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ORIGINAL RESEARCH ARTICLE

Impact of admission hyperglycaemia on clinical outcomes in non-diabetic heart failure with preserved ejection fraction

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Abstract

Aims At present, the clinical significance of admission hyperglycaemia in heart failure with preserved ejection fraction (HFpEF) patients remains unknown. This study was designed to evaluate the relationship between admission hyperglycaemia and clinical outcome in HFpEF patients, especially in non-diabetic patients.

Methods and results We enrolled 486 non-diabetic HFpEF (left ventricular ejection fraction ≥50%) patients hospitalized due to acute decompensated heart failure from the PURSUIT-HFpEF registry, a prospective, multicentre observational study. We divided non-diabetic patients into two groups, an admission hyperglycaemia group whose blood glucose on admission was ≥7.0 mmol/L (148 patients) and a normoglycaemic group whose blood glucose on admission was <7.0 mmol/L (338 patients). The primary endpoint was all-cause mortality, and the secondary endpoints were heart failure death and other causes of cardiac death. During a mean follow-up period of 400 ± 335 days, all-cause mortality was 69 patients. Twenty-five patients suffered cardiac death. All-cause mortality (P = 0.002), cardiac death (P = 0.009), and heart failure death (P = 0.001) were significantly more frequent in the admission hyperglycaemia group than in the normoglycaemic group. Admission hyperglycaemia was independently and significantly associated with all-cause mortality and cardiac death (HR 2.01, 95% CI 1.20–3.34, P = 0.008 and HR 3.03, 95% CI 1.35–6.96, P = 0.007, respectively).

Conclusions Non-diabetic HFpEF patients with admission hyperglycaemia when hospitalized for heart failure had poorer clinical outcomes than normoglycaemic patients.

Keywords Heart failure with preserved ejection fraction; Admission blood glucose; Hyperglycaemia; Prognosis

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Introduction

Heart failure (HF) is a global pandemic which affects 26 million people around the world annually.[1] HF is classified according to left ventricular ejection fraction (LVEF) as HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF).[2] The number of patients with HFpEF is markedly increasing with the increase in superaging populations.[3] HFpEF is increasing and is now recognized as

accounting for up to half of HF cases.[4] Several reports have examined prognostic factors in HFpEF,[5–8] but no evidence-based treatment has been found to reduce hospitalization and improve mortality in these patients. The reason for these disappointing results may be due to extracardiac co-morbidities among patients with HFpEF.[9]

Previous studies demonstrated that admission hyperglycaemia with acute heart failure was associated with a higher incidence of re-hospitalization, and with in-hospital, short-term and long-term mortality.[10–12] In nondiabetic patients with acute heart failure, admission hyperglycaemia was an independent predictor of one-year mortality, despite diabetes mellitus (DM) itself not carrying this prognosis.[13] The association between admission hyperglycaemia and clinical outcome in nondiabetic HFpEF patients has not been elucidated.

Here, we evaluated the relationship between admission hyperglycaemia and clinical outcomes in real-world patients with HFpEF using data from a prospective multicentre observational study of patients with HFpEF (PURSUIT-HFpEF registry).

Methods

The PURSUIT-HFpEF registry

We enrolled patients from the PURSUIT HFpEF (Prospective, mUlticenteR, obServational stUdy of patIenTs with Heart Failure with Preserved Ejection Fraction) registry. The PURSUIT-HFpEF is a prospective, multicentre (32 hospitals, details are shown in Appendix) observational study among collaborating hospitals in the Osaka region, Japan (UMIN-CTR ID: UMIN000021831).[14,15] The enrolled patients were hospitalized with acute decompensated heart failure (ADHF) as diagnosed by the Framingham criteria, with an LVEF $\geq$50% on transthoracic echocardiography and brain natriuretic peptide $\geq$100 ng/L or N-terminal pro brain natriuretic peptide (NT-pro BNP) $\geq$ 400 ng/L on admission. Exclusion criteria were (i) severe aortic stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural changes of the valve detected by transthoracic echocardiography; (ii) age $<$20 years; (iii) acute coronary syndrome on admission; (iv) $\leq$6 month prognosis due to non-cardiac diseases; (v) status post heart transplantation.

We followed each patient and collected outcome data on mortality, cause of death, and number and causes of hospitalization. All patients provided written informed consent to participate in the study, which was approved by the ethics committees of all participating hospitals. The investigation conforms with the principles outlined in the Declaration of Helsinki. The present study protocol was approved by the institutional review boards of all participating hospitals.

Study population

Heart failure with preserved ejection fraction patients from the PURSUIT-HFpEF registry were enrolled between June 2016 and February 2020. Patients who had no measurement of glucose level on admission or had a history of DM or HbA1c $>$ 6.2% during hospitalization were excluded from this study. Finally, we enrolled patients who without a history of DM and an HbA1c $\leq$ 6.2% on admission. We defined admission hyperglycaemia as blood glucose on admission $\geq$7.0 mmol/L and admission normoglycaemia as blood glucose on admission $<$7.0 mmol/L based on one of the diagnostic criteria of DM.[16] Previous studies defined normoglycaemia as no previous history of DM and HbA1c $<$ 6.4% or 6.5%.[13,17] Previous report demonstrated that the ethnic differences in the relationship between insulin sensitivity and insulin response and the genetic background of East Asians are susceptible to diabetes than Caucasians.[18] That is the reason why abnormal glucose metabolism is likely to occur even if the value of HbA1c is normally high in East Asians. In the present study, we defined normoglycaemia as HbA1c $\leq$ 6.2, which was stricter than in previous reports, to exclude patients with mild glucose intolerance which affects myocardial dysfunction.

