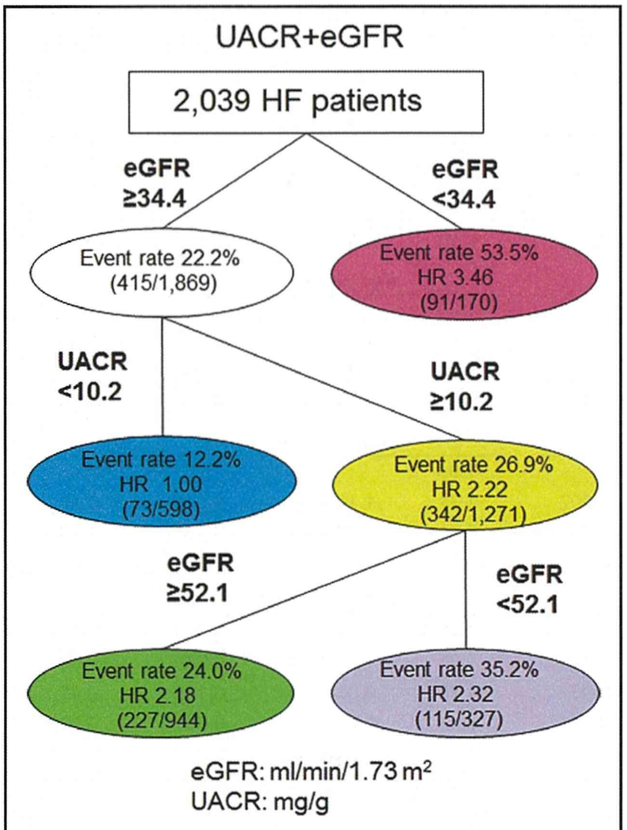

Figure 6. Classification and regression tree analysis identified the first and the second discriminating points as glomerular filtration rate (GFR) 34.5 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ and urinary albumin/creatinine ratio (UACR) 10.2 mg/g. HF, heart failure; HR, hazard ratio.

less of microalbuminuria, microalbuminuria or macroalbuminuria (**Figure 3C**). There was no difference in composite endpoints in patients with severely reduced GFR among the 4 groups (**Figure 3D**).

Figure 5 shows the results of non-adjusted and adjusted Cox proportional hazard regression models for composite endpoints. As compared with patients with normoalbuminuria (reference), multivariate adjusted Cox models showed that the patients with subclinical microalbuminuria, microalbuminuria and macroalbuminuria had 1.70-, 2.39- and 2.49-fold higher risk for composite endpoints, respectively (all $P<0.001$). In the patients with preserved GFR, the adjusted hazard ratio (HR) and 95%CI for composite endpoints was 1.90 (1.23–2.92), 2.50 (1.64–3.80) and 3.15 (1.71–5.81) for subclinical microalbuminuria, microalbuminuria and macroalbuminuria, respectively. Similarly, in patients with mildly reduced GFR, the adjusted HR (95% CI) was 2.29 (1.45–3.62), 2.24 (1.43–3.49) and 2.40 (1.36–4.24) in patients with subclinical microalbuminuria, microalbuminuria and macroalbuminuria, respectively. On subgroup analysis for composite endpoints, subclinical microalbuminuria was significantly associated with poor prognosis regardless of age, LVEF, hypertension or diabetes (**Table 2**). There was no significant interaction regarding sex and medications on subclinical microalbuminuria for mortality (**Table 2**). In a model using both eGFR and UACR, CART analysis showed that the first discriminating points for composite endpoints was eGFR=34.5 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ and the next split point was UACR=10.2 mg/g (**Figure 6**).

Discussion

The novel findings of the present study are the follows. First, among the patients with stage C/D CHF, CART analysis showed that UACR=27.4 mg/g and 10.2 mg/g were the first and the second discriminating points to stratify risk for composite endpoints, respectively, suggesting the clinical importance of subclinical microalbuminuria in addition to microalbuminuria and macroalbuminuria. Second, approximately one-quarter of the CHF patients had subclinical microalbuminuria, which was associated with poor prognosis regardless of renal function. Importantly, subclinical microalbuminuria had a similar prognostic impact to microalbuminuria and macroalbuminuria in CHF patients with mildly impaired renal function. To the best of our knowledge, the present study is the first to demonstrate the clinical importance of subclinical microalbuminuria in the management of CHF patients in real-world practice.

