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Description	**〈概要〉** 研究グループは、大腿部の筋肉内脂肪が非虚血性心筋症による心不全の予後に影響を与えることを初めて明らかにしました。本研究成果により、大腿部の筋肉内脂肪を測定することで心不全の予後を推測できる可能性が示されました。 皮下脂肪や内臓脂肪以外の脂肪組織のことを異所性脂肪と呼び、主なものとしては心臓周囲脂肪や筋肉内脂肪があります。異所性脂肪の一つである心臓周囲脂肪が狭心症や心筋梗塞といった冠動脈疾患や心房細動を引き起こすとの報告はありましたが、身体の他の部位の異所性脂肪が心不全に与える影響についての報告は今までほとんどありませんでした。大腿部の筋肉内脂肪が糖尿病など生活習慣病の発症に影響を与えているという報告は既にあったため、今回、大腿部の筋肉内脂肪が心不全患者の予後に関係するかを調査しました。 本研究グループは、2017 年 9 月から 2020 年 1 月に大阪公立大学医学部附属病院で、心機能が低下した心不全の精査目的に入院し冠動脈疾患が否定された連続 93 例を対象とし、CT で大腿部のスキャンを行い、筋肉量と筋肉内脂肪を測定して筋肉内脂肪比を算出しました。筋肉内脂肪比を中央値で 2 群に分類し、それぞれの群で心血管死もしくは心血管系の病気による予期しない入院の発生率に差があるか検討を行いました。その結果、筋肉内脂肪比が高い群の方が発生率が高く、筋肉内脂肪比が独立した予後規定因子であることが明らかになりました。 ‘筋肉内脂肪が多いと心不全予後が悪くなることを明らかに―筋肉量や筋力以外に筋肉の質も心不全に影響―’ 大阪公立大学. https://www.omu.ac.jp/info/research_news/entry-00438.html (参照 2022-04-08)

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Abstract

Skeletal muscle atrophy is an independent prognostic predictor for patients with chronic heart failure, and the concept of sarcopenia is drawing attention. Furthermore, the importance of not only muscle mass but also ectopic fat has been pointed out. However, there is a lack of consensus on the implications of ectopic fat for the prognosis in patients with non-ischemic cardiomyopathy. We investigated whether ectopic fat in the thigh affects the prognosis with non-ischemic cardiomyopathy. This prospective study recruited 145 patients diagnosed with nonischemic cardiomyopathy between September 2017 and January 2020. Finally, 93 patients with a reduced ejection fraction (EF) were enrolled. The clinical endpoints were cardiovascular death or unexpected rehospitalization because of a cardiac event. Using computed tomography, the percentage of intramuscular fat (%IMF) in the thigh was measured in all patients. Patients were divided into two groups based on the median %IMF. The results of Spearman correlation coefficient analysis revealed a correlation among %IMF and peak oxygen uptake (Spearman $r=-0.221$, $p = 0.036$). Kaplan–Meier analysis results showed significantly higher risk of adverse events in the high %IMF group (log-rank $p = 0.013$). Multivariate Cox regression analysis results revealed the %IMF as an independent factor for adverse events (hazard ratio, 1.361; 95% confidence interval, 1.043–1.745; $p = 0.018$). In conclusion, %IMF may have adverse consequences such as increased cardiac events in patients with nonischemic cardiomyopathy with a reduced EF.

Keywords: heart failure, nonischemic cardiomyopathy, intramuscular fat, prognosis

Sarcopenia, which is characterized by the loss of muscle mass, is a prognostic factor for heart failure (HF).[1] Recent studies have reported that not only the muscle mass but also its quality is important, and ectopic fat such as intramuscular fat (IMF) has garnered scientific attention.[2, 3] Ectopic fat secretes hormones and adipocytokines as internal secretion and has a role in accumulating fat.[4, 5] Ectopic fat has been reported to cause various diseases, and pericardial fat, a type of ectopic fats, causes coronary artery disease and atrial fibrillation.[6, 7] However, no consensus has been achieved regarding the correlation of HF with ectopic fat in other parts of the body. To our knowledge, no studies have demonstrated a correlation between HF prognosis and thigh IMF. This study, therefore, explored the correlation between thigh IMF and the prognosis of nonischemic cardiomyopathy with a reduced ejection fraction (EF).

