ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 100–110
Published online 23 September 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14162

ORIGINAL ARTICLE

Aetiology of chronic heart failure in patients from a super-aged society: the KUNIUMI registry chronic cohort

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Abstract

Aims With the rapidly increasing ageing population, heart failure is an urgent challenge, particularly in developed countries. The study aimed to investigate the main aetiologies of chronic heart failure in a super-aged society.

Methods and results The KUNIUMI registry chronic cohort is a community-based, prospective, observational study of chronic heart failure in Awaji Island, Japan. Inhabitants of this island aged ≥65 years accounted for 36.3% of the population. In the present study, data from patients with symptomatic heart failure were extracted from the registry. A total of 1646 patients were enrolled from March 2019 to March 2021, accounting for ~1.3% of the inhabitants of Awaji Island. We analysed 852 patients with symptomatic heart failure. The mean age was high (78.7 ± 11.1 years), with 357 patients (41.9%) being female. The proportion of women increased significantly with advancing age and constituted more than half of the patients aged 85 years and older ($P < 0.01$). The prevalence of atrial fibrillation, and in particular long-standing persistent atrial fibrillation, increased at 70 years of age ($P < 0.01$). The proportion of patients with heart failure with preserved ejection fraction increased to ~60% when age was over 75 years. Although ischaemic heart disease accounted for 35.0% of chronic heart failure aetiologies, valvular heart disease was the most common cause of chronic heart failure (49.8%). The major types of valvular heart disease were mitral regurgitation and tricuspid regurgitation (27.2% and 21.7%, respectively), both of which increased significantly with age ($P < 0.01$). The incidence of aortic valve stenosis increased markedly over the age of 85 years ($P < 0.01$). Atrial functional mitral regurgitation increased with age and was the major cause of mitral regurgitation in patients aged >75 years. Patients with atrial functional mitral regurgitation had a higher prevalence of atrial fibrillation (especially long-standing persistent atrial fibrillation) and a larger left atrial volume index when compared with patients with other types of mitral regurgitation ($P < 0.001$, respectively).

Conclusions The KUNIUMI registry chronic cohort showed a change in heart failure aetiology to valvular heart disease in a super-aged society. Effective and comprehensive countermeasures are required to prepare for the rapid rise in heart failure incidence in a super-aged society.

Keywords Chronic heart failure; Aetiology; Epidemiology; Ageing society; Atrial functional mitral regurgitation

Received: 13 February 2022; Revised: 25 August 2022; Accepted: 10 September 2022
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Introduction

With an increasing ageing population, the number of patients with heart failure (HF) is rapidly growing worldwide.[1–4] Due to the imminence of a super-aged society, HF is likely to become a major burden on the health systems and a worldwide challenge in the near future. In the Japanese HF registry during the late 2000s, ischaemic heart disease (IHD) was the leading cause of HF [Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD),[5] Acute Decompensated Heart Failure Syndromes (ATTEND),[6] and Chronic Heart Failure Registry and Analysis in the Tohoku District-2 (CHART-2)],[7] similar to that in Europe and America [EuroHeart Failure Survey II (EHFS II)[8] and the Acute Decompensated Heart Failure National Registry (ADHERE)].[9] Conversely, although it has been reported that the prevalence of valvular heart disease (VHD) increases with age,[10–12] the burden of VHD in a super-aged society in the near future is not well known.

Although the ageing population is growing worldwide, Japan will be the first to have a super-aged society, with more than 21% of the population being 65 years and older.[13] Particularly, Awaji Island, one of the largest outlying islands in Japan, has a super-aged population. Inhabitants of this island aged ≥65 years accounted for 36.3% of the population in 2019. This ageing rate is similar to the projected proportion of those who will be aged ≥65 years in Japan 20 years later. We previously performed a cross-sectional study on acute HF syndrome, titled 'Estimating incidence of acute heart failure syndromes in Japan—an analysis from the Kobe University heart failure registry in Awaji medical center (KUNIUMI registry) acute cohort', which estimated the future situation of acute HF in Japan.[14] The patient characteristics of individuals aged 80 years and younger in the KUNIUMI registry acute cohort were relatively similar to those in not only the Japanese but also the European HF registries (male: 65.3%, 65.8%, and 66.0%; hypertension (HT): 60.1%, 50.1%, and 61.0%; and diabetes mellitus (DM): 37.9%, 33.5%, and 34.0%; KUNIUMI,[14] JCARE-CARD,[12] and EHFS II,[15] respectively). Therefore, the current status of chronic HF (CHF) on Awaji Island could reflect the future of Japan's rapidly ageing society, as well as that of Western countries. Recently, we initiated a community-based, prospective, cohort study of patients with CHF titled 'The KUNIUMI registry chronic cohort'. In the present study, because there are few data on the aetiology of HF in a super-aged society, we analysed data from the KUNIUMI registry chronic cohort.

