Construction of a Heart Failure Database Collating Administrative Claims Data and Electronic Medical Record Data to Evaluate Risk Factors for In-Hospital Death and Prolonged Hospitalization

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Supplementary Material

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3. **Data extraction**

Patients with the following conditions in the diagnosis procedure combination (DPC) data during a 38-month period from November 2011 to December 2015 were extracted as inpatients with heart failure (HF) from 3 acute care hospitals in Japan (Saiseikai Kumamoto Hospital: 388 beds, Saiseikai Yokohamashi Tobu Hospital: 560 beds, and Saiseikai Fukuoka General Hospital: 360 beds). Patients under 20 years of age were excluded to match the condition with the registry representing Japan[1,2]:

1) Hospitalization with HF (International Classification of Diseases, Tenth Revision [ICD]-10: I50) coded as primary diagnosis, diagnosis that triggered hospitalization, or diagnosis with the highest medical cost

2) Hospitalization with any disease involving symptoms of HF (**Supplementary Table 2**,

Diagnosis), such as acute myocardial infarction or ischemic heart disease, coded as diagnosis with the highest medical cost and prescription of any drug for HF (**Supplementary Table 2**, Agents) during hospitalization

4. RECOMEND cohort

Based on the definition of the protocol criteria, 7215 inpatients (10,297 hospitalizations) were extracted. Clinical experts made comprehensive judgments on the extracted patient data, and a database of 3864 inpatients with HF (5247 hospitalizations) was created as the RECOMEND cohort. In this cohort, 232 cases had no disease code of HF in the DPC and were also unclear from the values of brain natriuretic peptide (BNP) and left ventricular ejection fraction (LVEF) (**Supplementary Table 3**). However, as a result of review of the patient-by-patient treatment flow chart by 2 cardiologists, the HF hospitalized group was considered to have 1 or more of the following 5 criteria.

1) Prescription of cardiotonic (C01C2*) agent (intravenous [iv]): 189 hospitalizations,
2) New York Heart Association (NYHA) Class III or IV: 12 hospitalizations,
3) Canadian Cardiovascular Society (CCS) Class IV: 12 hospitalizations,
4) Killip Class IV: 26 hospitalizations,
5) Acute myocardial infarction or tachyarrhythmia or valvular disease or myocarditis (as diagnosis with most costed medication) and prescription of diuretics (C03A2*, C03A9*) or carperitide (C01X0*): 149 hospitalizations.

Moreover, comprehensive judgment by clinical experts for medical treatment, outcomes, and other Hospital Information System (HIS)/electronic medical record (EMR) data of all cases were obtained.

5. Definitions of derived variables

Of the variables used in this study, body mass index (BMI), Charlson Comorbidity Index (CCI), Barthel Index, LVEF, estimated glomerular filtration rate (eGFR), Geriatric Nutritional Risk Index (GNRI), lymphocyte count, glycated hemoglobin (HbA1c), presence or absence of anemia, chronic kidney disease (CKD) stage, presence or absence of hyponatremia, presence or absence of hypoalbuminemia, and presence or absence of diabetes were derived from variables in hospital-specific databases to create a database for the

RECOMEND cohort as described below:

- CCI was calculated by summing up scores for given diseases using ICD-10 codes in Style 1, "Comorbidities at admission" in the hospital DPC data. Since up to 4 comorbidities at admission can be entered into the DPC data, some comorbidities used to calculate CCI may not be included.[3]

- Barthel Index was calculated by summing up scores for questions in Style 1, "Activities of daily living (ADL) at admission" in the hospital DPC data. If any answer was unknown or not described, the Barthel Index was assessed as not calculable.[4]

- LVEF was derived from left ventricular end-diastolic diameter (LVDd) and left ventricular end-systolic diameter (LVDs) according to the following formula:

  LVEF=(left ventricular end-diastolic volume [LVEDV] − left ventricular end-systolic volume [LVESV])/LVEDV × 100

  LVEDV=7.0/(2.4+LVDd) × LVDd

  LVESV=7.0/(2.4+LVDs) × LVDs

- eGFR was derived from gender, age, and creatinine according to the following formula:

  eGFR (male)=$194 \times [\text{creatinine}]^{-1.094} \times [\text{age}]^{-0.287}$

  eGFR (female)=$194 \times [\text{creatinine}]^{-1.094} \times [\text{age}]^{-0.287} \times 0.739$

- GNRI was derived from height at admission, weight at admission, and albumin according to the following formula:[5]

  GNRI=[14.89 × [albumin (g/dL)]+[41.7 × %IBW]

  %IBW=max (1, [weight at admission]/[22 × (height at admission [m])^2])

  where IBW=ideal body weight

- Lymphocyte count was derived from white blood cell count and lymphocyte subsets.

