Effectiveness of guideline-directed medical therapy for heart failure in frail elderly patients with malnutrition

by

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Abstract

Background: The early introduction of guideline-directed medical therapy (GDMT) has been shown to improve the prognosis of heart failure with reduced ejection fraction (HFrEF). However, the appropriateness of GDMT in the malnourished elderly patients is unclear due to comorbidities and polypharmacy. This study aims to assess the effects of GDMT on HFrEF in this specific population using the Geriatric Nutritional Risk Index (GNRI).

Methods: We retrospectively collected data of patients over 75 years old, who were admitted to St. Luke's International Hospital for acute heart failure with reduced ejection fraction from 2011 to 2022. Malnutrition was defined as a GNRI score below 92. GDMT was defined as the prescription of three or more of the following medications at the time of discharge: Beta-blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors. The primary endpoints were all-cause mortality at one year after discharge and HF readmission.

Results: Among 471 patients (mean age 83.9 ± 6.0 years), 323 patients (68.6%) had malnutrition. There was no significant difference in GDMT implementation rates between the low GNRI group and high GNRI group (38.7% vs 38.5%, p=1.00). In the low GNRI group, GDMT was associated with a significant reduction in all-cause mortality at one year (HR 0.43; 95% CI, 0.22-0.83), but not in HF readmission (HR 0.78; 95% CI, 0.50-1.22) at one year after discharge. In the high GNRI group, GDMT

was not significantly associated with these outcomes (all-cause mortality: HR 0.55; 95% CI, 0.15-2.03, HF readmission: HR 0.64, 95%CI, 0.32-1.30).

Conclusion: Implementation of GDMT in HFrEF may enhance prognosis, even among elderly patients with malnutrition.

Keywords: Heart failure, Guideline-directed medical therapy, Malnutrition, Geriatric Nutritional Risk Index, Elderly

List of abbreviations

GDMT	Guideline-directed medical therapy
HFrEF	Heart failure with reduced ejection fraction
GNRI	Geriatric Nutritional Risk Index
ACE-Is	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
ARNI	Angiotensin receptor-neprilysin inhibitor
MRAs	Mineralocorticoid receptor antagonists
SGLT2-Is	Sodium-glucose cotransporter 2 inhibitors
BP	Blood pressure
COPD	Chronic obstructive pulmonary disease
eGFR	estimated glomerular filtration rate
NTproBNP	N-terminal pro-B type natriuretic peptide
HR	Hazard ratio
CI	Confidence interval
RCTs	Randomized controlled trials

1. INTRODUCTION

1.1. Background Information

Heart failure is a public health problem with a high mortality rate, despite technological advancements in treatment. [1] Moreover, the incidence of heart failure increases with age, and as the population ages, the number of heart failure patients is expected to rise.[2] In this context, several pieces of evidence have emerged regarding drug therapy that improve prognosis and are recommended in guidelines for the treatment of heart failure with reduced ejection fraction (HFrEF).[3] Beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is) / angiotensin receptor blockers (ARBs) / angiotensin receptor-neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2-Is) are among the specific drugs recommended. The early introduction of guideline-directed medical therapy (GDMT) using these agents has been shown to improve the prognosis of HFrEF. [4]

On the other hand, the appropriateness of GDMT in the elderly needs to be carefully considered. This is because heart failure in the elderly is characterized by several comorbidities, frailty, and cognitive dysfunction, and is affected by adverse drug reactions and polypharmacy.[5,6] In particular, elderly patients with malnutrition may be at high risk for these GDMT-related adverse effects, although this is not yet known.

1.2. Objectives

This study aimed to examine the impact of GDMT on heart failure in frail elderly patients with malnutrition, using the Geriatric Nutritional Risk Index (GNRI), a nutritional index related to the prognosis of HFrEF.[7,8]

2. METHODS

2.1. Study design and patient population

This study was a retrospective, single-center cohort study wherein patients over 75 years old, admitted to St. Luke's International Hospital for acute heart failure with reduced ejection fraction from January 2011 to May 2022, were enrolled. Acute heart failure was diagnosed according to the Framingham criteria.[9] This study was conducted in conformation with the Declaration of Helsinki and the Japanese Ministry of Health, Labor and Welfare's Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol was approved by the Ethics Committee of St Luke's International Hospital.

