Early Initiation of Feeding and In-Hospital Outcomes in Patients Hospitalized for Acute Heart Failure

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Extensive data on early nutrition support for patients requiring critical care are available. However, whether early initiation of feeding could be beneficial for patients hospitalized for acute heart failure (HF) remains unclear. We sought to compare outcomes of early and delayed initiation of feeding for hospitalized patients with acute HF using a nationwide inpatient database. We retrospectively analyzed data from the Diagnosis Procedure Combination database. We included patients hospitalized for HF between January 2010 and March 2018. We excluded patients with length of hospital stay ≤2 days, those patients who underwent major procedures under general anesthesia, and those requiring advanced mechanical supports within 2 days after admission including intubation, intra-aortic balloon pumping, and extracorporeal membrane oxygenation. Propensity score matching and instrumental variable analyses were conducted to compare in-hospital mortality, complications and length of stay between the early and delayed feeding groups. Among 432,620 eligible patients, 403,442 patients (93%) received early initiation of feeding (within 2 days after admission) and 29,178 patients (7%) received delayed initiation of feeding. Propensity score matching created 29,153 pairs and delayed initiation of feeding was associated with higher in-hospital mortality (odds ratio 1.32; 95% confidence interval 1.26 to 1.39), longer hospital stay and higher incidence of pneumonia and sepsis. The instrumental variable analysis also showed patients with delayed initiation of feeding had higher in-hospital mortality (odds ratio 1.34; 95% confidence interval 1.28 to 1.40). In conclusion, our analysis suggested a potential benefit of early initiation of feeding for in-hospital outcomes in hospitalized patients hospitalized for acute HF. Further investigations are required to confirm our results and to clarify the underlying mechanisms. **(Am J Cardiol 2021;145:85−90)**

Heart failure (HF) is a major cause of death and morbidity worldwide. In particular, hospital admission due to acute HF is a critical healthcare issue, and real-world data indicated that patients hospitalized for acute HF have a high in-hospital mortality.[1,2] Patients with acute HF frequently have various co-morbidities and are at high risk for various lethal complications (cardiac and noncardiac).[3−5] Intensive hospital care is therefore indispensable for the management of patients hospitalized for acute HF. With regard to intensive care, early nutrition support and enteral nutrition are recommended for critically ill patients.[6,7] Patients with advanced HF frequently have malnutrition and cachexia, which are known to be associated with worse outcomes in these patients.[8−10] Therefore, early nutrition support may thus potentially benefit hospitalized patients for acute HF. However, the role of early nutrition support for acute HF patients remains unknown. In this study, we aimed to investigate the association of early nutrition support, particularly early initiation of feeding, with in-hospital clinical outcomes of patients hospitalized for acute HF using a nationwide inpatient database.

Methods

We performed a retrospective cohort study using data from the Diagnosis Procedure Combination database, a nationwide inpatient database in Japan. The data collected include administrative claims and clinical data for approximately 8 million hospitalized patients per year from more than 1,200 participating hospitals including all 82 academic hospitals.[11,12] These hospitals were distributed across all 47 prefectures in Japan. The Diagnosis Procedure Combination database represents approximately 50% of all acute inpatients and covers more than 90% of all tertiary-care

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See page 89 for disclosure information.

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emergency hospitals in Japan. Academic hospitals are required to participate in this database. However, participation of community hospitals is voluntary. The database collates main diagnoses, co-morbidities present at admission, and complications during hospitalization using the International Classification of Disease and Related Health Problems 10th Revision codes (ICD-10 codes).

Early initiation of feeding was defined as initiation of feeding within 2 days after hospital admission,[13−15] and delayed initiation of feeding as initiation of feeding after 3 or more days after hospital admission.

The primary outcome was in in-hospital mortality. Secondary outcomes included (1) requirement of life-supporting procedures (intubation, hemodialysis, intra-aortic balloon pumping, and extracorporeal membrane oxygenation) after admission; (2) infectious complications (pneumonia and sepsis) during hospitalization; (3) length of hospital stay; and (4) medicals costs.

This study was approved by the Institutional Review Board of the University of Tokyo [Approval number: 3501-(3)]. It was conducted in accordance with the Declaration of Helsinki. Because of the anonymous nature of the data used, the need for obtaining informed consent was waived.

