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Increased Mortality Rate after Hospitalization Among Chronic Hemodialysis Patients: A Prospective Cohort Study

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Keywords
Dialysis · Hospitalization · Mortality · Epidemiology · Infection

Abstract
Background/Aims: Hemodialysis patients are at high risk of hospitalization and their condition may worsen with repeated hospitalization. The aim of this study was to evaluate the impact of the cumulative number of hospitalizations on post-discharge mortality. ***Methods:*** This study was a prospective cohort study. We examined 3,359 adult patients on hemodialysis for at least 90 days who participated in the Japanese Dialysis Outcomes and Practice Patterns Study phases 3 and 4 (2005–2012). The patients hospitalized within 3 months before enrollment were excluded. The main exposure was the time-varying cumulative number of hospitalizations during the follow-up period. Hazard ratios (HRs) for all-cause mortality rate after discharge were estimated by time-dependent Cox regressions after adjusting for potential confounders. ***Results:*** The median follow-up time was 2.7 years, and 873 (26%) patients experienced at least 1 hospitalization during follow-up. The hospitalization rate was 0.23 per person-year and the mortality rate was 0.036 per person-year. The HR and 95% CI for post-discharge mortality increased as the cumulative number of hospitalizations increased: once, 1.41 (0.99–2.00); and twice or more, 2.27 (1.59–3.23). The cause-specific hospitalization categories, "infectious disease" and "cancer," affected post-discharge mortality HRs in a similar manner: 2.41(1.32–4.41) and 2.70 (1.23–5.93), respectively. ***Conclusion:*** A higher cumulative number of hospitalizations is associated with increased post-discharge mortality in chronic hemodialysis patients. The cause-specific hospitalizations category of "infectious disease" showed an impact on mortality similar to that of hospitalization for "cancer." Therefore, physicians should pay more attention to reducing preventable hospitalizations.

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Introduction

Patients on chronic hemodialysis are at high risk of hospitalization. Among the general population, the hospitalization rate was 0.14 per person-year in the United Kingdom (2011) [1] and 0.12 per person-year in the United States (2012) [2]. Among chronic hemodialysis patients, however, the hospitalization rate was much higher, at 1.74 per person-year in the United States (2013–2014) and 0.99 per person-year in Europe, ranging from 0.75 per person-year in Spain to 1.43 per person-year in France (2000) [3, 4]. In a recent report, the cost of hospitalization for end-stage renal disease patients in the United States contributed to one-third of total Medicare costs, and the 2 leading causes were infection (27%) and cardiovascular diseases (24%) [3]. Multiple comorbidities or interventions associated with dialysis treatment could lead to large differences in hospitalization rates between patients on chronic dialysis and the general population.

The condition of patients may change throughout hospitalization. The worsening of physical function occurs commonly and persists after discharge, especially among elderly people [5–9]. Among those discharged from the hospital, those who experienced re-hospitalization showed a much higher risk of long-term physical dysfunction [6]. Hospitalization might also be associated with cognitive decline and incident depression after admission [7, 10]; functional disability, cognitive impairment, and untreated depression were each shown to have an association with a higher risk of mortality [7, 11–16]. From this viewpoint, even if a hospital admission was due to a nonprogressive or nonmalignant disease, the hospitalization experience and its frequency may worsen the prognosis of patients who have survived hospitalization. In some previous studies, the frequency of hospitalizations due to worsening of the disease has been reported to be associated with increased mortality in some chronic conditions, such as end-stage renal failure and congestive heart failure [17–19]. In these previous studies, the frequency of hospitalizations was treated as a surrogate marker of progression of specific diseases or only hospitalization due to limited causes. This study aimed to examine the hypothesis that repeated hospitalization would aggravate post-discharge outcomes in the population of dialysis patients, regardless of the reason for hospitalizations. Therefore, we counted the cumulative number of all-cause hospitalizations and examined the association between the time-varying number of hospitalizations and mortality.