2.2. Data collection and definition

Patients' sociodemographic characteristics, laboratory data, and information on survival and hospitalization were extracted from St. Luke's International Hospital's electronic medical records.

HFrEF was defined as a left ventricular ejection fraction of less than 40% based on recent guidelines, and patients meeting that criterion on echocardiography at admission were included in this study. Nutritional status was evaluated using the GNRI, an index of nutritional assessment and calculated using the following formula: 14.89 × serum albumin (g/dL) + 41.7 × body mass index/22. The low GNRI will be defined as less than 92 based on previous studies.[7,8] GDMT was defined as the inclusion of at least three of the following drugs in the discharge prescription: beta-blockers, ACE-Is/ARBs/ARNI, MRAs and SGLT2-Is.

2.3. Endpoint

In this study, first, the association between GNRI and GDMT was examined. Then, the association between GDMT and all-cause mortality or HF readmission at one year after discharge was examined in patients with low and high GNRI scores, respectively.

2.4. Statistical analysis

Patient baseline characteristics were presented as percentages for categorical variables and means ± standard deviation for continuous variables. Patient characteristics between the two GNRI groups were analyzed using an independent sample t-test or $\chi 2$ test as appropriate. The event-free period was plotted using the Kaplan-Meier method and analyzed with the log-rank test. In addition, association between GDMT and all-cause mortality and readmission at one year after discharge were examined using separate Cox proportional hazards model. All

analyses were conducted using R Studio and a p-value <0.05 was considered as statistically significant.

3. RESULTS

3.1. Baseline characteristics

A total of 471 patients were included in the analysis. Of these, 323 (68.6%) were in the low GNRI group. The baseline characteristics of the patients by GNRI status (low and high GNRI groups) are shown in Table 1. The overall mean age was 83.9 years, and the low GNRI group was significantly older than the high GNRI group. Left ventricular ejection fraction and frequency of comorbidity did not differ between the two groups except for atrial fibrillation, which was higher in the high GNRI group. Regarding laboratory data, distribution of renal function test was similar, but NTproBNP was significantly higher in the low GNRI group than in the high GNRI group. Overall, heart failure medication prescription rates at discharge were 84.3% for beta-blockers, 68.6% for ACE-Is/ARBs/ARNI, 52.9% for MRAs, and 7.2% for SGLT2-Is. The overall GDMT achievement rate at discharge was 38.6%. Medication prescription for heart failure and GDMT did not differ significantly between the two groups at discharge.

The baseline characteristics of the low GNRI group by GDMT status (GDMT and non-GDMT groups) are shown in Table 2. The GDMT group was significantly younger than the non-GDMT group. The non-GDMT group was significantly more male than the GDMT group.

Blood pressure and left ventricular ejection fraction, and frequency of comorbidity did not differ between the two groups. Regarding laboratory data, Renal function was significantly worse in the non-GDMT group than in the GDMT group, and NTproBNP was significantly higher in the non-GDMT group than in the GDMT group. Regarding medications at discharge, the prescription rate of loop diuretics was significantly higher in the GDMT group than in the non-GDMT group.

Table 1: Patient characteristics by GNRI status

	Total (n=471)	Low GNRI group (n=323)	High GNRI group (n=148)	P-value
Age, years	83.9 ± 6.0	84.8 ± 6.2	82.0± 5.1	<0.001
Sex, male, %	259 (55.0)	169 (52.3)	90 (60.8)	0.105
Body weight (kg)	53.3 ± 12.1	49.1 ± 10.2	62.3 ± 10.9	<0.001
Clinical parameters at admission				
Systolic BP (mmHg)	133.1 ± 26.9	134.0 ± 27.8	131.0 ±24.7	0.245
Diastolic BP (mmHg)	72.7 ± 18.4	71.4 ± 18.3	75.6 ±18.5	0.023
Heart rate (beats/min)	94.4 ± 22.2	93.9 ±21.7	95.4 ±23.5	0.527
GNRI	87.3 ± 10.4	82.0 ± 7.2	98.9 ± 5.7	<0.001
LVEF (%)	29.1 ± 7.4	29.2 ± 7.4	28.9 ± 7.6	0.671
Medical history				
Hypertension, n (%)	413 (87.7)	278 (86.1)	135 (91.2)	0.154
Diabetes mellitus, n (%)	245 (52.0)	159 (49.2)	86 (58.1)	0.091
Dyslipidemia, n (%)	268 (57.0)	176 (54.5)	92 (62.2)	0.144
Atrial fibrillation, n (%)	193 (41.0)	118 (36.5)	75 (50.7)	0.005
COPD, n (%)	21(4.5)	15 (4.6)	6 (4.1)	0.962
Cerebral infarction, n (%)	145 (30.8)	98 (30.3)	47 (31.8)	0.84
Prior HF admission, n (%)	197 (41.8)	140 (43.3)	57 (38.5)	0.376
Dementia, n (%)	53 (11.3)	42 (13.0)	11 (7.4)	0.106
Laboratory data at admission				

