

Serial Changes in Clinical Presentations and Outcomes of 5,740 Patients Requiring Repeated Hospital Admissions (Four or More Times) due to Worsened Heart Failure

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Summary

Heart failure (HF) is a major cause of death and hospitalization worldwide. In particular, hospital readmission due to worsened HF occurs frequently after the onset of HF. However, the association of repeated hospital admission with clinical manifestations and outcomes is unclear. The aim of this study was to clarify the serial changes in presentation and clinical course of patients requiring repeated hospital admission due to worsened HF. Among 466,921 patients who were admitted and discharged between January 2010 and March 2018, with the main discharge diagnosis of HF, we studied 5,740 patients who were hospitalized 4 times or more, using the Diagnosis Procedure Combination database. We evaluated serial changes in continuous data using the Jonckheere trend test, and categorical data using the Cochran-Armitage trend test. The median age of the patients was 78 years, and 3,326 patients (58%) were male. Body mass index and Barthel Index decreased with increased numbers of admissions. Patients requiring respiratory support and hemodialysis increased, whereas patients undergoing intra-aortic balloon pumping decreased with increased numbers of admissions. The length of hospital stay was prolonged and the interval between hospitalizations was shortened with increased numbers of hospital admissions. The in-hospital mortality rate was 8.8% at the fourth admission. In conclusion, this is the first large-scale real-world study on the serial changes in characteristics and outcomes of HF patients requiring repeated hospitalization, suggesting that repeated hospitalization might adversely affect the general status of patients with HF and result in a vicious clinical cycle.

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Key words: Acute Heart Failure, Readmission, Epidemiology

Heart failure (HF) is a major cause of death and hospital admission worldwide.¹⁻³⁾ Hospital admission due to worsened HF is an important dimension of the clinical practice of patients with HF,^{4,5)} and readmission due to worsened HF occurs frequently after the onset of HF.^{2,6)} Furthermore, previous studies have showed that prior history of hospital admission was associated with poor clinical outcomes for HF patients.⁷⁻¹⁰⁾ Readmission due to worsened HF could affect the clinical presentation of patients with HF, and result in deteriorated outcomes. Although Gheorghide, *et al* indicated that a further decrease in cardiac function could occur with each hospital admission for acute HF, repeated episodes of worsened HF could also lead to non-cardiac damage, such as progression of cachexia, and a decrease in the activity

of daily living. However, little is known about the association of repeated admissions due to worsened HF with clinical manifestations such as body weight and activities of daily living, and in-hospital outcomes of patients with HF. In this study, we aimed to explore the serial changes in clinical presentation and outcomes of patients requiring repeated hospital admissions due to worsened HF using a nationwide inpatient database.

Methods

Data source and study design: We performed a retrospective cohort study using the Diagnosis Procedure Combination database, a nationwide inpatient database in Japan.¹¹⁻¹³⁾ The database includes administrative claims data

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Table I. Characteristics of Study Population

Variable	
Number of patients	5,740
Age (years)	78 (70-84)
20-59	421 (7.3)
60-69	921 (16.0)
70-79	1,842 (32.1)
80-89	2,101 (36.6)
90-	455 (7.9)
Male sex	3,326 (57.9)
Body weight (kg)	55.7 (47.2-65.1)
Body mass index (kg/m ²)	22.7 (20.2-25.5)
Lean	694 (12.1)
Normal	3,381 (58.9)
Overweight	1,319 (23.0)
Obese	346 (6.0)
Hypertension	3,627 (63.2)
Diabetes mellitus	1,983 (34.5)
Chronic renal failure	711 (12.4)
Chronic liver disease	193 (3.4)
Chronic respiratory disease	565 (9.8)
Cigarette smoking	1,867 (32.5)
New York Heart Association	
Class II	1,873 (32.6)
Class III	2,282 (39.8)
Class IV	1,585 (27.6)
Barthel Index	85 (40-100)
Barthel index < 60	2,056 (35.8)

Data are expressed as the median (interquartile range) or number (percentage).

and clinical data for approximately 8 million hospitalized patients per year from participating hospitals including all 82 academic hospitals in Japan. The main diagnosis, comorbidities on admission, and complications during hospitalization are recorded using the International Classification of Disease and Related Health Problems 10th Revision (ICD-10) codes. Chronic respiratory disease was defined as following ICD-10 codes; I27, J40-45, J47, J60-67, and J70. Chronic liver disease was defined as following ICD-10 codes; B18, K70-74, and K76.