Methods

Study design and populations

Awaji Medical Center (AMC) is the only hospital on Awaji Island where cardiologists are available full time. As the majority of patients with acute coronary syndrome are admitted to AMC[14] and because 70% of the total patients are hospitalized because of HF, a population low in bias and with generalizable data is available. In light of this, we initiated a community-based, prospective, cohort study of patients with CHF titled 'The KUNIUMI registry chronic cohort'.

The KUNIUMI registry chronic cohort was a single-centre, prospective, observational study. Patients who satisfied at least one of the inclusion criteria and none of the exclusion criteria were included in the registry (Supporting Information, *Table S1*). The inclusion criteria were the same as those used in the CHART-2 study,[7] which is one of the largest CHF cohort studies in Japan. Patients were then followed up semi-permanently at annual intervals (±3 months).

Patients were enrolled in the registry at the time of outpatient consultation or upon leaving the hospital. In this study, we investigated the aetiology of CHF in patients with Stages C and D.

For each patient, baseline data at enrolment included (i) existing HF stage and symptom severity, (ii) medical history (including history of hospitalization for HF), (iii) comorbidities exacerbating HF, (iv) treatment status (medications and treatment by device), and (v) laboratory findings [serum B-type natriuretic peptide (BNP) levels] and echocardiography.

Informed consent and ethical considerations

Written informed consent was obtained from all the patients. The principal investigator or sub-investigator provided potential participants with the opportunity to ask questions and ample consideration time before providing consent. They were required to confirm that the potential participants had a sufficient understanding of this study's protocol and what it involved before voluntarily consenting to participate. This study conformed to the principles outlined in the Declaration of Helsinki. Approval was obtained from the Ethics Review Board of the AMC (Approval No. 21-20, 5 October 2018). This study was registered with the Japan Registry of Clinical Trials (jRCT1050200024).

Patient data definitions

The staging categories of HF have been described in the literature.[7] HF with preserved ejection fraction (HFpEF) was defined as more than 50% of the left ventricular ejection fraction. Atrial fibrillation (AF) persisting for >1 year was defined as long-standing persistent AF.

Chronic HF aetiology was classified according to a previous study.[16] IHD was defined as a pre-existing history of myocardial infarction or coronary artery disease. VHD was specifically defined as having more than moderate valvular disease on echocardiography at the time of enrolment, using the

standard criteria.[16–19] The diagnosis of cardiomyopathy, such as dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), was made by the attending physicians at the time of patient enrolment. Hypertensive heart disease was considered as the aetiology when a patient did not have IHD, DCM, HCM, or VHD but had a history of HT. Patients with multiple aetiologies were permitted to fulfil these criteria.

Additionally, we classified the causes of mitral regurgitation (MR) into organic MR (OMR), ventricular functional MR (FMR-v), atrial functional MR (FMR-a), and others, as outlined in the literature.[18,20] OMR was defined as MR caused by abnormal leaflets with significant degenerative changes. Functional MR (FMR) was divided into FMR-v with ejection fraction (EF) $<40\%$ or EF $\geq$ 50% with regional wall motion abnormality, and FMR-a with EF $\geq 40\%$ with left atrial dilatation (left atrial volume index >48 mL/m^2) and no regional wall motion abnormality.

Echocardiography was performed on all patients by experienced technicians in accordance with the guidelines of the European Association of Cardiovascular Imaging.[21] The causes of MR were determined by two experienced cardiologists (J. I. and Su. O.).

Statistical analysis

Serum BNP levels are expressed as the median and interquartile range. Other continuous variables are expressed as the mean ± standard deviation. Differences between groups of continuous variables were evaluated using analysis of variance (ANOVA) or the Kruskal–Wallis test. Categorical variables are summarized as frequencies with percentages and were compared using the χ^2 test. The Cochran–Armitage test, ANOVA, or the Kruskal–Wallis test were used to assess the presence of a trend between patient characteristics and/or aetiology of HF and age groups; 95% confidence intervals of proportions were calculated using the Clopper–Pearson methods. All tests were two-tailed, and statistical significance was set at $P < 0.05$. SAS software (Version 9.4; SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

Patient characteristics

The study cohort comprised almost all participants who fulfilled the inclusion criteria at AMC from March 2019 to March 2021 (Supporting Information, *Figure S2*). Finally, a total of 1646 patients with CHF were enrolled, which accounted for ~1.3% of the population of Awaji Island. The baseline characteristics by stage are shown in Supporting Information, *Table S3*. Of the 1646 patients, we investigated 852 patients with CHF symptoms (Stages C and D), accounting for 51.8% of the entire cohort (*Figure 1*). *Table 1* shows the baseline data, medical history, and medications according to the age category. The mean age was high (78.7 ± 11.1 years), with 357 patients (41.9%) being female. The proportion of women increased significantly with advancing age and constituted more than half of the patients aged 85 years and older. The number of patients with a history of hospitalization due to HF also increased with age. The prevalence of AF, and in particular long-standing persistent AF, increased at 70 years of age. In contrast, the prevalence of DM decreased over the age of 80 years. The proportion of patients with HFpEF increased to ~60% when age was over 75 years. Anaemia and renal function worsened, and hypoalbuminaemia became evident in the advanced age group. An increase in the propor-

Figure 1 Study flowchart.