Methods

This single-center, prospective, observational study evaluated 145 patients admitted to Osaka City University Graduate School of Medicine between September 2017 and January 2020 because of nonischemic cardiomyopathy. The patients were consecutively enrolled after obtaining informed consent. Eligible patients had to be aged >18 years. All patients were diagnosed with HF based on the Framingham Diagnostic Criteria for HF, considering two major criteria or one major criterion and two minor criteria. All patients underwent cardiac catheterization, including coronary angiography, for the initial diagnosis of nonischemic cardiomyopathy. Exclusion criteria for this study were 1) patients with a left ventricular EF (LVEF) ≥40 %, 2) open heart surgery within the

preceding 3 months, 3) the presence of severe valvular heart disease, 4) inherited myopathy that appeared to have a strong impact on muscle quality, and 5) unwillingness to provide informed consent. The final study sample included 93 patients with HF with a diagnosis of nonischemic cardiomyopathy. The patients were followed until April 2021. The study protocol was approved by the institutional ethics committee of Osaka City University (approval number: 3785) and was conducted in accordance with the recommendations of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients.

Computed tomography (CT) was performed at baseline using a 64-slice CT scanner (LightSpeed VCT VISION, GE Healthcare Japan Co., Tokyo, Japan). Afterward, axial images were transferred to an offline workstation (Synapse Vincent, Fujifilm Medical Co., Tokyo, Japan) for postprocessing and image analysis. The measurement position of the thigh was set between the middle part of the femoral head and the midline of the patella. The edges of the muscle groups were carefully traced using Synapse Vincent to calculate the cross-sectional area of the muscle groups and the subcutaneous adipose tissue (SAT) of the thigh. The fat volume or area was defined as tissue with an attenuation of −200 to −30 HU. The thigh IMF area was defined as the fat interior to the thigh muscle. Thigh SAT was defined as the cross-sectional area of fat exterior to the muscle in the subcutaneous space. Muscle mass was defined based on the following formula:

Muscle mass = Overall area of the thigh – (IMF + SAT + bone marrow areas)

In the thigh muscle, the percentage of the IMF (%IMF) was evaluated based on the following

formula:

%IMF = (IMF area) / (IMF + muscle areas)

We measured the area of both the left and right thighs, and recorded the average value. CT image analysis was performed in a blinded manner.

Baseline clinical parameters and laboratory data were collected from the patients' medical records. Data on medication were collected at discharge. Routine laboratory analyses were performed for all patients at discharge. The estimated glomerular filtration rate (eGFR) was calculated using the modified IDMS–MDRD Study equation: eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine) − 1.094 × (age) − 0.287 × (0.739 for women).[8] Smoking was assessed as current tobacco smoking.

A symptom-limited cardiopulmonary exercise test (CPX) was conducted for all patients in clinically stable condition before discharge. The exercise stress tests were performed with an upright cycle ergometer (Strength Ergo 8; Fukuda Denshi, Tokyo, Japan) using a ramp protocol. After a 4-min rest on the cycle ergometer, the exercise began with a 4-min warm-up at 0 or 10 W, followed by an incrementally increasing work rate of 10 W every minute. The protocol was selected by the supervising physician depending on the presumed fitness level of the patient. Expired gas analysis was performed following the breath-by-breath method using an expired gas analyzer (Cpex-1; Inter Reha, Tokyo, Japan). Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured before, during, and after the exercise. The anaerobic threshold (AT)

was determined using the V-slope method.[9] Peak oxygen uptake (peak VO_2) was defined as the peak values during incremental exercise. Linear regression analysis revealed the slope of the relationship between VE and VCO_2 (VE/VCO_2 slope) as a marker of ventilator efficiency.

Grip strength and isometric knee extension muscle strength were measured as reference values for muscle strength on the same day as CPX. Grip strength was measured using a handgrip dynamometer (TAKEI GRIP-D [Digital Grip Dynamometer]; Takei Scientific Instruments Co. Ltd., Japan). Isometric knee extension muscle strength was measured with a hand-held dynamometer (JTech Commander PowerTrack II; JTech Medical, Salt Lake City, UT, USA). In each case, two measurements were taken on each left and right leg or arm, and the highest value obtained during measurement was recorded.[10]

Patients were followed up during their visit to the clinic, by reviewing their medical records, and through telephonic conversation with the patients or their physicians. The endpoint was cardiovascular (CV) death or unexpected rehospitalization because of cardiac events. The cardiac events were defined as worsening HF, cardiac resynchronization defibrillator implantation, and fatal arrhythmia. The patients were followed up for a mean period of 17.3 ± 12.7 months.

Continuous variables were described as mean ± standard deviation for normally distributed data and median with interquartile range for nonnormally distributed data. The normality of the data was evaluated using the Shapiro–Wilk normality test. Categorical variables were described as frequency (percentage). Baseline characteristics of those with the presence and absence of events

were compared using Student's *t*-test for normally distributed data, Mann–Whitney U test for nonnormally distributed data, and Pearson's chi-square test for categorical variables. The Spearman correlation coefficient between %IMF and each continuous variable was calculated. The Kaplan–Meier curves were constructed for time to death or hospitalization for worsening HF; the log-rank test was used for initial comparison. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify the predictors of prespecified endpoints. Univariate Cox proportional hazard analysis was performed with 25 clinical variables that are generally recognized parameters influencing HF, CPX, and muscle strength. We found a candidate variable with a $p < 0.10$ in univariate analysis and selected variables were considered clinically significant. These variables were entered into a multivariate model to identify independent predictors of death or hospitalization due to worsening HF. The results of the Cox proportional hazard models were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analyses were performed using the software package JMP version 13 (SAS Institute Inc., Cary, NC, USA). All p value <0.05 was considered significant.