Data collection

Investigative cardiologists and trained research nurses recorded the patient data such as medical history, substance history (such as smoking and alcohol), co-morbidities, exacerbation factors of HF, therapeutic procedures, and clinical events from the medical records and by direct interview of the patients and family members during their hospital stay. They also obtained vital signs, body mass index, New York Heart Association classification, echocardiographic data, admission laboratory data, and medications at discharge.

Clinical outcomes

After discharge, all patients were followed up by their treating hospital. Coordinators and investigators obtained clinical data by direct contact in an outpatient setting, telephone interview with patient families, or by mail. The primary endpoint for this study was all-cause mortality. The secondary endpoint was cardiac death and HF death.

Echocardiography

Left ventricular diastolic diameter (LVDd), left ventricular systolic diameter, interventricular septum thickness, left ventricular posterior wall thickness, left atrial diameter, and inferior

vena cava diameter were measured as previously described.[19,20] LVEF was measured by the modified Simpson method.[19] E/e′ was the mean of septal E/e′ and lateral E/e′. Left ventricular mass was calculated by linear methods as follows:

$$\text{Left ventricular mass} = 0.8 \times [1.04\,((\text{interventricular septum thickness diameter}) + (\text{LVDd}) + (\text{left ventricular posterior wall thickness diameter}))3 - (\text{LVDd})3] + 0.6.$$

Tricuspid regurgitation pressure gradient was measured by a simplified Bernoulli equation.[19]

Statistical analysis

JMP 15 statistical software (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis. Continuous variables are expressed as median [interquartile range]. Two-group comparisons were analysed by an unpaired two-tailed Student's *t*-test. Categorical data were expressed as a number (percentage) and compared using the χ^2 test or Fisher's exact test for categorical variables. Study endpoints were estimated using Kaplan–Meier curves, and statistical significance was determined using the log-rank test. Univariate analysis with a Cox proportional hazards regression model was performed, and *P*-values <0.05 were considered significant. Multivariate analyses with a Cox proportional hazards regression model for all-cause mortality and cardiac death were performed for those factors which had a *P*-value <0.05 on univariate analysis with the Cox proportional hazards regression model. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Results

Clinical characteristics

We enrolled 871 patients from the PURSUIT-HFpEF registry between June 2016 and February 2020. A total of 42 patients were excluded because of missing admission glucose values, and 343 patients were excluded because they had a history of DM or HbA1c $>$ 6.2%, respectively, leaving 486 patients with no history of DM or HbA1c $\leq$ 6.2% for analysis (*Figure 1*). Baseline characteristics of the patients with ADHF in the admission hyperglycaemia and normoglycaemic groups are shown in *Table 1*. Median age was 83 years [77, 88] and 43.4% of the population was female. The admission hyperglycaemia group showed higher systolic and diastolic blood pressure, higher heart rate, lower saturation of percutaneous oxygen under oxygen administration, higher white blood cell counts, a higher ratio of neutrophils, a lower ratio of lymphocytes, lower levels of sodium and chloride, higher C reactive protein and higher NT-pro BNP than the normoglycaemic group. The significantly different admission glucose levels resolved during the hospital stay, with no significant difference in glucose levels between the two groups at discharge.

Figure 1 Flow chart of the study patients. Among 871 HFpEF patients, we finally studied 486 patients. DM, diabetes mellitus.

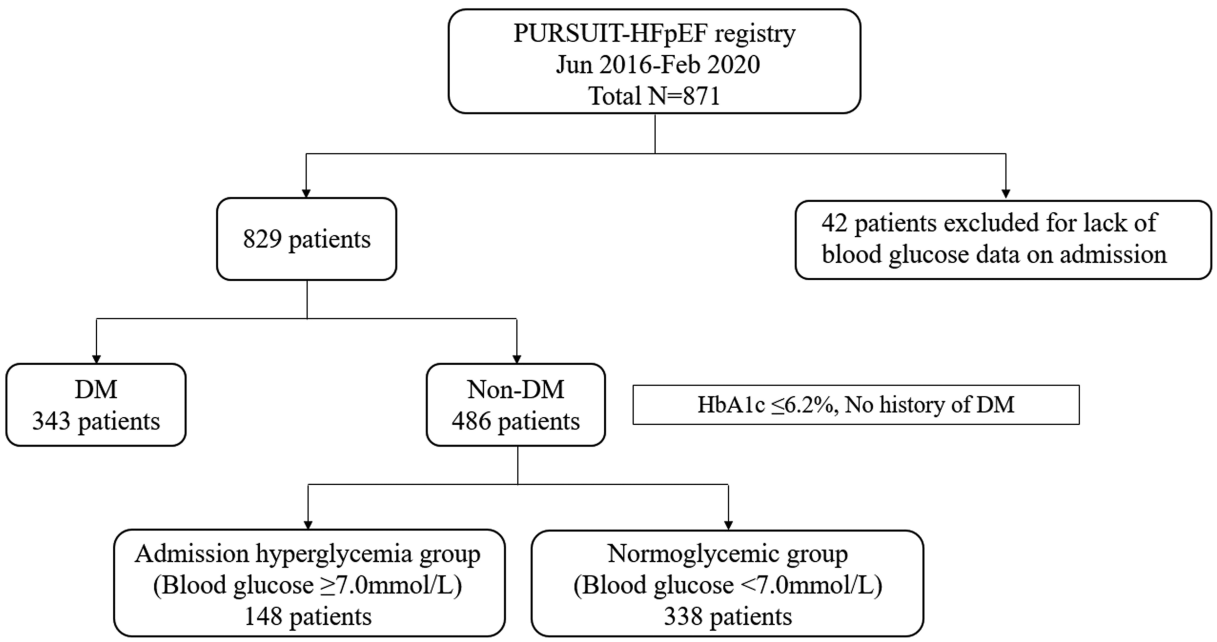

Table 1 Baseline characteristics of the HFpEF patients with acute decompensated heart failure stratified by blood glucose level on admission

