scientific reports

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Malnutrition stratified by marasmus and kwashiorkor in adult patients with heart failure

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Malnutrition is classified into marasmus and kwashiorkor in children. However, the clinical significance of these aspects is unclear in adult patients with heart failure (HF). We divided 2308 adult patients with HF into four groups according to marasmus type (body mass index < 18.5 kg/m^2) and kwashiorkor type (serum albumin < 3.4 g/dL) malnutrition: Group C (no malnutrition, n = 1511, 65.5%), Group M (marasmus type malnutrition, n = 133, 5.8%), Group K (kwashiorkor type malnutrition, n = 554, 24.0%) and Group MK (marasmic-kwashiorkor type malnutrition, n = 110, 4.8%). Group M showed the lowest blood pressure. Groups K and MK showed higher levels of B-type natriuretic peptide. Right atrial pressure was lowest in Groups M and MK. Kaplan-Meir analysis demonstrated that Group MK had the lowest event-free rate of all-cause death and cardiac death. In the multivariable Cox proportional hazard analysis, Groups M, K, and MK were associated with all-cause death (hazard ratio 1.790, 1.657 and 2.313, respectively) and cardiac death (hazard ratio 2.053, 1.855 and 3.001, respectively) compared to Group C as a reference. Marasmus type and kwashiorkor type malnutrition are associated with distinct profiles and high mortality, and marasmic-kwashiorkor type malnutrition has the poorest prognosis.

Malnutrition is one of the most common comorbidities of patients with heart failure (HF)[1]. Malnutrition in patients with HF is associated with metabolic alteration characterized by increased inflammation and decreased protein synthesis[2–4]. As malnutrition worsens, mortality progressively increases in these population independently of left ventricular systolic function[3,5,6]. Patients at risk of malnutrition should be identified by validated screening tools[7], and several criteria for malnutrition have been reported[8–11]. The components of criteria for malnutrition screening vary depending on the screening tools[8–11]. In patients with HF, both Mini-Nutritional Assessment Short-Form (MNA-SF), which includes body mass index (BMI)[9], and Geriatric Nutritional Risk Index, which is based on serum albumin levels and body weight[8], are associated with all-cause mortality[3,12]. However, these screening tools may reflect different heterogeneous pathophysiological conditions, such as dietary intake, weight loss, and inflammation, due to the different factors that are included in each set of criteria[13]. HF, especially HF with preserved ejection fraction, is a heterogeneous syndrome, and understanding the clinical phenotypes of HF may be beneficial with regard to different targeted intervention strategies[14].

Pathophysiological characteristics of malnutrition have been well categorized in children, namely marasmus, kwashiorkor, and a mixture (marasmic-kwashiorkor)[15]. Marasmus is clinically characterized by loss of subcutaneous fat and muscle wasting, whereas kwashiorkor presents with edema and abdominal distention[15,16]. However, the clinical implications of these phenotypes of malnutrition remain unclear in adult patients with HF. In the present study, we aimed to compare and elucidate the characteristics and prognosis of adult HF patients with/without marasmus and/or kwashiorkor type malnutrition.

Results

Among the total population, the median age was 70.0 (60.0–79.0) years, with 59.7% males. Comparisons of patient characteristics are shown in Table 1. Group MK had the oldest age and lowest proportion of male sex. Systolic blood pressure was lowest in Group M compared to the other groups. Heart rate was lowest in Group C, followed by Groups M, MK, and K, in order. The prevalence of malignant tumor was highest in Group MK, followed by Group M. Regarding medication, the usage of loop diuretics was the highest in Group MK, followed