Results

We analyzed the data of 93 patients who met the inclusion criteria. The baseline demographic and clinical characteristics are shown in **Table 1**. The flow chart of patients leading to the final cohort is shown in **Figure 1**.

Notably, the use of β-blockers and angiotensin-converting enzyme inhibitors or angiotensin

receptor blockers was very high at discharge. During the follow-up period, 23 patients had a CV death or unexpected rehospitalization due to cardiac events. In this population, the median %IMF was 2.8%. On the basis of the median value of %IMF, we divided patients into two groups: low or high %IMF. The baseline characteristics of these two groups were compared (**Table 1**). Patient demographics revealed that the percentage of HT was higher in the high %IMF group. The use of medications at discharge did not vary significantly between the two groups. No significant differences in laboratory, echocardiogram, and CT data (excluding %IMF) were observed between the two groups.

The exercise parameters in the CPX and the parameters of physical function are shown in **Table 2**. Cardiopulmonary function tended to decline in the high %IMF group; however, we noted no significant difference in any parameter between the two groups. Despite comparing ectopic fat in the thigh, leg extension strength did not differ between the two groups. However, the low %IMF group tended to have a weak grip strength.

Because of a large sex-based difference in muscle strength, additional analyses were performed for each sex-based group. When categorized by male and female, no significant difference in grip strength (male: $p = 0.303$; female: $p = 0.156$) and leg strength (male: $p = 0.934$; female: $P=0.062$) were noted between the two groups.

We evaluated the correlation between %IMF and each continuous variable (**Table 3**). The Spearman correlation coefficient analysis revealed no correlation between %IMF and the

demographic and clinical characteristics. The analysis of correlation between %IMF and exercise parameters showed a modest correlation between %IMF and peak VO_2. The Spearman correlation coefficient analysis revealed no significant correlation between %IMF and leg strength but revealed a significant correlation between %IMF and grip strength. CT data showed a slightly positive correlation between %IMF and the subcutaneous fat mass/body surface area.

The clinical endpoints were observed in 7 patients in the low %IMF group and 16 patients in the high %IMF group. There was a significant difference between the two groups ($p = 0.032$). Kaplan–Meier analysis results revealed that patients in the high %IMF group had a higher risk of CV death or unexpected rehospitalization due to cardiac events than those in the low %IMF group (**Figure 2**). When the endpoint was set to CV death only, four events were noted. Because of the small number of events, but no difference was observed between the two groups.

Univariate Cox regression analysis results revealed that AT, peak VO_2, peak working ratio, VE/VCO_2 slope, albumin, BNP, troponin T, grip strength, leg strength, and %IMF were significant predictors for CV death or unexpected rehospitalization for cardiac events, with a p value <0.05 (**Table 4**). Four statistically acceptable variables, including %IMF, were calculated based on the number of events. Therefore, we performed an analysis using a model that combined the predictors significant in the univariate analysis, and body mass index (BMI) to eliminate the influence of body size. The results of multivariate Cox regression analysis adjusted for BMI, peak VO_2, and leg strength revealed %IMF as an independent factor of adverse events. This result was similar when

compared with other components (**Table 4**).

Discussion

The key finding of our study was that muscle quality assessed by the %IMF in the thigh may be used to predict long-term outcomes of patients with nonischemic cardiomyopathy with a reduced EF. Recently, skeletal muscle atrophy has been reported to be an independent prognostic factor for chronic HF,[11] and the concept of sarcopenia has been gaining scientific attention. Furthermore, evidence shows that not only muscle mass but also muscle quality is important.[12] However, to our knowledge, no previous studies have quantitatively assessed IMF or evaluated its correlation with the prognosis of patients with nonischemic cardiomyopathy. To the best of our knowledge, this study is the first to explore this correlation.

A correlation was identified between the loss of muscle mass (a core factor in the diagnosis of sarcopenia) and the prognosis of patients with chronic HF. The loss of muscle mass has been reported to result in a poor prognosis.[13] Recently, the IMF of the quadriceps in older people has been shown to be strongly associated with decreased muscle strength, sit-up and sit-down abilities, and gait ability.[14, 15] Akazawa et al. reported that increased intramuscular adipose tissue mass of the quadriceps is more strongly associated with declines in activities of daily living (ADL) than muscle mass loss in older inpatients.[14] And a study reported that the prognosis is not associated with the loss of skeletal muscle mass itself in patients with HF with a reduced EF (HFrEF). [16] Therefore, not only muscle mass but muscle quality is important for the prognosis of patients in HFrEF. In this

study, %IMF and peak VO_2, which is an established marker of exercise tolerance, showed a negative correlation, suggesting that the decrease in IMF contributes to the improvement of ADL and exercise tolerance.

