Malnutrition in Hospitalized Heart Failure Patients with Reduced Ejection Fraction: Potential Association with Allocation of Guideline-Directed Medical Therapies

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Abstract

Background: Malnutrition is common in patients with heart failure with reduced ejection fraction (HFrEF) and may influence the long-term prognosis and allocation of guideline-directed medical therapy (GDMT).

Methods and Results: We reviewed 1,231 consecutive patient-level records from a multicenter Japanese registry of hospitalized HFrEF patients. Nutritional status was assessed using the geriatric nutritional risk index (GNRI). GDMTs were categorized based on the use of beta-blockers, renin-angiotensin system inhibitors, and mineralocorticoid receptor antagonists. The composite outcome of all-cause death and HF rehospitalization was assessed. The mean age was 72.0±14.2 years and 42.6% patients were malnourished (GNRI<92). At discharge, 43.6% and 33.4% of patients were receiving two (double therapy) and three (triple therapy) GDMT agents, respectively. Malnourished patients had lower rates of GDMT use. The standardized GNRI score was independently associated with the occurrence of adverse events (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.79–0.98; p=0.020). Regardless of the GNRI score, lower risk of adverse events was observed with triple therapy (HR: 0.44, 95% CI: 0.29–0.66; p<0.001) or double therapy (HR: 0.44, 95% CI: 0.29–0.66; p<0.001).

Conclusion: Malnutrition assessed by GNRI score predicts long-term adverse outcomes among hospitalized HFrEF patients. However, its prognosis may be modified with GDMT.

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] of ≤ 40%) affects over 2.5 million adults in the United States alone and is associated with high economic costs and rates of impaired health status, morbidity, and mortality [1–3]. Similar trends are observed in Japan [4], where more than 230,000 patients were hospitalized for HF in 2015. This number appears to be increasing by more than 10,000 cases each year, with one-half of these cases involving HFrEF [5]. High-quality evidence currently supports the treatment of HFrEF patients using guideline-directed medical therapy (GDMT), which has traditionally included beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) [5–7]. Novel disease-modifying therapies, such as angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is), have also been introduced, and these agents are expected to further improve the outcomes of HFrEF patients incremental to the backbone of GDMT listed above [8].

Previous studies have identified important barriers to the full implementation of GDMT, including renal dysfunction, hyperkalemia, hypotension, bradycardia, old age, and low functional status [9–11]. Malnutrition is also common among patients with HF and is independently associated with adverse outcomes, which are linked to both HF and mechanisms that are related to other chronic disease states [12]. In addition, malnutrition may reflect a state of abnormal drug metabolism, which may cause unfavorable treatment effects [13, 14]. Therefore, malnutrition can also negatively affect clinical decision-

making for patients with significant clinical conditions, such as cancer [15, 16]. However, contemporary large-scale randomized controlled trials (RCTs) have generally excluded malnourished patients, and there is limited data regarding the interaction between nutritional status and real-world use of HF-related GDMT [17, 18]. Given the typically stringent entry criteria for clinical trials, observational studies may provide a more realistic assessment of malnutrition among the HF patients.

This study evaluated the prevalence of malnutrition among HFrEF patients, their long-term outcomes, and whether their nutritional status was associated with the use of GDMT. The West Tokyo Heart Failure (WET-HF) registry in Japan has historically included HF patients who have lower body mass index or who are older (vs. Western HF studies [19]), thereby providing a unique opportunity to investigate this topic.

Methods

Study design

Patient-level data were extracted from the WET-HF registry [20, 21], which prospectively collected information on patients who were admitted to three university hospitals and three tertiary referral hospitals within the Tokyo metropolitan area (Japan) in 2006–2017. This multicenter registry was designed to collect data on the clinical characteristics and outcomes of patients hospitalized with a primary diagnosis of acute HF, which is defined as rapid-onset HF with changes in signs and symptoms that indicate an urgent need for hospitalization and therapy [22]. Clinical diagnoses were made by experienced cardiologists at each institution, who excluded patients who presented with acute coronary syndrome. A robust assessment of care and patient outcomes was facilitated by dedicated clinical research coordinators collecting baseline data and outcomes from medical records and querying attending physicians. Data were entered into an electronic data-capturing system that has a robust data query engine and system validations to ensure data quality. Exclusive on-site auditing by the investigators ensured proper registration of each patient. This study's retrospective protocol was approved by the Institutional Review Board of Keio University School of Medicine and conducted in accordance with the Declaration of Helsinki. And all patients provided informed consent for their treatment and research use of their data.

Patient population

This study evaluated prospectively collected data from 1,713 consecutive patients who were hospitalized for HFrEF. However, it excluded 73 patients who died during hospitalization, 51 dialysis patients, 124 patients who were lost to follow-up, 229 patients with missing albumin or body mass index data that prevented evaluation of nutritional status, and five patients with missing data regarding medication use at discharge. Thus, the study analyzed the complete data from 1,231 patients (Fig. 1).

Definitions of variables and outcomes

Baseline characteristics included age, sex, causes of HF, medical history, previous procedures, vital signs, laboratory data, echocardiographic data, and medications used at discharge. The definition of a reduced ejection fraction (EF ≤ 40%) was based on the universal definition and classification of HF [23].

Full GDMT use was defined as the prescription of BBs, RASis (ACEis or ARBs), and MRAs at the time of discharge. During the study period, ARNI, SGLT2i, and ivabradine for HF patients were not available in Japan. Thus, based on the medication(s) at discharge, we classified the patients as having received no GDMT (zero of the three agents), single therapy (one agent), double therapy (two agents), or triple therapy (all three agents).