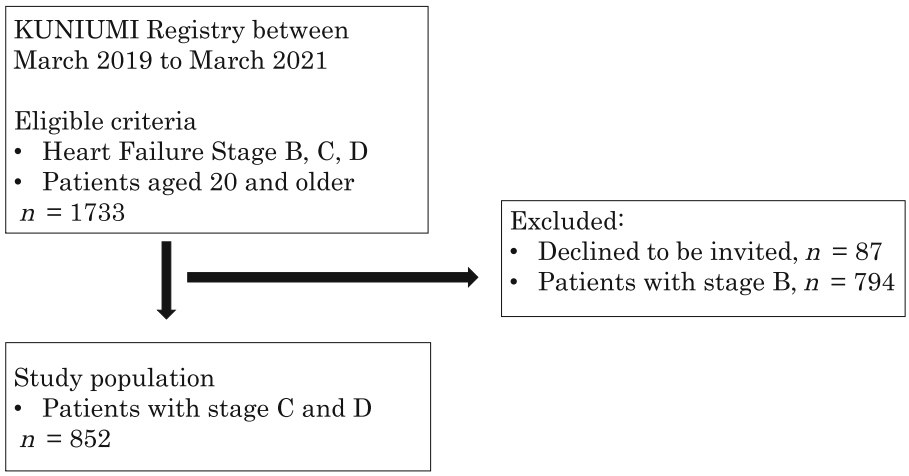


Table 1 Baseline characteristics

	Total	<70	70–74	75–79	80–84	≥85	*P* value
Number	852	148	105	145	149	305	
Age (years)	78.7 ± 11.1	60.1.8 ± 8.0	71.9 ± 1.5	77.0 ± 1.4	82.2 ± 1.4	89.2 ± 3.2	<0.01
Female (%)	41.9	25.0	33.3	44.1	41.6	52.1	<0.01
BMI (kg/m^2)	22.1 ± 4.4	24.7 ± 6.1	22.6 ± 4.1	22.0 ± 3.7	21.8 ± 3.3	21.0 ± 3.2	<0.01
Medical history (%)							
Prior hospitalization due to HF	63.3	58.1	54.3	60.0	61.1	71.5	<0.01
Hypertension	73.2	68.2	70.3	78.6	73.2	74.1	0.24
Diabetes mellitus	33.7	43.9	40.0	42.1	37.6	20.7	<0.01
Atrial fibrillation	46.2	30.4	50.5	49.0	48.3	50.2	<0.01
Long-standing persistent AF	26.8	10.1	26.7	28.3	32.9	31.2	<0.01
LVEF (%)	50.3 ± 14.0	45.9 ± 14.0	49.1 ± 14.2	51.2 ± 14.0	50.8 ± 13.3	52.1 ± 13.6	<0.01
LVEF ≥ 50% (%)	56.4	45.3	51.4	61.4	56.4	61.3	<0.01
Laboratory data							
Haemoglobin (mg/dL)	12.2 ± 2.2	13.4 ± 2.4	12.8 ± 2.4	12.2 ± 1.9	11.9 ± 2.0	11.4 ± 1.8	<0.01
eGFR (mL/min/1.73 m^2)	45.3 ± 22.9.	52.0 ± 27.2	48.9 ± 23.9	49.5 ± 25.2	43.0 ± 19.8	40.1 ± 18.7	<0.01
Albumin (mg/dL)	3.6 ± 0.6	3.9 ± 0.5	3.7 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	3.4 ± 0.6	<0.01
Total bilirubin (mg/dL)	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.4	0.6 ± 0.4	0.28
Sodium (mEq/L)	138.6 ± 3.3	138.4 ± 2.5	139.2 ± 3.2	138.8 ± 2.9	138.6 ± 3.4	138.5 ± 3.6	0.41
Potassium (mEq/L)	4.1 ± 0.5	4.1 ± 0.4	4.1 ± 0.5	4.1 ± 0.6	4.1 ± 0.5	4.2 ± 0.5	0.45
Total cholesterol (mg/dL)	165.6 ± 38.7	172.0 ± 34.2	169.7 ± 36.8	164.5 ± 38.8	164.4 ± 38.4	162.1 ± 40.6	0.10
HbA1c (%)	6.2 ± 0.9	6.4 ± 1.1	6.1 ± 0.9	6.2 ± 0.9	6.2 ± 0.8	6.0 ± 0.9	<0.01
BNP (pg/mL)	200.4 [85.3–409.8]	122.2 [50.4–364.3]	190.4 [94.1–414.3]	247.6 [115.7–733.7]	260.9 [138.3–488.8]	296.4 [167.3–502.9]	0.18
Medications							
No prescribed drugs	8.0 ± 3.1	7.2 ± 3.2	7.3 ± 3.1	8.8 ± 3.3	8.5 ± 3.1	8.1 ± 2.7	<0.01
Loop diuretic (%)	68.0	56.1	47.6	69.7	70.5	78.7	<0.01
MRA (%)	43.1	48.6	29.5	39.3	43.0	46.9	0.34
Beta-blocker (%)	72.4	85.1	77.1	75.2	70.5	64.3	<0.01
ACEI/ARB (%)	66.0	75.0	68.6	71.7	62.4	59.7	<0.01
Anti-coagulation (%)	43.4	32.4	47.6	49.7	54.0	39.3	0.39
SGLT-2 I (%)	9.6	15.5	12.4	9.7	11.4	4.9	<0.01