Ethics: This study was approved by the Institutional Review Board of the University of Tokyo [3501-(3)]. We conducted this study in accordance with the Declaration of Helsinki. Because of the anonymous nature of this database, the requirement for informed consent was waived.

Definition: We defined lean body weight, normal body weight, overweight, and obesity as body mass index < 18.5 kg/m², 18.5-24.9 kg/m², 25.0-29.9 kg/m² and ≥ 30 kg/m², respectively. Low Barthel Index was defined as < 60.¹⁴⁾

Statistical analysis: Continuous and categorical data are presented as the median (interquartile range) and number (percentage), respectively. We evaluated the serial changes during 4 admissions in continuous data using the Jonckheere trend test, and categorical data using the Cochran-Armitage trend test. A probability value of < 0.05 was considered to indicate a statistically significant difference. We performed statistical analysis using SPSS software (version 25, SPSS Inc., Chicago, IL, USA) and STATA (version 16, StataCorp LLC, College Station, TX, USA).

Results

We studied 466,921 patients aged ≥ 20 years with NYHA class ≥ II, admitted and discharged between January 2010 and March 2018 with the main discharge diagnosis of HF defined by ICD-10 codes I50.0, I50.1, and I50.9. Exclusion criteria were as follows: 1) length of hospital stay ≤ 2 days ($n = 15,270$) and 2) major procedures under general anesthesia ($n = 3,833$). The final number of patients analyzed in this study was 447,818. From among this total, we extracted 5,740 patients who were hospitalized 4 or more times.

Baseline clinical characteristics of the study population are summarized in Table I. The median age of the patients was 78 (70-84) years, and 3,326 patients (58%) were male. The median body mass index was 22.7 (20.2-25.5) kg/m². The incidences of hypertension, diabetes mellitus, and chronic renal failure were 63%, 35%, and 12%, respectively. Approximately 30% of the study population had New York Heart Association class IV symptoms. The median Barthel Index, which measures performance in activities of daily living, was 85 (40-100). Low Barthel Index was seen in 2,056 patients (36%).

Serial changes in clinical presentations at hospital admission are shown in Table II. Body weight and body mass index decreased with each hospital admission. Patients with a higher NYHA class increased with each admission. Barthel Index decreased and the proportion of low Barthel Index increased with each admission.

The serial changes in clinical outcomes are summarized in Table III. The proportion of patients receiving respiratory support (J045 of the medical reimbursement code), hemodialysis, and inotropic agents increased with each admission, while that of intra-aortic balloon pumping decreased with an increase in the number of admissions. Compared to the second admission, the length of hospital stay was prolonged at the third and fourth admissions. Furthermore, the interval between hospitalizations was shortened with an increased number of admissions. In-hospital mortality was 8.8% at the fourth admission.

Discussion

It is well known that acute events due to worsened HF lead to further deterioration of cardiac function and progression of HF.¹⁵⁾ However, there is a paucity of data on the association of repeated worsened HF with non-cardiac clinical presentations and outcomes of patients with HF. We studied 5,740 patients requiring 4 or more hospital admissions owing to worsened HF using a nationwide inpatient database, and found that the presentations and outcomes of the patients serially declined with each hospital admission.

Body weight decreased by approximately 1 kg with each admission. Accordingly, lean patients increased and overweight and obese patients decreased. Rossignol, *et al* reported that body weight loss during follow-up was associated with higher mortality and adverse cardiovascular and non-cardiovascular outcomes.¹⁶⁾ Further, given that several studies have showed that obesity paradox could be applicable for HF,¹⁷⁻²⁰⁾ a decrease in body weight could be