UACR for Risk Stratification in CHF

Microalbuminuria has been traditionally defined as 30–300 mg/g UACR in the previous studies and the current guidelines,[1] but this definition was originally derived from previous studies with small sample size that focused on determining the level of albuminuria to predict progression to overt proteinuria.[29,30] In the present study, we thus investigated UACR level to discriminate prognostic levels in the general practice of CHF patients. As a result, on CART analysis 27.4 mg/g and 10.2 mg/g were identified as the first and the second cut-off points of UACR, respectively, to discriminate cardiovascular risk of CHF patients. Especially, it is clinically important that we were able to identify UACR=27.4 mg/g as the primary cut-off point to determine prognosis in CHF patients, given that the primary cut-off point for the definition of microalbuminuria is around 30 mg/g in general practice. Furthermore, it is also important that we were able to identify UACR=10.2 mg/g as the secondary discriminating point, suggesting the prognostic impact of subclinical microalbuminuria in CHF patients in general practice.

Subclinical Microalbuminuria and Microalbuminuria in CHF

The present study is the first to demonstrate the prevalence of subclinical microalbuminuria in association with renal function. In the present study, the prevalence of normoalbuminuria (UACR ≤10.2 md/g) was decreased as eGFR increased. Of note, more than half of the patients with preserved or mildly reduced GFR had subclinical microalbuminuria or microalbuminuria associated with worse prognosis. It has been reported that the prevalence of microalbuminuria (UACR >30 mg/g) was 5% in apparently healthy individuals, 16% in patients with hypertension, and almost 30% in those with diabetes mellitus or CHF.[5,6] In the present study, the prevalence of microalbuminuria was approximately 30% overall in the CHF patients regardless of renal function, while that of subclinical microalbuminuria was approximately 20% in CHF patients with preserved or mildly reduced GFR, but <10% in those with reduced GFR (**Figure 2**).

UACR and CHF

The present study primarily showed that CHF patients with microalbuminuria had worse prognosis than those without it, a consistent finding of the previous studies that reported that subjects with microalbuminuria, traditionally defined as UACR 30–300 mg/g, had poorer prognosis regardless of diabetes, hypertension or renal function.[15–17] As reported in patients with hypertension or diabetes,[2–4] microalbuminuria is also important in CHF patients[6,31] because the disorder is likely to be associated with increased intravascular volume with resultant edema,[7] RAS activation and/or inflammation.[16] In addition, several studies reported that subclinical microalbuminuria (UACR <30 mg/g) was associated with cardiovascular events and HF in the general population and in patients with hypertension, diabetes and CVD.[5,8–14,32] For example, it was reported that the risk of cardiovascular death in patients with diabetes increased almost 10-fold when albuminuria rose from 10 to 30 mg/g,[32] and that this is also the case in the general population.[5] Although the underlying pathophysiology remains to be fully elucidated, subclinical microalbuminuria is considered to be associated with inflammation and hypertriglyceridemia,[5] LV hypertrophy,[7] and progression of atherosclerosis.[33] It was also reported that the mean or median UACR in the general population was around 10 mg/g.[5–7] Thus, it is reasonable to consider that subclinical microalbuminuria above the normal range is associated with poor prognosis.

In the present study, subclinical microalbuminuria was also associated with non-cardiovascular death. Although the underlying mechanisms remain to be elucidated, there are 2 possible explanations. First, it was reported that patients with advanced malignant tumor have a significantly higher urinary albumin excretion rate than those with localized disease.[34] Second, reduced eGFR and albuminuria are associated with increased risk for infection-related mortality.[35] Thus, it is conceivable that subclinical microalbuminuria was associated with non-cardiovascular death, at least in part, as a reflection of severer general condition in CHF patients in the present study.

To our knowledge, only 2 studies previously examined the association between CVD and increasing microalbuminuria in CHF patients.[18,19] Although these studies examined the impact of microalbuminuria, they did not specifically examine that of subclinical albuminuria in detail. The present study is the first to show that UACR=10.2 mg/g and 27.4 mg/g is useful for risk stratification of cardiovascular events in a large-scale observational cohort of CHF patients. In the present study, subclinical microalbuminuria was noted in approximately one-quarter of CHF patients with preserved or mildly reduced GFR (**Figure 2**), and the prognostic impact of subclinical microalbuminuria was similar to that of microalbuminuria and macroalbuminuria. Thus, the clinical importance of subclinical microalbuminuria should be further emphasized in real-world CHF management.