Categorical and continuous data are presented as percentages (%) and mean (mean ± standard deviation). Categorical and continuous variables were compared using chi-square and unpaired *t* tests. We performed propensity score matching using a 1:1 matching protocol width equal to 0.2 standard deviation of the logit of the propensity scores to account for differences in baseline clinical characteristics. We estimated the propensity scores by fitting a logistic regression model for receipt of delayed initiation of feeding as a function of patient demographics. Matched pairs were created without replacement. We compared the outcomes between the groups with early and delayed initiation of feeding before and after propensity score matching. The association of delayed initiation of feeding with in-hospital mortality was evaluated using a logistic regression analysis. We performed subgroup analyses according to baseline characteristics (age, sex, New York Heart Association [NYHA] class, Barthel Index, and intensive care unit (ICU) admission). We also performed instrumental variable analysis based on a 2-stage residual inclusion estimation to confirm the results of the propensity score analysis.[16] Propensity score analyses cannot remove the possibility of hidden biases due to unmeasured confounders. Instrumental variable analysis is a pseudorandomization process that can theoretically control for unmeasured confounders. In the present study, we used "hospital's preference for early initiation of feeding" as an instrument variable. For each hospital, we divided the number of patients with early initiation of feeding by the number of all eligible patients in each hospital. Hospital's preference for early initiation of feeding is presumably independent of patient characteristics. That is, receiving early initiation of feeding may have depended on the hospital at which the patient was treated, rather than on their specific risk factors. Hospital's preference for early initiation of feeding can be highly correlated with the treatment assignment, and do not directly affect patient outcomes, except through the treatment assignment. We used the F test as a weak-instrument identification test, and an F-statistic <10 was considered as a weak instrumental variable. We used this instrumental variable in a 2-stage residual inclusion method to compute the odds ratio for in-hospital mortality in the multivariable logistic regression model. We redefined early initiation of feeding as that within 1 day after hospital admission. We then conducted another propensity score matching analysis under this definition as a sensitivity analysis. p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software version 25 and Stata version 16.

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); (2) major procedures under general anesthesia (n = 3,833); (3) those requiring advanced mechanical supports within 2 days after admission including intubation, intra-aortic balloon pumping, and extracorporeal membrane oxygenation (n = 9,040); and (4) missing information on initiation of feeding (n = 6,158). Finally, 432,620 patients remained. Among them, 403,442 patients (93%) received early initiation of feeding and 29,178 patients (7%) received delayed initiation of feeding. Early initiation of feeding included oral feeding (n = 402,908), tube feeding (n = 474), and gastrostoma feeding (n = 60).

Table 1 shows the characteristics of the study population. Patients receiving delayed initiation of feeding were older and more likely to be female. NYHA class was higher and Barthel index was lower in patients receiving delayed initiation of feeding. After 1:1 propensity score matching, 29,153 pairs were matched, and both groups were well balanced.

Table 2 shows the primary and secondary outcomes of the study population. After propensity score matching, in-hospital mortality was higher in patients receiving delayed initiation of feeding than those receiving early initiation. The proportions of requiring life-supporting procedures were higher in patients receiving delayed initiation of feeding than those receiving early initiation of feeding, including intubation, hemodialysis, and intra-aortic balloon pumping. Patients with delayed initiation of feeding were more likely have pneumonia, and sepsis, and longer hospital stay.

Overall, delayed initiation of feeding was associated with higher in-hospital mortality (Figure 1). Figure 1 also shows the results of the subgroup analyses according to baseline clinical characteristics. The association between delayed initiation of feeding and in-hospital mortality was observed in all subgroups.

The F-statistic in the instrumental variable analysis was 16,301. According to the 2-stage residual inclusion estimation, in-hospital mortality was higher in patients receiving delayed initiation of feeding than those receiving early initiation of feeding (odds ratio 1.34; 95% confidence interval 1.28 to 1.40; p <0.001).

In the sensitivity analysis, 51,380 well-balanced pairs were matched after 1:1 propensity score matching (Supplementary Table 1). Trend in the association between delayed

Table 1
Characteristics of Patients Before and After Propensity Score Matching Between Early (within 2 days) and Delayed (≥3 days) Feeding Groups