	All (N = 486)	Admission hyperglycaemia group (N = 148)	Normoglycaemic group (N = 338)	P-value
Clinical data				
Age, years	83 [77, 88]	83 [77, 88]	83 [78, 88]	0.732
Male, *n* (%)	211 (43.4)	60 (40.5)	151 (44.7)	0.397
Body mass index, kg/m^2	22.6 [20.2, 25.7]	22.7 [19.8, 25.2]	22.6 [20.2, 25.8]	0.518
Smoking, *n* (%)	172 (35.4)	55 (37.2)	117(34.6)	0.589
Alcohol, *n* (%)	133 (27.4)	36 (24.3)	97 (28.7)	0.320
Systolic blood pressure, mmHg	146 [127, 168]	149 [129, 190]	144 [125, 166]	0.010
Diastolic blood pressure, mmHg	80 [65, 96]	81 [68, 108]	79 [65, 94]	0.030
Heart rate, b.p.m.	81 [65, 100]	88 [71, 118]	80 [63, 96]	<0.001
SpO2, %	95 [91, 97]	93 [88, 96]	95 [92, 97]	<0.001
NYHA classification ≥II, *n* (%)	311 (64.0)	96 (64.9)	215 (63.6)	0.791
Previous heart failure hospitalization, *n* (%)	120 (24.7)	37 (25.0)	83 (24.6)	0.917
Hypertension, *n* (%)	390 (80.2)	122 (82.4)	268 (79.3)	0.423
Dyslipidaemia, *n* (%)	160 (32.9)	44 (29.7)	116 (34.3)	0.322
Hyperuricaemia, *n* (%)	155 (31.9)	53 (35.8)	102 (30.2)	0.220
Chronic kidney disease, *n* (%)	179 (36.8)	48 (32.4)	131 (38.8)	0.183
Stroke, *n* (%)	63 (13.0)	15 (10.1)	48 (14.2)	0.219
Atrial fibrillation, *n* (%)	217 (44.7)	57 (38.5)	160 (47.3)	0.072
Echocardiographic data (on admission)				
LVDd, mm	46 [42, 50]	45 [42, 50]	46 [42, 50]	0.523
LVDs, mm	29 [26, 33]	29 [25, 34]	29 [26, 33]	0.793
IVSTd, mm	10 [8, 11]	10 [8, 11]	10 [8, 11]	0.267
LVPWTd, mm	10 [9, 11]	10 [9, 11]	9 [8, 11]	0.285
LADs, mm	44 [39, 50]	42 [38, 50]	45 [39, 51]	0.641
LVEF, %	60 [55, 65]	62 [57, 66]	60 [56, 64]	0.132
Left ventricular mass, g	152 [118, 184]	152 [118, 182]	152 [118, 184]	0.615
E/e′	15 [11, 20]	15 [11, 19]	15 [12, 20]	0.099
Inferior vena cava diameter, mm	18 [14, 22]	17 [14, 21]	18 [15, 22]	0.194
TRPG, mmHg	35 [27, 45]	34 [26, 44]	36 [29, 45]	0.658
Laboratory data (on admission)				
White blood cell, per μL	6200 [5000, 8200]	7700 [5800, 9700]	5900 [4600, 7400]	<0.001
Neutrophil, %	70 [62, 78]	72 [65, 82]	69 [61, 76]	0.003
Lymphocyte, %	18 [12, 25]	15 [9, 23]	19 [14, 26]	0.024
Haemoglobin, g/dL	11 [10, 13]	11 [10, 13]	11 [10, 12]	0.390
Sodium, mmol/L	140 [137, 142]	139 [135, 142]	141 [138, 143]	<0.001
Chloride, mmol/L	105 [102, 108]	103 [100, 108]	106 [103, 108]	<0.001
Potassium, mmol/L	4.1 [3.7, 4.4]	4.0 [3.6, 4.3]	4.1 [3.7, 4.5]	0.196
Creatinine, μmol/L	88 [71, 124]	88 [71, 133]	88 [71, 124]	0.676
eGFR, mL/min/1.73 m^2	45 [31, 59]	44 [29, 54]	45 [31, 60]	0.550
Uric acid, μmol/L	357 [291, 434]	357 [309, 428]	351 [291, 440]	0.633
Total bilirubin, μmol/L	12 [9, 19]	12 [9, 19]	12 [10, 17]	0.860
Albumin, g/dL	3.5 [3.2, 3.8]	3.7 [3.1, 3.9]	3.5 [3.2, 3.8]	0.142
Glucose (on admission), mmol/L	6.2 [5.4, 7.3]	8.3 [7.5, 9.8]	5.7 [5.2, 6.3]	<0.001
CRP, mg/dL	0.6 [0.2, 1.6]	0.7 [0.2, 3.9]	0.4 [0.1, 1.4]	<0.001
NT-pro BNP, ng/L	3323 [1740, 6550]	3913 [1950, 7530]	3250 [1633, 6220]	0.044
Laboratory data (at discharge)				
HbA1c, %	5.7 [5.4, 5.9]	5.7 [5.4, 5.9]	5.6 [5.4, 5.9]	0.607
Glucose (at discharge), mmol/L	5.1 [4.8, 5.7]	5.4 [4.8, 5.9]	5.1 [4.7, 5.6]	0.736
Medication (at discharge)				
ACEI, *n* (%)	93 (19.1)	25 (16.9)	68 (20.1)	0.405
ARB, *n* (%)	158 (32.5)	47 (31.8)	111 (32.8)	0.814
Beta blocker, *n* (%)	262 (53.9)	76 (51.4)	186 (55.0)	0.454
Diuretics (loop), *n* (%)	374 (77.0)	109 (73.6)	265 (78.4)	0.252
Aldosterone antagonist, *n* (%)	184 (37.9)	51 (34.5)	133 (39.3)	0.306
Statin, *n* (%)	131 (27.0)	45 (30.4)	86 (25.4)	0.257

