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BRIEF REPORT

Association Between Coexisting Constipation and Heart Failure Readmission in Patients With Heart Failure

— A Nationwide Database Study —

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Background: Constipation often coexists with heart failure (HF) and can cause increased blood pressure variability, which may increase the risk of repeated HF admissions. However, large-scale contemporary data regarding the prognostic effect of constipation in patients with HF are lacking.

Methods and Results: We retrospectively identified 556,792 patients admitted for HF for the first time and discharged alive in the fiscal years 2016–2021 using the Japanese Diagnosis Procedure Combination database. Constipation was defined as continued use of laxatives after discharge. We examined the association between constipation and 1-year HF readmission. The prevalence of constipation was 22.0% (n=122,670), which remained stable over the 6 years. Patients with constipation were older (82.7±10.1 vs. 79.3±12.8 years), more often female (53.5% vs. 48.0%), and received medications for HF more frequently at discharge compared with those without constipation. In the multivariable Cox proportional hazards model, constipation was significantly associated with a higher incidence of 1-year HF readmission (24.0% vs. 18.6%; adjusted hazard ratio [HR] 1.08; 95% confidence interval [CI] 1.06–1.10). This result was consistent with the result from the Fine-Gray model accounting for competing risk of death (subdistribution HR 1.08; 95% CI 1.06–1.09).

Conclusions: Constipation was associated with a higher risk of HF readmission after the first episode of HF hospitalization. Given the detrimental effect of constipation, further efforts are warranted to decrease constipation-related risk in patients with HF.

Key Words: Constipation; Epidemiology; Heart failure; Readmission

Constipation often coexists with heart failure (HF) owing to the advanced age of the patient population. It also develops during HF hospitalization due to decreased intestinal peristalsis with mucosal edema, diuretic use with restricted body fluid intake, and limited physical activity.[1] Excretion is one of the triggers for acute decompensated HF.[2] Constipation can cause increased blood pressure due to straining during defecation,[1,3] and mental stress, leading to increased sympathetic nervous activity.[4] However, few studies have examined the association between constipation and outcomes in patients with HF. We hypothesized that constipation was associated with a higher risk of HF readmission in patients with HF.

The objective of the present study was to examine the association between constipation and the risk of HF readmission after an episode of HF hospitalization using a large-scale nationwide database in Japan, the most rapidly aging country in the world.

Methods

Study Design and Data Source

This retrospective cohort study used the Japanese Diagnosis Procedure Combination (DPC) database.[5] This database contains annual data on >7 million hospitalizations at >1,000 acute care hospitals in Japan in a prespecified format. The details of the DPC database are described in the **Supplementary Methods**. The diagnoses and procedures

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Table. Characteristic of Patients With Heart Failure With Constipation vs. Without Constipation