Variable	Before propensity score matching				After propensity score matching		
	Early Feeding (n=403,442)	Delayed Feeding (n=29,178)	*P*-value	SMD	Early Feeding (n=29,153)	Delayed Feeding (n=29,153)	SMD
Age (years)	78.1±12.1	80.0±11.8	< 0.001	0.156	80.1±11.6	80.0±11.8	-0.006
Male sex	214,976 (53.3%)	14,217 (48.7%)	< 0.001	−0.091	14,068 (48.3%)	14,204 (48.7%)	0.009
Body mass index (kg/m^2)			< 0.001				
< 18.5	59,543 (14.8%)	5,164 (17.7%)		0.080	5,140 (17.6%)	5,158 (17.7%)	0.002
18.5-24.9	218,626 (54.2%)	14,407 (49.4%)		−0.096	14,534 (49.9%)	14,397 (49.4%)	−0.009
25.0-29.9	70,240 (17.4%)	4,193 (14.4%)		−0.083	4,154 (14.2%)	4,191 (14.4%)	0.004
≥30.0	21,437 (5.3%)	1,476 (5.1%)		−0.011	1,413 (4.8%)	1,475 (5.1%)	0.010
Missing	33,596 (8.3%)	3,938 (13.5%)		0.166	3,912 (13.4%)	3,932 (13.5%)	0.002
Hypertension	274,576 (68.1%)	17,697 (60.7%)	< 0.001	−0.155	17,680 (60.6%)	17,690 (60.7%)	0.001
Diabetes mellitus	126,853 (31.4%)	9,110 (31.2%)	0.433	−0.005	9,087 (31.2%)	9,102 (31.2%)	0.001
Chronic renal failure	59,013 (14.6%)	4,194 (14.4%)	0.236	−0.007	4,151 (14.2%)	4,192 (14.4%)	0.004
Chronic liver disease	15,906 (3.9%)	1,058 (3.6%)	0.007	−0.017	1,072 (3.7%)	1,057 (3.6%)	−0.003
Chronic respiratory disease	46,592 (11.5%)	2,782 (9.5%)	< 0.001	−0.066	2,702 (9.3%)	2,781 (9.5%)	0.009
Anemia	63,455 (15.7%)	5,581 (19.1%)	< 0.001	0.090	5,505 (18.9%)	5,571 (19.1%)	0.006
Stroke	7,356 (1.8%)	741 (2.5%)	< 0.001	0.049	723 (2.5%)	736 (2.5%)	0.003
Cancer	23,586 (5.8%)	1,616 (5.5%)	0.030	−0.013	1,598 (5.5%)	1,616 (5.5%)	0.003
Myocardial infarction	9,917 (2.5%)	1,302 (4.5%)	< 0.001	0.110	1,308 (4.5%)	1,297 (4.4%)	−0.002
Dilated cardiomyopathy	31,670 (7.8%)	1,453 (5.0%)	< 0.001	−0.117	1,463 (5.0%)	1,453 (5.0%)	−0.002
Smoking	131,073 (32.5%)	7,775 (26.6%)	< 0.001	−0.128	7,627 (26.2%)	7,769 (26.6%)	0.011
Prior hospital admission	109,148 (27.1%)	4,998 (17.1%)	< 0.001	−0.241	4,949 (17.0%)	4,998 (17.1%)	0.004
New York Heart Association Class			< 0.001				
II	121,055 (30.0%)	6,260 (21.5%)		−0.197	6,156 (21.1%)	6,260 (21.5%)	0.009
III	158,685 (39.3%)	9,136 (31.3%)		−0.168	9,313 (31.9%)	9,136 (31.3%)	−0.013
IV	123,702 (30.7%)	13,782 (47.2%)		0.345	13,684 (46.9%)	13,757 (47.2%)	0.005
Barthel Index			< 0.001				
≥ 60	181,212 (44.9%)	6,494 (22.3%)		0.494	6,424 (22.0%)	6,494 (22.3%)	0.006
< 60	149,093 (37.0%)	16,418 (56.3%)		0.395	16,539 (56.7%)	16,399 (56.3%)	−0.010
Missing	73,137 (18.1%)	6,266 (21.5%)		0.084	6,190 (21.2%)	6,260 (21.5%)	0.006
Barthel Index: Feeding			< 0.001				
0	67,479 (16.7%)	11,824 (40.5%)		0.546	11,814 (40.5%)	11,805 (40.5%)	−0.001
5	83,482 (20.7%)	4,900 (16.8%)		−0.100	4,917 (16.9%)	4,900 (16.8%)	−0.002
10	231,759 (57.4%)	8,984 (30.8%)		−0.557	8,960 (30.7%)	8,984 (30.8%)	0.002
Missing	20,722 (5.1%)	3,470 (11.9%)		0.244	3,462 (11.9%)	3,464 (11.9%)	0.000
Japan Coma Scale			< 0.001				
0	355,677 (88.2%)	21,220 (72.7%)		−0.397	21,354 (73.2%)	21,220 (72.8%)	−0.006
1 digit	41,991 (10.4%)	5,820 (19.9%)		0.268	5,852 (20.1%)	5,819 (20.0%)	−0.003
2 digits	4,570 (1.1%)	1,483 (5.1%)		0.229	1,413 (4.8%)	1,479 (5.1%)	0.010
3 digits	1,195 (0.3%)	655 (2.2%)		0.175	534 (1.8%)	635 (2.2%)	0.025
Missing	9 (0.0%)	0 (0.0%)		−0.007	—	—	–
Weekend Admission	67,883 (16.8%)	6,896 (23.6%)	< 0.001	0.170	6,860(23.5%)	6,883 (23.6%)	0.002
Medication within two days after admission							
Beta blocker	139,612 (34.6%)	5,525 (18.9%)	< 0.001	−0.360	5,395 (18.5%)	5,525 (19.0%)	0.011
Renin-angiotensin system inhibitor	156,570 (38.8%)	6,644 (22.8%)	< 0.001	−0.353	6,689 (22.9%)	6,644 (22.8%)	−0.004
Mineralocorticoid receptor antagonist	136,748 (33.9%)	6,077 (20.8%)	< 0.001	−0.296	6,013 (20.6%)	6,077 (20.8%)	0.005
Tolvaptan	44,447 (11.0%)	1,760 (6.0%)	< 0.001	−0.179	1,748 (6.0%)	1,760 (6.0%)	0.002
Intravenous inotropic agent	63,768 (15.8%)	6,857 (23.5%)	< 0.001	0.195	6,667 (22.9%)	6,834 (23.4%)	0.014
Intravenous nitrate	79,989 (19.8%)	8,084 (27.7%)	< 0.001	0.186	8,113 (27.8%)	8,071 (27.7%)	−0.003
Intravenous furosemide	274,033 (67.9%)	20,201 (69.2%)	< 0.001	0.028	19,898 (68.3%)	20,183 (69.2%)	0.021
Intravenous carperitide	164,780 (40.8%)	11,474 (39.3%)	< 0.001	−0.031	11,268 (38.7%)	11,467 (39.3%)	0.014
Procedures within two days after admission							
Respiratory support	40,523 (10.0%)	7,115 (24.4%)	< 0.001	0.387	7,020 (24.1%)	7,090 (24.3%)	0.006
Hemodialysis	6,771 (1.7%)	335 (1.1%)	< 0.001	−0.045	336 (1.2%)	335 (1.1%)	0.000
Intensive care unit stay within two days after admission	36,740 (9.1%)	4,785 (16.4%)	< 0.001	0.220	4,801 (16.5%)	4,771 (16.4%)	−0.003