Furthermore, little is known about the association between the cause of hospitalization and post-discharge prognosis and mortality risk. For instance, chronic hemodialysis patients were reported to have higher mortality after hospitalization due to fractures in comparison with chronic hemodialysis patients hospitalized for other reasons (0.43–0.91 per person-year vs. 0.38 per person-year) [20]. Further research to understand the impact of hospitalization and its repetition may affect patients' long-term prognosis and may guide preventive measures against hospitalization.

The main objective of this study was to examine the association between the cumulative number of hospitalizations and post-discharge mortality. We also evaluated the impact of cause-specific hospitalization on post-discharge mortality.

Methods

Study Design and Setting

We designed a retrospective cohort study. Data from The Japanese Dialysis Outcomes and Practice Patterns Study (J-DOPPS) phase 3 (2005–2008) and phase 4 (2009–2012) were used. DOPPS is an international prospective cohort study of patients 18 years or older on chronic hemodialysis. The patients were sampled randomly from a representative sample of dialysis facilities within each country. The detailed study design of DOPPS has been published elsewhere [21].

Participants

Participants were patients aged 18 years or older and on hemodialysis for 90 days or more. We excluded the patients who had been hospitalized within 3 months before enrollment. Patients with less than 2 days follow-up and those missing exclusion criteria or outcomes data were also excluded. Of 4,612 patients who were enrolled in J-DOPPS phases 3 and 4, 1,253 patients (227 due to missing data, 425 with dialysis vintage less than 90 days, 598 who had been hospitalized within 3 months before the enrollment, and 3 with less than 2 days follow-up) were excluded and 3,359 patients remained for analysis. Among them, 1,715 hospitalization records were identified and used for analysis. We conducted complete case analysis in the multivariate analysis, and data from 3,188 patients with available covariates data were used.

Exposure

The main exposure was the cumulative number of hospitalizations experienced during the follow-up period, which varied with time for a given patient, and was divided into 3 categories (none, once, twice or more).

The secondary exposure was cause-specific hospitalization experienced during the follow-up period. To code the cause of the admission for each hospitalization record, 144 diagnostic codes, grouped into 25 diagnostic categories, were predefined in the survey in the J-DOPPS study (online suppl. Table 1; for all online