	All (N=556,792)	Constipation (n=122,670)	No constipation (n=434,122)	SMD
Age (years)	80.0±12.3	82.7±10.1	79.2±12.8	0.299
Female	274,077 (49.2)	65,649 (53.5)	208,428 (48.0)	0.110
Ambulance use for admission	210,954 (37.9)	44,288 (36.1)	166,666 (38.4)	−0.047
BMI (kg/m²)				
<18.5	80,325 (14.4)	18,758 (15.3)	61,567 (14.2)	0.031
18.5–24.9	292,800 (52.6)	65,821 (53.7)	226,979 (52.3)	0.027
25.0–29.9	104,091 (18.7)	22,096 (18.0)	81,995 (18.9)	−0.023
≥30	36,500 (6.6)	6,918 (5.6)	29,582 (6.8)	−0.049
Missing	43,076 (7.7)	9,077 (7.4)	33,999 (7.8)	−0.016
Cognitive function				
Normal	351,871 (63.2)	74,572 (60.8)	277,299 (63.9)	−0.064
Mild dysfunction	115,866 (20.8)	29,495 (24.0)	86,371 (19.9)	0.100
Moderate/severe dysfunction	80,588 (14.5)	17,605 (14.4)	62,983 (14.5)	−0.004
Missing	8,467 (1.5)	998 (0.8)	7,469 (1.7)	−0.081
SBP at admission (mmHg)				
>140	183,945 (33.0)	38,201 (31.1)	145,744 (33.6)	−0.052
100–140	230,884 (41.5)	52,699 (43.0)	178,185 (41.0)	0.039
<100	39,569 (7.1)	9,700 (7.9)	29,869 (6.9)	0.039
Missing	102,394 (18.4)	22,070 (18.0)	80,324 (18.5)	−0.013
Cardiac disease				
Atrial fibrillation	215,845 (38.8)	48,753 (39.7)	167,092 (38.5)	0.026
CAD	151,375 (27.2)	35,942 (29.3)	115,433 (26.6)	0.060
DCM	12,716 (2.3)	2,373 (1.9)	10,343 (2.4)	−0.031
MR	32,353 (5.8)	6,609 (5.4)	25,744 (5.9)	−0.023
AS	26,299 (4.7)	6,189 (5.0)	20,110 (4.6)	0.019
AR	14,422 (2.6)	3,056 (2.5)	11,366 (2.6)	−0.008
Complete AV block	7,759 (1.4)	1,801 (1.5)	5,958 (1.4)	0.008
VT	11,647 (2.1)	2,689 (2.2)	8,958 (2.1)	0.009
Comorbidity				
Charlson Comorbidity Index				
1	194,643 (35.0)	37,404 (30.5)	157,239 (36.2)	−0.122
2	159,784 (28.7)	35,115 (28.6)	124,669 (28.7)	−0.002
3	108,325 (19.5)	25,848 (21.1)	82,477 (19.0)	0.052
≥4	94,040 (16.9)	24,303 (19.8)	69,737 (16.1)	0.098
Hypertension	341,126 (61.3)	76,569 (62.4)	264,557 (60.9)	0.030
Diabetes	153,645 (27.6)	35,500 (28.9)	118,145 (27.2)	0.038
Dyslipidemia	149,418 (26.8)	34,911 (28.5)	114,507 (26.4)	0.047
Prior stroke	36,118 (6.5)	9,566 (7.8)	26,552 (6.1)	0.066
Renal disease	74,144 (13.3)	18,420 (15.0)	55,724 (12.8)	0.063
Liver disease	16,651 (3.0)	3,900 (3.2)	12,751 (2.9)	0.014
Chronic pulmonary disease	52,857 (9.5)	13,629 (11.1)	39,228 (9.0)	0.069
Malignancy	35,461 (6.4)	9,083 (7.4)	26,378 (6.1)	0.053
Anemia	75,558 (13.6)	20,310 (16.6)	55,248 (12.7)	0.109
In-hospital management				
ICU admission	34,613 (6.2)	6,752 (5.5)	27,861 (6.4)	−0.039
HCU admission	49,498 (8.9)	10,542 (8.6)	38,956 (9.0)	−0.013
Dobutamine	52,263 (9.4)	11,623 (9.5)	40,640 (9.4)	0.004
Dopamine	20,450 (3.7)	5,240 (4.3)	15,210 (3.5)	0.040
Noradrenaline	17,060 (3.1)	3,248 (2.6)	13,812 (3.2)	−0.032
PDE III inhibitor	4,806 (0.9)	1,035 (0.8)	3,771 (0.9)	−0.003
Carperitide	134,606 (24.2)	29,175 (23.8)	105,431 (24.3)	−0.012
Intravenous nitrate	174,266 (31.3)	32,206 (26.3)	142,060 (32.7)	−0.142
PCI	15,937 (2.9)	3,606 (2.9)	12,331 (2.8)	0.006
PPM/ICD implantation	6,147 (1.1)	1,606 (1.3)	4,541 (1.0)	0.024
Red cell transfusion	37,465 (6.7)	9,449 (7.7)	28,016 (6.5)	0.049
Cardiac rehabilitation	277,613 (49.9)	63,631 (51.9)	213,982 (49.3)	0.052

(**Table** continued the next page.)