Several methods have been reported to reduce %IMF. Englund et al. have reported that physical activity and nutritional supplementation (whey protein and vitamin D) improve thigh intramuscular adipose tissue in community-dwelling, mobility-limited older people.[17] Regarding the effect of exercise on IMF, a previous study stated that the effect of reducing IMF is poor.[18] Conversely, another study reports that it is effective,[19] but the effect has not been determined. Several studies have demonstrated that aerobic and resistance training improves HF prognosis[20] and exercise may reduce %IMF. We speculate that an intervention aimed at improving nutritional status and physical activity is required to improve the thigh IMF.

The target patients in this study were limited to HFrEF. Comorbidities such as being overweight, abdominal obesity, and DM are common among patients with HF with a preserved EF (HFpEF) and those with HFrEF; however, these are more severe and occur more frequently in HFpEF than HFrEF.[21] Perhaps because of these differences, there is a clear difference in body composition between patients with HFpEF and those with HFrEF.[22] Among obese patients with HFpEF, a negative correlation was found between thigh IMF and exercise tolerance,[23] but owing to the difference in body composition between patients with these two pathologies, this study analysis was limited to HFrEF.

This study had a small sample size and was conducted at a single center. To further improve objectivity, multicenter prospective trials should be conducted. Furthermore, we analyzed patients with nonischemic cardiomyopathy with a reduced EF, which might have included several different HF etiologies. In fact, 25% of these patients had DM, and approximately 50% had a history of HT. Owing to the small number of patients in this study, it was not possible to adjust for all etiologies.

In conclusion, %IMF is an independent factor for predicting adverse cardiac events in patients with nonischemic cardiomyopathy with a reduced EF.

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Disclosures

None.

References

1. Kamiya K, Masuda T, Matsue Y, Inomata T, Hamazaki N, Matsuzawa R, Tanaka S, Nozaki K, Maekawa E, Noda C, Tojo MY, Matsunaga A, Izumi T, Ako J. Complementary Role of Arm Circumference to Body Mass Index in Risk Stratification in Heart Failure. *JACC Heart Fail* 2016;4(4):265-273.

2. Addison O, Drummond MJ, LaStayo PC, Dibble LE, Wende AR, McClain DA, Marcus RL. Intramuscular fat and inflammation differ in older adults: the impact of frailty and inactivity. J Nutr Health Aging 2014;18(5):532-538.

3. Marcus RL, Addison O, LaStayo PC. Intramuscular adipose tissue attenuates gains in muscle quality in older adults at high risk for falling. A brief report. J Nutr Health Aging 2013;17(3):215-218.

4. Hong ES, Lim C, Choi HY, Lee YK, Ku EJ, Moon JH, Park KS, Jang HC, Choi SH. Plasma fibroblast growth factor 21 levels increase with ectopic fat accumulation and its receptor levels are decreased in the visceral fat of patients with type 2 diabetes. BMJ Open Diabetes Res Care 2019;7(1):e000776.

5. Bornachea O, Vea A, Llorente-Cortes V. Interplay between epicardial adipose tissue, metabolic and cardiovascular diseases. Clin Investig Arterioscler 2018;30(5):230-239.

6. Sinha SK, Thakur R, Jha MJ, Goel A, Kumar V, Kumar A, Mishra V, Varma CM, Krishna V, Singh AK, Sachan M. Epicardial Adipose Tissue Thickness and Its Association with the Presence and Severity of Coronary Artery Disease in Clinical Setting: A Cross-Sectional Observational Study. J Clin Med Res 2016;8(5):410-419.

7. Gaeta M, Bandera F, Tassinari F, Capasso L, Cargnelutti M, Pelissero G, Malavazos AE, Ricci C. Is

epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis. Europace 2017;19(5):747-752.

8. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53(6):982-992.

9. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60(6):2020-2027.

10. Katoh M, Hiiragi Y, Hirano M, Gomi M, Tozawa R, Sakai Y, Tanaka M. Isometric knee muscle strength measurement using a belt-stabilized hand-held dynamometer and an isokinetic dynamometer with and without trunk fixation: investigation of agreement of measurement values and factors influencing measurement. *J Phys Ther Sci* 2019;31(11):878-883.

11. Yamada S, Kamiya K, Kono Y. Frailty may be a risk marker for adverse outcome in patients with congestive heart failure. *ESC Heart Fail* 2015;2(3):168-170.