Patients at risk of malnutrition can be identified using several risk indexes. The present study evaluated nutritional status based on the GNRI, which is a simple formula that has been demonstrated to be clinically useful among patients with various medical conditions [24, 25]. The GNRI score was calculated at the time of discharge as follows:

$14.89 \times \text{serum albumin (g/dL)} + 41.7 \times \text{body mass index (kg/m}^2\text{)} / 22$.

Clinical characteristics and mortality were compared between the following two groups: low GNRI group (< 92) with moderate or severe nutritional risk and high GNRI group (≥ 92) with low or no nutritional risk according to a previous report [26]. In the present study, patients with low GNRI score were defined as “malnourished.”

Ischemic etiology was defined as left ventricular dysfunction (EF of ≤ 40%) with a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or at least one major epicardial coronary artery with ≥ 75% stenosis. The eGFR was calculated using the Modification of Diet in Renal Disease Equation for Japanese Patients, which was proposed by the Japanese Society of Nephrology [27]. The EF was calculated using the modified Simpson’s method. Ultrasound cardiography was performed by highly experienced cardiologists or clinical technologists during the hospitalization. The NYHA functional class was evaluated at discharge by the treating cardiologists at each institution.

Follow-up data were mainly collected via telephone contact or a chart review. The primary outcome of interest was defined as a composite of all-cause death and HF rehospitalization after discharge, with the decision to rehospitalize the patient made by the treating physicians based on the usual standard of care. The first secondary outcome was the occurrence of death by any cause, and second secondary outcome was rehospitalization for HF. To ensure the accuracy of the adverse event ascertainment, the WET-HF registry is supported by a central study committee that adjudicates determination of the endpoint.

Statistical analysis

Data were reported as number and percentage for categorical variables and as median (interquartile range) for continuous variables. Continuous variables were compared using the Mann-Whitney U test and Kruskal-Wallis test, whereas categorical variables were compared using the Pearson’s chi-squared test.

A multivariable logistic regression model was used to evaluate whether GDMT use was related to different clinical variables. Models were adjusted for age, sex, serum potassium concentration, total cholesterol level, eGFR level, LVEF, systolic blood pressure, heart rate, history of HF hospitalization, atrial fibrillation, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, ischemic cardiomyopathy, and GNRI status. Survival curves were compared using the Kaplan-Meier method and log-rank test.

Multivariable Cox proportional hazard models were also created to assess the association between GDMT use (none, single, double, or triple therapy) and each endpoint, which was adjusted for age, sex, systolic blood pressure, and heart rate at discharge, renal dysfunction (eGFR < 60 mL/min/1.73 m^2), LVEF, history of HF hospitalization, ischemic etiology, atrial fibrillation, chronic obstructive pulmonary disease, stroke, diabetes mellitus, use of loop diuretics, statin use, and standardized GNRI score. Results were reported as HRs, 95% CIs, and p-values. We also created a 4-knot restricted cubic spline model of the HRs according to the GNRI status (continuous value), which was adjusted for the same factors as the Cox hazards model.

A sensitivity analysis was also performed after excluding patients with advanced renal impairment (eGFR < 30 mL/min/1.73 m^2) or higher mortality risk (an estimated mortality risk of > 10% based on a GWTG-HF risk score of > 57), considering the possibility of patients who may not benefit from or tolerate GDMTs [21]. All statistical analyses were performed using IBM SPSS software (version 26; IBM Corp., Armonk, NY, USA) and R software (version 3.6.3; Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The 1,231 HFrEF patients were predominantly men (62%) and had a median age of 72.0 years (interquartile range: 61.0–81.0 years). The baseline characteristics of patients divided into two groups according to their GNRI values are listed in Table 1. The low GNRI group had a higher proportion of female patients, tended to be older, had more severe symptoms (New York Heart Association [NYHA] III or IV), had lower hemoglobin and albumin concentrations, and had higher creatinine and B-type natriuretic peptide concentrations. There were no significant inter-group differences in terms of systolic blood pressure and heart rate at admission.

Table 1
Baseline characteristics of patients by nutritional status

Variables	Low GNRI (< 92) (n = 525)	High GNRI (GNRI ≥ *92)* (n = 706)	p value
Age, years	78 [69, 84]	68 [57, 77]	< 0.001
Female, n (%)	200 (38.1)	159 (22.5%)	< 0.001
Systolic blood pressure, mmHg	132 [110, 151]	132 [112, 155]	0.507
Heart rate, beats/min	94 [78, 114]	96 [78, 112]	0.814
LVEF, %	30 [25, 35]	30 [23, 35]	0.013
Ischemic etiology, n (%)	205 (39.0)	246 (34.8)	0.130
NYHA (III-IV)	432 (86.7)	553 (81.4)	0.015
Comorbidities			
Prior HF hospitalization, n (%)	188 (36.4)	246 (35.1)	0.642
Hypertension, n (%)	342 (65.1)	440 (62.3)	0.309
Diabetes mellitus, n (%)	201 (38.3)	270 (38.2)	0.988
Dyslipidemia, n (%)	193 (37.3)	319 (45.8)	0.003
Smoking, n (%)	209 (41.4)	357 (52.2)	< 0.001
Atrial fibrillation, n (%)	201 (38.4)	290 (41.1)	0.336
Stroke, n (%)	70 (13.3)	89 (12.7)	0.728
COPD, n (%)	26 (5.0)	24 (3.4)	0.173
Laboratory findings at admission			
Hemoglobin, g/dL	11.9 [10.4, 13.5]	13.4 [12.0, 15.0]	0.001
BUN, mg/dL	25.1 [18.2, 36.3]	20.3 [15.9, 27.4]	< 0.001
Creatinine, mg/dL	1.14 [0.81, 1.61]	1.04 [0.86, 1.31]	0.003
eGFR, ml/min/1.73 m^2	45.2 [29.8, 61.6]	53.6 [40.2, 66.5]	< 0.001
Sodium, mEq/L	139 [137, 142]	140 [138, 142]	< 0.001
Potassium, mEq/L	4.4 [3.9, 4.8]	4.3 [4.0, 4.7]	0.823
BNP, pg/mL	1155 [702, 1989]	707 [383, 1082]	< 0.001
Alb, mg/dL	3.4 [3.1, 3.7]	3.8 [3.6, 4.1]	< 0.001

