ORIGINAL RESEARCH ARTICLE

Differential effect of malnutrition between patients hospitalized with new-onset heart failure and worsening of chronic heart failure

Koichiro Matsumura[1,2]* (ID), Wakana Teranaka[1], Masanao Taniichi[1], Munemitsu Otagaki[1], Hiroki Takahashi[1], Kenichi Fujii[1], Yoshihiro Yamamoto[1], Gaku Nakazawa[2] and Ichiro Shiojima[1]

[1]*Department of Cardiology, Kansai Medical University, 10-15, Fumizono-cho, Moriguchi, 5708507, Japan;* [2]*Department of Cardiology, Kindai University, 377-2, Ohno-higashi, Osakasayama, 5898511, Japan*

Abstract

Aims   We aimed to investigate the differences in the prevalence, severity, and prognostic impact of malnutrition between patients with new-onset heart failure (HF) and worsening of chronic HF.
Methods and results   In older (≥60 years) hospitalized patients with acute HF, malnutrition was assessed according to the Geriatric Nutritional Risk Index (GNRI). A score <92 was defined as malnutrition. The primary endpoint was a composite endpoint, including cardiac death or rehospitalization for HF. Among 210 patients, 37% (52/142) of patients with new-onset HF and 31% (21/68) of patients with worsening of chronic HF had malnutrition (*P* = 0.41). The GNRI classification was comparable between the two groups. Kaplan–Meier analysis revealed a significant difference in the incidence of the composite endpoint in patients with new-onset HF (GNRI < 92 vs. GNRI ≥ 92: 50% vs. 32%, *P* = 0.007), but not in patients with worsening of chronic HF (GNRI < 92 vs. GNRI ≥ 92: 67% vs. 68%, *P* = 0.91). The adjusted Cox proportional hazards model demonstrated that a GNRI of <92 was an independent prognostic factor for the composite endpoint in patients with new-onset HF only.
Conclusions   Among older hospitalized patients with acute HF, the prevalence and severity of malnutrition were comparable between the two categories of patients. Malnutrition was an independent prognostic factor in patients with new-onset HF, while clinical prognosis was poor in patients with worsening of HF, irrespective of malnutrition. The prognostic impact of malnutrition differs between new-onset HF and worsening of chronic HF.

Introduction

Heart failure (HF) is a leading cause of mortality worldwide, with 64 million people diagnosed.[1,2] Patients with acute HF are classified into one of two categories, those with new-onset HF or those with worsening of chronic HF. These two categories have become recognized as being important conception, and several large studies have elucidated that patients with worsening of chronic HF have a higher proportion of men, with more ischaemic aetiology, and more co-morbidities, as well as higher rates of mortality and readmission compared with those with new-onset HF.[3,4] These new insights have led to changes in the treatment strategies for acute HF; however, the underlying mechanisms responsible for the difference in long-term prognosis between the two categories are currently unknown.

Malnutrition is a common complication in patients with HF. Factors associated with HF include loss of appetite, protein malabsorption due to gastrointestinal oedema, chronic inflammation, and loss of skeletal muscle mass, all of which can easily lead to malnutrition.[5] Malnutrition leads to an imbalance between catabolic and anabolic conditions, which, in turn, promotes geriatric conditions such as frailty and cardiac cachexia. Additionally, malnutrition itself yields worse

prognosis in patients with HF.[6] Therefore, we considered it important to clarify how malnutrition affects patients in each categories in order to better understand the pathophysiology of patients with new-onset HF and worsening of chronic HF. Accordingly, we used the Geriatric Nutritional Risk Index (GNRI) to investigate the prevalence, severity, and prognostic impact of malnutrition between new-onset HF and worsening of chronic HF in patients hospitalized with acute HF.

Methods

Study population and protocol

This was a single-centre, observational study that was conducted using a prospective database.[7] Patients aged ≥60 years who were admitted for acute HF with New York Heart Association Class III or IV at our hospital between May 2015 and December 2017 were included. We excluded patients who had malignant disease with a life expectancy of <1 year (*n* = 22), had end-stage renal disease requiring dialysis treatment (*n* = 17), and were lost to follow-up for at least 1 year (*n* = 11). This study conformed to the principles outlined in the 1975 Declaration of Helsinki. The study protocol was approved by the ethics committee of Kansai Medical University (No. 20130181) and was registered at the University Hospital Medical Information Network Clinical Trial Registry (unique identifier: UMIN000013445). All patients provided written informed consent.