- HbA1c (National Glycohemoglobin Standardization Program [NGSP]): if not available, HbA1c (Japanese Diabetes Society [JDS]) was converted to HbA1c (NGSP) according to the following formula:

  HbA1c (NGSP)=1.02 × HbA1c (JDS)+0.25

- Presence or absence of anemia: the patient was diagnosed with anemia based on gender and a hemoglobin level of <13 g/dL (male) or <12 g/dL (female) (World Health Organization criteria).

- CKD stage ≥G3b: The CKD stage was Grade 3b or higher if eGFR was

<45 mL/min/1.73 m^2.

- Presence or absence of hyponatremia: The patient was diagnosed with hyponatremia if sodium was <135 mEq/L.

- Presence or absence of hypoalbuminemia: The patient was diagnosed with hypoalbuminemia if albumin was ≤ 3.0 g/dL.

- Presence or absence of diabetes: The patient was diagnosed with diabetes if HbA1c (NGSP) at admission was $>6\%$ or any antidiabetic drug (Anatomical Therapeutic Chemical [ATC] code: A10C1, A10C2, A10C3, A10C5, A10D0, A10H0, A10J1, A10K1, A10K2, A10K3, A10L0, A10M1, A10M9, A10N1, A10N3, A10N9, A10P1, A10S0, and A10X9) was prescribed during hospitalization.

6. In-hospital mortality rate and proportion of patients hospitalized for a prolonged period by parameters early after admission

Among the risk factors for in-hospital mortality and those for long-term hospitalization, 5 variables were suggested to be strongly associated with in-hospital mortality and/or prolonged hospitalization: age (years), Barthel Index at admission, NYHA class, albumin, and creatinine. For the 5 variables, i.e., age (years), Barthel Index at admission, NYHA class, albumin, and gender-specific eGFR instead of creatinine, in-hospital mortality rate and number of days in hospital (only patients discharged alive) were calculated for each category. No tree diagram analysis was performed.

References

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Supplementary Table 1. List of laboratory, echocardiography, and vital sign items collected in the database

		Items
Laboratory values	Serum	Leukocyte, Erythrocyte, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean cell hemoglobin concentration, Platelet, Neutrophils, Eosinophil, Basophils, Monocyte, Lymphocytes, etc.
	Biochemical	Total protein, Albumin, Total bilirubin, Direct bilirubin, Total cholesterol, HDL cholesterol, LDL cholesterol, Triglyceride, HbA1c, Glucose, Sodium, Potassium, Chlorine, Calcium, Inorganic phosphorus, Iron, Total iron binding capacity, Amylase, Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Lactate dehydrogenase, Gamma-glutamyl transpeptidase, Cholinesterase, Creatine kinase, Uric acid, Creatinine, Blood urea nitrogen, C-reactive protein, Troponin T, Brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, etc.
	Urine	Urine specific gravity, Urine pH, etc.
	Blood gases	pH, Partial pressure of arterial carbon dioxide, Partial pressure of arterial oxygen, Bicarbonate ion, Arterial oxygen saturation, Sodium, Potassium, Chlorine, etc.
	Other	D-dimer, Activated partial thromboplastin time, Prothrombin time (%), Prothrombin time (second), prothrombin time-international normalized ratio, Procalcitonin, Thyroid stimulating hormone, Free thyroxine, etc.
Echocardiography indices		Left ventricular ejection fraction, Left ventricular end-diastolic diameter, Left ventricular end-systolic diameter, End-diastolic volume, End-systolic volume, Stroke volume, E-wave, A-wave, Deceleration time, e', Left atrial dimension, Left atrial volume, Left atrial volume index, etc.
Vital signs (only 1 site)		Body temperature, Systolic blood pressure, Diastolic blood pressure, Pulse/Heart Rate, Respiration rate, etc.