GNRI and outcomes

During a median follow-up period of 2.0 years (interquartile range: 0.8–3.1 years), the composite outcome was observed for 549 patients (44.6%), including 298 patients (24.3%) who died and 414 patients (33.6%) who were rehospitalized because of HF. The unadjusted Kaplan-Meier curves revealed that the low GNRI group had a higher risk of the composite outcome (**Supplementary Fig. S1**). The restricted cubic spline analysis also revealed a positive correlation between the GNRI score and long-term outcomes, particularly among patients with a GNRI score of < 100 **(**Fig. 2).

Factors influencing the implementation of fundamental therapy

At discharge, 49 patients (4.0%) were receiving no GDMT, 234 patients (19.0%) were receiving a single agent, 537 patients (43.6%) were receiving double therapy, and 411 patients (33.4%) were receiving triple therapy. The overall usage rates were 87.4% for BBs, 71.7% for RASis, and 51.0% for MRAs (**Supplementary Fig. S2)**. The triple therapy group (full GDMT) was younger, had a higher frequency of non-ischemic dilated cardiomyopathy, and had better renal function. Furthermore, the full GDMT group had a significantly higher median GNRI score (triple therapy: 96.7 [interquartile range: 88.5–104.8], double therapy: 94.5 [interquartile range: 87.3–102.9], single therapy: 91.2 [interquartile range: 82.3–98.2], and no therapy: 88.6 [interquartile range: 82.1–94.8]; $p < 0.001$).

The triple therapy as well as specific therapy groups (i.e., the BB, RASi, and MRA groups) were compared according to their nutritional risk using GNRI values. Lower GNRI values tended to be associated with lower administration rates of GDMTs (Fig. 3). The associations between specific therapy groups and clinical factors are described in Table 2. After multivariable adjustment, age was significantly associated with BB use (OR: 0.95, 95% confidence interval [CI]: 0.93–0.97; $p < 0.001$) and renal function was associated with RASi use (OR: 1.02, 95% CI: 1.02–1.03; $p < 0.001$) and MRA use (OR: 1.01, 95% CI: 1.00–1.02; $p = 0.004$). Furthermore, the GNRI score was significantly associated with BB use (OR: 1.02, 95% CI: 1.00–1.04; $p = 0.043$) and RASi use (OR: 1.03, 95% CI: 1.02–1.05; $p < 0.001$), but not with MRA use (OR: 1.00, 95% CI: 0.99–1.01; $p = 0.597$).

Table 2
Clinical variables contributing to GDMT administration

Variable	Beta-blockers		RAS-inhibitors		MRAs	
	OR [95%CI]	p value	OR [95%CI]	p value	OR [95%CI]	p value
Male, N (%)	0.57 [0.37–0.90]	0.016	0.84 [0.60–1.16]	0.287	0.83 [0.62–1.11]	0.209
Age (years)	0.95 [0.93–0.97]	< 0.001	0.99 [0.98-1.00]	0.164	0.99 [0.98–1.01]	0.234
Prior HF hospitalization, N (%)	1.06 [0.69–1.62]	0.805	1.12 [0.82–1.54]	0.473	1.61 [1.22–2.13]	< 0.001
Systolic blood pressure (mmHg)	1.00 [1.00-1.01]	0.512	1.00 [1.00-1.01]	0.202	0.99 [0.99-1.00]	0.310
Heart rate (beat/min)	1.01 [1.00-1.01]	0.171	1.00 [0.99-1.00]	0.149	1.00 [0.99–1.01]	0.469
eGFR (mL/min/1.72m^2)	1.00 [0.99–1.01]	0.912	1.02 [1.02–1.03]	< 0.001	1.01 [1.00-1.02]	0.004
Potassium level (mEq/L)	1.32 [0.88–1.98]	0.188	1.15 [0.86–1.54]	0.361	0.95 [0.73–1.24]	0.721
Total cholesterol level (mg/dL)	1.00 [0.99-1.00]	0.239	1.00 [1.00-1.01]	0.544	1.00 [1.00–1.00]	0.034
Atrial fibrillation, N (%)	0.97 [0.65–1.46]	0.882	1.20 [0.88–1.64]	0.247	0.92 [0.70–1.20]	0.528
Ischemic cardiomyopathy, N (%)	1.17 [0.77–1.77]	0.456	1.23 [0.90–1.68]	0.200	1.15 [0.87–1.51]	0.339
Diabetes mellitus, N (%)	1.02 [0.67–1.54]	0.946	0.78 [0.58–1.06]	0.782	1.20 [0.92–1.57]	0.178
Hypertension, N (%)	1.43 [0.94–2.16]	0.094	1.36 [0.99–1.88]	0.060	0.99 [0.75–1.31]	0.948
COPD, N (%)	0.61 [0.28–1.29]	0.228	1.41 [0.66–2.97]	0.374	0.67 [0.35–1.28]	0.228
LVEF (%)	0.98 [0.95–1.01]	0.103	1.00 [0.98–1.02]	0.855	0.97 [0.95–0.99]	0.002
GNRI	1.02 [1.00-1.04]	0.043	1.03 [1.02–1.05]	< 0.001	1.00 [0.99–1.01]	0.597