Acute HF was diagnosed according to the Framingham criteria.[8] Each patient was only included once in the study. All patients were prescribed standard therapy drugs for acute HF, such as loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, spironolactone, and sodium–glucose cotransporter 2, based on the discretion of the attending physician.

Data collection

The patient characteristics and medical histories were obtained from the hospital's medical records. The body mass index was calculated based on the patient's height and body weight upon admission. The New York Heart Association classification and laboratory parameters of each patient were collected upon admission. Echocardiography was performed by a cardiologist upon admission using either a Vivid 7 or Vivid E9 machine (GE Healthcare, Marlborough, MA, USA), and standard transthoracic and Doppler echocardiographic parameters were examined. The left ventricular ejection fraction was measured using the Simpson method. The oral medications of patients without in-hospital death upon discharge were collected from the hospital's medical records.

Assessment of nutritional status

The nutritional status was assessed using the GNRI, which is an objective and simple measure of nutritional assessment. The GNRI was calculated using the following formula: $14.89 \times$ serum albumin at admission (g/dL) $+ 41.7 \times$ body mass index at admission$/22$. A GNRI ≥ 98 was considered normal, while patients with GNRI scores of ≥92 to <98, ≥82 to <92, and <82 were at low risk, moderate risk, and severe risk of malnutrition, respectively. According to a previous report, patients with a GNRI score <92 were already considered malnourished.

Endpoint and follow-up

The primary endpoint was a composite endpoint, including cardiac death or rehospitalization for HF. The secondary endpoint was cardiac death and rehospitalization for HF. The incidence of these events was obtained from medical records or from questionnaires mailed to the hospitals where the patients attended follow-up appointments. Death certificates were prepared by two experienced physicians who were blinded to the endpoint classification. If the physicians disagreed on the classification of an event, a third party served as an arbiter.

Statistical analysis

Continuous variables with normal distributions are expressed as means ± standard deviations, data with skewed distributions are expressed as medians with inter-quartile ranges, and categorical variables are presented as percentages. The differences among continuous variables with normal distributions were analysed using Student's *t*-test, while the Wilcoxon test was used for continuous variables with skewed distributions. Categorical variables were compared using the χ^2 test. Kaplan–Meier survival analysis illustrated event-free rates, and log-rank test was used to make comparisons. Univariate and multivariate Cox proportional hazards models were used to evaluate the prognostic capability of the GNRI. The adjusted model was selected based on a previous report (the Acute Heart Failure Database score)[9] and included age, sex, atrial fibrillation, diabetes mellitus, serum creatinine, and B-type natriuretic peptide levels. JMP 14.2.0 software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. A *P*-value <0.05 was considered significant.

Results

Overall, 210 consecutive patients were observed during a median follow-up of 1.8 years (inter-quartile range,

1.1–2.9 years). Patients with new-onset HF had a significantly lower incidence of composite endpoints than those with worsening of chronic HF (39% vs. 68%, $P < 0.0001$). The incidence of cardiac death and rehospitalization for HF was significantly lower in patients with new-onset HF than in those with worsening chronic HF (16% vs. 31%, $P = 0.01$; 32% vs. 59%, $P < 0.001$, respectively).

Patient characteristics

The age, proportion of male sex, and body mass index were comparable between patients with new-onset HF and worsening of chronic HF (Table 1). There was no significant difference in the medical history of the two groups, with the exception of previous myocardial infarction and previous cardiac surgery. There was no significant difference in laboratory parameters, including haemoglobin, serum creatinine, serum albumin, B-type natriuretic peptide, and high-sensitive C-reactive protein between the two groups. The left ventricular ejection fraction was similar between the two groups. There was no significant difference in the rate of administration of standard medication for HF treatment at discharge between the two groups, with the exception of loop diuretics (Supporting Information, Table S1).