12. Hong ES, Lim C, Choi HY, Lee YK, Ku EJ, Moon JH, Park KS, Jang HC, Choi SH. Plasma fibroblast growth factor 21 levels increase with ectopic fat accumulation and its receptor levels are decreased in the visceral fat of patients with type 2 diabetes. BMJ Open Diabetes Res Care 2019;7(1):e000776.

13. Konishi M, Kagiyama N, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Misumi T, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Makino A, Oka K, Momomura SI, Matsue Y. Impact of sarcopenia on prognosis in patients with heart failure with

reduced and preserved ejection fraction. *Eur J Prev Cardiol* 2020;28(9):1022-1029.

14. Akazawa N, Kishi M, Hino T, Tsuji R, Tamura K, Moriyama H. Increased intramuscular adipose tissue of the quadriceps is more strongly related to declines in ADL than is loss of muscle mass in older inpatients. *Clin Nutr* 2021;40(3):1381-1387.

15. Akazawa N, Harada K, Okawa N, Tamura K, Moriyama H. Muscle mass and intramuscular fat of the quadriceps are related to muscle strength in non-ambulatory chronic stroke survivors: A cross-sectional study. *PLoS One* 2018;13(8):e0201789.

16. 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(6):4100-4107.

17. Englund DA, Kirn DR, Koochek A, Zhu H, Travison TG, Reid KF, Berens AV, Melin M, Cederholm T, Gustafsson T, Fielding RA. Nutritional Supplementation With Physical Activity Improves Muscle Composition in Mobility-Limited Older Adults, The VIVE2 Study: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Gerontol A Biol Sci Med Sci* 2017;73(1):95-101.

18. Ogawa M, Belavy DL, Yoshiko A, Armbrecht G, Miokovic T, Felsenberg D, Akima H. Effects of 8 weeks of bed rest with or without resistance exercise intervention on the volume of the muscle tissue and the adipose tissues of the thigh. *Physiol Rep* 2020;8(18):e14560.

19. Yoshiko A, Tomita A, Ando R, Ogawa M, Kondo S, Saito A, Tanaka NI, Koike T, Oshida Y, Akima H. Effects of 10-week walking and walking with home-based resistance training on muscle quality, muscle

size, and physical functional tests in healthy older individuals. *Eur Rev Aging Phys Act* 2018;15:13.

20. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Liifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301(14):1439-1450.

21. Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and Molecular Differences between HFpEF and HFrEF: A Step Ahead in an Improved Pathological Understanding. *Cells* 18;9(1):242.

22. Selvaraj S, Kim J, Ansari BA, Zhao L, Cvijic ME, Fronheiser M, Vanjarapu JMR, Kumar AA,Suri A, Yenigalla S, Satija V, Ans AH, Narvaez-Guerra O, Herrera-Enriquez K, Obeid MJ, Lee JJ, Jehangir Q, Seiffert DA, Car BD, Gordon DA, Chirinos JA. Body Composition, Natriuretic Peptides, and Adverse Outcomes in Heart Failure With Preserved and Reduced Ejection Fraction. *JACC Cardiovasc Imaging* 2021;14(1):203-215.

23. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, Upadhya B, Becton JT, Nelson MD, Chen H, Kitzman DW. Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction. *JACC Heart Fai*l 2018;6(8):640-649.

Figure legend

Figure 1. Patients flow diagram.

Figure 2. Kaplan–Meier estimates of risk of cardiac events.
The patients with high % intramuscular fat in the thigh had a higher risk of cardiovascular death or unexpected rehospitalization for cardiac events than those with low % intramuscular fat in the thigh (log-rank test $p = 0.0128$).