Values are given as median (IQR) or *n* (%). Age, co-morbidities, and echocardiographic parameters are given on admission. Laboratory data (HbA1c and glucose) and medications are given at discharge.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction: IVSTd, interventricular septum thickness at end-diastole; LADs, left atrial diameter at end-systole; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LVPWTd, left ventricular posterior wall thickness at end-diastole; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SpO2, saturation of percutaneous oxygen; TRPG, tricuspid pressure gradient.

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Outcomes

Average follow-up duration was 400 ± 335 days. Details of all-cause death in the two groups are shown in *Figure 2*. All-cause mortality occurred in 69 patients (admission hyperglycaemia group 31 patients (20.9%), normoglycaemic group 38 patients (11.2%)). Cardiac death occurred in 25 patients (admission hyperglycaemia group 13/31 patients, normoglycaemic group 12/38 patients). Heart failure death occurred in 15 patients (admission hyperglycaemia group 10/31 patients, normoglycaemic group 5/38 patients). Non-cardiac death occurred in 44 patients (admission hyperglycaemia group 18 patients, normoglycaemic group 26 patients). Factors which exacerbated HF resulting in hospitalization are shown in *Table 2*. Incidence of non-compliance with water and salt restrictions was significantly lower, and infection and hypertension were higher, in the admission hyperglycaemia group than in the normoglycaemic group (P = 0.013, P = 0.012, and P = 0.003, respectively).

Kaplan–Meier analysis demonstrated that the admission hyperglycaemia group had a significantly greater risk of all-cause mortality and cardiac death than the normoglycaemic group (*Figure 3*). Further, the risk of HF death was significantly higher in the admission hyperglycaemia group than the normoglycaemic group, although non-cardiac death did not significantly differ between the two groups (*Figure 3*).

Univariate Cox proportional hazards analysis showed that admission hyperglycaemia, age, sodium, albumin, and C reactive protein were significantly associated with all-cause mortality (*Table 3*). Multivariate Cox proportional hazards analysis showed that admission hyperglycaemia (HR 2.01, 95% CI 1.20–3.34, P = 0.008), age (HR 1.07, 95% CI 1.03–1.11, $P < 0.001$), albumin (HR 0.32, 95% CI 0.19–0.54, $P < 0.001$), and LVDd (HR 0.95, 95% CI 0.91–0.99, P = 0.009) were significantly associated with all-cause mortality (*Table 3*).

Univariate Cox proportional hazards analysis showed that admission hyperglycaemia, age, albumin, and LVDd were

Figure 2 Details of all-cause death in the two groups stratified by admission hyperglycaemia and normoglycaemia. All-cause mortality occurred in 69 patients (admission hyperglycaemia group: 31 patients, normoglycaemic group: 38 patients). Cardiac death occurred in 25 patients (admission hyperglycaemia group: 13/31 patients, normoglycaemic group: 12/38 patients). Heart failure death occurred in 15 patients (admission hyperglycaemia group: 10/31 patients, normoglycaemic group: 5/38 patients). Non-cardiac death occurred in 44 patients (admission hyperglycaemia group: 18 patients, normoglycaemic group: 26 patients).

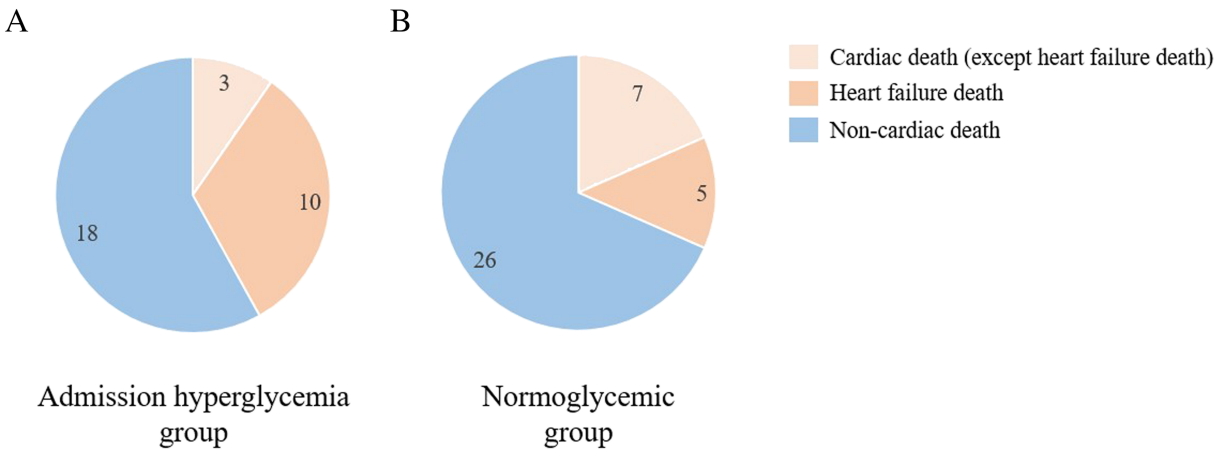

Table 2 Exacerbation factors of heart failure caused hospitalization

	Admission hyperglycaemia group (N = 148)	Normoglycaemic group (N = 338)	P-value
Non-compliance with water and salt restrictions, *n* (%)	27 (18.2)	98 (29.0)	0.013
Non-compliance with medications, *n* (%)	7 (4.7)	24 (7.1)	0.325
Physical overwork, *n* (%)	15 (10.1)	35 (10.4)	0.941
Infection, *n* (%)	37 (25.0)	52 (15.4)	0.012
Arrhythmia, *n* (%)	40 (27.0)	103 (30.5)	0.443
Exacerbation of ischaemia, *n* (%)	3 (2.0)	5 (1.5)	0.662
Hypertension, *n* (%)	31 (20.9)	37 (10.9)	0.003
Others, *n* (%)	36 (24.3)	91 (26.9)	0.548