Nutritional status

Malnutrition (GNRI < 92) was observed in 35% of the participants; the prevalence of malnutrition was similar and was present in 37% (52/142 patients) of patients with new-onset HF and 31% (21/68 patients) of patients with worsening of chronic HF ($P = 0.41$). The GNRI score was also similar in patients with new-onset HF (95.3 ± 11.8) and those with worsening of chronic HF (96.8 ± 12.2, $P = 0.38$) (Figure 1). The severity of nutritional status according to GNRI classification was not significantly different between the two groups (new-onset HF vs. worsening of chronic HF: normal 41% vs. 43%, $P = 0.80$; low 23% vs. 26%, $P = 0.53$; moderate 24% vs. 25%, $P = 0.87$; and severe 13% vs. 6%, $P = 0.13$).

Primary endpoint

Patients with a GNRI < 92 had a significantly higher incidence of composite endpoints than those with a GNRI ≥ 92 in patients with new-onset HF (50% vs. 32%, log-rank test $P = 0.007$) (Figure 2). However, no significant difference was observed in the composite endpoint between patients with a GNRI < 92 and those with a GNRI ≥ 92 in patients with worsening of chronic HF (67% vs. 68%, log-rank test $P = 0.91$).

Secondary endpoint

Patients with a GNRI < 92 had a significantly higher incidence of cardiac death and rehospitalization for HF than those with a GNRI ≥ 92 in patients with new-onset HF (27% vs. 10% and 38% vs. 28%, respectively) (Figure 3).

Table 1 Patient characteristics

	New-onset HF (n = 142)	Worsening of chronic HF (n = 68)	P-value
Age (years)	78 (69–84)	80 (74–88)	0.10
Male	75 (53)	32 (47)	0.43
Body mass index (kg/m^2)	22.8 (20.7–25.7)	23.0 (20.0–25.7)	0.76
NYHA Class IV	94 (66)	43 (63)	0.67
Medical history			
Hypertension	73 (51)	36 (53)	0.84
Diabetes mellitus	48 (34)	30 (44)	0.15
Past smoking	72 (51)	31 (46)	0.49
Atrial fibrillation	58 (41)	37 (54)	0.06
Previous myocardial infarction	23 (16)	25 (37)	<0.001
Previous cardiac surgery	3 (2)	24 (35)	<0.0001
Laboratory parameters			
Haemoglobin (g/dL)	11.2 (9.8–13.3)	10.9 (9.5–12.5)	0.14
Serum creatinine (mg/dL)	1.1 (0.8–1.7)	1.3 (0.9–1.7)	0.13
Serum albumin (g/dL)	3.4 (3.1–3.8)	3.5 (3.2–3.8)	0.22
BNP (pg/mL)	761 (414–1338)	818 (389–1593)	0.78
High-sensitive CRP (mg/dL)	0.70 (0.23–2.40)	0.93 (0.24–3.03)	0.48
LVEF (%)	47 (31–65)	47 (30–61)	0.48
LVEF < 50%	74 (52)	37 (54)	0.75

BNP, B-type natriuretic peptide; CRP, C-reactive protein; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Data are presented as median (25th to 75th percentiles) or number (%).