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT-2 I, sodium glucose co-transporter-2 inhibitor.
Values are presented as mean ± standard deviation, median (inter-quartile range), or absolute numbers.

tion of patients using diuretics was observed with age. In contrast, the prescription rates of cardioprotective agents, including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and sodium–glucose co-transporter-2 (SGLT-2) inhibitors, decreased with advancing age. Baseline characteristics according to the left ventricular ejection fraction are also shown in Supporting Information, *Table S4*.

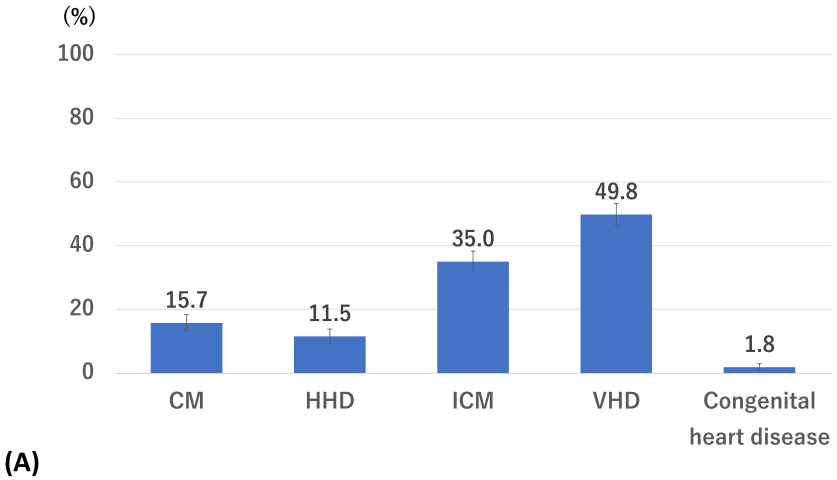
Aetiology of chronic heart failure

Figure 2A shows the distribution of CHF aetiologies. Although IHD accounted for 35.0% of CHF aetiologies, VHD was the most common cause of CHF in this registry (49.8%). This was influenced by the rapid increase in VHD in patients aged >75 years (*Figure 2B*). In contrast, the prevalence of cardiomyopathy decreased with age, whereas that of ICM declined in patients aged over 85 years ($P < 0.01$ and 0.05, respectively) (*Figure 2B*). Of the 852 patients with CHF symptoms, 152 patients (17.8%) had multiple aetiologies. The characteristics of patients with multiple aetiologies and the breakdown of co-existing aetiologies are shown in Supporting Information, *Tables S5* and *S6*, respectively.