Data are expressed as mean (standard deviation) or number (percentage). SMD, Standardized mean difference.

Table 2
Procedures and Outcomes Before and After Propensity Score Matching Between Early (within 2 days) and Delayed (≥3 days) Feeding Groups

Variable	Before propensity score matching			After propensity score matching		
	Early Feeding (n=403,442)	Delayed Feeding (n=29,178)	*P*-value	Early Feeding (n=29,153)	Delayed Feeding (n=29,153)	*P*-value
Intubation	3,577 (0.9%)	551 (1.9%)	< 0.001	405 (1.4%)	548 (1.9%)	< 0.001
Hemodialysis	9,748 (2.4%)	892 (3.1%)	< 0.001	665 (2.3%)	892 (3.1%)	< 0.001
Intra-aortic balloon pumping	1,195 (0.3%)	178 (0.6%)	< 0.001	135 (0.5%)	177 (0.6%)	0.017
Extra-corporeal membrane oxygenation	230 (0.1%)	19 (0.1%)	0.577	30 (0.1%)	19 (0.1%)	0.116
Pneumonia	9,360 (2.3%)	1,743 (6.0%)	< 0.001	1,055 (3.6%)	1,799 (6.2%)	< 0.001
Sepsis	1,879 (0.5%)	346 (1.2%)	< 0.001	212 (0.7%)	345 (1.2%)	< 0.001
Length of hospital stay (days)	22.0±21.3	35.5±37.3	< 0.001	24.3±24.7	35.5±37.3	< 0.001
Medical cost (JPY)	997,656 ±1,021,928	1,353,714 ±1,263,815	< 0.001	1,120,736 ±1079,383	1,352,129 ±1,260,575	< 0.001
Medical cost (USD)	9,378 ±9,606	12,725 ±11,880	< 0.001	10,535 ±10,146	12,710 ±11,849	< 0.001
In-hospital death	22,948 (5.7%)	3,744 (12.8%)	< 0.001	2,912 (10.0%)	3,737 (12.8%)	< 0.001

Data are expressed as mean (standard deviation) or number (percentage).

initiation of feeding and the outcomes was similar to that in the main analyses (Supplementary Table 2).