Figure 1 Nutritional status between new-onset heart failure (HF) and worsening of chronic HF according to Geriatric Nutritional Risk Index (GNRI). (A) Comparison of GNRI; no significant difference was observed between the two groups. (B) Distribution of GNRI classification. Patients with GNRI scores of ≥98, ≥92 to <98, ≥82 to <92, and <82 correspond to normal, low risk, moderate risk, and severe risk of malnutrition, respectively. No significant differences were observed between the two groups. The blue bar indicates patients with new-onset HF, and the red bar indicates patients with worsening of chronic HF.
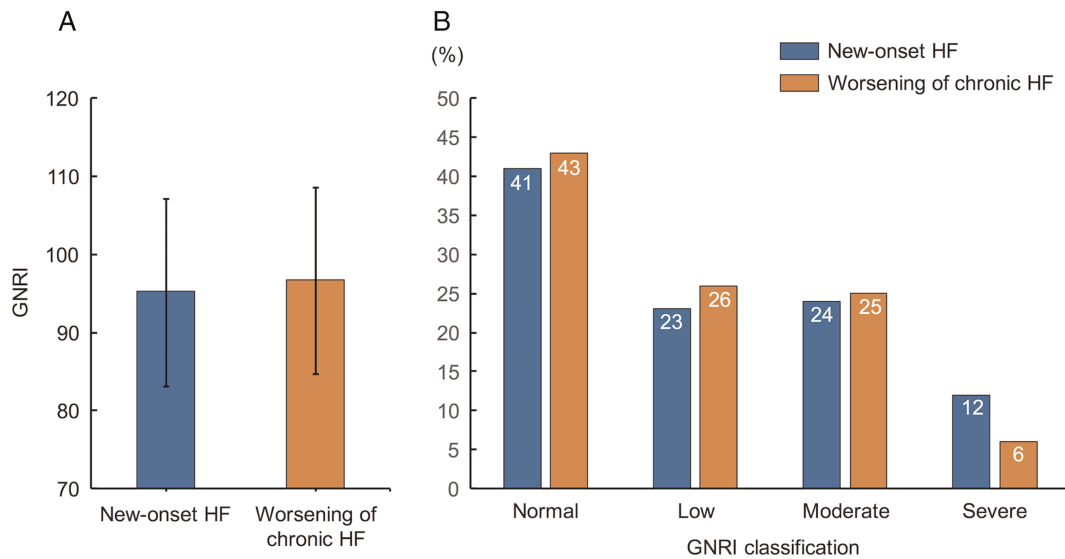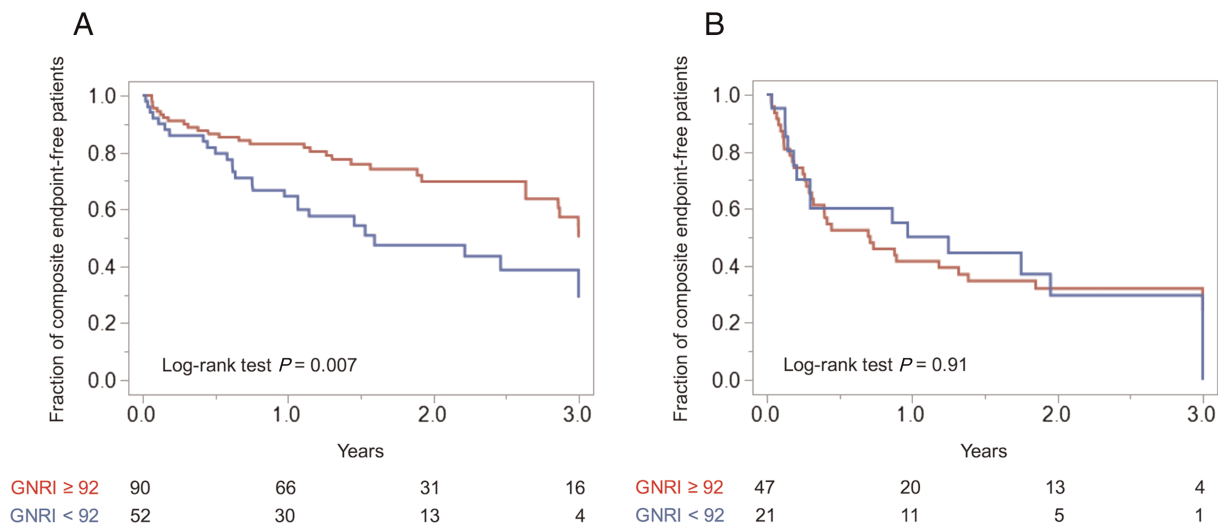

Figure 2 Kaplan–Meier analysis of patients who did not reach a composite endpoint, including those with cardiac death or rehospitalization for heart failure (HF). (A) Patients with new-onset HF; (B) patients with worsening of chronic HF. The red line indicates patients with Geriatric Nutritional Risk Index (GNRI) ≥92, and the blue line indicates patients with GNRI < 92.

However, no significant differences were observed in cardiac death and rehospitalization for HF between patients with worsening of chronic HF with a GNRI < 92 and those with a GNRI ≥ 92 (40% vs. 28% and 57% vs. 60%, respectively).