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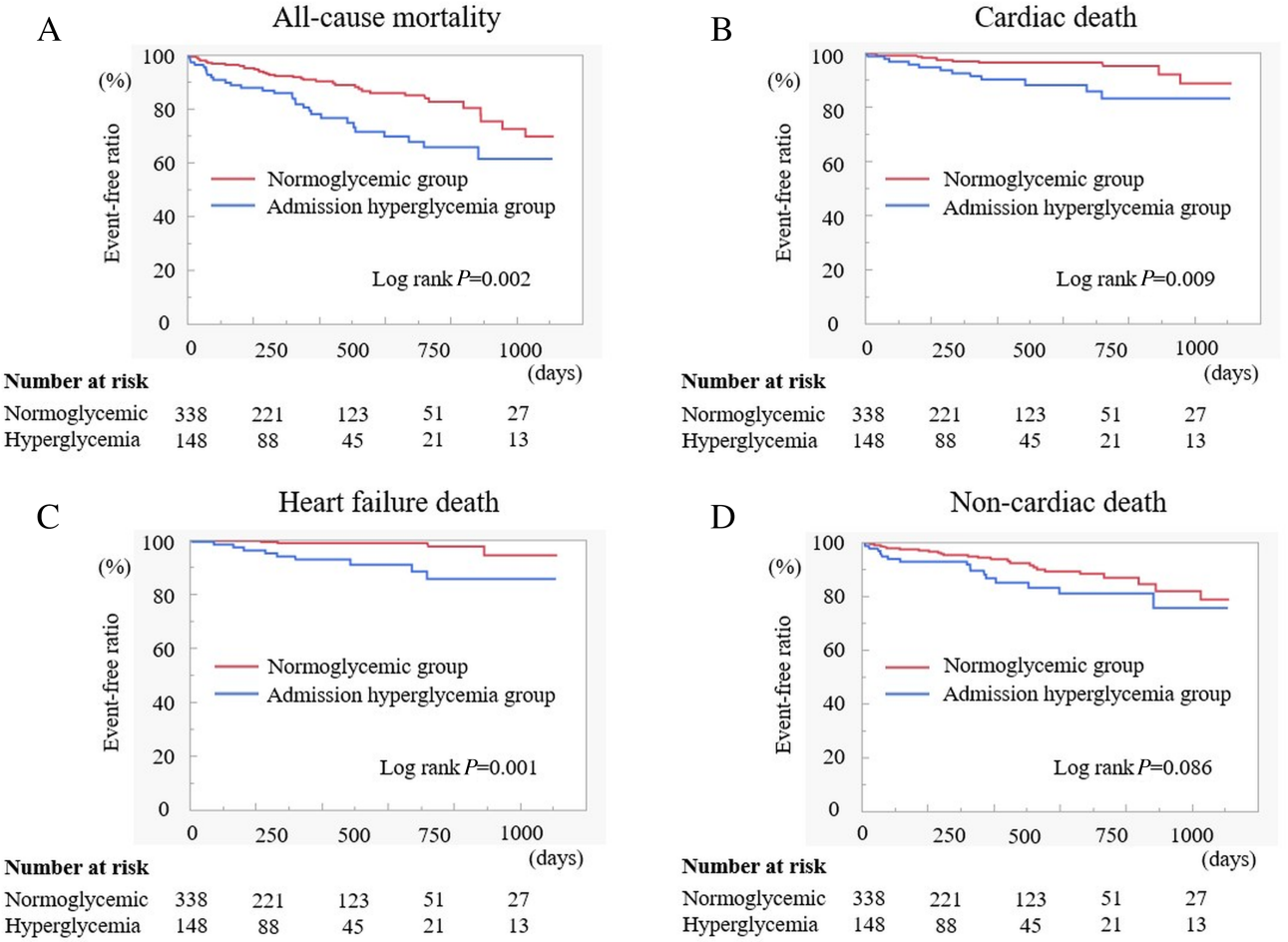
Figure 3 Kaplan–Meier analysis of (A) all-cause mortality, (B) cardiac death, (C) heart failure death, and (D) non-cardiac death between the admission hyperglycaemia and normoglycaemic groups.



significantly associated with cardiac death (*Table 4*). Multivariate Cox proportional hazards analysis showed that admission hyperglycaemia (HR 3.03, 95% CI 1.35–6.96, P = 0.007), albumin (HR 0.42, 95% CI 0.19–0.95, P = 0.033) and LVDd (HR 0.87, 95% CI 0.82–0.93, $P < 0.001$) were significantly associated with cardiac death (*Table 4*).