Implementation of GDMT and clinical outcomes

The unadjusted Kaplan-Meier curves revealed that patients who received more therapeutic agents had lower risks of the composite outcome (**Supplementary Fig. S3**). Among the malnourished, low GNRI group, the risks of the composite outcome decreased for patients who received single, double, and triple therapies (Fig. 4). The multivariable Cox proportional hazards model revealed that, regardless of the GNRI status, GDMT use was significantly associated with a lower risk of the composite outcome after adjustment for other patient characteristics. Compared with patients who received no GDMT therapy, the risk of the composite outcome was lower among those receiving triple therapy (adjusted hazard ratio [HR]: 0.44, 95% CI: 0.29–0.66; p < 0.001), double therapy (adjusted HR: 0.44, 95% CI: 0.29–0.66; p < 0.001), or single therapy (adjusted HR: 0.65, 95% CI: 0.43–0.99; p = 0.046). Furthermore, compared with those who received single therapy, the risk of the composite outcome was lower among those receiving triple therapy (adjusted HR: 0.67, 95% CI: 0.52–0.86; p = 0.002) or double therapy (adjusted HR: 0.68, 95% CI: 0.54–0.85; p < 0.001) (Table 3). Furthermore, the effects of GDMT appeared consistent in lowering risks of all-cause death (triple therapy: HR: 0.29, 95% CI: 0.17–0.49; p < 0.001 or double therapy: HR: 0.30, 95% CI: 0.19–0.49; p < 0.001) (**Supplementary Fig. S4**), and hospitalization for HF (triple therapy: HR: 0.43, 95% CI: 0.26–0.71; p < 0.001 or double therapy: HR: 0.44, 95% CI: 0.27–0.73; p < 0.001) (**Supplementary Fig. S5**), respectively.

Table 3
Multivariable Cox proportional hazards models of the primary outcome

Medication class	**Outcome analysis**	
None GDMT referenced	**HR [95%CI]**	**p value**
Triple therapy	0.44 [0.29–0.66]	< 0.001
Double therapy	0.44 [0.29–0.66]	< 0.001
Single therapy	0.65 [0.43–0.99]	0.046
Single therapy referenced		
Triple therapy	0.67 [0.52–0.86]	0.002
Double therapy	0.68 [0.54–0.85]	< 0.001

Sensitivity analysis

The results of our analyses were also similar in sensitivity analyses that excluded patients with advanced renal impairment (estimated glomerular filtration rate [eGFR]: <30 mL/min/1.73 m^2) or higher mortality risk (Get With The Guideline-Heart Failure [GWTG-HF] risk score: >57) (**Supplementary Fig. S6**). Compared with patients who received no GDMT therapy, the risk of the composite outcome was lower in patients receiving triple therapy (adjusted HR: 0.40, 95% CI: 025–0.64; p < 0.001), double therapy (adjusted HR: 0.38, 95% CI: 0.24–0.60; p < 0.001), or single therapy (adjusted HR: 0.58, 95% CI: 0.36–0.95; p = 0.031).

This tendency was consistent in the risk reduction of all-cause death (triple therapy: HR: 0.26, 95% CI: 0.14–0.46; p < 0.001 or double therapy: HR: 0.21, 95% CI: 0.12–0.38; p < 0.001) and HF rehospitalization (triple therapy: HR: 0.42, 95% CI: 0.23–0.77; p = 0.005 or double therapy: HR: 0.43, 95% CI: 0.24–0.78; p = 0.005).

Discussion

This study evaluated data from a contemporary multicenter registry of acute HF cases and revealed three main findings. First, among patients with HFrEF, malnutrition (based on a low GNRI score) was associated with significantly lower rates of GDMT use. Second, patients with malnutrition had an increased risk of the composite outcome that involved all-cause death and HF rehospitalization. Third, even among patients with malnutrition, increased use of GDMT was independently associated with lower risks of the composite outcome of rehospitalization or all-cause mortality.

Treatment for HF aims to prevent morbidities and prolong morbidity-free survival. Combination therapy using RASis (i.e., ACEis/ARBs/ARNIs and MRAs) with BBs is a guideline-recommended standard therapy for patients with HFrEF. However, despite increased awareness of this recommendation, a study of the CHAMP-HF registry demonstrated that prescription rates for these disease-modifying drugs remain lower than expected in the ambulatory setting and have not improved over 15 years since the Euro Heart Survey on Heart Failure [9, 28]. Similarly, a study on acute HF patients hospitalized with HFrEF from the Japanese Cardiac Registry of Heart Failure (2004–2005) revealed low proportions of drug use at discharge (BBs: 57.9%, ACEis: 4.3%, ARBs: 45.6%, MRAs: 46.0%) [29]. Aside from the rate of BB use, our findings are generally comparable and suggest that there is room for improvement in the treatment rates of ACEi/ARB and MRA, similar to that observed in Western countries. Additionally, the rate of MRA administration was similar across nutritional status. The purpose of its use may have been different than that of the other two agents and it may be prescribed as a potassium-sparing diuretic more frequently than as a cardioprotective agent. This may have influenced the relationship between its administration and GNRI value.