Ceatinine level (mg/dL)	1.83 ± 1.83	1.75 ± 1.64	2.01 ±2.17	0.199
eGFR (ml/min/1.73m^2)	41.5 ± 23.2	42.4 ± 18.3	39.4 ± 18.5	0.172
Albumin (g/dL)	3.13 ± 0.46	2.96 ± 0.39	3.50 ± 0.36	<0.001
NTproBNP (pg/mL)	18470.5 ± 31335.4	21631.0 ± 36104.7	11496.7 ± 14347.8	<0.001
Haemoglobin (g/dL)	10.8 ± 2.1	10.4 ± 2.0	11.7 ± 2.0	<0.001
Medication at discharge				
Beta-blockers, n (%)	397 (84.3)	272 (84.2)	125 (84.5)	1.000
ACE-Is/ARBs/ARNI, n (%)	323 (68.6)	219 (67.8)	104 (70.3)	0.668
MRAs, n (%)	249 (52.9)	170 (52.6)	79 (53.4)	0.959
SGLT2-Is, n (%)	34 (7.2)	18 (5.6)	16 (10.8)	0.065
Loop diuretics, n (%)	333 (70.7)	230 (71.2)	103 (69.6)	0.804
GDMT	182 (38.6)	125 (38.7)	57 (38.5)	1.000

BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; NTproBNP, N-terminal pro-B type natriuretic peptide; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; MRAs, mineralocorticoid receptor antagonists; SGLT2-Is, sodium-glucose cotransporter 2 inhibitors; GDMT, guideline-directed medical therapy

Table 2: Patient characteristics in the low GNRI group by GDMT status

	GDMT group (n=125)	non-GDMT group (n=198)	P-value
Age, years	83.8 ± 5.7	85.5± 6.5	0.014
Sex, male, %	56 (44.8)	113 (57.1)	0.042
Body weight (kg)	49.3 ± 10.5	49.0± 10.0	0.847
Clinical parameters at admission			
Systolic BP (mmHg)	134.4 ± 28.5	133.7 ±27.4	0.84
Diastolic BP (mmHg)	73.5 ± 20.0	70.1 ±17.0	0.119
Heart rate (beats/min)	96.1 ±20.1	92.6 ±22.6	0.149
GNRI	81.9 ± 7.1	82.0 ± 7.2	0.826
LVEF (%)	29.0 ± 6.9	29.4 ± 7.7	0.657
Medical history			
Hypertension, n (%)	104 (83.2)	174 (87.9)	0.309
Diabetes mellitus, n (%)	55 (44.0)	104 (52.5)	0.168
Dyslipidemia, n (%)	64 (51.2)	112 (56.6)	0.407
Atrial fibrillation, n (%)	44 (35.2)	74 (37.4)	0.782
COPD, n (%)	9 (7.2)	6 (3.0)	0.144
Cerebral infarction, n (%)	32 (25.6)	66 (33.3)	0.178
Prior HF hospitalization, n (%)	53 (42.4)	87 (43.9)	0.876
Dementia, n (%)	13 (10.4)	29 (14.6)	0.35
Laboratory data at admission			
Ceatinine level (mg/dL)	1.10 ± 0.48	2.16 ±1.96	<0.001