Discussion

In this nationwide large-scale database of patients hospitalized for acute HF, majority of acute HF patients received early initiation of feeding. Concretely, 88% of patients received initiation of feeding within 1 day after admission and 93% of patients received initiation of feeding within 2 days after admission. Patients receiving delayed initiation of feeding expectedly had relatively complex clinical characteristics compared with those receiving early initiation of feeding as shown in Table 1. Therefore, we conducted propensity score matching to adjust for the differences in the background characteristics. After propensity score matching, we obtained well-balanced 29,153 pairs and delayed initiation of feeding was associated with longer hospital stay and higher in-hospital mortality. The instrumental variable analysis confirmed the results of the propensity score matching analysis. Lastly, we confirmed our results by a sensitivity analysis as well.

The association between delayed initiation of feeding and higher in-hospital mortality was consistent in all subgroups (Figure 1). This association seemed evident in patients with low Barthel index and those admitted to general ward, suggesting that oral feeding could be initiated earlier in patients admitted to general ward even if they had

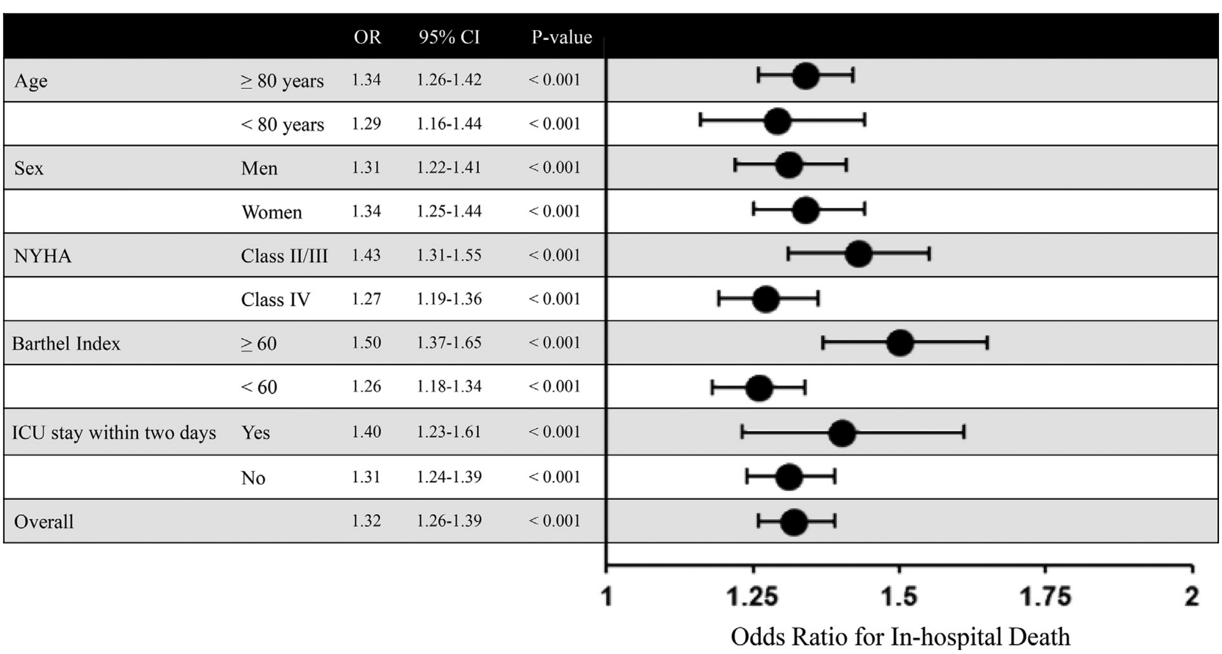

Figure 1. Odds ratios of in-hospital mortality associated with delayed initiation of feeding in the propensity score-matched cohort. Odds ratios of in-hospital mortality associated with delayed initiation of feeding in the propensity score-matched cohort. CI = confidence interval; ICU, intensive care unit; NYHA, New York Heart Association; OR = odds ratio.

low activities of daily living. Notably, the association of delayed initiation of feeding with in-hospital mortality was also observed in patients admitted to ICU with NYHA class IV symptoms. These results suggest that early initiation of feeding might be beneficial even in patients having NYHA class IV symptoms, with low Barthel Index, or admitted to ICU.