Prognostic value of the Geriatric Nutritional Risk Index

The Cox proportional hazards model revealed that a GNRI < 92 was associated with a 1.9-fold increased risk of composite

Figure 3 Kaplan–Meier analysis of patients who experienced cardiac death and rehospitalization for heart failure (HF). (A, C) Patients with new-onset HF; (B, D) patients with worsening of chronic HF. The red line indicates patients with Geriatric Nutritional Risk Index (GNRI) ≥92, and the blue line indicates patients with GNRI < 92.
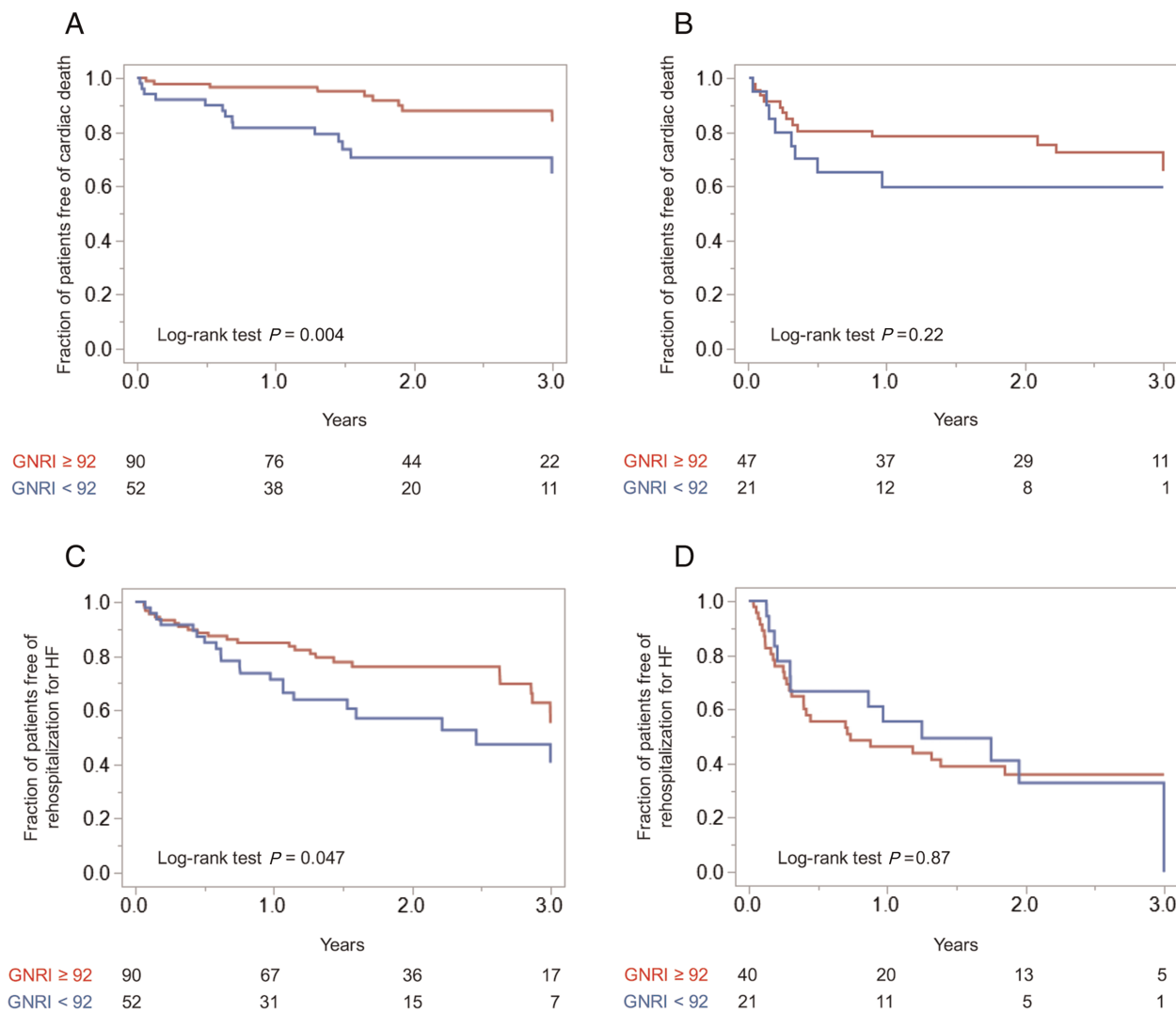

Panel A — Fraction of patients free of cardiac death (new-onset HF). Log-rank test *P* = 0.004

GNRI ≥ 92	90	76	44	22
GNRI < 92	52	38	20	11

Panel B — Fraction of patients free of cardiac death (worsening of chronic HF). Log-rank test *P* = 0.22