Microalbuminuria and CKD

According to the current classification of CKD, microalbuminuria is defined as a risk factor even though GFR was preserved.[12] In the present study, we were able to show for the first time that not only microalbuminuria (UACR ≥27.4 mg/g) but also subclinical microalbuminuria (UACR 10.2–27.3 mg/g) are significantly associated with poorer prognosis as compared with normoalbuminuria (UACR <10.2 mg/g), particularly in those with preserved or mildly reduced GFR. In the present study, on CART analysis both eGFR ($34.5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) and UACR were useful as the first discriminating point for the composite endpoints, indicating that the prognostic impact of eGFR $<34.5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ outweighed any classification with UACR (**Figure 6**). Interestingly, however, CART analysis also showed that UACR=10.2 mg/g was the next discriminating point to stratify risk for composite endpoints (**Figure 6**), suggesting the superiority of UACR ≥10.2 mg/g to stratify risk in those without severe renal dysfunction (eGFR $\geq 34.5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$). Among the patients with eGFR $\geq 34.5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, those with UACR ≥10.2 mg/g had increased incidence of cardiovascular events as compared with those without it (HR, 2.22; P<0.001; **Figure 6**). These results indicate that subclinical microalbuminuria is a therapeutic target in patients with preserved or mildly reduced GFR. Thus, we should pay more attention to subclinical microalbuminuria especially in patients with preserved or mildly reduced GFR, including those who are not classified as having CKD according to the current guidelines.

Study Limitations

Several limitations should be mentioned for the present study. First, in the present study, the patients with UACR data accounted for only approximately 50% of the total cohort. Patient background was considerably different between the patients with UACR measurement and those without it (**Table S1**). To minimize the influence of this selection bias, we performed a consistency analysis. Based on the propensity scores derived from 24 clinical variables, we randomly selected 1,440 individuals from the final subject group whose characteristics were similar to those of 2,591 patients excluded from the present study because of lack of UACR measurement. There were no difference in patient background or prognosis between the selected 1,440 patients with UACR measurement and excluded 2,591 patents without it (**Figure S1**; **Table S1**). Thus, we consider that no significant selection bias of patients was involved in the present study. Second, the present results were analyzed using data collected at study entry and we did not take into consideration the possible changes in UACR during the follow-up period. Third, all subjects in the CHART-2 Study were Japanese, which may limit extrapolation of the present results to patients in Western countries. Finally, given that the CHART-2 Study is an observational study, there might be unmeasured confounding factors influencing the present results. Thus, interpretation of the present results should be done carefully when generalizing it to other cohorts.

Conclusions

UACR=27.4 mg/g and 10.2 mg/g are the first and the second discriminating points to stratify risk in CHF patients regardless of renal function. Thus, the clinical importance of subclinical microalbuminuria should be underlined in the management of CHF patients in real-world practice, although studies are needed to further confirm the present results.

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References

1. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; **158:** 825–830.
2. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal

anaemia syndrome in systolic heart failure: Prevalence, clinical correlates, and long-term survival. *Eur J Heart Fail* 2011; **13:** 61–67.
3. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation* 2005; **112:** 969–975.
4. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE study. *Ann Intern Med* 2003; **139:** 901–906.
5. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, et al; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106:** 1777–1782.
6. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298:** 2038–2047.
7. Lieb W, Mayer B, Stritzke J, Doering A, Hense HW, Loewel H, et al. Association of low-grade urinary albumin excretion with left ventricular hypertrophy in the general population: The MONICA/KORA Augsburg Echocardiographic Substudy. *Nephrol Dial Transplant* 2006; **21:** 2780–2787.
8. Blecker S, Matsushita K, Köttgen A, Loehr LR, Bertoni AG, Boulware LE, et al. High-normal albuminuria and risk of heart failure in the community. *Am J Kidney Dis* 2011; **58:** 47–55.
9. Waheed S, Matsushita K, Sang Y, Hoogeveen R, Ballantyne C, Coresh J, et al. Combined association of albuminuria and cystatin C-based estimated GFR with mortality, coronary heart disease, and heart failure outcomes: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2012; **60:** 207–216.
10. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286:** 421–426.
11. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004; **110:** 32–35.
12. Romundstad S, Holmen J, Hallan H, Kvenild K, Ellekjaer H. Microalbuminuria and all-cause mortality in treated hypertensive individuals: Does sex matter? The Nord-Trøndelag Health Study (HUNT), Norway. *Circulation* 2003; **108:** 2783–2789.
13. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, et al. Microalbuminuria, cardiovascular risk factors and cardiovascular morbidity in a British population: The EPIC-Norfolk population-based study. *Eur J Cardiovasc Prev Rehabil* 2004; **11:** 207–213.
14. Romundstad S, Holmen J, Kvenild K, Hallan H, Ellekjaer H. Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: A 4.4-year follow-up study: The Nord-Trøndelag Health Study (HUNT), Norway. *Am J Kidney Dis* 2003; **42:** 466–473.
15. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 2009; **120:** 1577–1584.
16. Jackson CE, MacDonald MR, Petrie MC, Solomon SD, Pitt B, Latini R, et al. ALiskiren Observation of heart Failure Treatment (ALOFT) investigators. Associations of albuminuria in patients with chronic heart failure: Findings in the ALiskiren Observation of heart Failure Treatment study. *Eur J Heart Fail* 2011; **13:** 746–754.
17. Miura M, Shiba N, Nochioka K, Takada T, Takahashi J, Kohno H, et al; CHART-2 Investigators. Urinary albumin excretion in heart failure with preserved ejection fraction: An interim analysis of the CHART 2 study. *Eur J Heart Fail* 2012; **14:** 367–376.
18. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, et al. Albuminuria in chronic heart failure: Prevalence and prognostic importance. *Lancet* 2009; **374:** 543–550.
19. Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, et al; GISSI-HF Investigators. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: Data from the GISSI-Heart Failure trial. *Circ Heart Fail* 2010; **3:** 65–72.
20. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H; CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the CHART-2 study. *Circ J* 2011; **75:** 823–833.
21. Nochioka K, Sakata Y, Takahashi J, Miyata S, Miura M, Takada T, et al. Prognostic impact of nutritional status in asymptomatic patients with cardiac diseases: A report from the CHART-2 Study. *Circ J* 2013; **77:** 2318–2326.
22. Sakata Y, Miyata S, Nochioka K, Miura M, Takada T, Tadaki S, et al. Gender differences in clinical characteristics, treatments and long-term outcomes in patients with stage C/D heart failure: A report from the CHART-2 Study. *Circ J* 2014; **78:** 428–435.
23. Miura M, Sakata Y, Miyata S, Nochioka K, Takada T, Tadaki S, et al. Usefulness of combined risk stratification with heart rate and systolic blood pressure in the management of chronic heart failure: A report from the CHART-2 Study. *Circ J* 2013; **77:** 2954–2962.
24. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128:** 1810–1852.
25. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 1971; **285:** 1441–1446.
26. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11:** 41–50.
27. R Core Team. R: A language and environment for statistical computing. Austria: R Foundation for Statistical Computing, 2012.
28. Breiman L, Friedman J, Stone JC, Olshen AR. Classification and regression trees. Monterey, CA: Wadsworth, 1984.
29. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med.* 1984; **31:** 356–360.
30. Danziger J. Importance of low-grade albuminuria. *Mayo Clin Proc* 2008; **83:** 806–812.
31. van de Wal RM, Asselbergs FW, Plokker HW, Smilde TD, Lok D, van Veldhuisen DJ, et al. High prevalence of microalbuminuria in chronic heart failure patients. *J Card Fail* 2005; **11:** 602–606.
32. Rachmani R, Levi Z, Lidar M, Slavachevski I, Half-Onn E, Ravid M. Considerations about the threshold value of microalbuminuria in patients with diabetes mellitus: Lessons from an 8-year follow-up study of 599 patients. *Diabetes Res Clin Pract* 2000; **49:** 187–194.
33. Furtner M, Kiechl S, Mair A, Seppi K, Weger S, Oberhollenzer F, et al. Urinary albumin excretion is independently associated with carotid and femoral artery atherosclerosis in the general population. *Eur Heart J* 2005; **26:** 279–287.
34. Pedersen LM, Terslev L, Sorensen PG, Stokholm KH. Urinary albumin excretion and transcapillary escape rate of albumin in malignancies. *Med Oncol* 2000; **17:** 117–122.
35. Wang HE, Gamboa C, Warnock DG, Muntner P. Chronic kidney disease and risk of death from infection. *Am J Nephrol* 2011; **34:** 330–336.

Supplementary Files

Supplementary File 1

Table S1. Baseline patient characteristics vs. presence of UACR measurement

Figure S1. Prognostic impact of subclinical microalbuminuria in the matched patients with urinary albumin/creatinine ratio measurement.

Appendix S1. Organization of the CHART-2 Study

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0787

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ORIGINAL ARTICLE
Heart Failure

Prevalence, Predictors and Prognosis of Patients With Heart Failure Requiring Nursing Care

– Report From the CHART-2 Study –

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Background: Although the need for nursing care (NC) in heart failure (HF) patients is recognized, detailed information on the current status in Japan is lacking.

Methods and Results: In the CHART-2 Study, we obtained information on daily life, physical ability, nutrition and mental status for 4,174 patients (mean age, 67.1±10.8 years; 73.3% male) out of 10,219 patients. We examined the prevalence, baseline characteristics and clinical outcomes of stage B and C/D HF patients requiring NC. The prevalence of HF requiring NC was significantly higher in stage C/D (38.6%) than in stage B (30.4%; P<0.001). Among the reasons for requiring NC, physical dysfunction was most prevalent in both stage B (20.6%) and C/D (29.0%). Compared with the non-NC group, the NC group was characterized by higher age, higher prevalence of female gender and cerebrovascular disease, and increased plasma brain natriuretic peptide regardless of HF stage. During a median follow-up of 12.7 months after the survey, the NC group had a significantly higher mortality compared with the non-NC group (9.6% vs. 3.6%, P<0.001). On multivariate logistic analysis depressive mental status (hazard ratio [HR], 3.61; P<0.001) and dementia (HR, 2.70; P<0.001) were significantly associated with NC need.