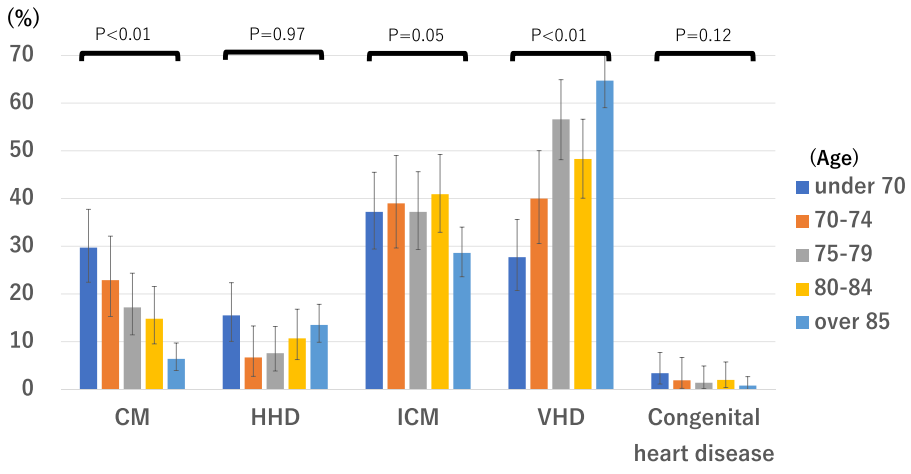
Types of valvular heart disease by age

As shown in *Figure 3A*, MR and tricuspid regurgitation (TR) were the major types of VHD in the present cohort (27.2%

Figure 2 (A) Aetiology of heart failure. (B) Aetiology of heart failure by age. CM, cardiomyopathy; HHD, hypertensive heart disease; ICM, ischaemic heart disease; VHD, valvular heart disease.



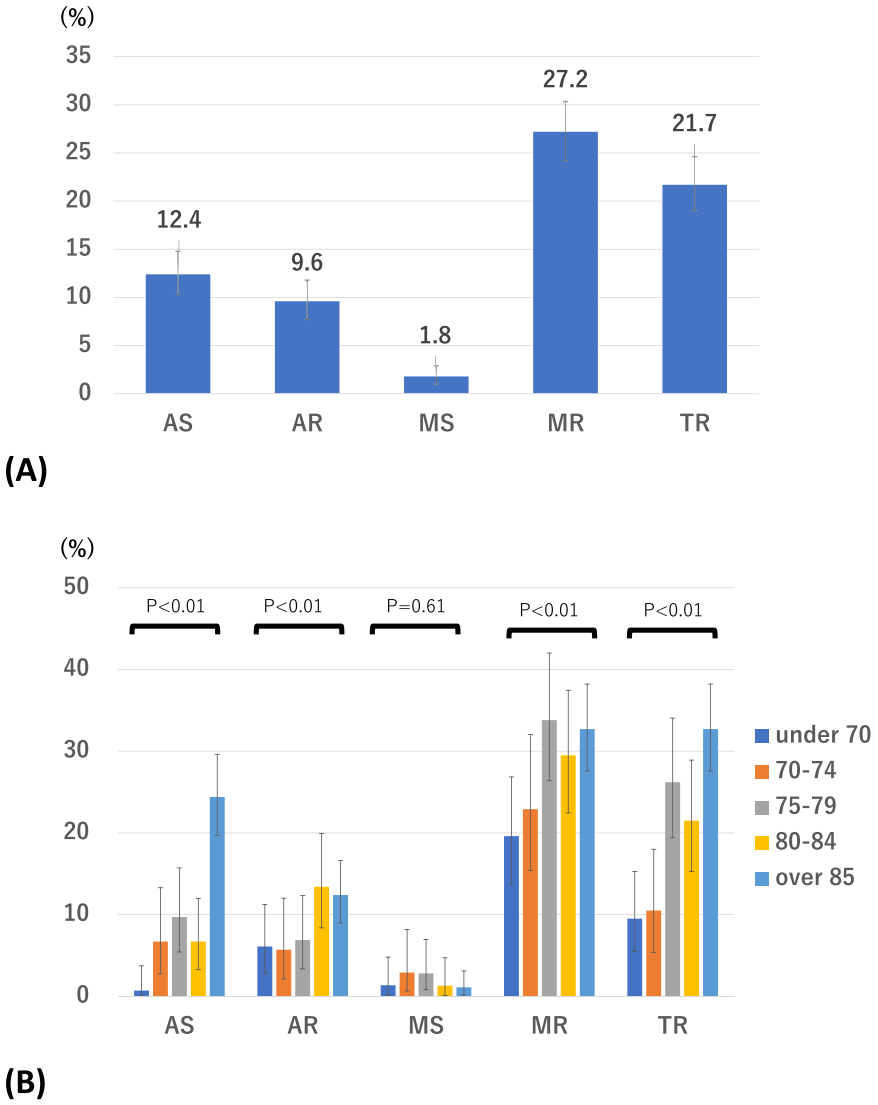
(A)



(B)

DOI: 10.1002/ehf2.14162

Figure 3 (A) Types of valvular heart disease. (B) Types of valvular heart disease by age. AR, aortic valve regurgitation; AS, aortic valve stenosis; MR, mitral valve regurgitation; MS, mitral valve stenosis; TR, tricuspid valve regurgitation.



and 21.7%, respectively). *Figure 3B* shows the types of VHD in the different age groups. Although a large proportion of patients with mitral stenosis were under 70 years of age, the incidence of other types of VHD increased with age. In particular, there was a significant increase in the rates of MR and TR (*Figure 3B*). In addition, the incidence of aortic valve stenosis (AS) increased markedly over the age of 85 years.