Table 1

Comparison of Baseline Characteristics of Study Patients Based on %IMF

	Total	Percent IMF Group		p value
		Low (≤2.891 %)	High (>2.891 %)	
	(n=93)	(n=47)	(n=46)	
Men	69 (74.2 %)	38 (80.9 %)	31 (67.4 %)	0.237
Age (years)	59.2±14.6	59.1±13.3	59.0±15.9	0.845
NYHA class Ⅰ	27 (29.0 %)	14 (29.8 %)	13 (28.2 %)	0.822
NYHA class Ⅱ	66 (71.0 %)	33 (70.2 %)	33 (71.8 %)	0.822
Current smoker	21 (22.6 %)	13 (27.7 %)	8 (17.4 %)	0.349
Hypertension	50 (53.8 %)	19 (40.4 %)	31 (67.4 %)	0.013
Dyslipidemia	28 (30.1 %)	13 (27.7 %)	15 (32.6 %)	0.656
Diabetes mellitus	23 (24.7 %)	9 (19.1 %)	14 (30.4 %)	0.237
BMI (kg/m²)	23.8±5.2	22.9±4.8	24.6±5.5	0.110
Heart rate (bpm)	72.8±14.3	73.1±13.3	72.3±14.3	0.825
Resting systolic BP (mmHg)	113.6±18.9	114.4±21.7	113.0±15.7	0.719
Resting diastolic BP (mmHg)	70.0±15.0	69.3±15.7	70.5±14.4	0.705
Hemoglobin (g/dl)	14.1±2.3	14.2±2.1	14.1±2.4	0.747
Serum sodium (mEq/L)	140.0±2.4	139.9±2.6	139.6±2.3	0.556
eGFR (mg/dl)	62.0±26.2	58.0±17.4	66.2±32.6	0.361
Albumin (g/dl)	3.92±0.51	4.00±0.47	3.83±0.55	0.125
High sensitive troponin T (ng/ml)	0.028±0.030	0.024±0.022	0.031±0.037	0.396
Log BNP (pg/ml)	2.20±0.48	2.18±0.49	2.17±0.46	0.948
Medication at discharge				
ACE inhibitor or ARB	80 (86.0 %)	40 (85.1 %)	40 (87.0 %)	0.773
β-blocker	88 (94.6 %)	46 (97.9 %)	42 (91.3 %)	0.361
MRA	67 (72.0 %)	38 (80.9 %)	29 (63.0%)	0.064
Loop diuretic	66 (71.0 %)	33 (70.2 %)	33 (71.7 %)	0.871
LVEDD (mm)	61.3±7.3	61.3±7.1	61.0±7.7	0.855
LVESD (mm)	53.0±8.6	52.8±8.6	52.9±9.0	0.953
LVEF (%)	25.0±6.6	24.7±6.9	25.4±6.5	0.644
e' (cm/s)	4.3±1.3	4.2±1.3	4.3±1.6	0.787
TRPG (mmHg)	26.4±11.2	24.8±10.9	28.2±11.4	0.171
Thigh muscle/BSA (cm^2/m^2)	68.9±11.4	70.8±10.4	67.0±12.3	0.112
Thigh SAT/BSA (cm^2/m^2)	29.4±16.9	26.4±16.4	32.4±17.2	0.093
%IMF in the thigh (%)	3.07±1.52	1.90±0.66	4.20±1.25	<0.001

Values are mean ± standard deviation, median (inter-quartile range), or n (%)

ACE = angiotensin converting enzyme; ARB = angiotensin type 1 receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BSA = body surface area; e' = early diastolic velocity of the medial mitral annulus; eGFR = estimated glomerular filtration rate; IMF = intramuscular fat; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MRA = Mineralocorticoid receptor antagonists; SAT = subcutaneous adipose tissue; TRPG = tricuspid regurgitation pressure gradient.

Table 2

Cardiopulmonary Exercise Test Data and Muscle Strength at Discharge

	Total	Percent IMF Group		p value
		Low (≤2.891 %)	High (>2.891 %)	
	(n=93)	(n=47)	(n=46)	
Peak WR (watt)	79.0±29.3	80.8±27.7	77.0±30.7	0.527
Anaerobic threshold (ml/min/kg)	13.1±2.6	13.3±2.4	12.8±2.9	0.342
Anaerobic threshold (%predicted)	84.7±16.1	86.3±14.8	83.2±17.6	0.313
Peak oxygen uptake (ml/min/kg)	18.9±4.9	19.6±4.6	18.3±5.3	0.207
Peak oxygen uptake (%predicted)	75.5±17.5	77.8±16.1	73.3±18.9	0.159
VE/VCO_2 slope	29.5±6.9	28.7±7.4	30.3±6.4	0.158
Muscle strength				
Grip strength (kg)	29.1±9.4	31.3±8.9	26.7±9.6	0.024
Leg strength (N)	287.4±108.1	300.8±102.4	273.3±114.6	0.242

Values are mean ± standard deviation

VE/VCO_2 slope = ventilatory equivalent versus carbon dioxide output slope; WR = work rate.

Table 4

Spearman Correlation Coefficient Analysis between %IMF in the Thigh and Each Continuous Variable

	Spearman r	p value
Age	0.082	0.435
BMI (kg/m²)	0.220	0.034
Heart rate (bpm)	0.039	0.712
Resting systolic BP (mmHg)	-0.002	0.985
Resting diastolic BP (mmHg)	0.004	0.967
Hemoglobin (g/dl)	-0.040	0.705
Creatinine (g/dl)	-0.086	0.421
High sensitive troponin T (ng/l)	0.200	0.083
Log BNP (pg/ml)	-0.045	0.667
LVEDD (mm)	0.038	0.719
LVESD (mm)	-0.008	0.939
LVEF (%)	0.089	0.399
e' (cm/s)	-0.064	0.549
TRPG (mmHg)	0.204	0.065
Peak working rate (watt)	-0.183	0.082
Anaerobic threshold (ml/kg/min)	-0.169	0.109
Peak oxygen uptake (ml/kg/min)	-0.221	0.036
Thigh muscle/BSA (cm^2/m^2)	-0.189	0.069
Thigh SAT/BSA (cm^2/m^2)	0.258	0.013
Grip strength (kg)	-0.298	0.005
Leg strength (N)	-0.208	0.054

BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BSA = body surface area; e' = early diastolic velocity of the medial mitral annulus; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SAT = subcutaneous adipose tissue; TRPG = tricuspid regurgitation pressure gradient.