Conclusions: In HF patients, NC need is considerably high and is associated with increased mortality regardless of HF stage in Japan. (*Circ J* 2014; **78:** 2276–2283)

Key Words: Heart failure; Nursing care; Prognosis

There are approximately 23 million patients with heart failure (HF) worldwide, and 2 million patients with HF are newly diagnosed every year.[1] Furthermore, given that the speed at which society is aging has been increasing since the 1970s in the developed countries, especially in Japan, it is expected that the number of HF patients will be increasing much faster.[2,3] In Japan, the number of HF patients in stage B (without prior history of HF but at high risk for HF development) and stage C/D (with overt HF) has been rapidly increasing due to westernization of dietary pattern, reduced physical ability, increased prevalence of obesity, diabetes and hypertension, and rapid society aging.[4,5]

Although the management of stage B and C/D HF has improved over the past decades, many patients with stage B and C/D HF are currently aging with progressive cardiac dysfunction and increased comorbidities, likely resulting in greater disability and need for nursing care (NC).[6] Gure et al reported that HF patients had a significantly greater burden of illness due to geriatric conditions, functional limitations, in-home caregiving needs, and nursing home admission.[7] Furthermore, HF patients who needed NC were characterized by urinary incontinence, injury by fall, and dementia.[7] Thus, it is important to develop medical and social systems that can help stage B and C/D HF patients stay healthier. Detailed information on the prevalence, baseline characteristics and clinical outcomes of HF patients requiring NC in Japan, however, is lacking. Thus,

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Table 1. NC Questionnaire

Daily life-1	
Q1	Do you usually travel by bus or train by yourself?
Q2	Do you go out and buy daily necessities by yourself?
Q3	Do you manage your own deposits and savings at the bank?
Q4	Do you often go out to visit your friends?
Q5	Do you consult with your family or friends about their problems?
Physical ability	
Q6	Are you able to go upstairs without holding rail or wall?
Q7	Are you able to stand up from the chair without any aids?
Q8	Are you able to keep walking for approximately 15 min?
Q9	Have you fallen during the past year?
Q10	Do you worry about falling down?
Nutrition and oral condition	
Q11	Have you lost more than 2–3 kg in the past 6 months?
Q12	Please fill out: your height (cm) and your weight (kg)
Q13	Compared with 6 months ago, do you have difficulty in eating hard food?
Q14	Do you choke when you drink tea or soup?
Q15	Do you often feel your mouth dry?
Daily life-2	
Q16	Do you go out more than once in a week?
Q17	Compared with last year, do you go out less often?
Q18	Do people around you say you repeat same thing and have become forgetful?
Q19	Do you make phone calls by yourself?
Q20	Do you find yourself not knowing today's date?
Mental status	
Q21	I don't feel any fulfillment in my life during the last 2 week.
Q22	I cannot enjoy things I used to enjoy during the last 2 weeks.
Q23	During the last 2 weeks, I am not willing to do what I could do easily before.
Q24	During the last 2 weeks, I do not feel I am useful to anyone.
Q25	During the last 2 weeks, I feel I am exhausted without any reason.

NC, nursing care.

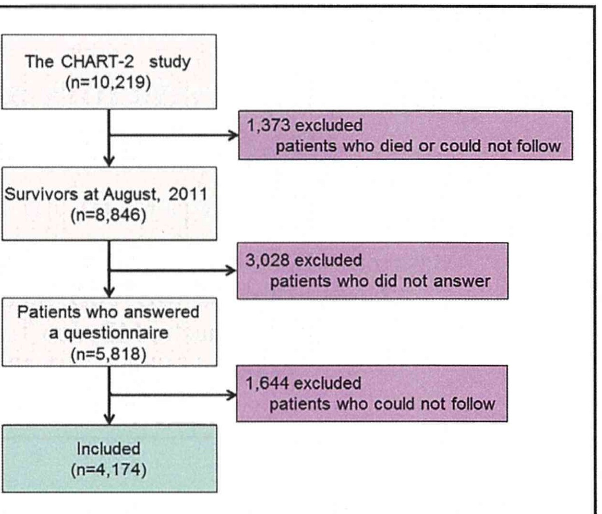

Figure 1. Study flow diagram.