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	Group C (n = 1511)	Group M (n = 133)	Group K (n = 554)	Group MK (n = 110)	P value
Age, years	69.0 (59.0–77.0)†	68.0 (60.0–78.0)†	73.5 (63.0–82.0)*	75.0 (67.0–84.0)*	< 0.001
Male sex	951 (62.9)	61 (45.9)	316 (57.0)	50 (45.5)	< 0.001
Body mass index, kg/m^2	23.5 (21.4–26.1)*†	17.4 (16.7–18.0)†	22.9 (21.1–25.3)*	17.2 (16.5–17.8)†	< 0.001
Systolic blood pressure, mmHg	123.0 (109.0–140.0)*	111.0 (98.0–126.0)†	125.5 (108.0–149.0)*	121.5 (106.0–144.0)*	< 0.001
Heart rate, bpm	72.0 (62.0–87.0)*†	76.0 (65.0–86.0)†	86.0 (70.0–101.0)*	85.0 (71.0–95.0)*†	< 0.001
NYHA class 3 or 4, n (%)	63 (4.2)	5 (3.8)	41 (7.4)	16 (14.5)	< 0.001
Atrial fibrillation, n (%)	589 (39.0)	52 (39.1)	215 (38.8)	42 (38.2)	0.998
CAD, n (%)	453 (30.0)	23 (17.3)	208 (37.5)	27 (24.5)	< 0.001
Stroke, n (%)	250 (16.5)	26 (19.5)	127 (23.0)	21 (19.1)	0.010
COPD, n (%)	386 (29.6)	35 (30.7)	113 (27.9)	24 (27.9)	0.888
Malignant tumor, n (%)	236 (15.9)	29 (22.0)	113 (20.5)	31 (28.2)	0.001
RASIs, n (%)	1087 (71.9)	75 (56.4)	387 (69.9)	67 (60.9)	< 0.001
Beta blockers, n (%)	1093 (72.3)	98 (73.7)	393 (70.9)	76 (69.1)	0.793
MRAs, n (%)	563 (37.3)	58 (43.6)	236 (42.6)	54 (49.1)	0.014
Loop diuretics, n (%)	923 (61.1)	91 (68.4)	423 (76.4)	92 (83.6)	< 0.001
Statins, n (%)	652 (43.2)	29 (21.8)	180 (32.5)	30 (27.3)	< 0.001
Antihyperuricemic agents, n (%)	365 (24.2)	27 (20.3)	108 (19.5)	16 (14.5)	0.022
ICD or CRT, n (%)	240 (15.9)	26 (19.5)	54 (9.7)	8 (7.3)	< 0.001
BNP, pg/mL	179.6 (63.5–439.9)*†	374.4 (100.3–595.8)†	543.9 (225.3–1048.0)*	598.6 (357.9–1097.1)*†	< 0.001
Hemoglobin, g/dL	13.3 (12.0–14.7)*†	12.7 (11.5–13.9)†	11.3 (9.7–13.1)*	10.5 (8.9–11.8)*†	< 0.001
Lymphocytes, %	24.0 (17.0–31.0)*†	22.0 (15.0–30.0)†	15.0 (9.0–21.0)*	13.5 (9.0–20.0)*†	< 0.001
Albumin, g/dL	4.0 (3.7–4.3)†	3.9 (3.6–4.2)†	3.0 (2.7–3.2)*	2.9 (2.6–3.1)*†	< 0.001
eGFR, mL/min/1.73m^2	60.3 (47.1–72.9)*†	59.3 (44.1–79.8)†	51.7 (35.5–68.5)*	58.3 (37.4–75.7)*†	< 0.001
Sodium, mmol/L	140.0 (138.0–142.0)*†	139.0 (137.0–141.0)†	139.0 (136.0–141.0)*	138.0 (134.5–141.0)*†	< 0.001
Uric acid, mg/dL	6.1 (5.1–7.4)	6.1 (4.6–7.6)	6.3 (4.8–8.0)	5.7 (4.5–7.2)	0.140
C-reactive protein, mg/dL	0.12 (0.05–0.38)*†	0.10 (0.05–0.28)†	1.54 (0.39–5.33)*	1.11 (0.28–4.53)*†	< 0.001
Total cholesterol, mg/dL	182.0 (157.0–210.0)*†	189.5 (167.0–211.0)†	154.0 (128.5–181.5)*	152.0 (127.0–189.0)*†	< 0.001
HbA1c, %	5.8 (5.5–6.3)*	5.7 (5.3–6.1)†	5.9 (5.4–6.5)*	5.7 (5.3–6.2)†	< 0.001
LVEF, %	55.0 (40.4–64.2)	57.0 (36.1–65.4)	54.0 (39.2–62.6)	56.5 (42.6–63.0)	0.427
Mean PAWP, mmHg§	12.0 (9.0–18.0)†	11.0 (8.0–15.5)†	15.0 (9.0–22.0)*	12.0 (6.0–17.5)†	< 0.001
Systolic PAP, mmHg§	32.0 (25.0–41.0)†	29.0 (23.0–39.0)†	34.0 (28.0–44.0)*	34.0 (25.5–44.0)	0.002
Diastolic PAP, mmHg§	14.0 (10.0–20.0)†	12.0 (8.0–16.0)†	17.0 (12.0–23.0)*	15.0 (9.5–20.0)	< 0.001
Mean PAP, mmHg§	21.0 (16.0–28.0)†	19.0 (15.0–26.0)†	24.0 (18.0–31.0)*	22.5 (16.0–29.0)	< 0.001
Mean RAP, mmHg§	6.0 (4.0–9.0)*†	5.0 (2.0–8.0)†	8.0 (5.0–12.0)*	5.0 (3.0–8.5)†	< 0.001
Cardiac index, L/min/m^2§	2.5 (2.2–3.0)†	2.5 (2.1–3.0)	2.4 (2.0–2.9)	2.4 (2.0–3.0)	0.026