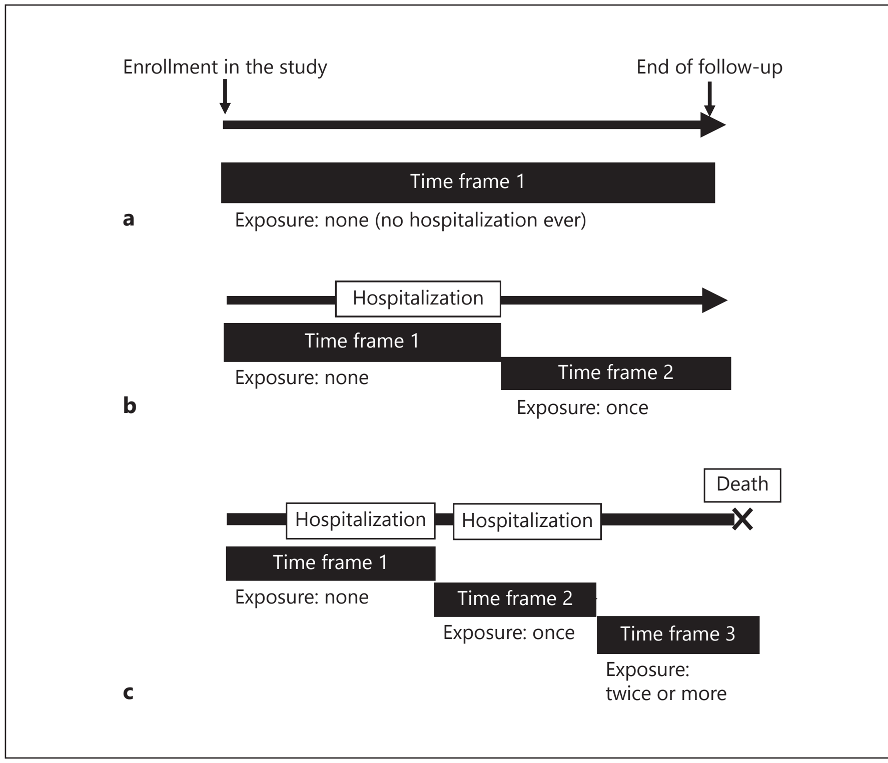

Fig. 1. Definition of time frame and exposure. A time frame starts at study enrollment or the day following the discharge date. A time frame ends at the day of death or censoring among patients never hospitalized. Among patients with hospitalizations, a time frame ends at the day of death, censoring, or discharge date. **a** Patient 1: The patient was never admitted for hospitalization during the follow-up period. Patient 1 has one time frame, an exposure of "none (no hospitalization)," and the outcome is survival. **b** Patient 2: The patient was admitted to hospital once. This patient has 2 time frames. During the first time frame, exposure is "none" and the outcome is survival. During the second time frame, the exposure is "once" and the outcome is survival. **c** Patient 3: The patient was admitted twice and died after the second discharge. This patient has 3 time frames. In the first time frame, exposure is "none" and the outcome is survival; in the second time frame exposure is "once" and the outcome is survival; in the third time frame exposure is "twice or more" and the outcome is death.

suppl. material, see www.karger.com/doi/10.1159/000492083). One hospitalization record could have more than one diagnosis code as the major cause for admission, for example, pneumonia (categorized into the category "infectious disease") and congestive heart failure (categorized into the category "cardiac or cardiovascular disease"). In this example, the cause of hospitalization was classified into both corresponding diagnosis categories, that is, hospitalization due to "infectious disease" and "cardiac or cardiovascular disease." For the secondary exposure, considering multiple diagnosis categories are independent variables, we defined the major exposure as a dichotomous variable, that is, the presence or absence of each cause-specific hospitalization, rather than as 3 levels of the primary analysis (none, once, twice or more), considering that only a small number of patients would exist at each level.

Time Frame

The exposure status changed when a patient experienced a new hospitalization. Therefore, the follow-up period was divided into several time frames depending on the number of admissions and discharges during the follow-up period (Fig. 1). We set either the enrollment date or day following discharge as the start of each time frame because our aim was to evaluate the impact of hospitalization or cause-specific hospitalization on post-discharge mortality, and not the impact on the acute phase after admission. During each time frame, the exposure status was defined by the hospitalization experienced until the start of the time frame (Fig. 1). For example, Patient 1, who was never admitted during the follow-up period, has one time frame and an exposure of "none (no hospitalization ever"; Fig. 1a). Patient 2, who was admitted once, was discharged, and remained alive at the end of follow-up, has 2 time frames (Fig. 1b); the second time frame began the day after the discharge date and ended on the last day of follow-up, and the exposure was "once." Likewise, Patient 3, who was admitted twice, has 3 time frames (Fig. 1c); the third time frame started the day following the second time frame and ended at the date of death, and the exposure was "twice or more."

The secondary exposure, cause-specific hospitalization, was defined by all diagnostic categories experienced before the start of the time frame. For example, if the first hospitalization of Patient 3 (Fig. 1c) was due to "infectious disease" and the second hospitalization was due to "cardiac disease," the exposure of "Time frame 2" was hospitalization due to "infectious disease" and that of "Time frame 3" was hospitalization due to "infectious disease" and "cardiac or cardiovascular disease."

Outcomes

The primary outcome was the post-discharge mortality rate, indicated by a hazard ratio (HR). Transfer to another facility, transfer to peritoneal dialysis, kidney transplantation during the follow-up period, and survival at the end of the time frame were defined as censoring.

Potential Confounders

Age, sex, dialysis vintage, cardiovascular disease (coronary artery, peripheral vascular, cerebrovascular, and other cardiovascular disease), congestive heart failure, diabetes mellitus, cancer, gastrointestinal bleeding, hepatitis, chronic lung disease, neurologic disease, albumin, and hemoglobin at enrollment were considered potential confounders. We used the fixed baseline values as covariates because the follow-up period values were considered intermediate factors.