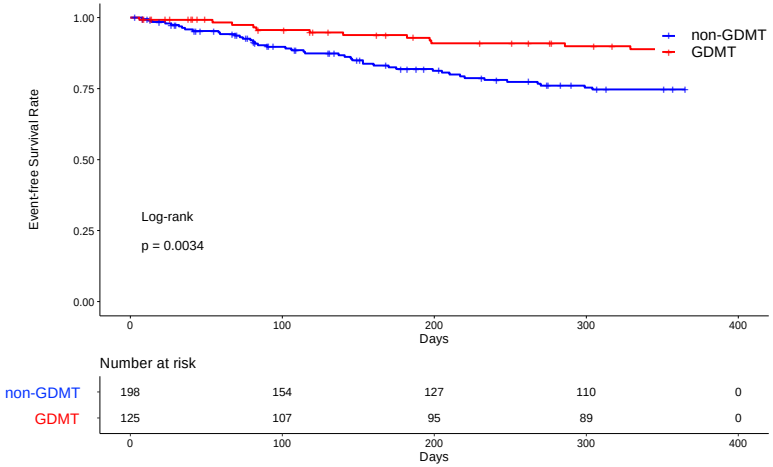
eGFR (ml/min/1.73m^2)	49.8 ± 20.9	37.7 ± 24.7	<0.001
Albumin (g/dL)	2.94 ± 0.41	2.97 ± 0.39	0.54
NTproBNP (pg/mL)	13520.7 ± 17582.1	27054.7 ± 43598.4	<0.001
Haemoglobin (g/dL)	10.8 ± 2.0	10.2 ± 1.9	0.007
Medication at discharge			
Beta-blockers, n (%)	125 (100)	147 (74.2)	<0.001
ACE-Is/ARBs/ARNI, n (%)	122 (97.6)	97 (49.0)	<0.001
MRAs, n (%)	124 (99.2)	46 (23.2)	<0.001
SGLT2-Is, n (%)	17 (13.6)	1 (0.5)	<0.001
Loop diuretics, n (%)	103 (82.4)	127 (64.1)	<0.001

BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; NTproBNP, N-terminal pro-B type natriuretic peptide; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; MRAs, mineralocorticoid receptor antagonists; SGLT2-Is, sodium-glucose cotransporter 2 inhibitors; GDMT, guideline-directed medical therapy

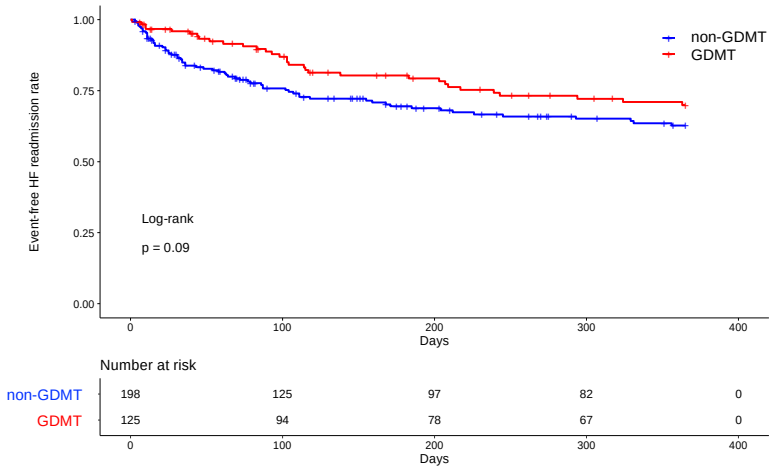
3.2. All-cause mortality and Heart Failure readmission

Sixty-seven patients died within one year; 55 in the low GNRI group and 12 in the high GNRI group. While 134 patients were readmitted due to heart failure within one year after discharge 96 in the low GNRI group and 38 in the high GNRI group. Kaplan-Meier curves for all-cause mortality and heart failure readmission are shown in Figure 1. In the low GNRI group, patients who received GDMT had significantly lower all-cause mortality. There was no significant difference in heart failure readmission rate between patients with and without GDMT. In the high GNRI group, there was no significant difference in all-cause mortality or heart failure readmission rate between patients who received GDMT and who did not receive it. Results based on Cox regression analysis are shown in Table 3. In the low GNRI group, GDMT was significantly associated with a lower all-cause mortality (HR 0.43; 95% CI, 0.22-0.83) but not with heart failure readmission (HR 0.78; 95% CI, 0.50-1.22) in the adjusted analysis. In the high GNRI group, GDMT was not significantly associated with either all-cause mortality (HR 0.55; 95% CI, 0.15-2.03) or heart failure readmission (HR 0.64; 95% CI, 0.32-1.30).