Aetiology of mitral regurgitation

In this study, of the 232 patients with MR, 78 patients had FMR-a, 77 had FMR-v, 31 had OMR, 40 had post-surgery MR, and 6 had other aetiologies. *Figure 4* shows the distribution of MR aetiologies by age. The number of patients with FMR-a increased with age, and it was most prevalent in patients aged >75 years. *Table 2* shows the patient characteristics according to MR aetiologies. Patients with FMR-a were older and had a higher prevalence of AF (especially long-standing persistent AF) and a larger left atrial volume index when compared with patients with other types of MR. In addition, all of the remaining 10 FMR-a patients with sinus rhythm were over the age of 75 years, with 8 patients being over the age of 85 years. In contrast, patients with FMR-v had a larger left ventricular diastolic diameter and increased prevalence of ICM.

Figure 4 Total number of patients with atrial functional mitral regurgitation (FMR-a), ventricular functional mitral regurgitation (FMR-v), and organic mitral regurgitation (OMR) by age.

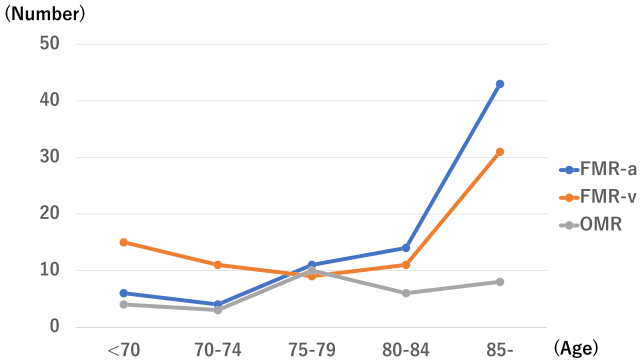


Table 2 Baseline characteristics by aetiology of mitral regurgitation

	FMR-a	FMR-v	OMR	*P* value
Number	78	77	31	
Age (years)	83.8 ± 8.3	78.9 ± 11.7	78.5 ± 9.6	0.012
Female (%)	51.3	45.5	64.5	0.200
BMI (kg/m^2)	21.6 ± 3.5	21.3 ± 3.7	21.2 ± 2.7	0.621
ICM (%)	12.8	44.2	3.2	<0.001
TR (%)	70.5	26.0	32.3	<0.001
Medical history (%)				
Prior hospitalization due to HF	59.0	84.4	38.7	<0.001
Hypertension	71.8	64.9	71.0	0.479
Diabetes mellitus	21.8	28.6	22.6	0.864
Atrial fibrillation	87.2	48.1	41.9	<0.001
Long-standing persistent AF	69.2	20.8	19.4	<0.001
LVEF (%)	56.9 ± 9.0	36.1 ± 12.7	60.7 ± 12.4	<0.001
LVDD (mm)	48.1 ± 7.6	56.0 ± 9.4	47.2 ± 6.4	<0.001
LAD (mm)	50.9 ± 9.8	46.4 ± 6.9	44.1 ± 6.4	<0.001
LAVI (mL/m^2)	88.2 ± 39.3	59.4 ± 22.0	61.3 ± 24.0	<0.001
Haemoglobin (mg/dL)	11.3 ± 1.9	12.1 ± 2.2	12.3 ± 1.5	0.006
eGFR (mL/min/1.73 m^2)	39.5 ± 18.4	40.8 ± 20.3	54.8 ± 49.0	0.001
Albumin (mg/dL)	3.6 ± 0.5	3.6 ± 0.5	3.7 ± 0.5	0.609
BNP (pg/mL)	316.2 [200.9–509.2]	488.8 [276.2–866.8]	154.5 [77.0–263.2]	0.002

AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FMR-a, atrial functional mitral regurgitation; FMR-v, ventricular functional mitral regurgitation; HF, heart failure; ICM, ischaemic cardiomyopathy; LAD, left atrial diameter; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; OMR, organic mitral regurgitation; TR, tricuspid regurgitation.
Values are presented as mean ± standard deviation, median (inter-quartile range), or absolute numbers.

Discussion

The KUNIUMI registry chronic cohort provides unique data on patients with CHF in a super-aged society, where 36.3% of the inhabitants were aged ≥65 years. To our knowledge, this is the first reported CHF registry created in a super-aged community. The information provided by this registry will be of use as a global reference as the world shifts towards a super-aged society.

The main findings were as follows: (i) the proportion of HFpEF increased with age; (ii) in a super-aged society, VHD was the main aetiology of CHF, especially MR and TR; and (iii) FMR-a increased with age, with a majority of the patients aged >75 years. These results may reflect the situation of CHF in the future in developed countries that are transitioning to a super-aged society.