Next, we evaluated the clinical significance of admission hyperglycaemia considering the modern HFpEF criteria (HFA-PEFF and H2FPEF score).[21,22] Our criteria are considered to match step 2 of the HFA-PEFF. The H2FPEF score were reported to be useful for the diagnosis of HFpEF,[23] but the ethnic-specific BMI cut-off value (definitely lower than Caucasian populations in the USA and Europe) for Asians, especially Japanese, should be discussed. The only 40 patients (8.2%) had BMI $\geq$ 30 in the present registry. We analysed the patients with H2FPEF score $\geq$4 considering the modern HFpEF criteria. Baseline characteristics of the patients are shown in Supporting Information, *Table S1*. Kaplan–Meier analysis demonstrated that the admission hyperglycaemia group had a significantly greater risk of all-cause mortality and cardiac death than the normoglycaemic group (log-rank P = 0.006 and Log-rank P = 0.038, respectively, *Figure 4*). Multivariate Cox proportional hazards analysis showed that admission hyperglycaemia was significantly associated with all-cause mortality and cardiac death (HR 2.98, 95% CI 1.58–5.61, $P < 0.001$ and HR 3.99, 95% CI 1.35–11.79, P = 0.012, respectively, Supporting Information, *Tables S2* and *S3*).

Discussion

Main findings

This study had three major findings: (i) 148 non-diabetic HFpEF patients (30.5%) had admission hyperglycaemia; (ii) the HFpEF patients with admission hyperglycaemia had a significantly greater risk of all-cause mortality, cardiac death, and HF death than normoglycaemic HFpEF patients; and (iii) admission hyperglycaemia was an independent predictor for

Table 3 Cox proportional hazard analysis for all-cause mortality

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Admission hyperglycaemia	2.08	1.29–3.34	0.003	2.01	1.20–3.34	0.008
Age	1.09	1.05–1.13	<0.001	1.07	1.03–1.11	<0.001
Female	0.90	0.56–1.44	0.648			
Systolic blood pressure	1.00	0.99–1.00	0.382			
Heart rate	1.00	0.99–1.01	0.902			
SpO2	0.97	0.93–1.02	0.199			
Hypertension	0.88	0.50–1.65	0.675			
Atrial fibrillation	0.81	0.49–1.30	0.382			
Haemoglobin	0.98	0.88–1.10	0.747			
Sodium	0.95	0.91–1.00	0.042	0.97	0.93–1.03	0.322
Creatinine	1.02	0.77–1.20	0.879			
Albumin	0.25	0.15–0.40	<0.001	0.32	0.19–0.54	<0.001
CRP	1.09	1.04–1.13	<0.001	1.03	0.98–1.08	0.251
NT-pro BNP	1.00	0.99–1.00	0.516			
LVDd	0.93	0.90–0.97	<0.001	0.95	0.91–0.99	0.009
LVEF	1.03	0.99–1.08	0.174			
E/e′	1.02	0.99–1.05	0.102			

CI, confidence interval; CRP, C reactive protein; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; HR, hazared ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; SpO2, saturation of percutaneous oxygen.

Table 4 Cox proportional hazard analysis for cardiac death

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Admission hyperglycaemia	2.74	1.25–6.00	0.012	3.03	1.35–6.96	0.007
Age	1.08	1.02–1.15	0.010	1.05	1.00–1.12	0.061
Female	1.63	0.72–3.99	0.256			
Systolic blood pressure	0.99	0.97–1.00	0.107			
Heart rate	1.00	0.98–1.01	0.804			
SpO2	0.97	0.91–1.06	0.478			
Hypertension	0.93	0.38–2.79	0.882			
Atrial fibrillation	0.82	0.36–1.81	0.632			
Haemoglobin	0.99	0.82–1.19	0.889			
Sodium	0.93	0.87–1.01	0.074			
Creatinine	1.07	0.71–1.33	0.634			
Albumin	0.32	0.14–0.73	0.006	0.42	0.19–0.95	0.033
CRP	1.02	0.91–1.11	0.636			
NT-pro BNP	1.00	0.99–1.00	0.366			
LVDd	0.88	0.82–0.93	<0.001	0.87	0.82–0.93	<0.001
LVEF	1.06	0.98–1.14	0.131			
E/e′	1.04	0.99–1.07	0.066			