Table 1. Patient characteristics (n = 2308). *P < 0.05 vs. Group M and †P < 0.05 vs. Group K. §Right heart catheterization was performed in patients selected by attending physicians (n = 1303). NYHA, New York Heart Association; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; RASI, renin-angiotensin system inhibitor; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; PAWP, pulmonary artery wedge pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure.

by Groups K, M, and C, in that order. In laboratory data, levels of B-type natriuretic peptide (BNP) increased and hemoglobin decreased in Groups C, M, K, and MK. According to right heart catheterization, Group K showed higher mean pulmonary artery wedge pressure, systolic/diastolic/mean pulmonary artery pressure, and mean right atrial pressure compared to Groups C and M.

Tables 2 and 3 show the results of the logistic regression analysis evaluating factors associated with marasmus type and kwashiorkor type malnutrition, respectively. According to the multivariable analysis, systolic blood pressure, use of renin-angiotensin system inhibitors and statins, and levels of hemoglobin, sodium, and glycated hemoglobin were negatively associated with marasmus type malnutrition, while levels of log-transformed BNP and estimated glomerular filtration rate were positively associated. On the other hand, levels of hemoglobin, lymphocytes, sodium, and total cholesterol were negatively associated with kwashiorkor type malnutrition, while levels of BNP and C-reactive protein were positively associated.

During the post-discharge follow-up period (median 1679 days), a total of 809 deaths from any cause, including 362 cardiac deaths, occurred. Kaplan–Meier analysis revealed that event-free survival from death from any cause was the lowest in Group MK, while Group C had the highest rate of survival (Fig. 1, log-rank P < 0.001). Regarding cardiac death, Group MK showed the lowest and Group C showed the highest event-free survival,

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.004 (0.995–1.014)	0.343	1.006 (0.992–1.019)	0.423
Male sex	0.530 (0.405–0.692)	< 0.001	0.779 (0.539–1.125)	0.182
Systolic blood pressure	0.992 (0.987–0.997)	0.001	0.990 (0.983–0.998)	0.013
Heart rate	1.003 (0.998–1.008)	0.238	NS	
NYHA class 3 or 4	1.783 (1.093–2.907)	0.020	1.064 (0.543–2.085)	0.857
Atrial fibrillation	0.989 (0.753–1.300)	0.939	NS	
Coronary artery disease	0.550 (0.398–0.761)	< 0.001	0.802 (0.493–1.305)	0.374
Stroke	1.073 (0.766–1.504)	0.682	NS	
COPD	1.014 (0.735–1.398)	0.933	NS	
Malignant tumor	1.593 (1.164–2.179)	0.004	1.438 (0.938–2.204)	0.096
RASIs	0.564 (0.429–0.740)	< 0.001	0.555 (0.386–0.799)	0.002
Beta blockers	0.983 (0.732–1.320)	0.907	NS	
MRAs	1.355 (1.037–1.770)	0.026	1.017 (0.676–1.530)	0.935
Loop diuretics	1.629 (1.201–2.211)	0.002	1.321 (0.830–2.104)	0.241
Statins	0.475 (0.350–0.645)	< 0.001	0.645 (0.419–0.993)	0.047
Antihyperuricemic agents	0.724 (0.512–1.022)	0.066	NS	
ICD or CRT	0.980 (0.668–1.437)	0.917	NS	
Log-BNP	2.051 (1.565–2.687)	< 0.001	1.648 (1.152–2.358)	0.006
Hemoglobin	0.820 (0.772–0.871)	< 0.001	0.871 (0.796–0.953)	0.003
Lymphocytes	0.982 (0.967–0.997)	0.019	0.998 (0.979–1.018)	0.873
eGFR	1.007 (1.001–1.012)	0.023	1.010 (1.002–1.019)	0.014
Sodium	0.920 (0.889–0.951)	< 0.001	0.931 (0.890–0.974)	0.002
Uric acid	0.916 (0.848–0.989)	0.025	0.977 (0.885–1.079)	0.647
C-reactive protein	1.021 (0.985–1.060)	0.225	NS	
Total cholesterol	1.000 (0.995–1.004)	0.859	NS	
HbA1c	0.710 (0.595–0.847)	< 0.001	0.724 (0.564–0.930)	0.011
LVEF	1.000 (0.989–1.010)	0.933	NS	