GNRI ≥ 92	47	37	29	11
GNRI < 92	21	12	8	1

Panel C — Fraction of patients free of rehospitalization for HF (new-onset HF). Log-rank test *P* = 0.047

GNRI ≥ 92	90	67	36	17
GNRI < 92	52	31	15	7

Panel D — Fraction of patients free of rehospitalization for HF (worsening of chronic HF). Log-rank test *P* = 0.87

GNRI ≥ 92	40	20	13	5
GNRI < 92	21	11	5	1

Table 2 Cox proportional hazards model for composite outcome

	Unadjusted			Adjusted[a]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Patients with new-onset HF						
GNRI < 92	2.05	1.20–3.49	<0.01	1.90	1.08–3.35	0.026
Patients with worsening of chronic HF						
GNRI < 92	0.96	0.51–1.81	0.91	0.69	0.35–1.36	0.28

CI, confidence interval; GNRI, Geriatric Nutritional Risk Index; HF, heart failure; HR, hazard ratio.
[a]Adjusted for age, sex, atrial fibrillation, diabetes mellitus, serum creatinine at admission, and B-type natriuretic peptide at admission.

endpoint in patients with new-onset HF adjusted by age, sex, atrial fibrillation, diabetes mellitus, serum creatinine at admission, and B-type natriuretic peptide at admission (*Table 2*).

Conversely, no association was shown between a GNRI < 92 and the incidence of composite endpoint in patients with worsening of chronic HF in the unadjusted and adjusted model.

Discussion

This study demonstrated several important findings. First, the prevalence and severity of malnutrition according to the GNRI were comparable between new-onset HF and worsening of chronic HF. Second, during a median follow-up period of 1.8 years, patients with worsening of chronic HF had a significantly higher incidence of composite endpoints, cardiac death, and rehospitalization for HF compared with those with new-onset HF. Third, malnutrition was an independent prognostic factor for worse clinical outcomes, including cardiac death or rehospitalization for HF in patients with new-onset HF; however, this association was not identified in patients with worsening of chronic HF. Our study found that the rate of malnutrition in patients with new-onset HF was as high as that in patients with worsening of chronic HF. Moreover, malnutrition may be a prognostic factor for the early phase of HF but may not be a strong determinant in patients with advanced HF.

Malnutrition is a long-term prognosticator and common complication in patients with acute HF.[10] In patients with acute HF, poor nutritional status results from multidimensional factors such as loss of appetite, malabsorption due to intestinal oedema, high-energy demand, and cytokine-induced hypercatabolism.[11] Earlier detection and initiation of treatment intervention for malnutrition during hospitalization with acute HF is crucial for improving long-term clinical outcomes. Body mass index is one of the most common prognostic factors for reflecting nutritional status, but its predictive value is insufficient in patients with HF.[12] GNRI emerged as a simple and useful nutritional scoring system consisting of serum albumin level, true body mass index, and ideal body mass index.[13] A previous single-centre retrospective study has identified that a GNRI < 92 was an independent prognostic factor for all-cause death in patients aged ≥65 years who were hospitalized for acute HF.[14] Additionally, the GNRI showed the greatest risk stratification capacity among other indicators, including body mass index, serum albumin level, lymphocyte count, and total cholesterol. Sze *et al*. have elucidated the prognostic capacity of nutritional scoring systems for all-cause mortality in patients with chronic HF.[13] As a result, in their baseline model (age, sex, diastolic blood pressure, heart rate, New York Heart Association classification, urea, log N-terminal pro-B-type natriuretic peptide, history of cerebrovascular disease, and history of peripheral vascular disease), addition of body mass index alone did not improve risk stratification performance of the basal model. By contrast, the GNRI showed the greatest incremental value in predicting clinical outcomes compared with other nutritional scoring systems. Because clinical parameters such as laboratory, physiological, and body composition measurements fluctuate during the acute phase of HF, evaluation of nutritional status using GNRI may not precisely reflect true nutritional status. In our study, body mass index and laboratory and echocardiographic parameters on admission were comparable between patients with new-onset HF and worsening of chronic HF. As multi-time point nutritional evaluation may be more favourable, further investigation of the optimal assessment method of nutritional status is warranted in patients with acute HF.[15]