	All (N=556,792)	Constipation (n=122,670)	No constipation (n=434,122)	SMD
Medications at discharge				
ACEi/ARB	235,242 (42.2)	59,384 (48.4)	175,858 (40.5)	0.159
ARNI	9,823 (1.8)	2,201 (1.8)	7,622 (1.8)	0.003
MRA	200,751 (36.1)	49,785 (40.6)	150,966 (34.8)	0.120
β-blocker	254,366 (45.7)	63,422 (51.7)	190,944 (44.0)	0.155
SGLT2 inhibitor	33,929 (6.1)	8,363 (6.8)	25,566 (5.9)	0.038
Loop diuretic	368,032 (66.1)	100,742 (82.1)	267,290 (61.6)	0.469
Thiazide	19,696 (3.5)	6,292 (5.1)	13,404 (3.1)	0.103
Tolvaptan	96,447 (17.3)	29,661 (24.2)	66,786 (15.4)	0.222
Digitalis	19,771 (3.6)	5,725 (4.7)	14,046 (3.2)	0.074
Ivabradine	991 (0.2)	207 (0.2)	784 (0.2)	−0.003
Amiodarone	22,444 (4.0)	6,768 (5.5)	15,676 (3.6)	0.091
Calcium channel blocker	145,508 (26.1)	44,166 (36.0)	101,342 (23.3)	0.280
DOAC	145,844 (26.2)	38,945 (31.7)	106,899 (24.6)	0.159
Warfarin	56,255 (10.1)	18,800 (15.3)	37,455 (8.6)	0.207
Aspirin	93,427 (16.8)	29,649 (24.2)	63,778 (14.7)	0.241
$P2Y_{12}$ inhibitor	50,563 (9.1)	15,051 (12.3)	35,512 (8.2)	0.135
Statin	124,235 (22.3)	36,703 (29.9)	87,532 (20.2)	0.227
Discharge status				
ADL at discharge				
Independence	260,994 (46.9)	48,511 (39.5)	212,483 (48.9)	−0.190
Partial dependence	167,460 (30.1)	44,806 (36.5)	122,654 (28.3)	0.177
Total dependence	72,200 (13.0)	15,811 (12.9)	56,389 (13.0)	−0.003
Missing	56,138 (10.1)	13,542 (11.0)	42,596 (9.8)	0.040
Length of hospital stay (days)	17.0 [11.0–27.0]	20.0 [14.0–31.0]	16.0 [11.0–26.0]	0.209
Discharge home	426,570 (76.6)	99,275 (80.9)	327,295 (75.4)	0.134
Home medical care after discharge				
No	503,429 (90.4)	105,965 (86.4)	397,464 (91.6)	−0.166
Yes	47,278 (8.5)	15,520 (12.7)	31,758 (7.3)	0.179
Missing	6,085 (1.1)	1,185 (1.0)	4,900 (1.1)	−0.016
Hospital characteristics				
University hospital	43,621 (7.8)	9,131 (7.4)	34,490 (7.9)	−0.019
Annualized hospital volume of any HF hospitalizations (cases/year)				
Low (≤107)	184,050 (33.1)	47,565 (38.8)	136,485 (31.4)	0.154
Intermediate (108–187)	187,800 (33.7)	39,321 (32.1)	148,479 (34.2)	−0.046
High (≥188)	184,942 (33.2)	35,784 (29.2)	149,158 (34.4)	−0.112
Fiscal year				
2016	111,851 (20.1)	25,437 (20.7)	86,414 (19.9)	0.021
2017	97,973 (17.6)	21,588 (17.6)	76,385 (17.6)	0.000
2018	93,319 (16.8)	20,398 (16.6)	72,921 (16.8)	−0.005
2019	83,735 (15.0)	18,090 (14.7)	65,645 (15.1)	−0.011
2020	87,638 (15.7)	19,360 (15.8)	68,278 (15.7)	0.001
2021	82,276 (14.8)	17,797 (14.5)	64,479 (14.9)	−0.010

Unless indicated otherwise, data are presented as n (%), median [IQR], or mean±SD. ACEi, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; AR, aortic regurgitation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AS, aortic stenosis; AV, atrioventricular; BMI, body mass index; CAD, coronary artery disease; DCM, dilated cardiomyopathy; DOAC, direct oral anticoagulant; HCU, high care unit; HF, heart failure; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; IQR, interquartile range; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; PDE, phosphodiesterase; PPM, permanent pacemaker; SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; SMD, standardized mean difference; VT, ventricular tachycardia.

in the DPC database have been well validated with high accuracy in prior studies.[6,7] While all university hospitals are obliged to participate in the database yearly, the other hospitals participate voluntarily in each fiscal year. A Japanese fiscal year spans 12 months, from April 1 of 1 calendar year to March 31 of the following year (e.g., the fiscal year 2016 covers the period from April 1, 2016, to March 31, 2017).