Statistical Analysis

The baseline characteristics were described in all participants and in patients classified by the presence or absence of hospitalization within the follow-up period. Continuous variables with a normal distribution were described by mean and standard deviation; continuous variables with non-normal distribution were represented by median and interquartile range (IQR). Categorical variables were presented as number and proportion (%). Observed time, number of hospitalizations within the follow-up period, days of hospitalization, and number of deaths were also summarized. Kaplan-Meier curves were used to estimate the time until the first hospitalization.

The primary analysis tested the association between the number of hospitalizations (none, once, twice or more) experienced before the time frame and survival time. Since the exposure status may have changed during the follow-up period, we treated the number of hospitalizations as a time-varying covariate in the Cox regression model and adjusted for potential confounding variables at baseline as fixed covariates. An age-stratified analysis was also conducted for patients under 65 years of age and those 65 years or older.

The secondary analysis tested the association between cause-specific hospitalization experienced before the time frame and survival time, using a time-dependent Cox regression model. Of 25 cause-of-hospitalization diagnosis categories, the higher frequency categories were treated as independent categories and lower frequency categories were combined into one category. To identify the patients with a higher risk of hospitalization, the association between baseline characteristics and any hospitalization during the follow-up period was also tested by a logistic regression model. To assess the impact of duration of hospital stay, we utilized the Kaplan-Meier survival curve after the first discharge during the study period stratified by the quartile of hospitalized days.

Sensitivity Analysis

As hospitalization duration lengthened, it may have affected the mortality rate before discharge. We conducted a sensitivity analysis using an end of time frame defined by whichever came first: the day of death, censoring, the discharge date, or 14 days after the admission date.

All statistical analyses were performed using STATA version 14.1 (Stata Corp., College Station, TX, USA). The significance level was 0.05 for 2-sided tests.

Results

Of 3,359 eligible patients, 2,486 patients (74%) were never admitted during the follow-up period. The remaining 873 patients (26%) experienced at least one admission and 1,715 hospitalizations in total. Patients who were hospitalized during the follow-up period tended to have longer dialysis vintage and more comorbidities (Table 1) [1, 2]. The hospitalization rate was 0.23 and 0.88 per person-year among all patients and the patients with at least 1 hospitalization during the follow-up period respectively. The mortality rate was higher among previously hospitalized patients compared to those without hospitalization (0.036 and 0.058 per person-year respectively). Online supplemental Figure 1 presents the time to the first hospitalization during the follow-up period; by 2 years follow-up, over one-fourth of the patients were estimated to experience hospitalization.

Online supplemental Table 2 shows the frequency of each diagnosis category at admission and hospitalized days per hospitalization. The 7 most frequent categories were "cardiac or cardiovascular disease," "vascular access," "gastrointestinal disease," "orthopedic disease," "infectious diseases," "neurologic or cerebrovascular disease," and "neoplastic disease or cancer." Categories other than these 7 were aggregated into the "Other" category (online suppl. Table 1) for the multivariate analysis.

As our primary analysis, we examined the association between post-discharge mortality and the cumulative number of hospitalizations. Table 2 demonstrates these results. The HR for post-discharge mortality increased as the cumulative number of hospitalizations increased. Hospitalization due to infectious disease and neoplastic disease/cancer showed a significantly higher risk of post-discharge mortality compared to other categories (HR and 95% CI 2.41 [1.32–4.41] and 2.70 [1.23–5.93] respectively). The age-stratified results are presented in Table 3. Of 1,686 patients under 65 years old, 90 (5.3%) died during the follow-up period. Two-hundred and nine patients (13.9%) of 1,502 total patients aged 65 years or older died during the follow-up period. Although similar trends were observed, the hospitalization exposure HRs were higher among the younger patients than the elderly patients. We collected details of diagnoses and their frequencies of hospitalizations due to infectious disease, as shown in online supplemental Table 3. Pneumonia was the most frequent diagnosis. Sensitivity analysis of the time frame showed the same tendency (online suppl. Table 4).