One of the key questions from our study is why was there no association between malnutrition and long-term prognosis in patients with worsening of chronic HF? This may be explained by the fact that patients with worsening of chronic HF have long-term exposure to HF. Indeed, previous studies have shown that this long-term exposure is closely linked to not only cardiac dysfunction, including myocardial remodelling and low cardiac output, but also the frailty cycle, including physical inactivity, exercise intolerance, increased insulin resistance, decreased growth hormone secretion, and neurohormone regulatory dysfunction due to systemic congestion.[15,16] However, in the current study, the left ventricular ejection fraction was comparable between the two groups. Accordingly, differences in the effects of malnutrition on long-term prognosis between patients with new-onset HF and worsening of chronic HF may be related to differences in frailty progression. Because of the lack of evidence, further studies are needed to elucidate the clinical implications of frailty among patients with new-onset HF and worsening of chronic HF.

A DPC-based nationwide study found that 52% of patients had new-onset HF. They also suggested that patients with worsening of chronic HF had a significantly higher incidence of composite endpoints, including all-cause death and rehospitalization for HF, than those with new-onset HF during a 4 year observational period.[4] Another large trial reported that 27% of patients had new-onset HF, and patients with worsening of chronic HF had increased 180 day mortality compared with those with new-onset HF; our findings are in line with those of this previous study. However, the ratio of two categories of patients with acute HF varies widely by study because of differences in country, demographic characteristics, definition, and data capture.[17] According to Global REPORT-HF (International Registry to Assess Medical Practice with Longitudinal Observation for Treatment of HF), the rates range from 20% in North America to 79% in Southeast Asia.[18] Our research is a single-centre study, and it is natural that the ratio of the two categories differs from that of the nationwide study.

The potential implications of the two categories for demographic characteristics and long-term prognosis in patients with acute HF have not been well studied. However, the number of cases of new-onset HF is increasing annually, and it is necessary to carry out therapeutic intervention and risk stratification while being aware of the differences between the two categories.[19,20] Based on our study, nutritional intervention targeted to patients with new-onset HF has the potential to provide better clinical outcome compared with patients with worsening of chronic HF. Future research is warranted to clarify the difference in clinical prognoses and treatment

response for geriatric conditions, including frailty and cardiac cachexia between patients with new-onset HF and worsening of chronic HF.

The current study has two limitations. First, the study population was relatively small, and the study itself was conducted in a single centre; thus, our findings need to be confirmed in a larger population. However, the prevalence of cardiac events in patients with new-onset HF and worsening of chronic HF in our study was consistent with that reported in previous large trials.[3,4] This is the first study to investigate the influence of malnutrition on long-term clinical outcomes according to differences in HF duration. Second, our study has the potential for patient treatment bias as the treatment strategy used during hospitalization was at the discretion of the attending physician; thus, older patients with greater co-morbidities might have avoided interventional treatment. However, no significant difference in the rate of guideline-recommended optimal medical therapy was observed between the two groups.

In patients aged ≥60 years who were hospitalized for acute HF, the prevalence and severity of malnutrition were comparable between those with new-onset HF and worsening of chronic HF. Malnutrition was an independent prognostic factor in patients with new-onset HF, but not in those with worsening chronic HF. It is important to be aware of the differences between the categories of new-onset HF and worsening of chronic HF when treating acute HF.

Acknowledgement

Conflict of interest

None declared.

Funding

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Oral medication at hospital discharge in patients without in-hospital death

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789–1858.

2. Mamas MA, Sperrin M, Watson MC, Coutts A, Wilde K, Burton C, Kadam UT, Kwok CS, Clark AB, Murchie P, Buchan I, Hannaford PC, Myint PK. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. *Eur J Heart Fail* 2017; **19**: 1095–1104.

3. Greene SJ, Hernandez AF, Dunning A, Ambrosy AP, Armstrong PW, Butler J, Cerbin LP, Coles A, Ezekowitz JA, Metra M, Starling RC, Teerlink JR, Voors AA, O'Connor CM, Mentz RJ. Hospitalization for recently diagnosed versus worsening chronic heart failure: from the ASCEND-HF trial. *J Am Coll Cardiol* 2017; **69**: 3029–3039.