The gaps in GDMT use in this setting may be related to various factors, including physician aversion and inertia, patient intolerance, and side effects [9]. Frailty, a possible reason for physicians being hesitant to change therapy, is also strongly related to malnutrition, but has different features that require investigation and call for further evaluation of the interaction and its association with HF treatment and outcomes, since either of the two may lead to a vicious cycle of physical impairment. In previous studies, patients with low GNRI were more likely to have characteristics of frailty, which represents a state of increased vulnerability to stressors resulting from multisystem dysregulation and is associated with a higher risk of impaired physical function and mortality [30]. As our study showed that GDMT use was associated with better outcomes even in patients with low GNRI, it may be possible to improve their prognoses.

Malnutrition may make physicians reluctant to alter a patient's treatment considering the medicine's side-effects during liver dysfunction [16], as it decreases oxidative metabolism in the liver, which is performed by cytochrome P-450 isoenzymes, via depletion of nicotinamide adenine dinucleotide phosphate reserves. Other liver metabolic pathways can also be impaired, which can decrease drug clearance, thereby increasing drug exposure and potentially resulting in harmful side effects. There are also concerns regarding drug absorption changes due to poor nutritional status (e.g., because of vitamin and/or mineral deficiency), which may influence the physician's decisions based on the medication's effectiveness and potential side effects [31] and partially explain the present study's findings. Moreover, the existing RCTs have generally excluded malnourished patients, who are often older and have more comorbidities. Thus, although there is still limited evidence regarding whether nutritional status influences the effectiveness and side effects of GDMT, our results suggest that even malnourished patients with HFrEF can benefit from a more complete prescription of GDMT.

Malnourished patients are often older and tend to have a greater number of comorbidities, including renal dysfunction, which may make physicians hesitant to add new medications [32]. We have previously reported that RASi prescriptions were more appropriate for patients with better renal function (eGFR: >30 mL/min/1.73 m^2), and RASi prescription was associated with lower risks of all-cause death and HF rehospitalization, although RASi use was not significantly associated with adverse outcomes among patients with a lower eGFR [33]. Similar results have been reported for MRA use, as data from the GWTG-HF registry revealed that spironolactone was less frequently prescribed for HFrEF patients with advanced renal impairment (serum creatinine: 1.5–2.0 mg/dL) than for patients with serum creatinine concentrations of < 1.5 mg/dL [34]. Another report based on the OPTIMIZE-HF registry revealed that MRA use was associated with good clinical outcomes, even among older patients, if their eGFR was > 30 mL/min/1.73 m^2 [35]. Ferreira et al. also evaluated MRA prescription patterns in a sub-analysis of data from RCTs and reported that lower MRA doses were prescribed to patients with chronic kidney disease [36]. This may be because these patients experience more frequent episodes of worsening renal function during MRA treatment, which necessitates close surveillance and dose adaptations. Nevertheless, patients still benefited at lower MRA doses. Clinicians must consider the risks and benefits of any specific treatment strategy, especially for patients with chronic kidney disease, who are frequently encountered in clinical practice.

Strengths and limitations

This study highlights the real-world challenges of HF management in malnourished patients, although it also has several inherent limitations. First, the retrospective observational nature is prone to bias and confounding by unmeasured or unidentified variables, although we adjusted the analyses for relevant clinical characteristics and tested different cut-offs as sensitivity analyses. Although well-designed RCTs would be needed to ensure the efficacy of GDMT, especially triple therapy, given the strength of the evidence for GDMT among non-malnourished patients, there may be ethical questions regarding testing these therapies against placebo in clinical trials. Also, the registry did not contain data regarding the

specific doses of each agent, which precluded dose-related analyses. Future studies should evaluate whether malnourished patients benefit from lower drug doses. Finally, frailty can coexist with malnutrition, although we were unable to consider the relationship between these two conditions because of the lack of data regarding frailty.

Conclusion

Malnourished HFrEF patients, who are typically excluded from clinical trials, exhibited poorer prognoses and GDMT prescription rates, when compared with patients with better nutritional status. However, our study revealed that GDMT was independently associated with favorable outcomes regardless of nutritional status. Effective approaches to increase GDMT utilization are needed.

Declarations

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Author contributions:

The author contributions are started as follows; Y.K., Y.S., and S.K. drew the manuscript. Y.K. and N.N. prepared images. Y.S., S.K., T.K., A.G., Y.N., Y.N., M.S., M.T., Y.I., S.N., and T.Y. collected patient information. T.K., A.G., Y.N., Y.N., M.S., M.T., Y.I., N.N., A.T.S.S., S.N., T.Y. and K.F. provided a critical revision of the manuscript for the key intellectual content of supervision. All the authors have approved all aspects of our work, read, and approved the manuscript.

Competing interest:

Dr. Shiraishi is affiliated with an endowed department by Nippon Shinyaku Co., Ltd., Medtronic Japan Co., Ltd., and BIOTRONIK JAPAN Inc. and received research grants from the SECOM Science and Technology Foundation and the Uehara Memorial Foundation and honoraria from Otsuka Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd.. Dr. Kohsaka has received an unrestricted research grant from the Department of Cardiology, Keio University School of Medicine, Bayer Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., and Novartis Pharmaceutical Co., Ltd.. The remaining authors have no conflicts of interest to disclose. There are no patents, products in development, or marketed products to declare. Dr. Sandhu receives research support from the US National Heart, Lung, and Blood Institute (1K23HL151672-01).

Data availability:

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

Ethics approval and participant's consent:

The study's retrospective protocol was approved by the Institutional Review Board of Keio University School of Medicine and conducted in accordance with the Declaration of Helsinki. And all patients provided informed consent for their treatment and research use of their data.

Consent to participate/Consent to publish:

This study's retrospective protocol was approved by each center's ethics review committee, and all patients provided informed consent for their treatment and research use of their data.