Table II. Serial Changes in Clinical Presentations

	1st Admission (n = 5,740)	2nd Admission (n = 5,740)	3rd Admission (n = 5,740)	4th Admission (n = 5,740)	P-value
Body weight (kg)	55.7 (47.2-65.1)	54.8 (46.4-64.0)	53.8 (45.5-62.7)	52.9 (44.6-61.8)	< 0.001
Body mass index (kg/m ²)	22.7 (20.2-25.5)	22.3 (19.8-25.1)	22.0 (19.6-24.7)	21.7 (19.3-24.5)	< 0.0001
Lean	694 (12.1)	814 (14.2)	928 (16.2)	1,055 (18.4)	
Normal	3,381 (58.9)	3,466 (60.4)	3,492 (60.8)	3,455 (60.2)	
Overweight	1,319 (23.0)	1,152 (20.1)	1,047 (18.2)	978 (17.0)	
Obese	346 (6.0)	308 (5.4)	273 (4.8)	252 (4.4)	
New York Heart Association					< 0.001
Class II	1,873 (32.6)	1,725 (30.1)	1,615 (28.1)	1,456 (25.4)	
Class III	2,282 (39.8)	2,449 (42.7)	2,486 (43.3)	2,416 (42.1)	
Class IV	1,585 (27.6)	1,566 (27.3)	1,639 (28.6)	1,868 (32.5)	
Barthel index	85 (40-100)	85 (40-100)	75 (40-100)	65 (30-100)	< 0.0001
Feeding	10 (5-10)	10 (5-10)	10 (5-10)	10 (5-10)	
Transfer	15 (10/15)	15 (10-15)	10 (10-15)	10 (5-15)	
Grooming	5 (0-5)	5 (0-5)	5 (0-5)	5 (0-5)	
Toilet use	10 (5-10)	10 (5-10)	10 (5-10)	5 (0-10)	
Bathing	5 (0-5)	5 (0-5)	0 (0-5)	0 (0-5)	
Mobility	15 (0-15)	15 (0-15)	10 (0-15)	10 (0-15)	
Ascending/Descending stairs	5 (0-10)	5 (0-10)	5 (0-10)	5 (0-10)	
Dressing	10 (5-10)	10 (5-10)	5 (5-10)	5 (0-10)	
Bowel control	10 (5-10)	10 (5-10)	10 (5-10)	10 (5-10)	
Bladder control	10 (5-10)	10 (5-10)	10 (5-10)	10 (5-10)	
Barthel index < 60	2,056 (35.8)	2,056 (35.8)	2,254 (39.3)	2,531 (44.1)	< 0.001

Data are expressed as the median (interquartile range) or number (percentage).

Table III. Serial Changes in Clinical Outcomes

	1st Admission (n = 5,740)	2nd Admission (n = 5,740)	3rd Admission (n = 5,740)	4th Admission (n = 5,740)	P-value
Respiratory support	755 (13.2)	760 (13.2)	813 (14.2)	976 (17.0)	< 0.0001
Hemodialysis	42 (0.7)	42 (0.7)	60 (1.0)	123 (2.1)	< 0.0001
Intra-aortic balloon pumping	32 (0.6)	12 (0.2)	12 (0.2)	13 (0.2)	< 0.0001
Extra-corporeal membrane oxygenation	2 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)	0.532
Inotropic use	2,065 (36.0)	2,093 (36.5)	2,197 (38.3)	2,493 (43.4)	< 0.0001
Length of hospital stay (days)	16 (11-25)	16 (11-24)	16 (11-26)	18 (11-29)	< 0.0001
Interval (days)	-----	120 (39-320)	85 (33-226)	80 (30-207)	< 0.0001
In-hospital death	-----	-----	-----	503 (8.8)	-----

Data are expressed as the median (interquartile range) or number (percentage).

recognized as a sign of a dismal prognosis. Malnutrition and cardiac cachexia, which are known as poor prognostic determinants of patients with HF,²¹⁻²³⁾ could coexist in patients with body weight loss. Further, Barthel Index decreased with each hospital admission and the proportion of low Barthel Index values increased from 35.8% at 1st admission to 44.1% at 4th admission, suggesting the deterioration of activities of daily living with each admission due to worsened HF. Activities of daily living are also associated with the outcomes of patients with HF.^{14,24)} These results might mirror the continuous deterioration of the non-cardiac general condition of HF patients with each hospital admission.

Regarding in-hospital outcomes, an increase in patients requiring advanced supports with each admission is thought to reflect that the proportions of patients developing life-threatening conditions increased with each admission. The proportion of patients undergoing hemodialysis increased with each admission. Although the detailed reason for hemodialysis could not be assessed in this study,

worsened renal function during hospitalization has been associated with the adverse outcomes of patients with HF.²⁵⁻²⁷⁾ Furthermore, patients requiring inotropic agents also increased from 36.0% at the 1st admission to 43.4% at the 4th admission. Cardiogenic shock and low blood pressure were also reported to be associated with the adverse clinical outcomes of hospitalized HF patients.^{28,29)}