4. Butt JH, Fosbøl EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, Gustafsson F, Madelaire C, Kristensen SL, Gislason GH, Torp-Pedersen C, Køber L, Schou M. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. *Eur J Heart Fail* 2020; **22**: 1777–1785.

5. Curcio F, Testa G, Liguori I, Papillo M, Flocco V, Panicara V, Galizia G, Della-Morte D, Gargiulo G, Cacciatore F, Bonaduce D, Landi F, Abete P. Sarcopenia and heart failure. *Nutrients* 2020; **12**: 211.

6. Lena A, Ebner N, Anker MS. Cardiac cachexia. *Eur Heart J Suppl* 2019; **21**: L24–L27.

7. Matsumura K, Teranaka W, Matsumoto H, Fujii K, Tsujimoto S, Otagaki M, Morishita S, Hashimoto K, Shibutani H, Yamamoto Y, Shiojima I. Loss of skeletal muscle mass predicts cardiac death in heart failure with a preserved ejection fraction but not heart failure with a reduced ejection fraction. *ESC Heart Fail* 2020; **7**: 4100–4107.

8. 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.

9. Spinar J, Jarkovsky J, Spinarova L, Mebazaa A, Gayat E, Vitovec J, Linhart A, Widimsky P, Miklik R, Zeman K, Belohlavek J, Malek F, Felsoci M, Kettner J, Ostadal P, Cihalik C, Vaclavik J, Taborsky M, Dusek L, Littnerova S, Parenica J. AHEAD score—long-term risk classification in acute heart failure. *Int J Cardiol* 2016; **202**: 21–26.

10. Lin H, Zhang H, Lin Z, Li X, Kong X, Sun G. Review of nutritional screening and assessment tools and clinical outcomes in heart failure. *Heart Fail Rev* 2016; **21**: 549–565.

11. Saitoh M, Rodrigues Dos Santos M, von Haehling S. Muscle wasting in heart failure: the role of nutrition. *Wien Klin Wochenschr* 2016; **128**: 455–465.

12. Gastelurrutia P, Lupón J, de Antonio M, Zamora E, Domingo M, Urrutia A, Altimir S, Coll R, Díez C, Bayes-Genis A. Body mass index, body fat, and nutritional status of patients with heart

failure: the PLICA study. *Clin Nutr* 2015; **34**: 1233–1238.

13. Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, Clark AL. Prevalence and prognostic significance of malnutrition using 3 scoring systems among outpatients with heart failure: a comparison with body mass index. *JACC Heart Fail* 2018; **6**: 476–486.

14. Honda Y, Nagai T, Iwakami N, Sugano Y, Honda S, Okada A, Asaumi Y, Aiba T, Noguchi T, Kusano K, Ogawa H, Yasuda S, Anzai T, NaDEF investigators. Usefulness of geriatric nutritional risk index for assessing nutritional status and its prognostic impact in patients aged ≥65 years with acute heart failure. *Am J Cardiol* 2016; **118**: 550–555.

15. Kinugawa S, Fukushima A. Malnutrition in heart failure: important but undervalued issue. *JACC Heart Fail* 2018; **6**: 487–488.

16. Yin J, Lu X, Qian Z, Xu W, Zhou X. New insights into the pathogenesis and treatment of sarcopenia in chronic heart failure. *Theranostics* 2019; **9**: 4019–4029.

17. Khan MS, Butler J, Greene SJ. The real world of de novo heart failure: the next frontier for heart failure clinical trials? *Eur J Heart Fail* 2020; **22**: 1786–1789.

18. Filippatos G, Angermann CE, Cleland JGF, Lam CSP, Dahlström U, Dickstein K, Ertl G, Hassanein M, Hart KW, Lindsell CJ, Perrone SV, Guerin T, Ghadanfar M, Schweizer A, Obergfell A, Collins SP. Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure. *JAMA Cardiol* 2020; **5**: 401–410.

19. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015; **17**: 884–892.

20. Kin H, Matsumura K, Yamamoto Y, Fujii K, Otagaki M, Takahashi H, Park H, Yoshioka K, Yokoi M, Sugiura T, Shiojima I. Renoprotective effect of tolvaptan in patients with new-onset acute heart failure. *ESC Heart Fail* 2020; **7**: 1764–1770.