We explored possible associations between patient baseline characteristics and any hospitalization during the follow-up period (online suppl. Table 5). Sex, cardiovascular disease, congestive heart failure, diabetes mellitus, and hepatitis were significantly associated with hospitalization.

Finally, a Kaplan-Meier survival curve after the first discharge during the study period stratified by the quartiles of the hospitalized days (1–3, 4–10, 11–21, 22

Table 1. Participant baseline characteristics, hospitalization, and mortality

	Total (n = 3,359)	Hospitalization	
		never n = 2,486 (74%)	one or more n = 873 (26%)
Age, years, mean (SD)	63 (12)	63 (12)	64 (12)
65 years old or older, n (%)	1,569 (47)	1,147 (46)	422 (48)
Gender, male, n (%)	2,107 (63)	1,581 (64)	526 (60)
Dialysis vintage, years, median (IQR)	5.2 (1.8–11.0)	5.1 (1.6–11.0)	5.5 (2.4–11.0)
Cause of ESRD, n (%)			
Diabetes mellitus	990 (29)	700 (28)	290 (33)
Missing data	125 (4)	101 (4)	24 (3)
Comorbidity, n (%)			
Cardiovascular disease	1,934 (58)	1,345 (54)	589 (67)
Congestive heart failure	714 (21)	469 (19)	245 (28)
Diabetes mellitus	1,140 (34)	801 (32)	339 (39)
Malignancy	321 (10)	229 (9)	92 (11)
Gastrointestinal bleeding	123 (4)	89 (4)	34 (4)
Hepatitis	346 (10)	216 (9)	130 (15)
Chronic lung disease	99 (3)	78 (3)	21 (2)
Neurologic disease	266 (8)	181 (7)	85 (10)
Albumin, g/dL, mean (SD)	3.8 (0.4)	3.8 (0.4)	3.8 (0.4)
Missing data, n (%)	158 (5)	105 (4)	53 (6)
Hemoglobin, g/dL, mean (SD)	10.5 (1.2)	10.5 (1.2)	10.5 (1.2)
Missing data, n (%)	22 (0.7)	16 (0.6)	6 (0.7)
Observed time			
Total years	7,428	5,477	1,951
Years per person, median (IQR)	2.7 (1.7–2.8)	2.7 (1.6–2.8)	2.7 (1.8–2.8)
Hospitalization during the follow-up period			
Number per person, median (IQR)	0 (0–1)	–	1 (1–2)
Number per one person-year	0.23	–	0.88
Total days	50,624	–	50,624
Days per one person-year	6.8	–	25.9
Death, n (%)	309 (9)	196 (8)	113 (13)
Mortality rate (per 100 person-year)	4.2	3.6	5.8

ESRD, end-stage renal disease; IQR, interquartile range.

and over) is shown in online supplemental Figure 2. We found that longer hospital stay was associated with higher post-discharge mortality rate (Log-rank test $p <$ 0.01). We also found that post-discharge death rate seems to be consistent over time (no difference between immediate post-discharge period and late discharge period).

Discussion

In this study, we describe the incidence and cause of hospitalization among 3,359 chronic hemodialysis patients. We also examine the association between the cumulative number of hospitalizations and post-discharge mortality. The incidence of hospitalization was high among chronic dialysis patients when compared to that in the general population [1, 2] (Table 1). Cardiac or cardiovascular disease, vascular access, and gastrointestinal disease were the leading causes for admission (online suppl. Table 2). The cumulative number of hospitalizations and the cause-specific hospitalization categories of malignancy and infectious disease were associated with post-discharge mortality (Table 2). The same result was confirmed in the age-stratified analysis, and it suggested that the younger population faces a higher risk of post-discharge mortality due to hospitalization (Table 3).