Table 2. Logistic regression analysis for marasmus type malnutrition (n = 243/2,308 patients). Age, male sex, and variables with P values of < 0.05 were entered into multivariable model. OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; RASI, renin-angiotensin system inhibitor; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; Log-BNP, log-transformed B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; NS, not selected. Age, systolic blood pressure, heart rate, log-BNP, hemoglobin, lymphocytes, eGFR, sodium, uric acid, C-reactive protein, total cholesterol, HbA1c, and LVEF were analyzed as continuous variables.

while Groups M and K demonstrated intermediate survival (Fig. 2, log-rank P < 0.001). Table 4 summarizes the results of the Cox proportional hazard analysis performed to assess the association between malnutrition and event-free survival time, adjusting for the potential confounding factors. In the univariable analysis, Groups M, K, and MK were associated with both death from any cause and cardiac death, compared to Group C as a reference, respectively. After adjustment for prespecified covariables, Groups M (hazard ratio 1.790, P = 0.011), K (hazard ratio 1.657, P = 0.004), and MK (hazard ratio 2.313, P = 0.002) were associated with the primary endpoint, respectively (Table 4A). Similarly, Groups M (hazard ratio 2.053, P = 0.029), K (hazard ratio 1.855, P = 0.021), and MK (hazard ratio 3.001, P = 0.004) were also associated with the secondary endpoint, respectively (Table 4B).

Discussion

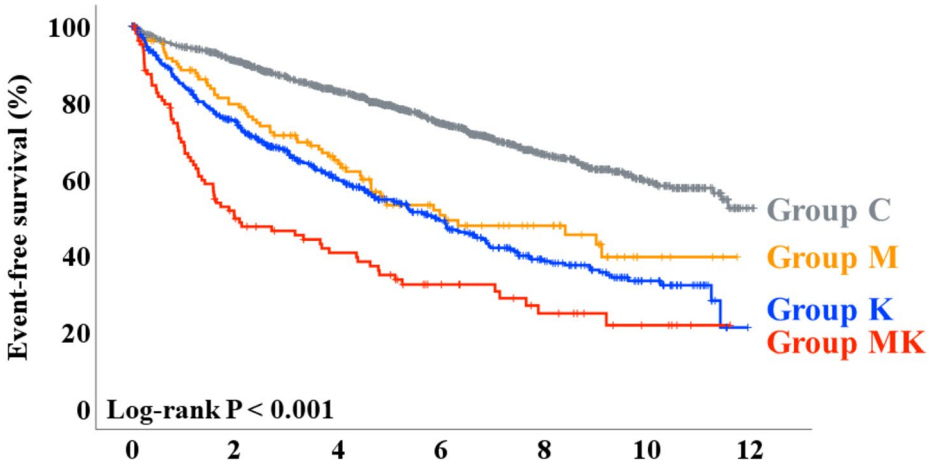
In the present study, we investigated the clinical characteristics and outcomes of a cohort of patients with HF, categorized into four distinct groups based on a combination of marasmus type and/or kwashiorkor type malnutrition. We revealed that approximately 35% of patients with HF had at least marasmus type malnutrition, kwashiorkor type malnutrition, or both. Although combined marasmic-kwashiorkor type malnutrition was rare in adult patients with HF, these patients had the worst prognosis.

In children, protein-energy malnutrition occurs as a result of inadequate protein and energy supply[15,16]. Marasmus, one of the two main extreme forms of protein-energy malnutrition, results from calorie and energy deficiency mainly in children younger than 5 years[15,16]. Children with marasmus present with loose skin due to the loss of subcutaneous fat, muscle wasting, hypotension, bradycardia, and absence of edema[15]. Although the present study defined marasmus type malnutrition simply based on low BMI, Group M showed some important characteristics that are similar to those in children with marasmus. Blood pressure was the lowest in Group M