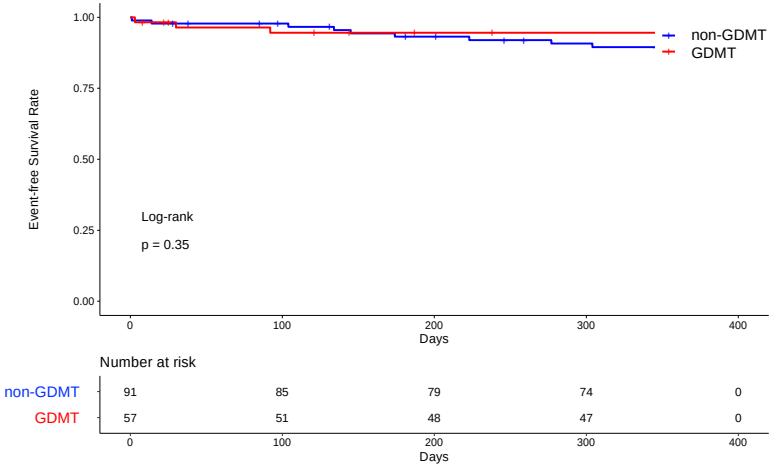
A. All-cause mortality (low GNRI group)



B. HF readmission (low GNRI group)



C. All-cause mortality (High GNRI group)



D. HF readmission (High GNRI group)

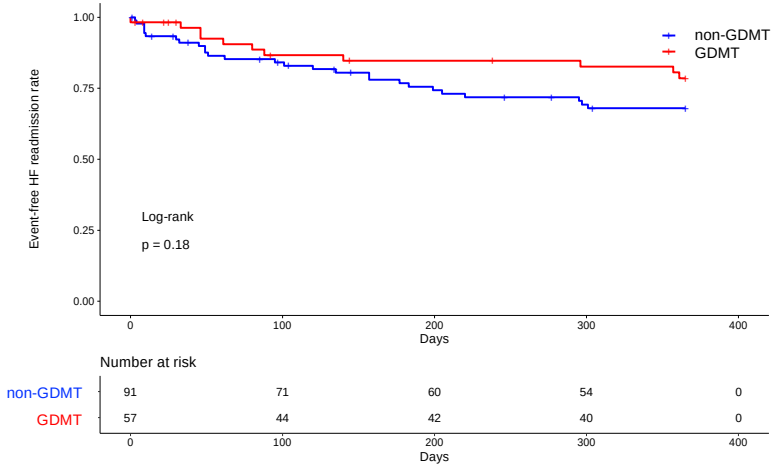


Figure1: Kaplan-Meier analysis for all-cause mortality and HF readmission by GDMT use

A and B, Kaplan-Meier curves in low GNRI group. C and D, Kaplan-Meier curves in high GNRI group. GNRI, geriatric nutritional risk index; HF, heart failure; GDMT, guideline-directed medical therapy

Table 3: Results of Cox regression analysis based on GDMT use and all-cause mortality or HF readmission

	All-cause mortality			HF readmission		
	HR	95% CI	P-value	HR	95%CI	P-value
Low GNRI group						
Unadjusted	0.40	0.21-0.75	0.005	0.69	0.45-1.06	0.092
Adjusted	0.43	0.22-0.83	0.012	0.78	0.50-1.22	0.277
High GNRI group						
Unadjusted	0.54	0.15-2.01	0.361	0.62	0.31-1.25	0.184
Adjusted	0.55	0.15-2.03	0.365	0.64	0.32-1.30	0.220

All-cause mortality and HF readmission in low GNRI group: adjusted by age, sex, prior HF admission and eGFR, and prescription for loop diuretics. All-cause mortality and HF readmission in high GNRI group: adjusted by age, sex. HF, heart failure; GDMT, guideline-directed medical therapy; GNRI, geriatric nutritional risk index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

4. DISCUSSION

This study examined the effect of discharge GDMT in elderly malnourished patients hospitalized for acute heart failure with reduced left ventricular ejection fraction, as measured by GNRI. The results showed that, in malnourished patients with low GNRI, GDMT was significantly associated with a reduction in all-cause mortality after one year of discharge. In contrast, GDMT was not associated with prognosis in patients who were not malnourished.