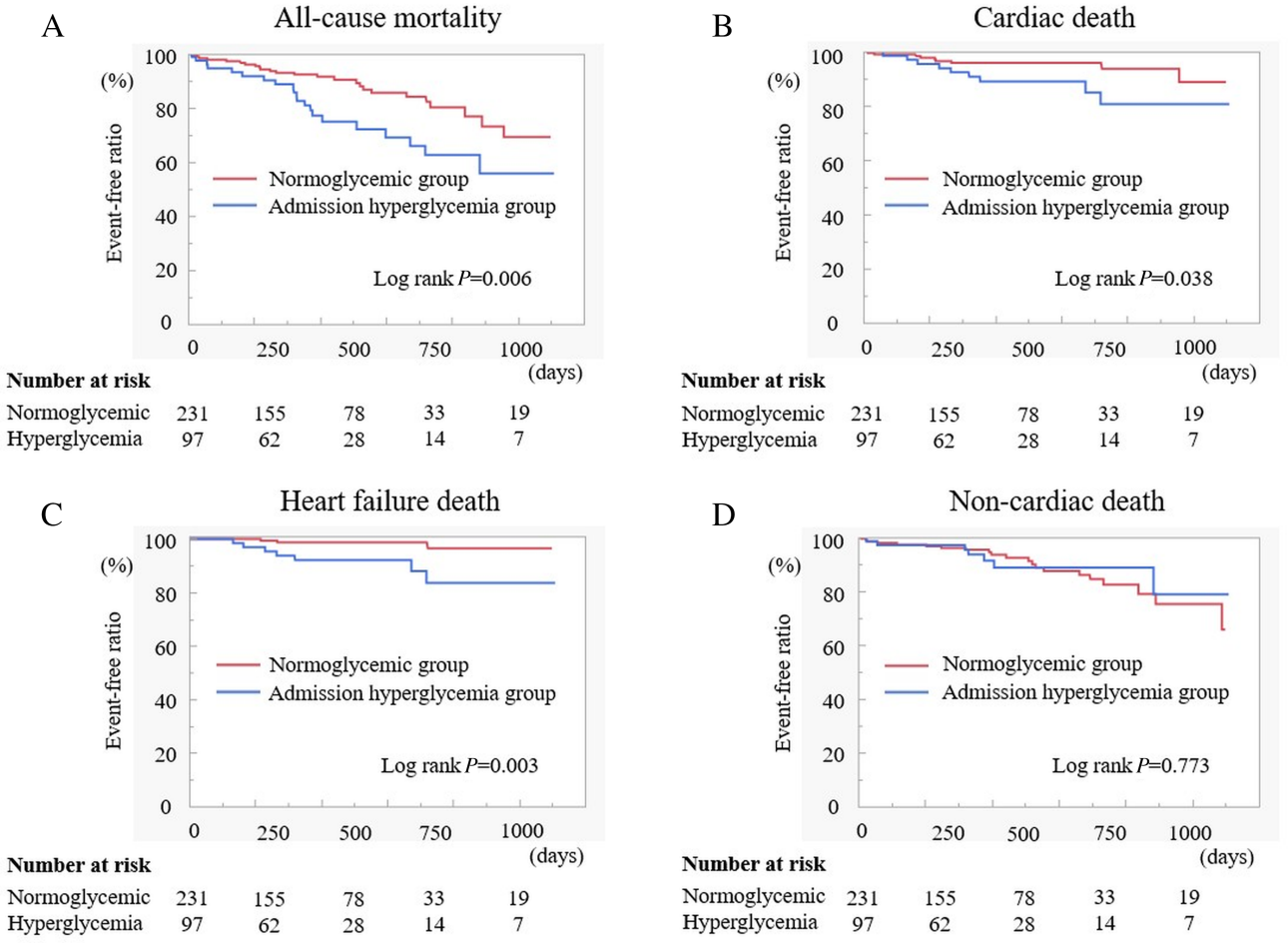
CI, confidence interval; CRP, C reactive protein; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; HR, hazared ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; SpO2, saturation of percutaneous oxygen.

all-cause mortality and cardiac death in non-diabetic HFpEF patients. These findings suggest admission hyperglycaemia was a simple and useful marker for predicting clinical outcome in non-diabetic HFpEF patients.

Sympathetic nervous system and hyperglycaemia

Previous studies showed the relationship between admission hyperglycaemia and the prognosis in AHF patients. Kosiborod *et al*. showed no significant association between admission glucose levels and mortality in a large cohort of patients hospitalized with heart failure.[24] In this study, 23.9% had left ventricular systolic dysfunction and 41.8% of enrolled patients had DM, while our enrolled patients were only non-diabetic HFpEF patients. Other reports have shown that admission hyperglycaemia is associated with hospital and short-term mortality in AHF patients.[10] Sud *et al*. have also showed that hyperglycaemia is associated with 30 day mortality and hospitalization in acute heart failure patients with no pre-existing DM.[11] In acute myocardial infarction patients, admission hyperglycaemia is an important factor of worse short-term and long-term prognosis.[25] In critical disease as mentioned earlier, the stress response is accompanied by the release of cortisol, catecholamines, glucagon, and growth hormones, which may induce continuous glucometabolic

Figure 4 Kaplan–Meier analysis of (A) all-cause mortality, (B) cardiac death, (C) heart failure death, and (D) non-cardiac death between the admission hyperglycaemia and normoglycaemic groups in the patients with H2FPEF score ≥4.



abnormalities.[26,27] Activation of these pathways provokes transient elevation of blood glucose levels, so-called 'stress hyperglycaemia'. Acute hyperglycaemia induces an increase in inflammatory cytokines with accompanying oxidative stress and endothelial dysfunction.[28–30] Oxidative stress plays a critical role in the induction of insulin resistance and beta cell dysfunction.[31] In acute heart failure, activation of the sympathetic nervous system is the major neurohormonal mechanism in the progression of HF. Another study showed that severe HF was associated with the development of myocardial insulin resistance caused by decreased myocardial adenosine triphosphate levels and reduction in glucose transporter-4 translocation.[32] Sympathetic nervous system activation due to decreased cardiac output causes inhibition of insulin release and direct stimulation of carbohydrate metabolism such as glycogenesis and gluconeogenesis.[33]

In our present study, admission hyperglycaemia was shown to be an independent predictor of cardiac death. The fact that systolic and diastolic blood pressure and heart rate on admission were significantly higher in the admission hyperglycaemia group than in the normoglycaemic group suggests increased sympathetic nervous system activation, in addition to evidence of more severe HF as demonstrated by low sodium and low oxygen saturation (*Table 1*).

Possible pathophysiology of acute decompensated status in the admission hyperglycaemia group of heart failure with preserved ejection fraction patients

Multivariate analysis for Cox proportional hazards analysis showed that low albumin levels and small LVDds, in addition to admission hyperglycaemia, were independently and significantly associated with all-cause mortality and cardiac death (*Table 4*).

Low albumin levels

Hypoalbuminemia is associated with infection as previously reported.[34] Infection in the elderly is likely to be fatal and is also an important factor that exacerbates heart failure. Median age in our registry was 83 years, and 89 patients (18.3%) had infection as the exacerbating factor on admission (*Table 2*). Considering the characteristics of our registry, low albumin might have a large impact on all-cause mortality and cardiac death.