the aim of the present study was to address these important issues in HF patients registered in our HF registry, the Chronic Heart Failure Analysis and Registry in the Tohoku District Study-2 (CHART-2; NCT00418041, n=10,219).[5,8–10]

Methods

Subjects and Inclusion Criteria

Details of the design, purpose and basic characteristics of the CHART-2 Study have been described previously.[5,8–10] Briefly, eligible patients were aged ≥20 years with significant coronary artery disease or in stage B, C or D defined by the American College of Cardiology/American Heart Association guidelines for the diagnosis and management of HF in adults.[11] Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[12] The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively recruited after written informed consent was obtained. The CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients registered from the 24 participating hospitals.[5] All data and events will be surveyed at least once a year until March 2018.[5]

We conducted a questionnaire survey, regarding daily life, physical ability, nutritional status, and mental status for the patients in the CHART-2 study in August 2011. The questionnaire consisted of 25 questions (**Table 1**). Questions (Q) 1–5 and 16–20 were related to daily life, Q6–10 physical ability, Q11–Q15 to nutrition and oral condition, and Q21–Q25 to mental status. These questions were based on the questionnaire of NC prevention published by the Japanese Ministry of Health, Labour and Welfare (JMHLW).[13] In Q1–8, 16, 20, if applicable, patients answered 'No'. In Q9–11, 13–15, 17, 18 and Q20–25, if applicable, patients answered 'Yes'. Need for NC, according to the JMHLW definition, was defined as follows: (1) ≥10 questions from Q1 to Q20; and (2) physical dysfunction (≥3 questions in the physical ability section; Q6–10); and (3) poor nutrition (both Q11 and body mass index [BMI] <18.5); or (4) poor oral condition (≥2 questions in the oral condition section; Q13–15).[13] According to the questionnaire results, the patients were divided into 2 groups as follows: those who needed NC (NC group) and those who did not (non-NC group). Furthermore, we considered the patients for whom at least 1 question was applicable among Q18–20 as high risk for dementia, and those for whom at least 2 questions were applicable among Q21–25 as high risk for depression according to the JMHLW definition.[13]

Figure 1 shows the study flow. Among 10,219 patients registered in the CHART-2 study, we sent the questionnaire to 8,846 patients who were alive in August 2011. At the end of 2011, we received a reply from 5,818 patients (65.8%). Among the 5,818 patients, we finally included the 4,174 patients who were eligible for the follow-up survey by the end of May 2013.

Follow-up Survey and Study Outcome

We conducted the follow-up survey for survival from January to May in 2013, and the median follow-up period was 12.7 months after the questionnaire. The outcome of this study was

Table 2. Baseline Subject Characteristics

	All patients (n=4,174)	Stage B (n=2,380)		P-value	Stage C/D (n=1,794)		P-value
		NC (n=723)	Non-NC (n=1,657)		NC (n=692)	Non-NC (n=1,102)	
Age (years)	67.1±10.9	71.3 ±10.2	65.4±10.6	<0.001	70.8±9.7	64.4±10.9	<0.001
Male	73.3	62.1	78.6	<0.001	63.0	79.1	<0.001
History of admission for HF	23.1	0.0	0.0	–	58.5	50.7	0.001
Comorbidity							
Hypertension	73.4	76.8	73.5	0.09	72.4	71.7	0.74
Diabetes	22.1	24.1	19.3	0.009	25.1	23.1	0.33
Hyperuricemia	32.9	24.6	28.2	0.07	40.6	40.6	0.99
AF	22.4	16.8	16.3	0.94	33.8	28.0	0.02
Coronary artery disease	56.5	60.3	61.8	0.49	48.0	51.3	0.17
Cerebrovascular disease	14.7	19.6	11.5	<0.001	20.7	12.5	<0.001
Clinical status							
NYHA class 3 and 4	2.8	0.1	0.3	<0.001	11.1	3.4	<0.001
BMI (kg/m^2)	24.2±3.4	24.0±3.4	24.4±3.2	0.008	23.7±3.8	24.2±3.4	0.003
SBP (mmHg)	128±18	130±18	129±17	0.86	126±19	126±17	0.91
DBP (mmHg)	74±11	74±11	75±11	<0.001	71±12	74±11	<0.001
Heart rate (beats/min)	70±13	70±12	69±13	0.16	72±15	71±14	0.12
Measurement							
LVEF (%)	62.0±13.6	66.1±11.0	65.6±11.2	0.34	57.0±15.0	57.2±14.9	0.85
Hemoglobin (g/dl)	13.7±1.8	13.3±1.6	13.9±1.6	<0.001	13.0±1.8	13.8±2.1	<0.001
BUN (mg/dl)	17.1±6.6	16.9±6.2	15.9±5.1	<0.001	19.8±8.9	17.3±6.4	<0.001
GFR (ml·min^{-1}·1.73m^{-2})	66.3±21.6	65.6±21.1	69.1±17.4	<0.001	59.9±19.9	66.5±27.1	0.001
Serum sodium (mEq/L)	141±2.5	141±2.5	141±2.2	0.23	141±2.6	141±2.6	0.86
Serum potassium (mEq/L)	4.3±0.4	4.4±0.4	4.3±0.4	0.20	4.1±0.4	4.4±0.4	0.31
BNP (pg/ml)	56†	55†	36†	<0.001	108†	72†	<0.001
Medications							
RAS inhibitor	63.0	54.1	57.2	0.16	69.7	73.2	0.10
β-blocker	42.5	34.0	34.8	0.73	52.5	53.6	0.63
Calcium channel blocker	46.6	53.8	51.2	0.25	42.5	37.4	0.03
Diuretics	29.7	19.8	11.8	<0.001	58.4	44.9	<0.001
Aldosterone inhibitor	12.2	6.5	3.2	<0.001	26.7	20.2	0.001
Statin	44.8	47.9	42.9	0.02	39.5	44.8	0.03
Digitalis	14.2	8.4	7.9	0.66	23.3	21.9	0.49