There is evidence that GDMT improves prognosis in many patients with HFrEF.[10, 11] However, observational studies are important to confirm the efficacy of GDMT only in the elderly population, as evidence-generating randomized controlled trials (RCTs) involve people of different ages, including young people. Previous observational studies have shown that the combination of ACE-Is /ARBs and beta-blockers was associated with a favorable prognosis in elderly patients hospitalized for acute heart failure.[12, 13] Other observational studies have shown that the triple combination of ACE-Is/ARBs, beta-blockers and MRA was also associated with a better prognosis in elderly and frail patients.[14,15] In contrast, one study reported that the triple combination therapy did not reduce mortality or readmission and increased the risk of fall-related adverse events. [16] Together, these studies implicate that the use of three or more heart failure medications in combination in the elderly is controversial. In this study, we included the relatively new heart failure drugs ARNI and SGLT2-Is to examine the effects of three and four heart failure drugs in combination therapy. The GNRI was also used to focus on malnourished patients, who may be more susceptible to adverse events.

Previous studies have shown that heart failure patients with low GNRI (indicating malnutrition) have a poorer prognosis.[17] To the best of our knowledge, this is the first observational study which examined GDMT efficacy data generated by RCTs based on elderly population at high risk of malnutrition. The effect of SGLT2-Is and ARNI may account for the better prognosis with more heart failure medications in this high-risk population prone to polypharmacy and adverse drug reactions. It has been proposed that the early diuretic effect of SGLT2i may reduce the risk of worsening heart failure associated with beta-blockers.[18] In addition, the neprilysin inhibitory effects of ARNI and SGLT2-Is may improve renal function and potassium homeostasis and reduce MRA-induced adverse effects.[18]

GDMT may be effective in frail elderly patients with HFrEF, but the GDMT achievement rate in this study was low at approximately 40%, regardless of nutritional status. The low prescription rate of SGLT2-Is may be due to the fact that it is a new induction agent, whereas the low prescription rates of ACE-Is/ARBs/ARNI and MRAs may reflect actual clinical practice. Previous studies reported that frail and elderly patients with HFrEF had lower number of heart failure medications.[15,19] Possible reasons include, a healthcare provider assumption that older adults are less tolerant of heart failure medications, lack of knowledge about managing medication side effects, and clinical inertia.[19] Addressing these issues on the healthcare provider side requires thorough heart failure education for healthcare providers and clinical decision support based on electronic health records.[20]

4.1. Limitations

First, this constituted a single-center investigation involving a limited patient cohort. Specifically, the restricted number of subjects within high GNRI group potentially hindered the detection of statistically significant differences in the endpoints for this group. Second, given the observational nature of the study, covariate adjustments were made. However, unmeasured or unknown confounders may have influenced the results. Some of the variables that differed in patient background (e.g., NT-proBNP) could also not be adjusted for due to the limited number of endpoints. Third, patients may have died or were admitted for heart failure in other healthcare institutions. Fourth, the consideration of patients' pre-admission utilization of heart failure medications was omitted. Additionally, an evaluation of the patients' ability to adhere to prescribed heart failure medications post-discharge during the follow-up period was not conducted. Finally, the dosage of heart failure medications was not taken into account in the analysis.

4.2. Implications for Practice

In this study, we were able to provide evidence that can be used as a reference for appropriate treatment of heart failure in vulnerable elderly patients. In practical setting, there are many situations in which providers hesitate to prescribe heart failure medications to elderly heart failure patients. Based on the results of this study, physicians may consider to use a

combination of multiple heart failure medications aggressively in this population. As a result, this study may provide an opportunity to improve the quality of heart failure care in the elderly.

5. Conclusions

GDMT improved all-cause mortality in malnourished elderly patients hospitalized with HFrEF. These results may provide a basis for recommending GDMT to frail elderly heart failure patients. However, there was no significant association between GDMT and reduced heart failure rehospitalization in this population. As the results are based on small observational study, future observational studies based on a larger patient population as well as experimental studies are needed to replicate the results generated in this study and establish appropriate treatment strategies in elderly heart failure patients.

6. References

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