Small left ventricular diastolic diameter

A previous study reported that left ventricular end-diastolic volume was increased, and pulmonary capillary wedge pressure was slightly increased during submaximal exercise in normal subjects, whereas left ventricular end-diastolic volume did not increase in HFpEF patients and pulmonary capillary wedge pressure markedly increased.[35] In our study, small LVDd was a risk factor for cardiac death in non-diabetic HFpEF patients. These results suggest that instability of the compensatory mechanism due to small LVDd facilitates pulmonary capillary wedge pressure elevation. DM itself promotes cardiomyocyte hypertrophy according to the following mechanism: impairment of myocardial nitric oxide pathway, coronary microvascular dysfunction, increased inflammation, and oxidative stress.[36] Although we enrolled only non-DM patients, we showed that the influence of insufficient left ventricular dilatation under stress on clinical outcomes was important in the hyperglycaemic group.

Clinical implications

Our study showed that admission hyperglycaemia was an important and simple predictor of all-cause mortality and cardiac death in non-diabetic HFpEF patients. We excluded HFpEF patients with DM in this study because blood glucose on admission was not reliable due to insulin resistance and beta cell dysfunction in HFpEF patients with DM. Several studies have investigated the control of hyperglycaemia in patients with acute myocardial infarction, but the results showed that intensive insulin therapy did not reduce all-cause mortality.[37,38] In HF patients, increases in blood glucose since admission were associated with increased 30 day mortality.[39] Few studies showed a positive correlation between controlling hyperglycaemia and clinical outcome in HF.[40–42] The present results have the potential efficacy of reduction in blood glucose as a therapeutic target in HFpEF patients. Recent studies showed that SGLT-2 inhibitors had a lower risk of cardiovascular death or hospitalization for heart failure than those in the control group.[40–42] SGLT-2 inhibitors had various beneficial effects not only on reduction of blood glucose but also on improvement insulin resistance.[43] Insulin resistance alters the systemic and neurohumoural milieu leading to changes in metabolism and signalling pathways in the heart that may induce to myocardial dysfunction.[44] Insulin resistance is one of the strong predictors of incident heart failure, especially HFpEF.[45] The aforementioned studies enrolled only in HFrEF patients, but pleiotropic effects of SGLT2 inhibitors may have a cardioprotective actions especially in HFpEF patients. Recently, McMurray *et al*. showed the novel algorithm for sequencing of fundamental treatment in HF patients.[46] They proposed the beta-blocker and SGLT-2 inhibitor as an initial treatment in HFrEF patients because SGLT2 inhibitor have potentially early diuretic action and may mitigate the short-term risk of worsening heart failure. However, few evidence of the efficacy of SGLT2 inhibitors on HFpEF were shown, and it remains unclear when SGLT2 inhibitor starts. Our results suggest that reduction of blood glucose itself in acute phase due to SGLT2 inhibitor may improve the present study endpoints because of diuretic action, improvement of insulin resistance, and amelioration of glucometabolic abnormalities. Because low albumin levels were independently and significantly associated with all-cause mortality and cardiac death in HFpEF patients, it is important to thoroughly improve nutritional status and prevent infection.

Study limitations

This study has several limitations. First, we enrolled only patients with admission hyperglycaemia and only slightly elevated HbA1c levels and selection bias in the target population could not be excluded. Second, we defined blood glucose on admission $\geq$7.0 mmol/L as admission hyperglycaemia based on the one of the diagnostic criteria of DM, but there may be other cut-off values of blood glucose on admission to predict clinical outcomes. There were few studies of admission hyperglycaemia only for non-diabetic patients. Tziomalos *et al*. defined stress hyperglycaemia as blood glucose level $\geq$7.0 mmol/L in non-diabetic DM patients.[47] It is considered applicable that diagnostic cut-off value of admission hyperglycaemia is ABG $\geq$ 7.0 mmol/L. Third, we did not perform oral glucose tolerance examinations in all enrolled patients. Fourth, we could not evaluate the status of food intake in the enrolled patients before admission. Evaluation of our findings in various populations is therefore required. Fifth, the readmissions was related to a poor quality of life and an increased mortality risk in heart failure patients,[48] but in our study, the incidence of the prior HF hospitalizations did not significantly relate to the endpoints. Approximately 50% of the enrolled patients had a history of prior HF hospitalizations in the previous report,[48] while 120 patients (24.7%) had prior HF hospitalizations in

our cohort. The lower incidence of prior HF hospitalizations might not have affected the poor prognosis in our cohort.

Conclusions

Non-diabetic HFpEF patients with admission hyperglycaemia had a significantly higher risk of all-cause mortality and cardiac death than those who were normoglycaemic.

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Conflict of interest

Daisaku Nakatani has received honoraria from Roche Diagnostics. Shungo Hikoso has received personal fees from Daiichi Sankyo Company, Bayer, Astellas Pharma, Pfizer Pharmaceuticals and Boehringer Ingelheim Japan, and received grants from Roche Diagnostics, FUJIFILM Toyama Chemical and Actelion Pharmaceuticals. Yasushi Sakata received personal fees from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation and Actelion Pharmaceuticals, and received grants form Roche Diagnostic, FUJIFILM Toyama Chemical, Abott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation and Biotronik. Other authors have no conflicts of interest to disclose.

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Supporting information

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

Table S1 Baseline characteristics of the HFpEF patients with acute decompensated heart failure and H2PFEF score ≥4 stratified by blood glucose level on admission.
Table S2 Cox proportional hazard analysis for all-cause mortality in the patients with H2PFEF score ≥4.
Table S3 Cox proportional hazard analysis for cardiac death in the patients with H2PFEF score ≥4.

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Appendix A

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