A-wave, peak atrial filling velocity; e', peak early diastolic velocity of the mitral annulus; E-wave, peak early diastolic filling velocity; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Supplementary Table 2. MDC and ATC code list of the RECOMEND cohort

Diagnosis (MDC code)	Agents (ATC code)	
Acute myocardial infarction (050030)	**Intravenous agents:**	**Oral agents:**
Angina pectoris, Chronic ischemic heart failure (050050)	Digoxin (C01A1)	Eplerenone (C03A1)
Cardiomyopathy (050060)	Deslanoside (C01A1)	Spironolactone (C03A1)
Tachyarrhythmia (050070)	Amiodarone hydrochloride (C01B0)	Azosemide (C03A2)
Valvular disease (050080)	l-isoprenaline hydrochloride (C01C1)	Torasemide (C03A2)
Endocarditis (050090)	Etilefrine hydrochloride (C01C1)	Piretanide (C03A2)
Myocarditis (050100)	Noradrenaline (C01C1)	Bumetanide (C03A2)
Acute pericarditis (050110)	Phenylephrine hydrochloride (C01C1)	Furosemide (C03A2)
Constrictive pericarditis (050120)	Dopamine hydrochloride (C01C2)	Indapamide (C03A3)
Hypertensive disease (050140)	Dobutamine hydrochloride (C01C2)	Trichlormethiazide (C03A3)
Hypertensive cardiac disease with congestive heart failure (ICD-10: I110)	Dipyridamole (C01D0)	Hydrochlorothiazide (C03A3)
Hypertensive cardiac renal disease with congestive heart failure (ICD-10: I130)	Nicorandil (C01D0)	Tolvaptan (C03A9)
Hypertensive cardiac renal disease with congestive heart failure and renal failure (ICD-10: I132)	Nitroglycerin (C01E0)	
Heart failure (050130)	Isosorbide dinitrate (C01E0)	
	Olprinone hydrochloride hydrate (C01F0)	
	Milrinone (C01F0)	
	Carperitide (genetic recombination) (C01X0)	

Potassium canrenoate (C03A1)

Piretanide (C03A2)

Bumetanide (C03A2)

Furosemide (C03A2)

Landiolol hydrochloride (C07A0)

Diltiazem hydrochloride (C08A0)

Nicardipine hydrochloride (C08A0)

Verapamil hydrochloride (C08A0)

ATC, Anatomical Therapeutic Chemical; ICD-10, International Classification of Diseases, Tenth Revision; MDC, Major Diagnosis Category.

Supplementary Table 3. Presence of heart failure code (ICD-10: I50) in the DPC data and diagnostic criteria of chronic heart failure by BNP and LVEF of the RECOMEND cohort

		BNP ≥100 pg/mL[*], NT-proBNP ≥400 pg/mL[*], or LVEF ≥40%[**]				
		Yes, n	No, n	Total, n	PPV	NPV
Coded HF in DPC data[***]	Yes	2651	155	2806	0.945	
	No	823	232	1055		0.78
Total		3474	387	3861		
Sensitivity		0.76				
Specificity			0.6			

[*]Maximum value between 60 days before admission and discharge date. [**]Minimum value between 60 days before admission and discharge date. [***]Coded HF: hospitalizations which were coded as "Heart Failure" in DPC data.

BNP, brain natriuretic peptide; DPC, diagnosis procedure combination; ICD-10, International Classification of Diseases, Tenth Revision; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PPV, positive predictive value, NPV, negative predictive value.