Compared to all patients in J-DOPPS phase 3 and phase 4, the eligible study patients demonstrated simi-

Table 2. Association between hospitalization and post-discharge mortality (n = 3,188)

	Any hospitalization		Cause-specific hospitalization	
	HR	95% CI	HR	95% CI
Cumulative number of hospitalizations				
None	Reference			
Once	1.41	0.99–2.00		
Twice or more	2.27	1.59–3.23		
Diagnosis category at admission				
Cardiac/cardiovascular			1.23	0.73–2.06
Vascular access			0.80	0.43–1.49
Gastrointestinal			1.08	0.57–2.04
Orthopedic			0.87	0.40–1.89
Infectious diseases			2.41	1.32–4.41
Neurologic/cerebrovascular			1.87	0.93–3.76
Neoplastic/cancer			2.70	1.23–5.93
Other			1.50	1.05–2.13

Adjusted for age, sex, dialysis vintage, comorbidity (cardiovascular disease, congestive heart failure, diabetes mellitus, cancer, gastrointestinal bleeding, hepatitis, chronic lung disease, neurologic disease), albumin and hemoglobin.
HR, hazard ratio.

Table 3. Association between hospitalization and post-discharge mortality stratified by age

	Any hospitalization				Cause-specific hospitalization			
	<65 years old (n = 1,686)		65 years or older (n = 1,502)		<65 years old (n = 1,686)		65 years or older (n = 1,502)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Cumulative number of hospitalizations								
None	Reference		Reference					
Once	1.63	0.89–2.99	1.33	0.85–2.07				
Twice or more	3.35	1.82–6.20	1.96	1.26–3.04				
Diagnosis category at admission								
Cardiac/cardiovascular					1.33	0.56–3.16	1.05	0.53–2.08
Vascular access					0.70	0.21–2.31	0.92	0.44–1.93
Gastrointestinal					1.71	0.52–5.62	1.22	0.57–2.60
Orthopedic					0.88	0.20–3.81	1.05	0.42–2.63
Infectious diseases					5.06	1.87–13.7	1.52	0.68–3.41
Neurologic/cerebrovascular					2.08	0.62–7.01	2.11	0.89–4.97
Neoplastic/cancer					6.16	1.46–25.9	2.71	1.04–7.03
Other					1.84	1.04–3.25	1.33	0.84–2.09

Adjusted for age, sex, dialysis vintage, comorbidity (cardiovascular disease, congestive heart failure, diabetes mellitus, cancer, gastrointestinal bleeding, hepatitis, chronic lung disease, neurologic disease), albumin and hemoglobin.
HR, hazard ratio.

lar age and sex distributions (64 vs. 63 years old and 63 vs. 63%, respectively). On the other hand, the proportion of end-stage renal disease caused by diabetes mellitus (29 vs. 32%) and mortality rate (0.042 vs. 0.053 per person-year) were lower among the eligible patients. This could be due to the exclusion of patients who had been on hemodialysis for less than 90 days or hospitalized within 3 months before the enrollment.

The prognosis for hemodialysis patients after cause-specific hospitalization is poor for several diseases. For instance, the crude mortality rate of hemodialysis patients after admission due to infection or heart failure were both reported to be as high as 0.29 per person-year [22, 23]. One-year mortality rate among patients hospitalized for pneumonia and traumatic brain injury were 45 and 77% respectively [23, 24]. However, there have been few studies that examine the impact of hospitalization on post-discharge prognosis, that also consider repeated hospitalization(s). Our results suggest that preventing unnecessary hospitalization or re-hospitalization may improve patient prognosis.

Regarding the associations between cause-specific hospitalizations and post-discharge mortality, we found relatively strong associations between higher mortality rate and hospitalizations due to cancer and infectious disease. In addition to the progressive nature of cancer, a higher mortality rate after hospitalization due to cancer might be explained by the high burden of cancer treatment (surgery or chemotherapy). Some patients might continue to receive cancer treatment after discharge. However, we could not assess the type of treatments that patients received during the hospitalization and after the discharge in this study. Even if the treatment for infectious disease might have been completed at the time of discharge, appetite loss or decreased activity due to acute illness may lead to a decline in physical and cognitive function and post-discharge mortality [7].