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.017 (1.011–1.024)	< 0.001	1.000 (0.985–1.015)	0.969
Male sex	0.767 (0.639–0.920)	0.004	0.754 (0.493–1.153)	0.192
Systolic blood pressure	1.003 (1.000–1.006)	0.031	1.005 (0.998–1.012)	0.126
Heart rate	1.017 (1.013–1.021)	< 0.001	1.003 (0.995–1.011)	0.504
NYHA class 3 or 4	2.175 (1.511–3.131)	< 0.001	0.497 (0.189–1.308)	0.157
Atrial fibrillation	0.988 (0.821–1.189)	0.899	NS	
Coronary artery disease	1.344 (1.110–1.628)	0.002	1.209 (0.745–1.963)	0.443
Stroke	1.424 (1.139–1.782)	0.002	1.184 (0.738–1.901)	0.484
COPD	0.916 (0.729–1.150)	0.448	NS	
Malignant tumor	1.420 (1.132–1.782)	0.002	0.755 (0.463–1.232)	0.261
RASIs	0.897 (0.738–1.090)	0.273	NS	
Betablockers	0.915 (0.750–1.116)	0.380	NS	
MRAs	1.277 (1.064–1.534)	0.009	0.968 (0.636–1.474)	0.880
Loop diuretics	2.147 (1.745–2.643)	< 0.001	1.168 (0.722–1.891)	0.527
Statins	0.654 (0.541–0.792)	< 0.001	0.683 (0.443–1.053)	0.084
Antihyperuricemic agents	0.733 (0.585–0.919)	0.007	0.853 (0.539–1.350)	0.497
ICD or CRT	0.534 (0.398–0.715)	< 0.001	0.774 (0.453–1.323)	0.349
Log-BNP	4.869 (3.903–6.073)	< 0.001	3.595 (2.356–5.487)	< 0.001
Hemoglobin	0.658 (0.626–0.693)	< 0.001	0.797 (0.721–0.882)	< 0.001
Lymphocytes	0.910 (0.898–0.922)	< 0.001	0.955 (0.932–0.977)	< 0.001
eGFR	0.989 (0.985–0.994)	< 0.001	1.006 (0.997–1.016)	0.189
Sodium	0.893 (0.870–0.916)	< 0.001	0.932 (0.884–0.983)	0.009
Uric acid	1.023 (0.972–1.076)	0.384	NS	
C-reactive protein	1.446 (1.371–1.525)	< 0.001	1.361 (1.229–1.506)	< 0.001
Total cholesterol	0.981 (0.977–0.985)	< 0.001	0.991 (0.986–0.997)	< 0.001
HbA1c	1.108 (1.013–1.213)	0.025	1.075 (0.881–1.311)	0.475
LVEF	0.995 (0.988–1.002)	0.144	NS	

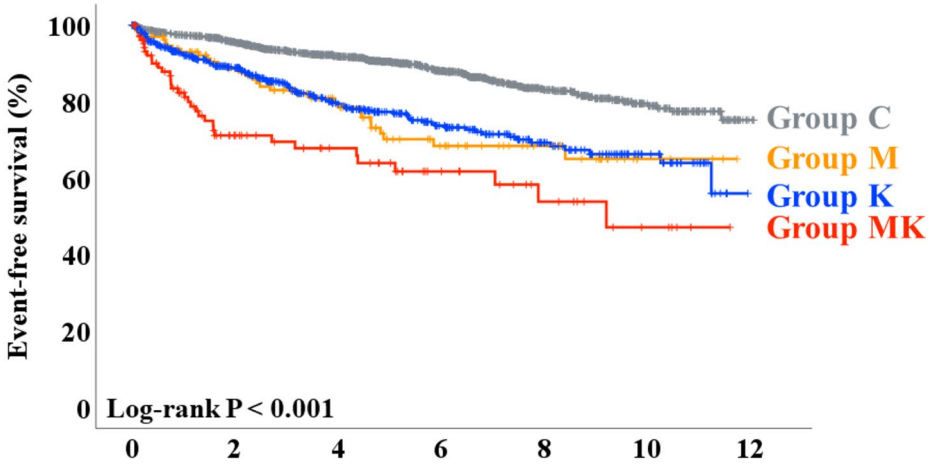
Table 3. Logistic regression analysis for kwashiorkor type malnutrition (n = 664/2308 patients). Age, male sex, and variables with P values of < 0.05 were entered into multivariable model. OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; RASI, renin-angiotensin system inhibitor; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; Log-BNP, log-transformed B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; NS, not selected. Age, systolic blood pressure, heart rate, log-BNP, hemoglobin, lymphocytes, eGFR, sodium, uric acid, C-reactive protein, total cholesterol, HbA1c, and LVEF were analyzed as continuous variables.