We obtained ethical approval from the Institutional Review Board of The University of Tokyo (approval no. 3501-[5]), which waived the requirement for informed consent due to the anonymized and de-identified data. This

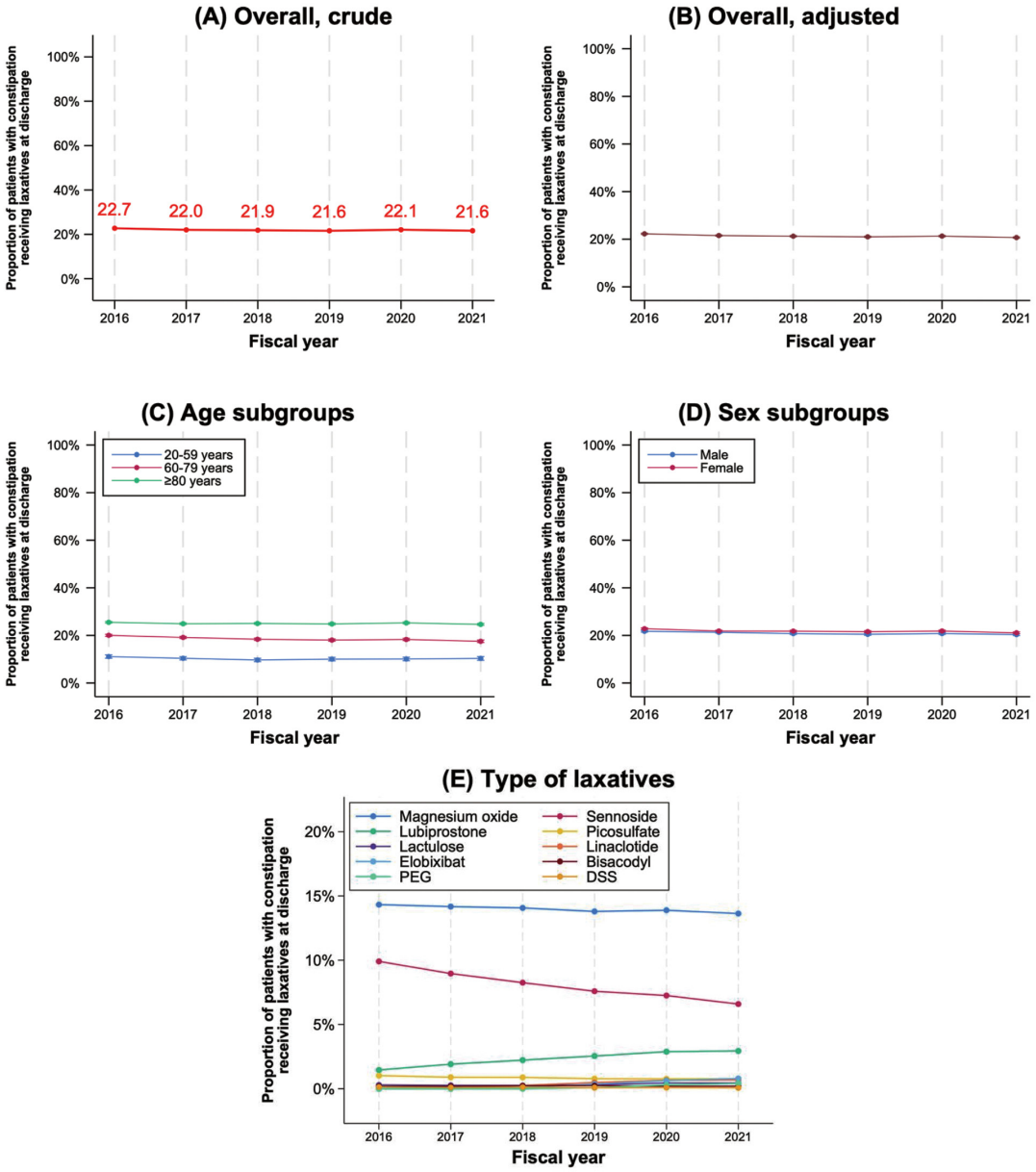

Figure 1. Trend of prevalence of constipation and types of laxatives prescribed at discharge in patients hospitalized with heart failure. (**A**) Crude proportions of patients with constipation receiving laxatives in the overall population. (**B**) Adjusted proportions and 95% confidence intervals (CIs) of patients with constipation receiving laxatives in the overall population on the modified Poisson regression model adjusted for age and sex. (**C**,**D**) Interaction plots showing predictive margins estimated with the selected subgroup variables (age [**C**] and sex [**D**]) on the proportion of patients with constipation receiving laxatives. (**B**–**D**) Data show point estimates, with error bars representing 95% CIs. (**E**) Types of laxatives prescribed at discharge in patients with HF and constipation. A Japanese fiscal year spans 12 months, from April 1 of one calendar year to March 31 of the following year. DSS, dioctyl sodium sulfosuccinate; PEG, polyethylene glycol.

study was conducted in accordance with the Declaration of Helsinki.

Study Participants