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Figures

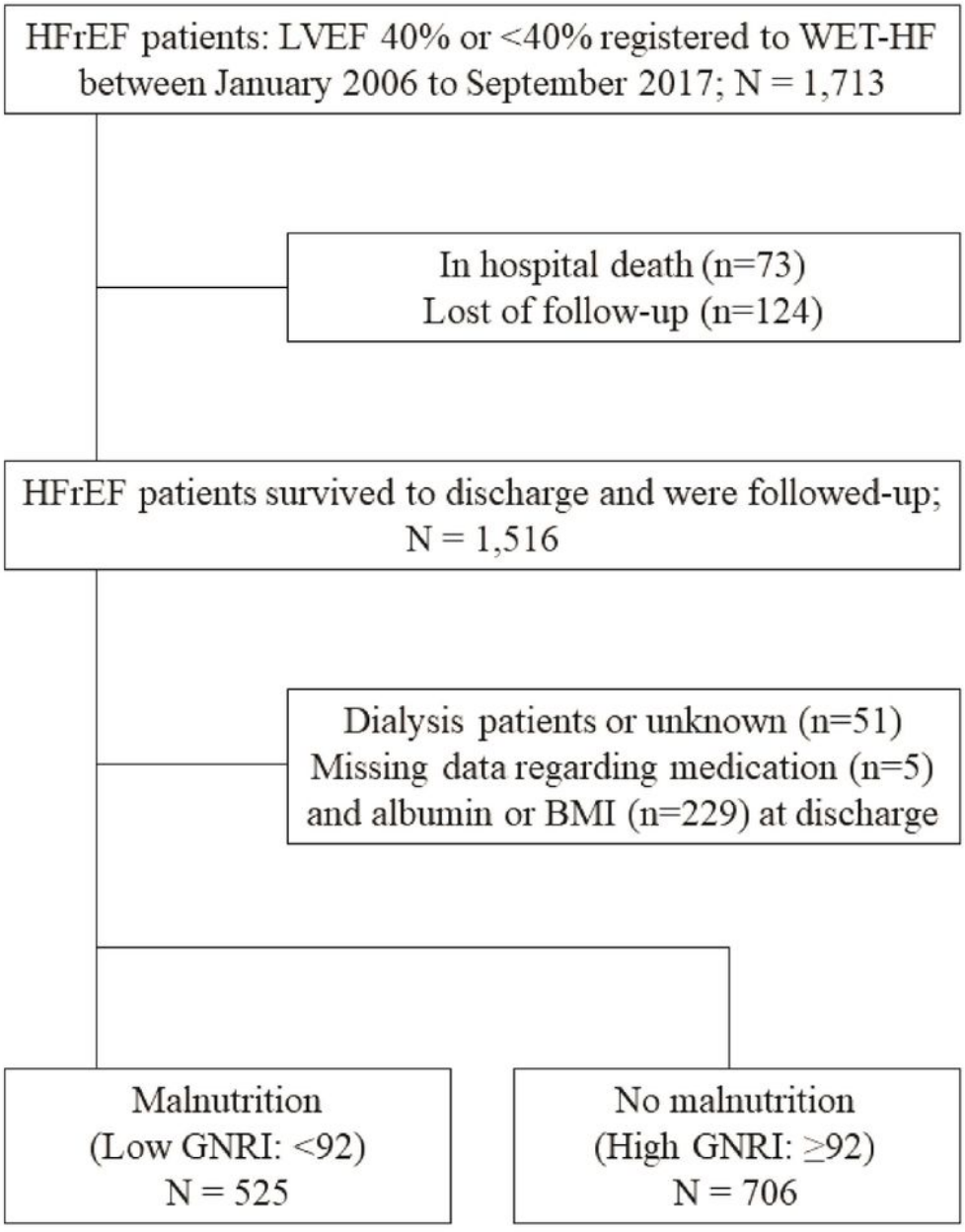

Figure 1

Study flowchart. The HFrEF patients were categorized according to their GNRI score into groups with malnutrition (low GNRI) or normal nutritional status (high GNRI). HFrEF, heart failure with reduced ejection fraction; WET-HF, West Tokyo Heart Failure, GNRI; geriatric nutritional risk index.