and heart rate was lower than in those with kwashiorkor type malnutrition. The lower use of loop diuretics and lower levels of BNP compared to those in Groups K and MK indicated that congestion was less severe in Group M. The results of right heart catheterization support this interpretation. The main features of the HF patients with marasmus type malnutrition included low BMI, lower blood pressure, and higher prevalence of malignant tumor as a comorbidity. These characteristics suggest greater significance of frailty, sarcopenia, and cachexia in those populations[1,17–19]. HF Patients with frailty sarcopenia, and/or cachexia are at high risk of application of implantable cardioverter-defibrillator and/or cardiac resynchronization therapy, impaired exercise capacity, and high mortality[17,20–23]. Considering these pathophysiologies, treatment for HF patients with marasmus type malnutrition should be multifactorial and include exercise training, nutritional supplementation, and treatment for comorbidities[1,19]. Although the causal relationship was unclear, the logistic regression analysis revealed several important factors that were associated with marasmus type malnutrition. Patients with lower systolic blood pressure were at risk of marasmus type malnutrition, suggesting that advanced HF is associated with marasmus type malnutrition[1,19,24]. The use of renin-angiotensin receptor inhibitors showed a protective effect on the presence of marasmus type malnutrition. Angiotensin II type 1 receptors are present in skeletal muscle fibers and increased renin-angiotensin system signaling promotes skeletal muscle wasting[25]. The results of the present study were consistent with those of previous studies reporting potential therapeutic effects of renin-angiotensin receptor inhibitors for sarcopenia[26–30]. There is a lack of evidence regarding the effectiveness of statins to prevent marasmus type malnutrition. The use of statins has been reported to be protective for sarcopenia[31], but has not been proven to be effective for frailty and cachexia[32,33]. Since routine administration of statins in patients with HF without other indications is not recommended by the guidelines[19], the priority of the use of statins seemed



Number at risk							
Group C	1,511	1,263	957	612	321	135	3
Group M	133	98	66	38	25	5	0
Group K	554	379	241	149	77	32	0
Group MK	110	48	35	21	12	5	0

Figure 1. Primary outcome: Kaplan–Meier analysis. Kaplan–Meier analysis demonstrated that event-free survival of death from any cause was lowest in Group MK while Group C showed the best prognosis.



Number at risk							
Group C	1,511	1,263	957	612	321	135	3
Group M	133	98	66	38	25	5	0
Group K	554	379	241	149	77	32	0
Group MK	110	48	35	21	12	5	0

Figure 2. Secondary outcome: Kaplan–Meier analysis. Shown are the results of the Kaplan–Meier analysis which revealed that event-free survival of cardiac death was the lowest in Group MK, whereas Groups M and K showed intermediate prognosis.

to be low in HF patients with marasmus type malnutrition, which showed lower prevalence of coronary artery disease and stroke.

Kwashiorkor is another extreme form of protein-energy malnutrition that mainly occurs in older infants and young children suffering from a diet with inadequate protein but reasonably normal caloric intake[15,16]. Children with kwashiorkor are characterized by edema, abdominal distension, hepatomegaly, dermatosis, and

(A) Death from any cause (event n = 809)	Hazard ratio (95% CI)	P value
Group C	Reference	–
Group M (unadjusted)	2.053 (1.568–2.688)	< 0.001
Group M (model 1)	2.287 (1.743–2.999)	< 0.001
Group M (model 2)	1.790 (1.141–2.810)	0.011
Group K (unadjusted)	2.451 (2.102–2.857)	< 0.001
Group K (model 1)	2.251 (1.928–2.628)	< 0.001
Group K (model 2)	1.657 (1.172–2.344)	0.004
Group MK (unadjusted)	4.112 (3.193–5.296)	< 0.001
Group MK (model 1)	3.718 (2.879–4.801)	< 0.001
Group MK (model 2)	2.313 (1.375–3.893)	0.002
(B) Cardiac death (event n = 362)	**Hazard ratio (95% CI)**	**P value**
Group C	Reference	–
Group M (unadjusted)	2.363 (1.622–3.443)	< 0.001
Group M (model 1)	2.627 (1.798–3.838)	< 0.001
Group M (model 2)	2.053 (1.074–3.922)	0.029
Group K (unadjusted)	2.236 (1.770–2.826)	< 0.001
Group K (model 1)	2.102 (1.661–2.661)	< 0.001
Group K (model 2)	1.855 (1.096–3.139)	0.021
Group MK (unadjusted)	4.282 (2.965–6.183)	< 0.001
Group MK (model 1)	4.030 (2.780–5.843)	< 0.001
Group MK (model 2)	3.001 (1.419–6.345)	0.004

Table 4. Cox proportional hazard analysis for the primary and secondary outcomes (n = 2308). CI, confidence interval. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, New York Heart Association class 3 or 4, left ventricular ejection fraction, systolic blood pressure, coronary artery disease, use of renin-angiotensin system inhibitors, beta blockers, mineralocorticoid receptor antagonists, statins, and antihyperuricemic agents, implantable cardioverter-defibrillator and/or cardiac resynchronization therapy, and levels of log-transformed B-type natriuretic peptide, estimated glomerular filtration rate, hemoglobin, lymphocytes, uric acid, total cholesterol, and sodium. Age, left ventricular ejection fraction, systolic blood pressure, and levels of log-transformed B-type natriuretic peptide, estimated glomerular filtration rate, hemoglobin, lymphocytes, uric acid, total cholesterol, and sodium were analyzed as continuous variables.