Table 4 Table 4

Univariate and Multivariate Analyses for all-cause Death or Rehospitalization for Heart Failure

	Univariate Analysis			Multivariate Analysis								
				Model 1			Model 2			Model 3		
	HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value
Age	1.026	0.995-1.061	0.112									
Male gender	0.785	0.334-2.047	0.595									
BMI (kg/m^2)	0.958	0.867-1.045	0.360	0.915	0.806-1.023	0.144				0.952	0.856-1.045	0.328
Heart rate (bpm)	0.969	0.943-0.998	0.033									
Resting systolic BP (mmHg)	0.989	0.971-1.006	0.293							0.995	0.969-1.019	0.690
Resting diastolic BP (mmHg)	0.972	0.939-1.003	0.085									
Diabetes mellitus	1.206	0.434-2.917	0.695									
LVEDD (mm)	1.034	0.973-1.093	0.258									
LVESD (mm)	1.027	0.975-1.080	0.303									
LVEF (%)	0.989	0.925-1.053	0.728				0.944	0.872-1.016	0.142			
e' (cm/s)	1.070	0.793-1.428	0.649									
TRPG (mmHg)	1.027	0.991-1.062	0.131									
Anaerobic threshold (ml/kg/min)	0.789	0.646-0.943	0.014				0.952	0.768-1.164	0.637			
Peak oxygen uptake (ml/kg/min)	0.851	0.753-0.949	0.006	0.856	0.752-0.961	0.013						
Peak WR (watt)	0.980	0.961-0.998	0.042									
VE/VCO_2 slope	1.116	1.064-1.168	<0.001									
Hemoglobin (g/dl)	0.854	0.707-1.026	0.095									
Serum sodium (mEq/l)	0.924	0.786-1.094	0.350									
Albumin (g/dl)	0.331	0.152-0.746	0.006							0.352	0.150-0.842	0.017
eGFR ($ml/min/1.73m^2$)	0.997	0.978-1.011	0.705									
Log BNP (pg/ml)	4.928	1.926-13.962	0.002				5.614	1.827-19.256	0.004			
High sensitive troponin T (ng/l)	1.013	1.001-1.021	0.011									

Grip strength (kg)	0.947	0.916-0.981	0.002									
Leg strength (N)	0.996	0.992-0.999	0.019	1.004	0.998-1.010	0.204						
Thigh muscle/BSA (cm^2/m^2)	0.982	0.946-1.020	0.348									
Thigh SAT/BSA (cm^2/m^2)	0.999	0.971-1.023	0.916									
%IMF in the thigh (%)	1.379	1.089-1.724	0.006	1.361	1.043-1.745	0.018	1.47	1.108-1.967	0.008	1.33	1.054-1.657	0.013

Abbreviations as in Table 1 and 2. CI, confidence interval; HR, hazard ratio.

BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BSA = body surface area; e' = early diastolic velocity of the medial mitral annulus; eGFR = estimated glomerular filtration rate; IMF = intramuscular fat; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SAT = subcutaneous adipose tissue; TRPG = tricuspid regurgitation pressure gradient; VE/VCO_2 slope = ventilatory equivalent versus carbon dioxide output slope; WR = work rate.