We identified patients aged ≥20 years admitted for a primary diagnosis of HF (International Classification of Diseases, 10th Revision code: I50.x) and discharged alive between April 1, 2016 and March 31, 2022 (fiscal years 2016–2021 in Japan). The first hospitalization for HF during the study period was regarded as the index hospitalization for HF in each patient.

We excluded patients who fulfilled any of the following exclusion criteria, in line with an ongoing randomized trial for HF:[8] (1) receipt of coronary artery bypass grafting, valve surgery/intervention, or cardiac resynchronization therapy within 90 days prior to or during index hospital-

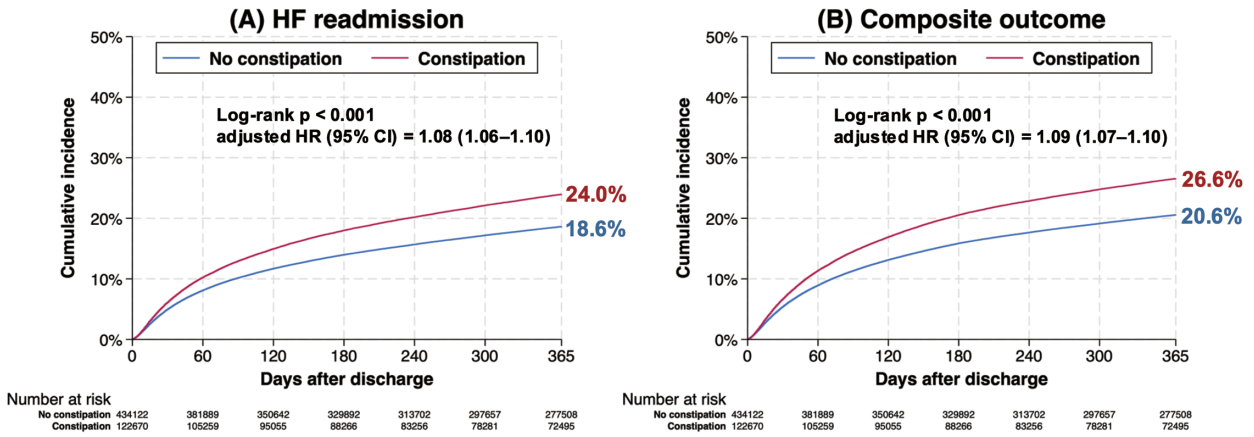

Figure 2. Kaplan-Meier curves comparing the cumulative incidence of outcomes between patients with heart failure (HF) with and without constipation. (**A**) The 1-year HF readmission and (**B**) composite outcome between the constipation and no-constipation groups in patients with HF. CI, confidence interval; HR, hazard ratio.

ization; (2) ventricular assist device recipients; (3) heart transplantation recipients; (4) congenital heart/vascular disease; (5) acute coronary syndrome; (6) end-stage renal failure; (7) receipt of mechanical circulatory support during index hospitalization; (8) pregnancy or delivery within 90 days prior to or during index hospitalization; and (9) receipt of palliative care within 90 days prior to or during index hospitalization.

