


Multilevel analysis of hemodialysis-associated infection among end-stage renal disease patients: results of a retrospective cohort study utilizing the insurance claim data of Fukuoka Prefecture, Japan

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Abstract

The presence of comorbid conditions along with heterogeneity in terms of healthcare practices and service delivery could have a significant impact on the patient's outcomes. With a strong interest in social epidemiology to examine the impact of health services and variations on health outcomes, the current study was conducted to analyse the incidence of hemodialysis-associated infection (HAI) as well as its associated factors, and to quantify the extent to which the contextual effects of the care facility and regional variations influence the risk of HAI.

A total of 6111 patients with end-stage renal disease who received hemodialysis treatment between 1 October 2015 and 31 March 2016 were identified from the insurance claim database as a population-based, close-cohort retrospective study. Patients were followed for one year from April 1, 2016 to March 31, 2017. A total of 200 HAI cases were observed during the follow-up and 12 patients died within 90 days of the onset of HAI. Increased risks for HAI were associated with moderate (HR 1.73, 95% confidence interval [CI] 1.00–2.98) and severe (HR 1.87, 95% CI 1.11–3.14) comorbid conditions as well as malignancy (HR 1.36, 95% CI 1.00–1.85). Increased risk was also seen among patients who received hemodialysis treatment from clinics (HR 2.49, 95% CI 1.1–5.33). However, these statistics were no longer significant when variations at the level of care facilities were statistically controlled. In univariate analyses, no statistically significant association was observed between 90-day mortality and baseline patients, and the characteristics of the care facility.

The results of the multivariate, multilevel analyses indicated that HAI variations were only significant at the care facility level (σ^2 2.07, 95% CI 1.3–3.2) and were largely explained by the heterogeneity between care facilities. The results of this study highlight the need to look beyond the influence of patient-level characteristics when developing policies that aim at improving the quality of hemodialysis healthcare and service delivery in Japan.

Abbreviations: CI = confidence interval, ESRD = end-stage renal disease, HAI = hemodialysis-associated infection, HR = hazard ratio.

Keywords: care facility, hemodialysis-associated infection, hemodialysis, infection, insurance claim data, multilevel, variations

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Over two million people worldwide are currently receiving dialysis treatment.^[1] In Japan, the number of patients receiving dialysis treatment has increased by more than 300,000 and the number has increased steadily over the last 3 decades.^[2] With an estimate of 1 in every 450 persons in Japan who are affected by chronic kidney disease (CKD), an annual national survey conducted by the Japanese Society for Dialysis Therapy recorded a total of 334,505 patients requiring dialysis treatment at the end of the year 2017, with the prevalence rate of 2640 per million population.

Japan is not the only country with a high number of treated patients with end-stage renal disease (ESRD). According to the 2018 United States Renal Data System (USRDS) report, the reported number was by far the highest in the United States with 709,501 patients treated, followed by Japan and Brazil with an estimated cohort of 180,000 prevalent patients. The prevalence of ESRD in Taiwan was 3392 per million population in 2016, whereas the prevalence of ESRD in the United States was 2,196.^[3]

The Japanese healthcare system recognizes individuals who require constant dialysis care as patients with physical disabilities.^[4,5] Therefore, healthcare services are provided free of charge regardless of medical conditions that a patient may have. A total of 4321 dialysis facilities with 13,358 dialysis units have been established in Japan, particularly for dialysis care. With an annual cost of ¥5 million per patient, approximately ¥1.6 trillion were spent each year – accounting for 4% of total healthcare expenditure in Japan.^[5]

Comparing the statistics obtained from the annual survey, hemodialysis remains the main treatment option for ESRD, despite a steady increase in the number of patients who have opted for hemodiafiltration (HDF) treatment in recent years. Regardless of the type of dialysis treatment received, approximately 25,000 dialysis patients die every year due to various CKD complications.^[6–9] Data compiled from the year 2015 until 2017 suggest that more than 6000 cases of infection have been reported each year. In addition to the statistics, infection has consistently been ranked as the main disease leading to death among dialysis patients – ranked only second after heart failure. By comparison, in 2017 alone, a total of 7484 patients died of health failure, 6556 patients died of infection, and 2802 patients died of malignancy.^[6]

Despite these alarming statistics, only a few studies to date specifically looked at the incidence of hemodialysis-associated infection (HAI) in Japan.^[10–13] Earlier studies were heavily focused on finding clinical and pathological associations, ignoring possible correlations of socio-demographic, organizational and geographical variations, and health outcomes. Furthermore, the populations studied were mostly confined to a single healthcare facility, making the results difficult to generalize to the population level. Multicenter studies, on the other hand, mainly looked at HAI factors using fixed-effect models, ignoring the possible confounding effects of care facilities and geographical variations on HAI incidence and mortality. As a result, motivated by an increasing interest in examining the contextual effects of care facilities and geographical variations in health outcomes, the current study attempted to address the existing gap in literature by analyzing population-based data using a multilevel approach.