Figure

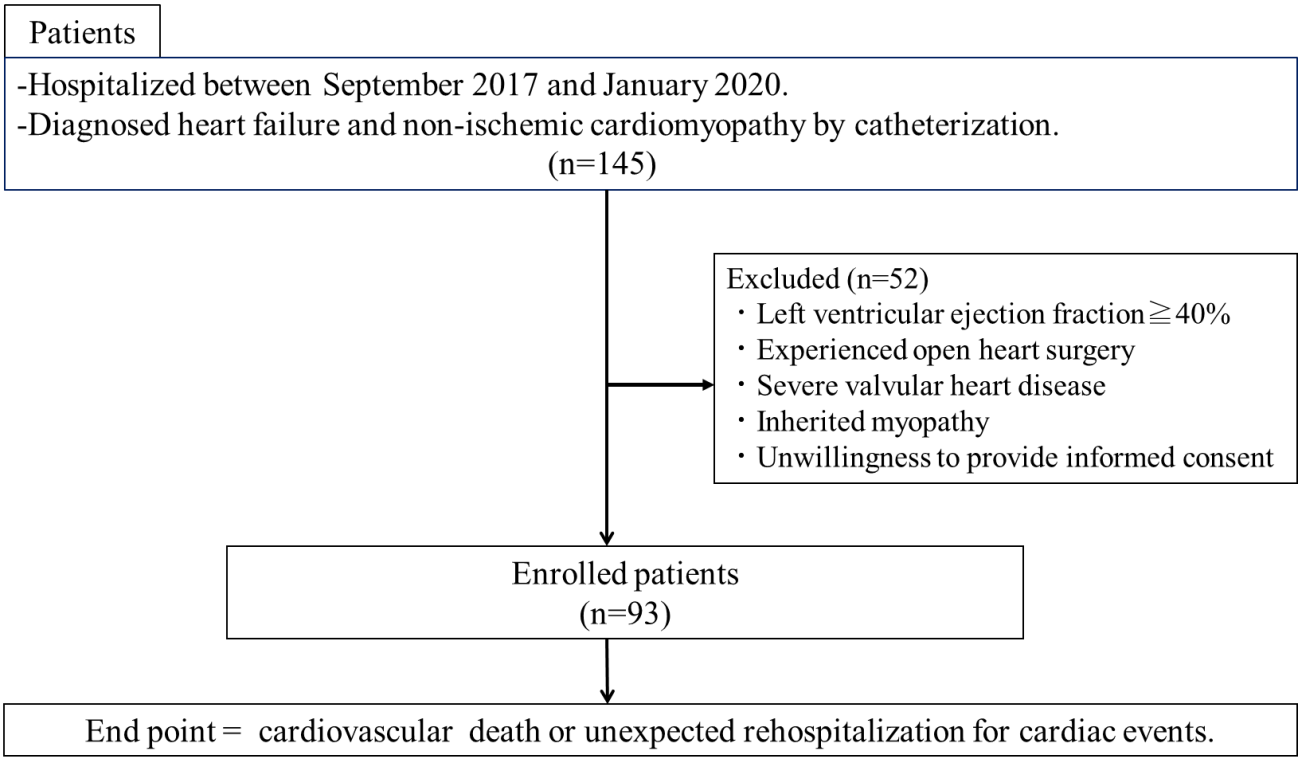
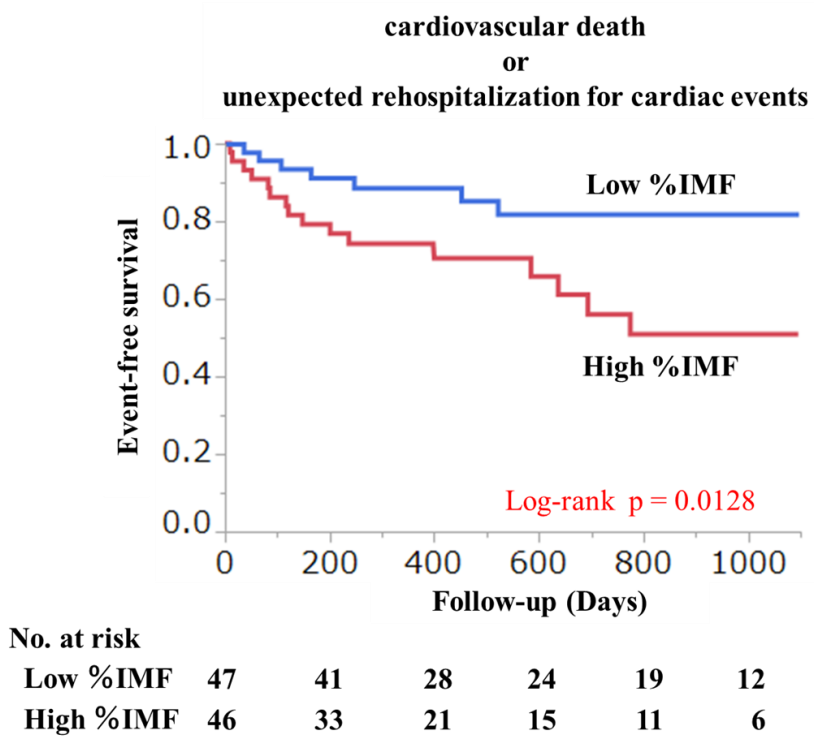


Figure 1. Patients flow diagram.

Figure



No. at risk						
Low %IMF	47	41	28	24	19	12
High %IMF	46	33	21	15	11	6

Figure 2. Kaplan-Meier estimates of risk of cardiac events**.** The patients with high % intramuscular fat in the thigh had a higher risk of cardiovascular death or unexpected rehospitalization for cardiac events than those with low % intramuscular fat in the thigh (log-rank test p = 0.0128).

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