Exposure and Baseline Characteristics

The exposure of interest was constipation, defined as continued use of laxatives (magnesium oxide, sennoside, picosulfate, bisacodyl, lubiprostone, linaclotide, elobixibat, polyethylene glycol, lactulose, and dioctyl sodium sulfosuccinate[9]) after discharge. We extracted baseline characteristics from the database (see **Supplementary Methods**), including age, sex, ambulance use for admission, body mass index, cognitive function, systolic blood pressure at admission, cardiac diseases, Charlson Comorbidity Index, several specific comorbidities (**Supplementary Table 1**), in-hospital management for HF (intensive/high-care unit admission, intravenous medications, cardiac interventions, and cardiac rehabilitation[10,11]), laxatives and HF/other medications at discharge, discharge status (activities of daily living at discharge [**Supplementary Table 2**], length of hospital stay, discharge home, and home medical care after discharge), hospital characteristics (type of hospital [university hospital or not] and annualized hospital volume of HF hospitalizations), and fiscal year of discharge.

Outcome Measures

The primary outcome was HF readmission within 1 year after discharge from the index HF hospitalization. The secondary outcome was a composite of HF readmission and death within 1 year after discharge. The DPC database allowed for the identification of readmissions using a unique identifier assigned to each patient at each hospital in the database. Thus, it was possible to detect readmissions to the index hospital (where a patient was initially admitted for HF) and deaths occurring during the readmissions. Each patient was followed up until 1 year after discharge, death during any-cause readmission, or the last date of follow up, whichever came first. Since participation in the DPC database was voluntary for non-university hospitals each fiscal year, some hospitals occasionally failed to submit data to the database for 2 consecutive fiscal years. If a patient was discharged from a hospital in a given fiscal year (fiscal year of discharge; e.g., fiscal year 2016) and the hospital did not participate in the database for the following fiscal year (e.g., fiscal year 2017), the maximum follow-up period of the patient was considered to end on March 31 in the fiscal year of discharge (e.g., March 31, 2017).

Statistical Analyses

We described trends of the prevalence of constipation and types of laxatives prescribed at discharge among patients hospitalized for HF over the 6 fiscal years of 2016–2021. We obtained predictive margins from the modified Poisson regression to estimate the adjusted proportions and 95% confidence intervals (CIs) of patients with constipation receiving laxatives over the 6 fiscal years after adjustment for age and sex. We also estimated the predictive margins with the age and sex subgroups on the proportion of patients with constipation receiving laxatives.[12] We compared baseline characteristics between patients with HF with and without constipation using standardized mean differences, of which the absolute value <0.1 represents a negligible difference between the two groups.

Kaplan-Meier curves were presented to describe the cumulative incidence of outcomes with the log-rank test. We examined the association between constipation and outcomes using a multivariable Cox proportional hazards model, adjusting for the 60 variables listed in **Table**. We estimated adjusted hazard ratios (HRs) and 95% CIs of constipation compared with no constipation for outcomes.

As a sensitivity analysis, a Fine-Gray subdistribution hazard model was used to account for competing risk of death and to estimate a subdistribution HR and 95% CI for 1-year HF readmission.[13] We set a two-sided significance level of 0.05 and conducted all statistical analyses using Stata version 18 (StataCorp, College Station, TX, USA).

Results

Prevalence of Constipation in Patients With HF

We identified 556,792 eligible patients (mean age 80.0±12.3 years; females 49.2%) admitted for HF and discharged alive (**Supplementary Figure**). The prevalence of constipation was 22.0% (n=122,670) and remained stable over the 6 years, regardless of age and sex (**Figure 1**). Magnesium oxide was the most frequently used laxative over the 6 years, with the proportion being approximately 14%. The use of sennoside decreased over the years, whereas the use of lubiprostone increased.