Data given as mean±SD, % or †median.
AF, atrial fibrillation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood presure; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system; SBP, systolic blood pressure. Other abbreviation as in Table 1.

a composite of all-cause death, admission for HF, acute myocardial infarction (AMI) and stroke.

Statistical Analysis

Statistical analysis was done for both non-HF (stage B) and HF (stage C/D) patients. Comparison of data between 2 groups was done using chi-squared test and Student's t-test. Continuous data are described as mean±SD. Kaplan-Meier curves were plotted to evaluate the association between NC and composite outcome. We also constructed the following 3 Cox proportional hazard regression models: (1) unadjusted; (2) adjusted for age and sex; and (3) fully adjusted including medical treatment. In model (3) we included the following covariates that can potentially influence outcome: age, sex, New York Heart Association class, history of malignant tumor, BMI, systolic blood pressure, heart rate, serum sodium, serum albumin, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), comorbidities (anemia defined as hemoglobin <12 g/dl in women and <13 g/dl in men, diabetes mellitus, hyperuricemia, atrial fibrillation and cerebrovascular disease), left ventricular ejection fraction (LVEF), ischemic etiology of HF, and treatment (β-blocker, renin-angiotensin system inhibitors and aldosterone antagonists). We also performed subgroup analyses based on age (<median age or ≥median age), sex, cause of HF (ischemic HF vs. non-ischemic HF) and history of cerebrovascular disease. Finally, we also constructed a logistic regression model to elucidate the predictors for NC need. We included several covariates, including age, sex, HF stage, history of malignant tumor, BMI, systolic blood pressure, heart rate, eGFR, serum albumin, comorbidities (anemia, diabetes mellitus, hyperuricemia, atrial fibrillation, and cerebrovascular disease), LVEF, ischemic etiology, and risk of dementia and that of depression.

Statistical analysis was done using SPSS Statistics 19.0 (SPSS, Chicago, IL, USA) and statistical significance was defined as 2-sided P<0.05.