Anticipated from this study, the outcome could raise the awareness of the magnitude of the burden of HAI and quantify

the extent to which patients, care facilities and geographical characteristics influence variations in HAI risk and associated mortality. As the understanding increases, the information generated from the study would help in the development of policy and informed clinical practice on the prevention and control of infection.

2. Method

2.1. Study design and patient selection

The current study was designed as a retrospective closed-cohort study. Therefore, all hemodialysis patients receiving care were identified from October 1, 2015 to March 31, 2016. The follow-up covered a one-year period from April 1, 2016 to March 31, 2017. Data for analysis were mainly obtained from data on insurance claims submitted to the Fukuoka Prefecture Association of Latter Stage Elderly Healthcare. In Japan, citizens who are 75 years old or older are automatically eligible for the Latter Stage Elderly Healthcare Insurance scheme.^[3] This insurance scheme is also extended to cover those aged 65 to 74 years old with specific disabilities, including ESRD, which requires long-term care for dialysis. Using the International Classification of Disease, 10th revision (ICD-10) to identify patients with CKD (ICD-10 code: N18.0), and procedure codes 140007710, 140036710, 140051010, 140051110, and 140029850 to confirm hemodialysis maintenance status, a total of 7435 patients were identified.

Patients with a previous history of HAI within 6 months before follow-up ($n=203$) and those younger than 65 years old by 31 March 2016 ($n=385$) were excluded from the study. Patients who had received less than 12 hemodialysis sessions during the 6-month recruitment period were also excluded ($n=648$) as we could not rule out such sessions to address chronic kidney failure or for any other medical reasons. In this study, we also excluded data from one specific hospital as outliers because 11 cases of HAI were identified among 29 patients in the hospital and their inclusion would have a statistical and significant impact on the outcome of the study. Each patient was followed from April 1, 2016 to the date of first HAI, death, emigration from the study area (ie, Fukuoka prefecture) or March 31, 2017, whichever came first.

In Fukuoka prefecture, 11,634 patients are currently receiving hemodialysis treatment, representing 5% of patients with hemodialysis in Japan.^[6] Facilities providing hemodialysis treatment are organized according to ‘Secondary Tier of Medical Care’ (STM) locations. Figure 1 depicts the organization of health care services and facilities throughout Fukuoka prefecture according to 13 ‘secondary tier of medical care’ (STM) locations. Color saturation represents the density of the insured population by March 31, 2017.

Figure 2 provides a diagrammatic presentation of the study design and patient selection process. The study was approved by the Institutional Review Board of Kyushu University (Clinical Bioethics Committee of the Graduate School of Medical Sciences, Kyushu University).

Claim data used in the current study were anonymized. Therefore, the requirement to obtain informed consent was waived in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan [https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf].