Characteristics and Outcomes of Patients With Constipation

Compared with patients without constipation, those with constipation were older, more often female, and received medications for HF and others more frequently at discharge (**Table**). Overall, HF readmissions occurred in 102,221 patients (27,162 and 75,059 with and without constipation, respectively), deaths occurred during readmissions in 30,823 patients (8,967 and 21,856 with and without constipation, respectively), and the composite outcome occurred in 114,661 patients (30,681 and 83,980 with and without constipation, respectively). Constipation was significantly associated with a higher incidence of 1-year HF readmission (constipation vs. no constipation, Kaplan-Meier estimates 24.0% vs. 18.6%; adjusted HR 1.08; 95% CI 1.06–1.10) and the composite outcome of HF readmission and death (26.6% vs. 20.6%; adjusted HR 1.09; 95% CI 1.07–1.10; **Figure 2**). Results of the 1-year HF readmission were consistent with the results from the Fine-Gray model (subdistribution HR 1.08; 95% CI 1.06–1.09).

Discussion

This nationwide study demonstrated that constipation commonly coexisted with HF in approximately 1 out of 5 patients hospitalized with HF and was significantly associated with a higher incidence of 1-year HF readmission.

Constipation is more prevalent with increasing age and affects approximately 10% of individuals aged >80 years in the general population.[14] A recent study reported that patients hospitalized with HF were 2 times more likely to develop constipation during hospitalization compared with those with other medical diseases.[15] A single-center study reported that 32.2% of patients admitted with acute HF had constipation.[16] However, there are no contemporary nationwide data, to our knowledge, on the incidence of constipation in patients with HF. Although the prevalence of constipation may vary according to its definition,[17] our definition is reasonable in identifying patients with HF suffering from constipation as it is similar to previous studies.[16,18] Notably, the prevalence of constipation remained high at approximately 20% in patients with HF over the 6 years of the study, highlighting that constipation is a common issue in patients with HF.

The present study revealed that constipation status was significantly associated with a higher incidence of HF readmission in patients with HF. This is consistent with the result from a single-center study.[16] A possible explanation for this association is that straining may trigger acute decompensated HF via increased blood pressure.[1] Straining is the most common and distressing symptom in patients with constipation due to reduced bowel movements and hard stools.[19] Another explanation for the increased risk of HF readmission may be that a change in intestinal microbiota induced by constipation may promote atherosclerosis through the enhanced production of trimethylamine-N-oxide, a dietary phosphatidylcholine metabolite.[20]

Although the mechanism of increased HF readmission risk induced by constipation remains to be elucidated, our findings highlight the importance of managing constipation in patients with HF. No laxatives or other agents for constipation have been proven to be effective in improving the prognosis of HF. Nonetheless, laxatives may potentially improve clinical outcomes, as well as gastrointestinal symptoms and related mental stress, in patients with HF and constipation if the appropriate use of laxatives is established, warranting further studies on the effectiveness of laxatives.

Several limitations should be acknowledged in the present study. First, the present study may have been subject to inherent biases related to the retrospective study design using an administrative claims database. Clinical information, such as symptoms and laboratory and imaging findings, was unavailable in the DPC database, similar to that of other administrative databases. Such unmeasured factors might have affected our results. Second, there might have been some patients who were readmitted for HF to hospitals that were different from the index hospital or did not participate in the database, resulting in the underestimation of readmissions. However, it is unlikely that the underestimation would bias our results because we do not believe that such readmissions to another hospital would be common or more likely to occur in either group.

Conclusions

This nationwide cohort study demonstrated that constipation was common in patients with HF and was associated with an increased risk of HF readmission. Further efforts are warranted to decrease the risk of constipation-related adverse events in patients with HF.

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Disclosures

T.I. and A.M. have an academic affiliation with the Department of Health Services Research, which is a cooperative program between The University of Tokyo and Tsumura & Company. N.M. and H.M. had an academic affiliation with the Department of Health Services Research. A.O. has an academic affiliation with the Department of Prevention of Diabetes and Lifestyle-Related Diseases, which is a cooperative program between The University of Tokyo and the Asahi Mutual Life Insurance Company. Tsumura & Company and the Asahi Mutual Life Insurance Company played no roles in the design of the study, the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to publish the results. The other authors declare no conflicts of interest.

IRB Information

The Institutional Review Board of the University of Tokyo approved the present study and waived the requirement for informed consent

from individual patients because all patient data were anonymized and de-identified (approval no. 3501-[5]).

Data Availability

The data used in the present study are not publicly available owing to contracts with hospitals that provide data to the database.

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Supplementary Files

Please find supplementary file(s);
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