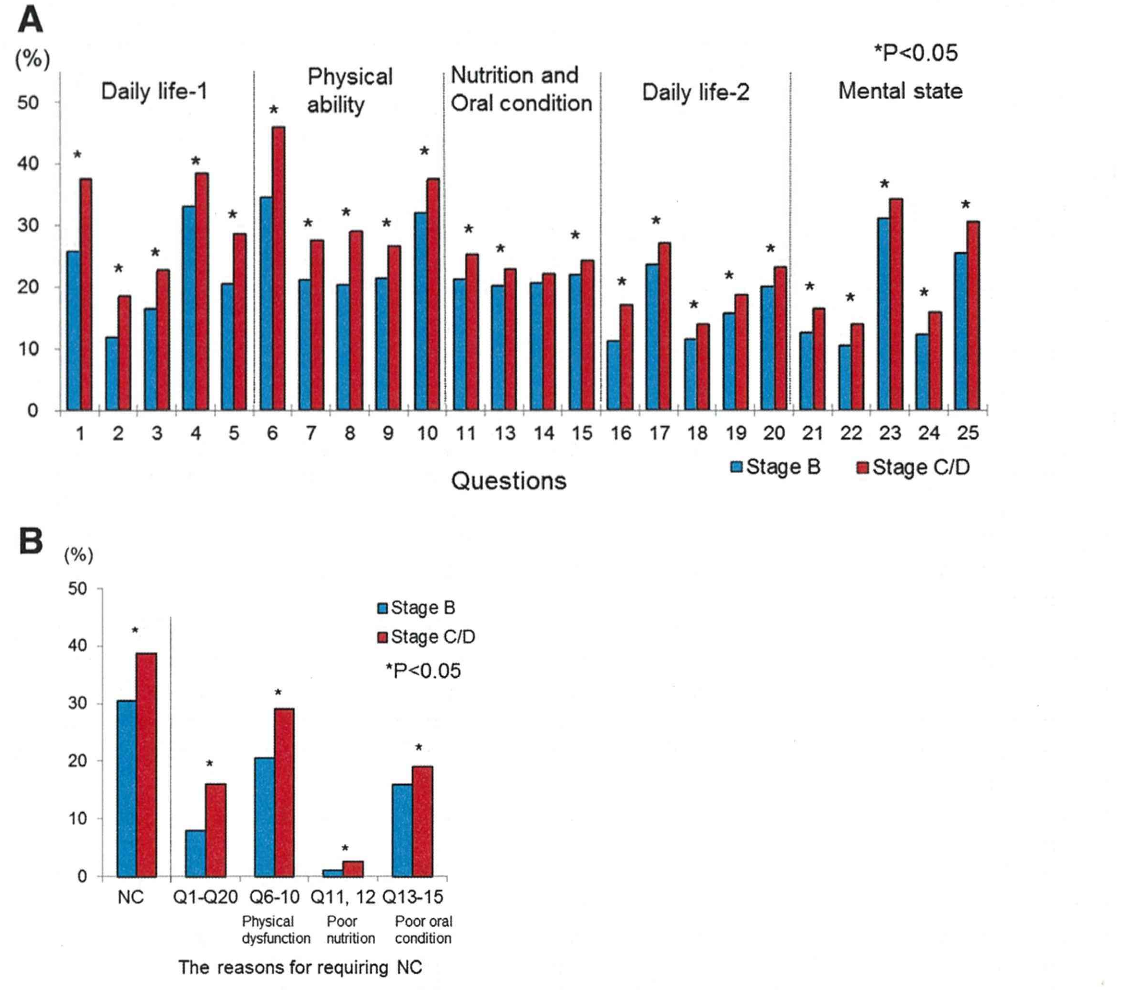

Figure 2. (**A**) Questionnaire results: stage B vs. stage C/D. Q1–8, 16, 20 are answered 'No'. Q9–11, 13–15, 17, 18, 20–25 are answered 'Yes'. (**B**) Prevalence of and reasons for nursing care (NC) need in stage B vs. stage C/D. Q11, Q12: 'Yes' and body mass index <18.5, respectively. *P<0.05.

Results

Prevalence of NC and Baseline Patient Characteristics

Mean age was 67.1±10.9 years and male patients accounted for 73.3% of the subjects. Female patients were older than male patients (68.3±11.5 vs. 66.6±10.6 years, P<0.001). Coronary artery disease was noted in 56.5% and mean LVEF in 62.0±13.6%. The prevalence of cerebrovascular disease was 14.7%. The prevalence of NC was significantly higher in stage C/D (38.6%) than in stage B (30.4%; P<0.001; **Table 2**; **Figure 2B**).

More than 30% of the patients in stage C/D did not go out by themselves using bus or train (Q1), did not visit their friend's house (Q4), could not go upstairs without holding onto the railing (Q6), and had serious concerns and/or fears for falling (Q10; **Figure 2A**). Furthermore, approximately one-quarter of the patients in both stage B and C/D had an experience of falling (Q9).

Among the reasons for requiring NC, physical dysfunction (Q6–10) was the most prevalent in both stage B and C/D (**Figure 2B**). Female patients had a higher prevalence of impaired physical activity (female 38.3% vs. male 19.1%, P<0.001), and impaired oral condition (female 20.6% vs. male 15.9%, P<0.001). The baseline characteristics of the NC patients are listed in **Table 2**. In both stage B and C/D, the patients who needed NC were characterized by older age, higher prevalence of female gender and history of cerebrovascular disease, lower BMI and hemoglobin, and higher BUN and B-type natriuretic peptide. In both stage B and C/D, the patients who needed NC were more frequently treated with diuretics.

Impact of NC on Composite Outcome

During the median follow-up period of 12.7 months after the questionnaire, the composite outcome occurred in 234 patients (5.6%). In stage B patients, 90 composite outcomes occurred, including all-cause death in 38 (42.2%), AMI in 7 (7.8%), admission for HF in 25 (27.8%), and stroke in 20 (22.2%). In stage C/D patients, 144 composite outcomes occurred, including all-cause death in 68 (47.2%), AMI in 5 (3.4%), admission for HF in 55 (38.2%), and stroke in 17 (11.8%).