Increase in heart failure with preserved ejection fraction patients with ageing

Similar to the results of a previous report, the number of patients with HFpEF increased with age in this registry.[22] The prognosis of patients with HFpEF was worse than that of pa-

tients with HF with reduced EF (HFrEF),[23] and effective treatment was limited, unlike that for HFrEF. Recently, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) demonstrated that empagliflozin, an SGLT-2 inhibitor, reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF, regardless of the presence or absence of DM.[24] However, the efficacy and safety of SGLT-2 inhibitor in older patients are not well known. Because older patients with HFpEF tend to present with multiple comorbidities, such as frailty and undernutrition,[25] multidisciplinary interventions are required.

Aetiology of heart failure

In the Japanese CHF registry during the early 2000s, cardiomyopathy was the major cause of HF.[26] However, with the accelerated westernization of lifestyle and increase in the number of survivors following acute coronary events,[27] the prevalence of coronary artery disease as an aetiology in patients with HF dramatically increased in Japan during the late 2000s.[7] Hereinafter, we will face the new era of a super-aged society. According to literature, older patients are more likely to develop VHD.[11,12,28] In this registry of a super-aged society, VHD was the most common aetiology, accounting for 49.8% of patients with overt HF. The prevalence of VHD in this study was much higher than that in the Japanese acute HF registry (27.7%),[5] CHART-2 (23.8%),[7] and European CHF registry (34%) from 2004 to 2005.[15] Furthermore, in this CHF registry of a super-aged society, MR was the most common type of VHD identified in patients with symptomatic HF, which increased with age (~30% in patients aged 75 years and older). In the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry, the largest pan-European cohort providing contemporary generalizable information about 'real-world' patients with CHF, MR was also the most frequently encountered VHD (MR: 31.2%; AS: 3.7%; aortic valve regurgitation: 4.7%; and TR: 19.2%).[29] The EuroHeart Failure Survey I also demonstrated that MR was more common in older patents (36.1% in individuals aged 80 years and older vs. 31.6% in those under 80 years).[30] Furthermore, a population-based study also identified MR as the most frequently encountered VHD and observed a significant increase in the prevalence of MR with ageing.[11]

Additionally, similar to previous results,[11] the number of patients with AS also increased with age, especially in those aged over 85 years. The Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial was a randomized controlled trial that evaluated the safety and efficacy of surgical aortic valve replacement in the treatment of asymptomatic patients with severe AS. This study demonstrated that early intervention reduced cardiovascular events, including HF hospitalization, when compared with conservative treatment.[31] Early intervention in patients with severe AS may be desirable in the HF pandemic era. However, as most patients in the AVATAR trial were under 85 years of age, it is difficult to reflect its generalizability to the real-world practice in a super-aged society. Recently, the use of transcatheter aortic valve replacement (TAVR) has increased, greater operator experience, and improved outcome.[32] TAVR is a less invasive alternative to traditional surgical aortic valve replacement in super-aged patients with AS. Early intervention with TAVR may contribute to the prevention of HF exacerbation in older patients with AS.

Causes and mechanisms of mitral regurgitation

It has been recognized that MR can occur without significant degenerative changes in the mitral leaflets. This type of MR is FMR, in contrast to degenerative MR (OMR), which is caused by organic changes in the mitral valve itself.[33] Two types of FMR were recognized: FMR-v, which was caused by a dilated or ischaemic left ventricle with mitral leaflet tethering, and FMR-a, which was caused by a dilated left atrium or mitral annulus without obvious left ventricular systolic dysfunction.[34–36]

Atrial functional MR was assumed to occur in relation to AF and/or HFpEF.[34] In the present study, 87.2% of FMR-a patients had a history of AF. All remaining FMR-a patients with sinus rhythm were over 75 years of age. Dziadzko *et al*. examined the aetiology and mechanisms in all MR cases in a super-aged community, where OMR and FMR were 32% and 65%, respectively; FMR-v and FMR-a were 38% and 27%, respectively.[20] Similar to previous results, this registry showed that the rate of FMR was higher than that of OMR, and the prevalence of FMR-a was comparable with that of FMR-v, owing to the increase in patients with FMR-a with ageing. As previously reported,[20] patients with FMR-a were the oldest among the three groups; therefore, the burden of FMR-a increases in a highly aged society. To prevent the occurrence of FMR-a, early detection of AF using advanced technologies, such as implantable and optical sensor-enabled wearable devices,[37,38] is imperative. Interventions for the prevention of transition to long-standing AF, including control of HT and DM, management of obesity and chronic kidney disease, and the detection and treatment of sleep apnoea, are also assumed to contribute to preventing FMR-a.[39]