Hospitalization due to "cardiac or cardiovascular disease" or "orthopedic disease" was not significantly associated with post-discharge mortality, whereas hemodialysis patients hospitalized due to "heart failure" or "fracture" showed high crude mortality in previous studies [20, 23]. Though it was pragmatic to summarize diagnoses into a limited number of categories to evaluate the impact of cause-specific hospitalization, diagnoses with less severe etiology may have a lower impact on post-discharge mortality. For this reason, the diagnosis categories with lower risk should not be ignored.

Although we found consistent associations of hospitalizations with higher post-discharge mortality between age groups, the point estimates of the HRs were higher in the younger population (<65 years) compared with that in the older population (65 years or older; Table 3). This may be because the baseline mortality rate was higher in the older population (6.4 per 100 person-years) than in the younger population (2.3 per 100 person-years), and hospitalization status provided minimal additional prognostic information for the older population. These results are consistent with those in patients with chronic heart failure [17].

Interventions to prevent hospital readmission, such as hospital discharge planning and intensive monitoring after discharge, have proven effective [25–27]. Several treatments specific to hemodialysis patients, such as controlling anemia, or administration of vitamin D after discharge [28], could prevent readmission and reduce the number of hospitalizations. Among hospitalizations due to infectious disease, pneumonia (30%) was the leading cause. Hospitalization due to infectious disease can be reduced by interventions such as pneumococcal or influenza vaccines [29, 30]. Although these interventions are an already recognized important public health practice and the associated infectious diseases are curable, we re-emphasize their importance, considering the possible burden of hospitalization on patients' post-discharge mortality. Furthermore, while these results are from chronic hemodialysis patients, they could be applied to the general elderly population, who demonstrate a similar increased tendency to multiple comorbidities with age.

There are several strengths of this study. To start with, this is the first study to demonstrate the impact of the cumulative number of hospitalizations on post-discharge prognosis. For this purpose, the study design and analysis treated the major exposure as a time-dependent variable. Second, the sampling method was such that participants were chosen to be representative of the chronic hemodialysis patients. Third, we confirmed the robustness of our results by both stratified analysis and sensitivity analysis.

Our study also presents some limitations. First, the judgment of admission or discharge was not predefined and could vary depending on the physician or facility. However, the data reflected real-world practices and the results might thus be interpreted for the daily practice setting. Second, the disease category definitions may introduce variability. Since there is no standard for disease category definitions, we used the categories from the original survey. Third, hospitalizations that occurred before enrollment could affect prognosis during the study period. To reduce this effect, we excluded patients who had experienced hospitalization within 3 months before enrollment. There were no details about hospitalizations more than 3 months before enrollment, thus we were unable to consider such exposures. Fourth, other residual confounders, such as medication compliance or family structure, could exist.

In conclusion, the cumulative number of hospitalizations was associated with increased post-discharge mortality rate in chronic hemodialysis patients. The cause-specific hospitalization category "infectious disease" showed a similar impact on mortality compared to the "cancer" category. Physicians should aim to reduce preventable hospitalizations.

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Ethics Statement

We conducted this study in compliance with the Declaration of Helsinki. In J-DOPPS, all participants provided informed consent. This study was approved by institutional review boards as required by each facility and by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee.

Disclosure Statement

S. Shimizu and T. Ikenoue have no relevant financial interests. S. Fukuma and S. Fukuhara have acted as scientific advisors to Kyowa Hakko Kirin. T. Akizawa has consultancy agreements with Astellas Pharma, Kyowa Hakko Kirin, Bayer Health Care Pharmaceuticals, JT Pharmaceuticals Corporate, Kissei Pharmaceutical, Ono Pharmaceutical, and is a member of the Astellas advisory panel. T. Akizawa is also a scientific advisor of Bayer HealthCare Pharmaceuticals and a member of the speaker's bureau of Bayer HealthCare Pharmaceuticals, Kyowa Hakko Kirin, Chugai Pharmaceutical, and Torii Pharmaceutical.

Author Contributions

Research idea and study design, data acquisition, data analysis/interpretation: S. Shimizu, S. Fukuma; drafting the article: S. Shimizu; supervision or mentorship: S. Fukuma, T. Ikenoue, S. Fukuhara, T. Akizawa. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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