hypopigmented hair[15]. Low protein intake leads to a reduction in serum albumin and ferritin levels, causing hypoalbuminemia and anemia, respectively[16]. Hypoalbuminemia decreases oncotic pressure resulting in edema[16], which occurs in adult patients with HF due to diminished intake of protein as in children, but several other mechanisms also exist[34,35]. Previous studies have reported that inflammation (reflected by increased levels of C-reactive protein)[35], along with lower levels of lymphocytes[35], hemoglobin[36,37], sodium[36,37], and total cholesterol[36,37], are associated with hypoalbuminemia in patients with HF. BMI is not a determinant of hypoalbuminemia[35–37]. The results of logistic regression analysis in the present study were consistent with these reports. In addition, higher levels of BNP were also independently associated with kwashiorkor type malnutrition. Patients with this type of malnutrition in the present study showed a higher use of loop diuretics and higher levels of BNP, pulmonary artery wedge pressure, pulmonary artery pressure, and right atrial pressure, suggesting that their congestion was more severe. In those populations, congestion may lead to hypoalbuminemia by hemodilution and decreased liver synthesis due to congestive liver[34,38,39]. Lower levels of estimated glomerular filtration rate were derived from renal congestion in some patients with kwashiorkor type malnutrition[40,41]. Thus, more aggressive decongestion targeting levels of serum albumin should be considered in patients with kwashiorkor type malnutrition[42–44].

The present study had some limitations. The definition of marasmus type malnutrition was based solely on BMI. Body composition (e.g., skeletal muscle and fat) should be assessed in further studies. Detailed information of malignant tumor was not recorded. Right heart catheterization was performed in selected patients based on the decision by their attending cardiologists. Patients with chronic liver disease and/or chronic kidney disease not requiring maintenance dialysis were not excluded.

Conclusion

HF patients with marasmus type malnutrition and those with kwashiorkor type malnutrition demonstrate distinct characteristics. Classifying the nutritional status based on these phenotypes is useful for understanding their underlying pathophysiology and determining the appropriate treatment. HF patients with marasmic-kwashiorkor type malnutrition are at the highest risk of death from any cause and cardiac death.

Methods

Study population

This was an observational study. The patient flow chart is shown in Fig. 3. We recruited a total of 2484 hospitalized patients with acute decompensated HF who were discharged alive between Jan. 2010 and Mar. 2021. Diagnosis of acute decompensated HF was confirmed by attending cardiologists based on the established HF guidelines[19,24,45–48]. Among them, patients for whom we lacked data on levels of serum albumin (n = 8) and those on maintenance dialysis (n = 168) were excluded. Finally, a total of 2308 patients were enrolled. In the present study, we defined marasmus type malnutrition as a BMI of < 18.5 kg/m^2 and kwashiorkor type malnutrition as serum albumin of < 3.4 g/dL, based on previous studies[35,37,49–51]. The patients were divided into four groups according to the presence/absence of marasmus type and kwashiorkor type malnutrition: Group C (those with neither marasmus type nor kwashiorkor type malnutrition [control group], n = 1511, 65.5%), Group M (those with only marasmus type malnutrition, n = 133, 5.8%), Group K (those with only kwashiorkor type malnutrition, n = 554, 24.0%), and Group MK (those with both marasmus type and kwashiorkor type malnutrition [marasmic-kwashiorkor type malnutrition], n = 110, 4.8%). We compared the patients' characteristics and prognosis after discharge. Demographic data, including BMI and medication, were obtained at discharge. BMI was calculated by dividing weight (kg) by height (m) squared[49,52]. Levels of serum albumin were measured using a bromocresol purple dye-binding method. Levels of plasma BNP were measured using a chemiluminescent immunoassay method. Levels of serum total cholesterol, C-reactive protein, uric acid, creatinine were measured using enzymic method, latex agglutination immunoassay method, uricase-peroxidase method, and enzymic method, respectively. Estimated glomerular filtration rate was determined by a 3-variable Japanese equation using levels of serum creatinine and age[53]. Laboratory tests were blindly performed by clinical laboratory technologists using Siemens Atellica CH at Fukushima Medical University Hospital. The results of laboratory data and echocardiography were based on data recorded within 1 week prior to discharge. We recruited data on right heart catheterization in some patients performed in a stable condition on medical judgement[39]. The decision to perform catheterization was left to the attending cardiologists. The primary and secondary outcomes were post-discharge death from any cause and cardiac death, respectively. We considered death as cardiac death if the attending physician judged the death was due to worsening HF, ventricular fibrillation, or acute coronary syndrome. The investigation conforms with the principles outlined in the *Declaration of Helsinki*[54]. The study protocol was approved by the ethical committee of Fukushima Medical University. All patients gave written informed consent to participate in this study.