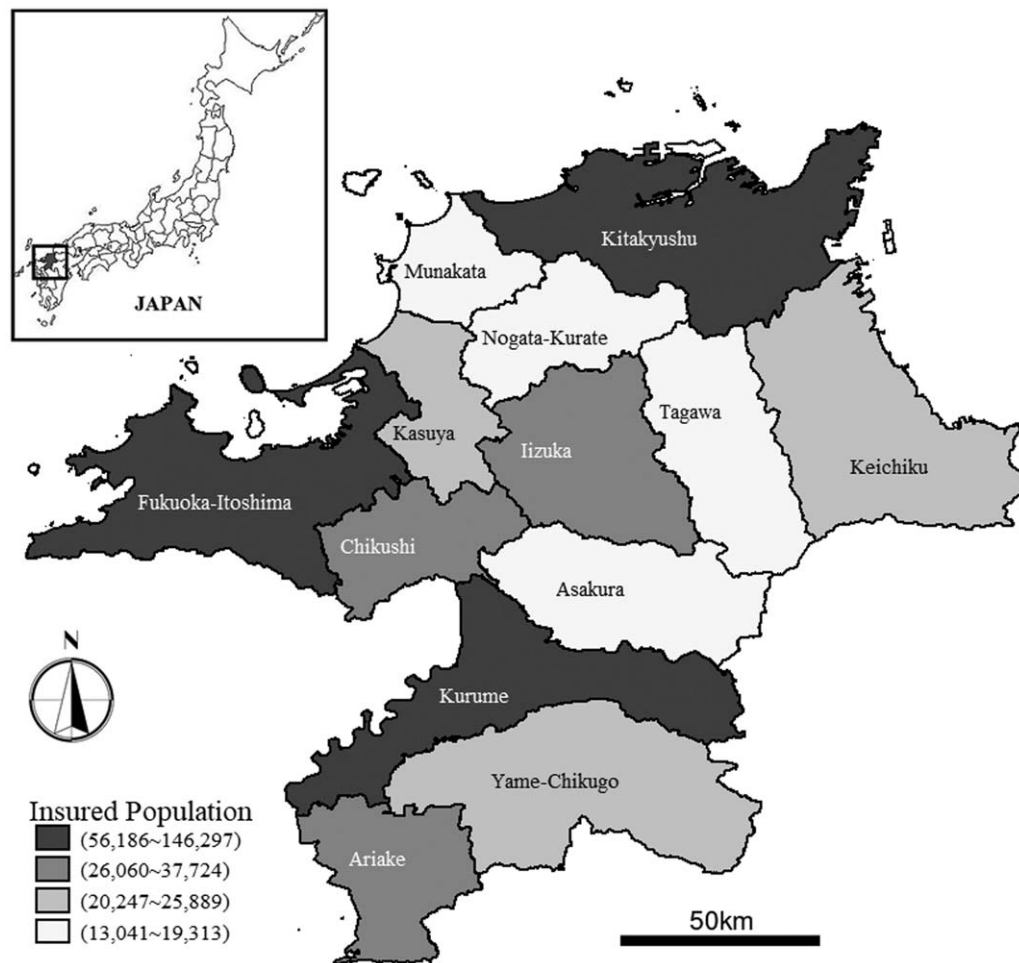


Figure 1. Secondary tier of medical care (STM) in Fukuoka Prefecture. STM refers to the unit of secondary care that a prefecture governs according to Japan Medical Service Law. Small inset shows the location of the study area in Japan. Care facilities located in Fukuoka prefecture are organized according to 13 STMs. By 31 March, 2017, the STM in Fukuoka Prefecture had provided care to a total of 579,419 insured residents.

2.2. Definition of variables

Claim data provided comprehensive information regarding the demographic and medical history of patients. In this study, patients were categorized by sex and 5 age categories: (65–69 years old, 70–74 years old, 75–79 years old, 80–85 years old, and ≥ 85 years old). The co-morbidity status was identified using ICD-10 codes. The status included the presence of diabetes mellitus (E10–E15), hypertensive diseases (I10–I15), nephritis (N10–N16) and malignancy (C00–C97). The comorbidities were assessed according to the Charlson comorbidity index (CCI). This validated instrument assigns weight (1, 3 or 6) to each of 19 major disease categories according to their potential impact on treatment prognosis and mortality.^[14,15] In this study, the weight was modified to exclude chronic kidney disease. The summated weights assigned to each patient were further categorized into 3 groups representing the degree of severity: mild, with *m*-CCI score ≤ 1 ; moderate, with *m*-CCI score of 2–6; severe, with *m*-CCI score ≥ 7 .

Claim data were linked to a unique ID that allowed for the retrieval of information on care facilities. At the regional level, STMs were identified using the codes for care facilities. Likewise, codes were used to link the database of the care facility in

identifying the address, the type of facility and the number of beds in possession. Since hemodialysis patients might receive treatment from multiple facilities, only information on the primary facility that patients are frequently treated would be analyzed.

2.3. Definition of outcome

The primary outcome was the development of HAI after the index date (April 1, 2016). Contextually, HAI was defined as an infection caused by vascular devices, implants, grafts or hemodialysis-related vascular access devices. Diagnosis code 8845140 was used to identify cases. The date of diagnosis was recorded and considered to be the onset of infection. Infection diagnosis was considered valid only when evidence of intravenous antibiotics administration (of vancomycin, ciprofloxacin, amikacin, linezolid, teicoplanin, daptomycin, quinolones, or carbapenems) was available. If a patient had multiple episodes of HAI, only the first episode of HAI would be considered and analyzed.