Supplementary Figure 1. Distribution of baseline LVEF values
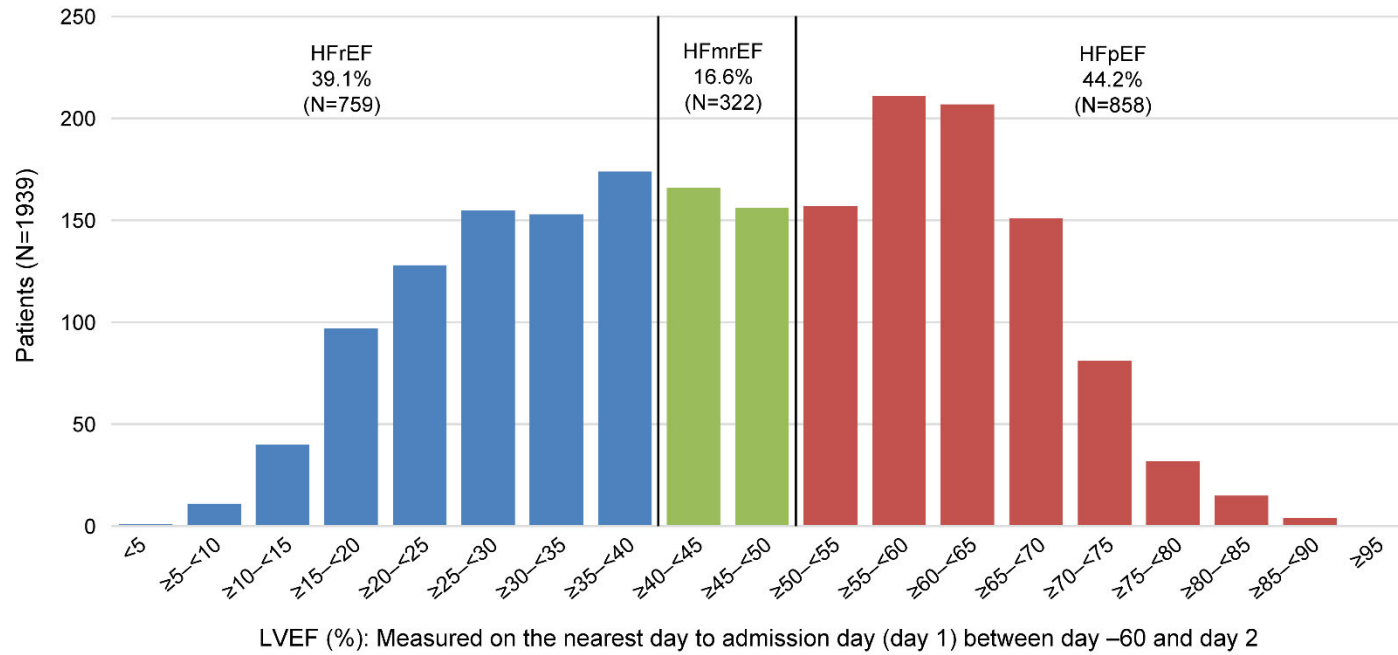
HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

Supplementary Figure 2. Chart of in-hospital death and median hospitalization days by risk factors at admission

In-hospital death chart
In-hospital death rate (%)

Creatinine (mg/dL)	Sodium (mEq/L)	CRP (mg/dL)	Age (years)							
			<80				≥80			
			NYHA class				NYHA class			
			I+II		III+IV		I+II		III+IV	
			Albumin (g/dL)		Albumin (g/dL)		Albumin (g/dL)		Albumin (g/dL)	
			>3.5	≤3.5	>3.5	≤3.5	>3.5	≤3.5	>3.5	≤3.5
≥1.1	<135	≥0.6	4.8	8.4	11.8	19.4	12.4	20.4	27.1	40.3
		<0.6	2.6	4.7	6.7	11.5	7.1	12.1	16.8	26.8
	≥135	≥0.6	3.5	6.1	8.7	14.8	9.2	15.5	21.1	32.7
		<0.6	1.9	3.4	4.9	8.6	5.2	9	12.6	20.8
<1.1	<135	≥0.6	2.9	5.1	7.2	12.4	7.6	13	17.9	28.4
		<0.6	1.6	2.8	4	7.1	4.3	7.5	10.6	17.6
	≥135	≥0.6	2.1	3.7	5.3	9.2	5.6	9.7	13.5	22.1
		<0.6	1.1	2	2.9	5.2	3.1	5.5	7.8	13.3

Hospitalization days chart
Long-term hospitalization rate (%)
(patients discharged alive)

Albumin (g/dL)	CRP (mg/dL)	LDH (IU/L)	NYHA class							
			I+II				III+IV			
			Barthel Index				Barthel Index			
			>60		≤60		>60		≤60	
			BNP or NT-proBNP (pg/mL)		BNP or NT-proBNP (pg/mL)		BNP or NT-proBNP (pg/mL)		BNP or NT-proBNP (pg/mL)	
			Other	High	Other	High	Other	High	Other	High
≤3.5	≥0.6	≥350	47.9	53.3	62	67	54	59.3	67.6	72.1
		<350	43.3	48.7	57.6	62.8	49.4	54.8	63.4	68.2
	<0.6	≥350	43.4	48.7	57.6	62.8	49.4	54.8	63.4	68.3
		<350	38.9	44.1	53.1	58.4	44.8	50.2	59.1	64.2
>3.5	≥0.6	≥350	38.8	44.1	53	58.3	44.8	50.1	59	64.1
		<350	34.6	39.6	48.4	53.8	40.2	45.5	54.5	59.7
	<0.6	≥350	34.6	39.6	48.4	53.8	40.3	45.6	54.5	59.8
		<350	30.5	35.3	43.8	49.2	35.9	41	49.9	55.3

High: BNP ≥200 pg/mL or NT-proBNP ≥900 pg/mL.

BNP, brain natriuretic peptide; CRP, C-reactive protein; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.