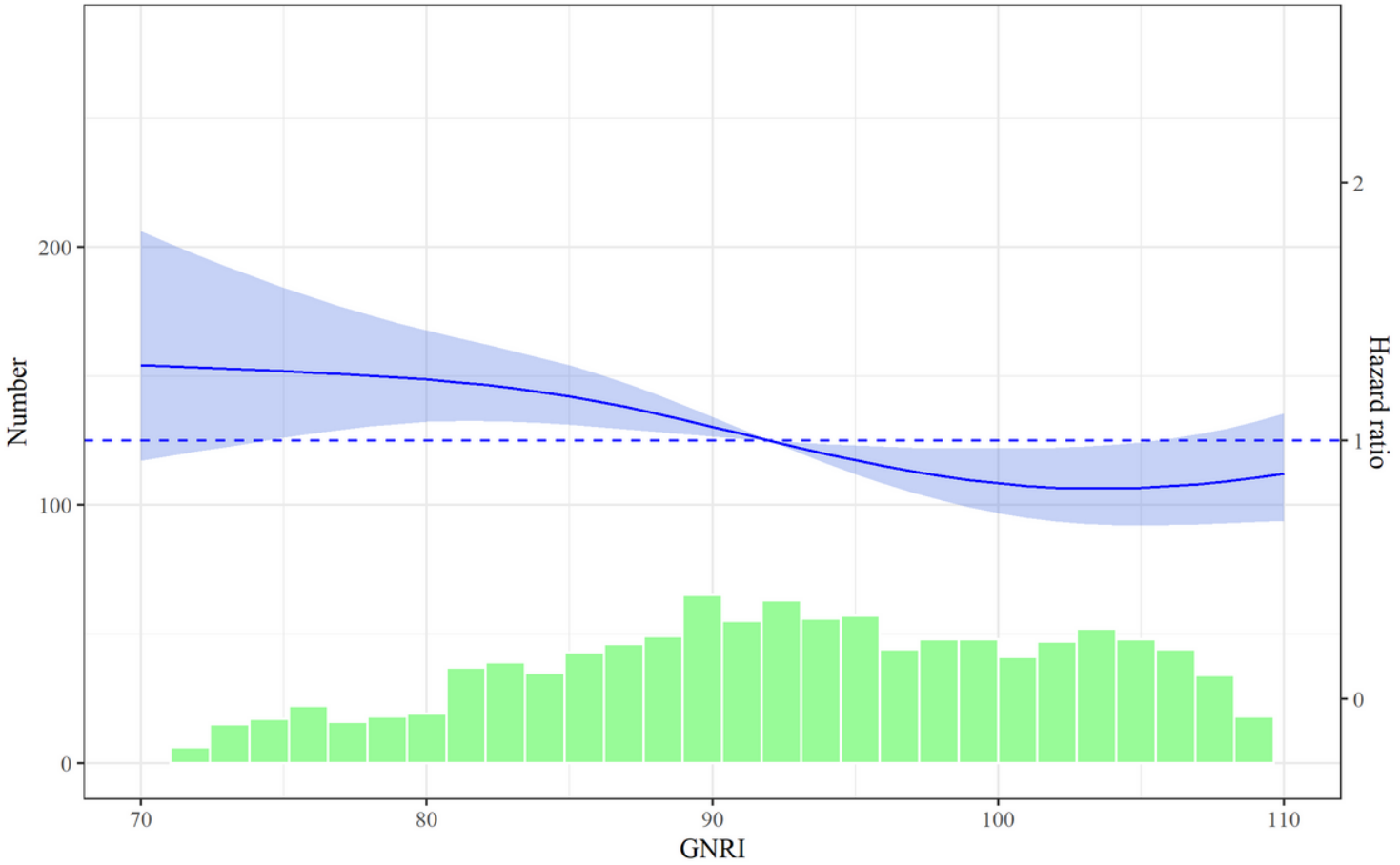

Figure 2

Hazard ratios for the composite outcome (all-cause death and heart failure rehospitalization) according to the Geriatric Nutritional Risk Index score. The blue line represents the continuous hazard ratio (HRs) and the light blue area represents the 95% confidence intervals. The green bars represent the numbers of patients with each Geriatric Nutritional Risk Index (GNRI) score.