In association with these various changes in clinical presentations and outcomes with each hospital admission, the length of hospital stay was prolonged and the interval of hospitalization was shortened with each hospital admission. As a consequence, in-hospital mortality was approximately 9% at the fourth admission, which was higher than that in a recent Japanese study.³⁰⁾

This study has several clinical implications. Although repeated hospital admissions due to worsened HF are common in our daily clinical practice, detailed information on the serial changes in clinical presentations and outcomes of patients with repeated hospital admissions has been scarce. We believe that our results could clearly

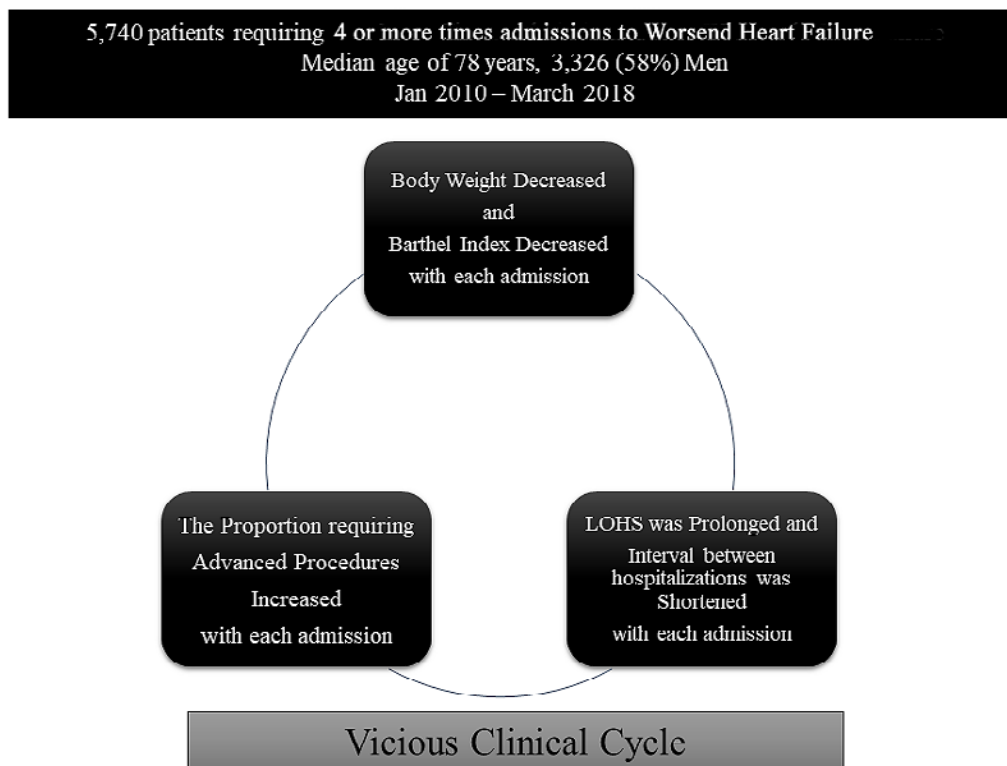


Figure. Summary of Study. Summarizes the main results of this study. LOHS indicates length of hospital stay.

demonstrate how the clinical presentations of the patients declined with each hospital admission and led to adverse outcomes (Figure). Furthermore, it is also important to share these concrete data with healthcare professionals, patients and their families, and to reconfirm the significance of prevention of HF readmission.

There are several limitations to this study. Although the validity of the diagnoses and procedures in our database was reported to be high,³¹⁾ recorded diagnoses are generally considered less well validated because of the nature of administrative data and retrospective studies. Our database lacked information on several factors that were potentially associated with the outcomes, including blood pressure, HF etiology, and left ventricular ejection fraction. Therefore, the applicability of our findings on which types of heart failure such as HF with reduced ejection fraction, HF with preserved ejection fraction, ischemic cardiomyopathy, and non-ischemic cardiomyopathy remains unclear. Generally, body weight and the Barthel Index decrease with age, so we were unable to separate the impact of physiological aging and repeated hospital admissions on the changes in body weight and Barthel Index. Further investigations are required to clarify the determinants of changes in these clinical manifestations of patients with HF.

Conclusion

This is the first large-scale real-world study on the serial changes in clinical characteristics and outcomes of HF patients requiring repeated hospital admissions due to

worsened HF, suggesting that repeated hospital admissions might adversely affect not only cardiac function but also the non-cardiac general status of patients with HF and lead to a vicious clinical cycle.

Disclosure

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Conflicts of interest: None to declare.

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