The secondary outcome was HAI-associated mortality. In this study, we defined any mortality case that occurs within 90 days following the onset of an infection as HAI-associated.

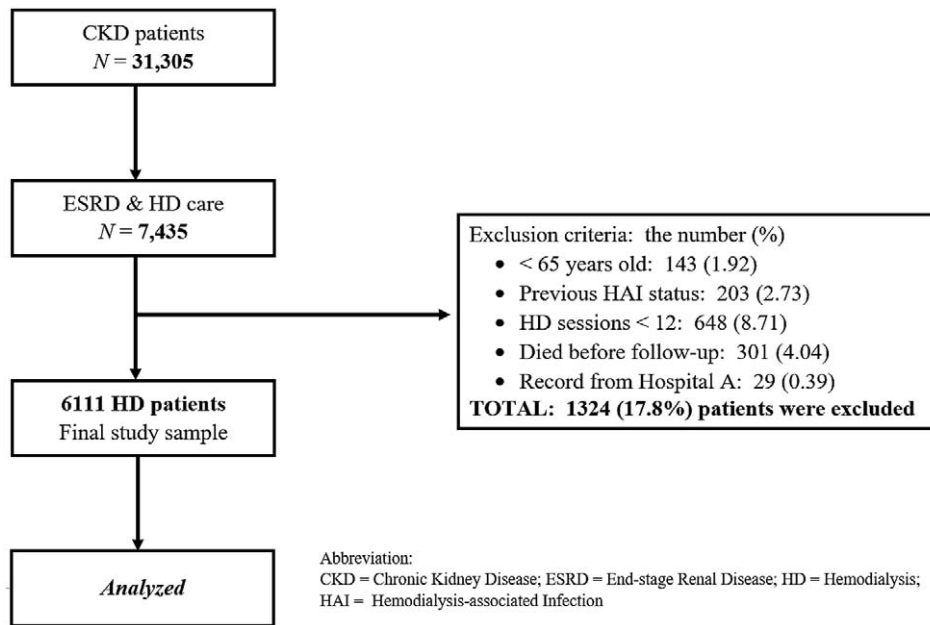


Figure 2. Study design and patient selection. A total of 6111 patients with end-stage renal disease requiring continuous hemodialysis were identified and were found to meet the inclusion criteria. Each patient was followed from 1 April, 2016 to the date of first HAI, death, emigration from the study area, or 31 March, 2017, whichever came first.

2.4. Exposure Variables

The exposure variables were grouped into 2 categories:

1. patient-level characteristics and
2. care facility-level characteristics.

Patient-level characteristics include age categories, sex, and comorbidity status (nephritis, diabetes mellitus, hypertension and malignancy). The severity of comorbid events, which was assessed by a modified version of Charlson Comorbidity Index (*m*-CCI), was also used as an exposure variable. At facility-level, the variables assessed include the ownership of care facility (categorized as either public or private) and the size of facility (categorized based on the number of beds available).

2.5. Statistical analysis

The results of the descriptive analysis are expressed as numerical values and percentages for categorical variables. The comparison of sex, age groups, morbidity status (nephritis, diabetes, hypertension, and malignancy) and *m*-CCI categories by infection and mortality status was based on the log-likelihood Chi-squared test. The incidence of HAI was assessed according to STM by dividing the number of new HAI cases, with the number of hemodialysis populations living in a specific STM. Risk ratio refers to the ratio of HAI cases reported in a specific STM compared to the total number of hemodialysis populations living in Fukuoka prefecture. The 95% confidence interval (CI) values for both the incidence rate and ratio were calculated. A similar method was used to calculate the rate and ratio for STM- mortality cases.

The univariate hazard ratio (HR) with a 95% CI was calculated to estimate the risk of HAI and 90-day mortality using the Cox proportional hazards model with a baseline survival function according to patient-level and facility-level covariates. Likewise, the risk was also estimated by STMs.