However, there is limited evidence on therapeutic options for the management of FMR-a. Gertz *et al*. reported that FMR improved if sinus rhythm was restored by AF ablation through the shrinkage of the enlarged left atrium.[36] Additionally, Wu *et al*. showed that patients with AF and FMR-a who were treated with catheter ablation had a lower combined risk of HF-related hospitalization and stroke than a matched cohort of patients receiving drug therapy alone.[40] However, the effectiveness of rhythm control by itself might be limited

in patients with a markedly dilated left atrium because maintaining a sinus rhythm and reverse remodelling is more difficult with a large left atrium.[41,42] Therefore, surgical treatment may be the most reliable treatment option for FMR-a with highly advanced enlargement of left atrium.[10,43] Okamoto *et al*. revealed that TR was an independent prognostic factor of FMR-a[18] that co-existed with FMR-a at a high rate (70.5%); therefore, surgical treatment was reasonable because MR and TR were treated at the same time. However, because patients with FMR-a tend to be older and have a high surgical risk or many comorbidities, catheter-based interventions, such as MitraClip, are useful alternative treatment choices. More intensive therapeutic options have been proposed; however, no conclusive data are available to date. Further evidence is required to confirm this hypothesis.

Limitations

The present study had several limitations. First, 1646 patients with CHF were recruited in the registry, but not all patients with CHF on Awaji Island were included. This was attributed to only 2 years having passed since the start of this registry and the refusal of some patients to enrol. Okura *et al*. had estimated that 1.2% of the Japanese population would have HF by 2040 when ~36% of people would be more than 65 years old.[44] In the present study, 1.3% of total inhabitants had been enrolled, indicating the enrolment of most patients with HF on the Awaji Island. Second, the KUNIUMI registry was a single-centre cohort registry. However, because AMC is the only hospital that has full-time practising cardiologists on Awaji Island, lower-bias cardiological patients were gathered in this hospital. Third, all participants in the KUNIUMI registry chronic cohort were inhabitants of Awaji Island, which may not completely represent the typical Japanese patient population or that of any developed country. However, Awaji Island is not isolated. Located near large cities, this island offers a reasonable model for the future Japanese population. In fact, we found that the characteristics of non-aged patients (65–74 years) were similar to that in CHART-2, which is the largest CHF registry in Japan to date (DM 40.1% vs. 43.0%, AF 48.1% vs. 44.7%, and history of percutaneous coronary intervention 31.4% vs. 33.6%, in the KUNIUMI chronic cohort and CHART-2,[16] respectively). Considered together, these findings are assumed to reflect the status of Japan's super-ageing society in the near future. In contrast, comparing the HF background between Japan and Europe, body mass index and ischaemic aetiology were lower in Japan.[2] These dissimilarities should be considered when extrapolating the present findings to a model for future super-aged societies in other countries.

Fourth, we excluded patients with CHF Stage B. As patients without symptoms are liable to fail to visit a hospital for a medical check-up, we deemed that the present study design was inadequate to investigate the aetiology of patients with Stage B HF. Supporting Information, *Figure S7* shows the aetiology of patients with CHF Stage B; however, the findings may be misleading. Finally, we included cases with multiple aetiologies because it was sometimes difficult to determine which aetiology was responsible for HF.

Conclusion

The KUNIUMI registry chronic cohort showed a change in the predominant HF aetiology to VHD, especially MR, in a super-aged society. Based on the results of this study, effective and comprehensive countermeasures must be investigated to prepare for the rapid increase in HF incidence.

Acknowledgements

The authors would like to thank Shiho Fukushima, Haruka Okada, Michiko Iwasaki, and Yoko Fujimoto for collecting and managing data.

Conflict of interest

R.T., M.N., and K-I.H. belong to the Division of Evidence-based Laboratory Medicine, Kobe University Graduate School of Medicine, which was established by an endowment fund from Sysmex Corporation. H.T. is a consultant for AstraZeneca plc, Ono Pharmaceutical Co., Ltd., Pfizer Inc., Otsuka Pharmaceutical Co., Ltd., and Novartis International AG. K-I.H. received an honorarium from Kowa Company, Ltd. and Novo Nordisk Pharma Ltd.

Funding

This work was financially supported by the Osaka Gas Group Welfare Foundation, Japan.

Supporting information

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

Table S1. Eligible criteria for the KUNIUMI registry chronic cohort.
Figure S2. Time course of patient recruitment in the KUNIUMI registry chronic cohort.
Table S3. Baseline characteristics by stages.

Table S4. Baseline characteristics by left ventricular ejection fraction.

Table S5. Baseline characteristics of patients with or without multiple aetiologies.

Table S6. Co-existing aetiology in patients with multiple aetiologies.

Figure S7. Aetiology of heart failure in stage B patients.

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