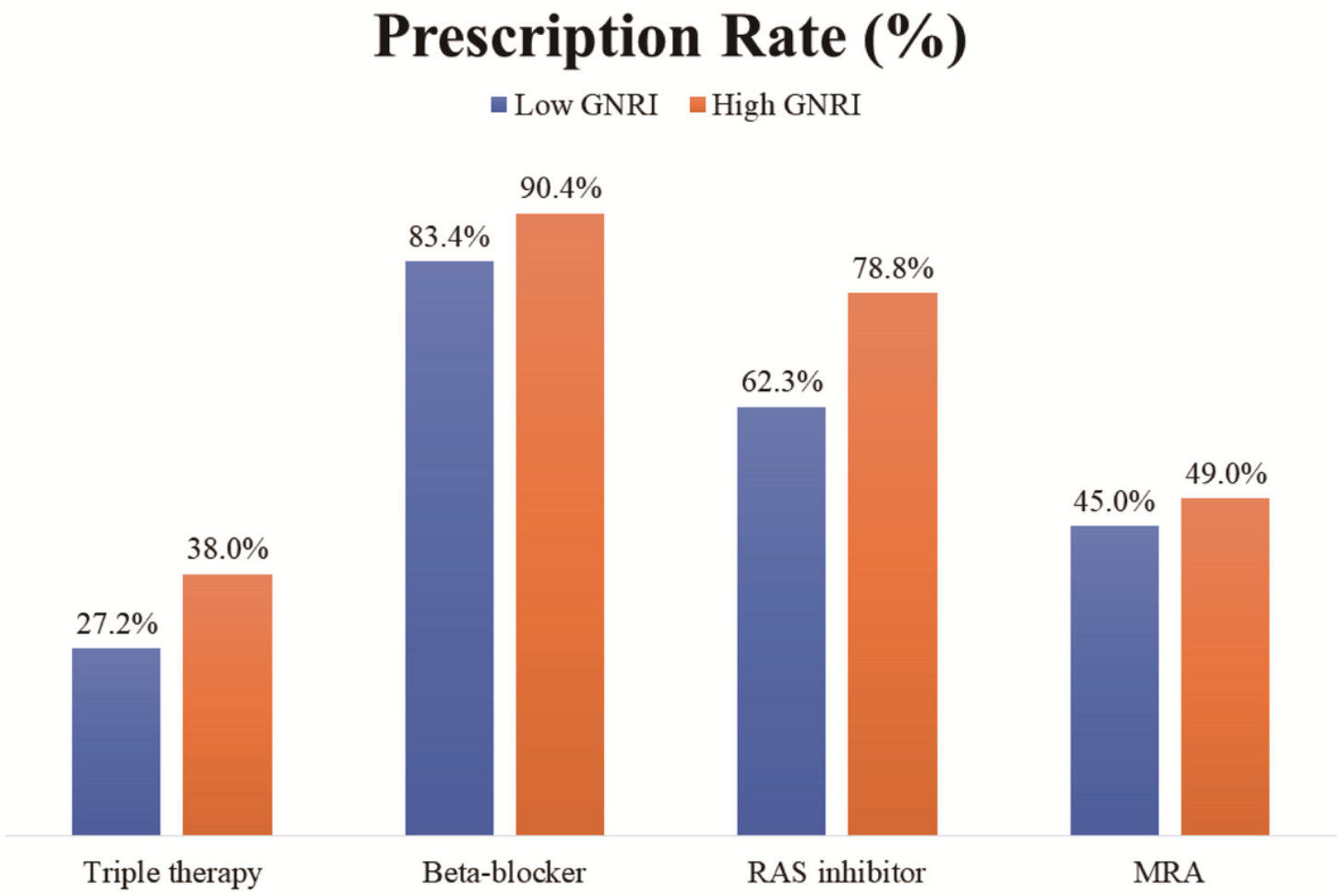

Figure 3

Prescription rate of each agent according to Geriatric Nutritional Risk Index: Low GNRI for moderate or severe nutritional risk with GNRI<92, and high GNRI for low or no nutritional risk with GNRI≥92. Abbreviation : GNRI, Geriatric Nutritional Risk Index; RASi, renin-angiotensin-system inhibitor; MRA, mineralocorticoid receptor antagonist; GNRI, Geriatric Nutritional Risk Index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist

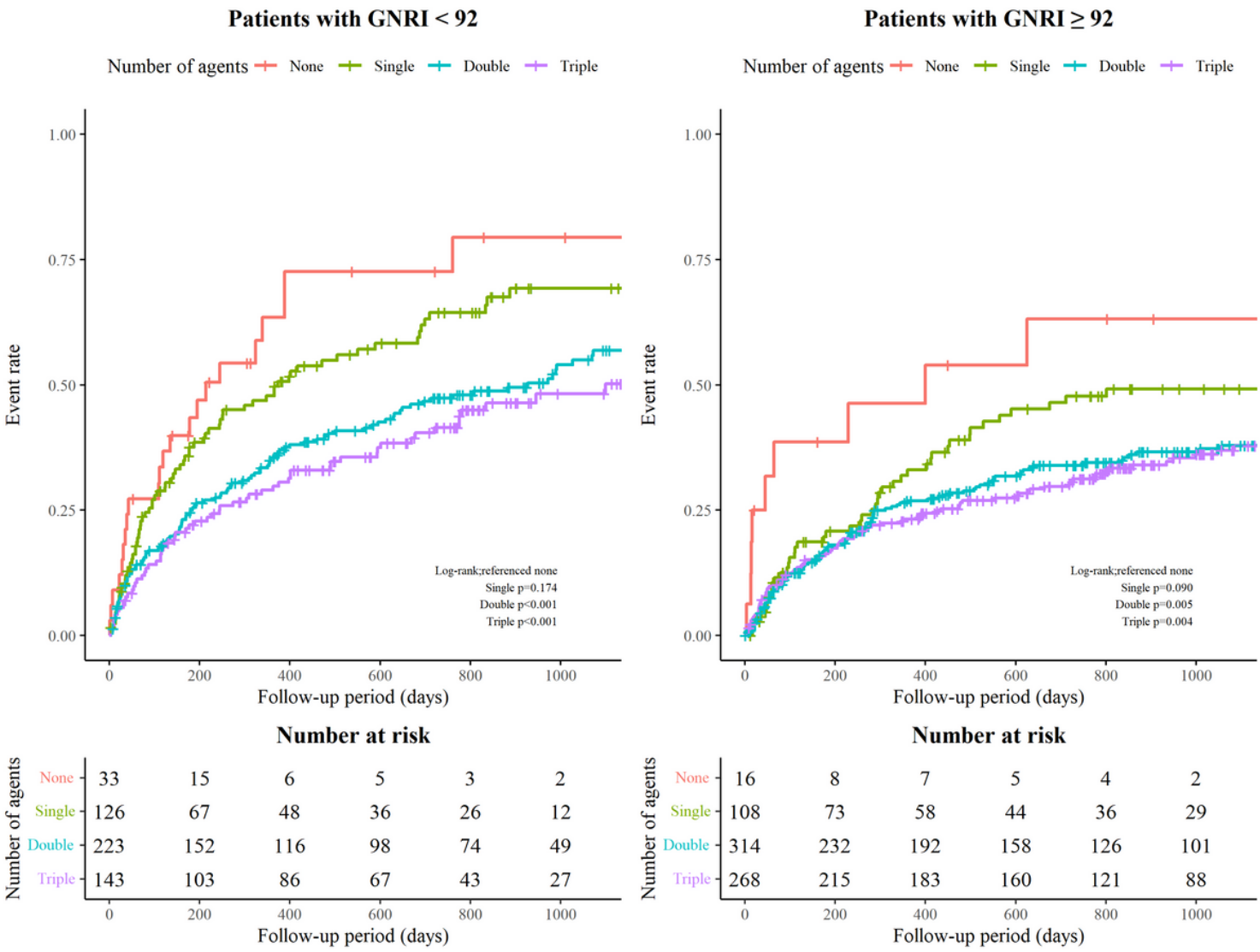

Figure 4

Unadjusted Kaplan-Meier curves for the composite outcome (all-cause death and heart failure rehospitalization) in each treatment group (no, single, double, and triple therapy) according to Geriatric Nutritional Risk Index score (GNRI: <92 vs. ≥92).