Although the timing of initiation of feeding is difficult to determine in patients hospitalized for acute HF, our study could present the beneficial potential of early initiation of feeding, which is consistent with the other recent study.[17] Postponement of initiation of feeding without any solid clinical reasons may even be potentially harmful. In contrast, delaying enteral nutrition is recommended in critically ill patients with uncontrolled shock, uncontrolled hypoxemia, and acidosis.[6] These lethal conditions are frequently observed in patients with acute HF; therefore, a careful assessment for the indication of initiation of feeding is without doubt required.

Several possible explanations could be suggested for our results. The lower proportions of infectious complications in patients receiving early initiation of feeding could contribute to the results. Infectious complications are common and associated with adverse outcomes in patients with acute HF.[12,18] Early enteral nutrition could reduce infectious complications, and early enteral nutrition is recommended for critically ill patients.[6,19] Our results are in line with preceding studies.[20,21] Enteral nutrition is known to be associated with mucosal immunological function, gastrointestinal mucosa integrity, tissue repair process, and infectious complications.[22–25] In addition, even after propensity score matching, patients requiring intubation, hemodialysis, and intra-aortic balloon pumping were more common in patients receiving delayed initiation of feeding. Delayed initiation of feeding may have been directly or indirectly associated with cardiorespiratory instability in patients with acute HF. However, due to the nature of the retrospective observational study, we are unable to conclude the causal relation and determine the biological basis of our results. Further studies are warranted to confirm our results and to clarify the pathological mechanisms of our results.

We acknowledge several limitations of this study. Although we conducted propensity score matching analysis and an instrumental variable analysis to exclude the influence of unmeasured confounders and residual bias as much as possible, sicker clinical backgrounds of patients with delayed initiation of feeding could have influenced the results. Reasons for delayed initiation of feeding and detailed information on feeding such as completeness of nutrition and calorie intake were unclear due to limited available data of our database and the nature of the retrospective design. Well-designed prospective studies are required to overcome these fundamental limitations of the retrospective study. We were unable to obtain several important information including blood pressure, heart rate, left ventricular ejection fraction, HF etiology, initial nutritional status, presence and type of malnutrition, amount and type of feeding, intensity of systemic inflammation, and the nutritional management, which could have affected the results. We used body weight at hospital admission to assess BMI in this study, which might not necessarily have reflected the BMI in the stable conditions. The majority of patients categorized in the early initiation of feeding group received oral feedings. Therefore, further data are needed to assess the relation between tube feeding and clinical outcomes in hospitalized patients for acute HF. Similarly, further studies are needed to compare enteral nutrition and parenteral nutrition in hospitalized patients for acute HF. Data on swallowing function and dysphagia were not available in our database.

In conclusion, our analysis of a nationwide inpatient database showed that delayed initiation of feeding was associated with higher in-hospital mortality in patients hospitalized for acute HF, suggesting a beneficial potential of early initiation of feeding in acute HF. Further investigations are required to verify our results and to establish the optimal nutrition support strategy in patients with acute HF.

Authors' Contribution

Hidehiro Kaneko: Conception and design or analysis and interpretation of data. Drafting of the manuscript. Hidetaka Itoh: Analysis of data. Kojiro Morita: Analysis and interpretation of data. Tadafumi Sugimoto: Conception and design or analysis and interpretation of data. Drafting of the manuscript. Masaaki Konishi: Conception and design or analysis and interpretation of data. Drafting of the manuscript. Kentaro Kamiya: Revising it critically for important intellectual content. Hiroyuki Kiriyama: Revising it critically for important intellectual content. Tatsuya Kamon: Analysis of data. Katsuhito Fujiu: Revising it critically for important intellectual content. Nobuaki Michihata: Analysis and interpretation of data. Taisuke Jo: Data collection. Analysis and interpretation of data. Norifumi Takeda: Revising it critically for important intellectual content. Hiroyuki Morita: Revising it critically for important intellectual content. Hideo Yasunaga: Conception and design or analysis and interpretation of data. Final approval of the manuscript submitted. Issei Komuro: Final approval of the manuscript submitted.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.082.

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