Statistical analysis

All continuous variables were assessed for normality using the Shapiro–Wilk test and were determined to be non-normally distributed. Continuous variables were expressed as median (interquartile range) and compared using the Kruskal–Wallis test, followed by the Steel–Dwass post-hoc test if significant. Categorical variables were expressed as numbers (percentages) and compared using the chi-square test. Variables associated with the presence of marasmus type and kwashiorkor type malnutrition were evaluated by the logistic regression analysis. Age, sex, and other significant variables were further entered into multivariable model. Event-free survival after discharge was compared using Kaplan–Meier analysis with the log-rank test. The prognostic impact of marasmus type and kwashiorkor type malnutrition was evaluated using the Cox proportional hazard analysis with Group C as a reference. Hazard ratios were adjusted in two steps to account for the influence of confounding factors. Model 1 was adjusted for age and sex. Model 2, based on the Seattle Heart Failure Model[55,56], was adjusted for age, sex, New York Heart Association class 3 or 4, left ventricular ejection fraction, systolic blood pressure, coronary artery disease, use of renin-angiotensin system inhibitors, beta blockers, mineralocorticoid receptor antagonists,

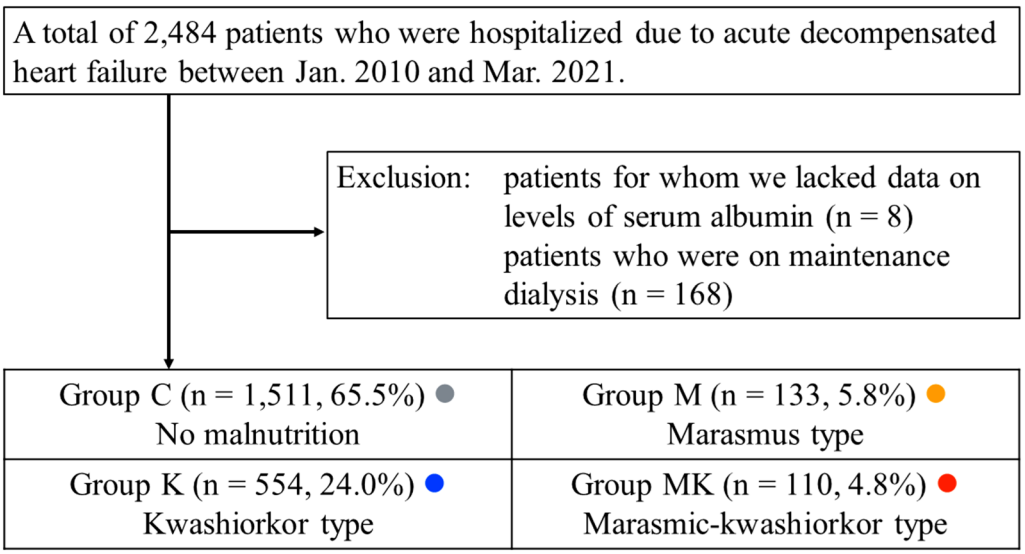


Figure 3. Patient flow chart.

statins, and antihyperuricemic agents, implantable cardioverter-defibrillator and/or cardiac resynchronization therapy, and levels of log-transformed BNP, estimated glomerular filtration rate, hemoglobin, lymphocytes, uric acid, total cholesterol, and sodium.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 14 January 2024; Accepted: 14 August 2024
Published online: 25 August 2024

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Acknowledgements

The authors thank Kumiko Watanabe, Yumi Yoshihisa, Shiori Togashi, and Tomiko Miura for their technical assistance. The acquisition of data was supported by Ayumi Haneda, Akito Endo, Mari Hoshi, Manami Akimoto, Mimori Itami, Shiori Urayama, and Yuuichi Yokoyama from the Office for Diversity and Inclusion, Fukushima Medical University, Fukushima, Japan. The present study was supported in part by grants-in-aid for Scientific Research (Nos. 20K07828 and 22K15670) from the Japan Society for the Promotion of Science.

Author contributions

Y.Sa., A.Y., Y.Su., T.M., T.S., T.K., M.O., A.K., T.Y., K.N., and Y.T. contributed to the conception or design of the work. Y.Sa., A.Y., Y.Su., T.M., T.S., T.K., M.O., A.K., T.Y., K.N., and Y.T. contributed to the acquisition, analysis, or interpretation of data for the work. Y.Sa., A.Y., and Y.T. drafted the manuscript. Y.Sa., A.Y., Y.Su., T.M., T.S., T.K., M.O., A.K., T.Y., K.N., and Y.T. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Competing interests

The authors declare no competing interests.

Additional information

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