Attempts to quantify the magnitude of regional variations and contextual effects of care facility on both HAI risks were made by performing multilevel analyses, with patients nesting in care facilities and nesting within 13 STMs. To analyze survival data using a multilevel approach, the follow-up period was divided into intervals based on unique failure times. Subsequently, data were fitted into Poisson regression with a random intercept. Units contributing to the likelihood of given intervals correspond to the ‘risk set’ of Cox proportional hazards model.^[16,17]

In order to facilitate the assessment of contextual effects, 3-level multilevel models with random intercept were fitted, setting the patient-level characteristics at level 1, care facility-level characteristics as level 2 and STMs at level 3. The first model (null model) did not contain any explanatory variable. This model was fitted to decompose the total variance into its care facility-level and STM-level component. The second model (model 1) expanded the empty model by including only patient-level covariates (sex, age categories, nephritis, diabetes, hypertension, malignancy, and *m*-CCI score categories), whereas the third model (model 2) included only care facility-level covariates (ownership and facility size). A full model (model 3) was fitted to incorporate all explanatory variables (including both patient-level and care facility-level covariates) into the multilevel analysis.

Two important statistical measures of clustering and heterogeneity – Median HR (MHR) and Inter-class Correlation Coefficient (ICC) – were computed. As an analog to Median Odds Ratio (MOR) in multilevel logistic regression analysis, MHR is appropriate for use with survival or time-to-event outcomes when Cox frailty models are fitted to reflect the clustered nature of the data.^[18] MHR refers to the median value of HR between 2 individuals who are randomly chosen from 2 different regions. As such, it normally takes a value greater than 1, where larger values reflect greater variability.^[18] The computed measure of association of Poisson regression is the

incidence rate ratio. However, when the follow-up period was divided based on failure times, the unit contributing to the probability for given intervals would correspond to the 'risk set' of Cox's regression hazards ratio (HR). According to Rabe-Hesketh and Skrondal^[16,17] and Austin et al,^[18] the formula to calculate MHR is as follows:

$$HR_{\text{median}} = \exp\left(\sqrt{2\sigma^2\Phi^{-1}(0.75)}\right) \quad (1)$$

Additionally, the Inter-class Correlation coefficient (ICC) was computed. It is an important measure of the relatedness of clustered data within levels. Simply put, it provides information regarding the proportion of total variance in the outcome attributable to care facility-level and STMs. The formula of exact calculation methods for poisson regression was adopted to calculate the ICC.^[19,20]

$$ICC = \frac{\exp(2\beta X + 2\sigma^2) - \exp(2\beta X + 2\sigma^2)}{\exp(2\beta X + 2\sigma^2) - \exp(2\beta X + 2\sigma^2) + \exp\left(\beta X \frac{\sigma^2}{2}\right)} \quad (2)$$

$$ICC = \frac{\sigma^2(2)}{[\sigma^2(2) + \sigma^2(1)]} \quad (3)$$

Unlike the popular method that assumes an underlying latent response (ie, linear threshold model/latent variable), calculation of the ICC in formula

(2) incorporates any offset variables (ie, βX) into the linear predictor. Apart from technicalities, the ICC value is the ratio between the cluster-level variance [$\sigma^2(2)$] and the total variance [$\sigma^2(2) + \sigma^2(1)$], as simplified in formula (3).

Another important measure calculated was the proportional change in variance (PCV). It estimates the percentage of change in variance explained by the introduction of the additional variable. Considering 2 fitted models: the empty model and model 1 that only include patient-level variables, PCV for model 1 can be calculated using a formula provided by Merlo et al,^[21] where:

$$PCV_1 = \frac{(V_{N-1} - V_{N-2})}{V_{N-1}} \quad (4)$$

V_{N-1} in formula (4) refers to the variance in the empty model, whereas V_{N-2} is the variance in model 1 that includes patient-level variables. The percentage can therefore be concluded as the variance in the empty model attributable to the compositional factors considered with reference to patient-level variables. All reported P -values were 2-tailed, and the level of significance was set at $P < .05$. Stata statistical software released 14 (StataCorp, College Station, TX) was used to perform the analyses.

3. Result

3.1. Descriptive analysis

3.1.1. Baseline patient's characteristics. The demographic and care facility data for 6111 hemodialysis patients were first analyzed using descriptive statistics. Overall, the number of male patients was higher than the number of female patients. The median age was 75 years old (mean 75.1, SD 7.03) and the oldest age reported was 98 years old. Most patients were reported living with hypertensive diseases ($n=5778$; 95%) and about 57% ($n=3463$) of patients were also diabetic. Hemodialysis patients with malignancy accounted for 23% ($n=1419$) of the population studied. The computed m -CCI score indicated that a large number of patients were considered to be living with moderate ($n=2021$, 32.92%) to severe comorbid conditions ($n=3285$, 53.50%). Analysis of care facility data indicated that more patients received treatment from private hemodialysis facilities than from public hospitals. Small hemodialysis clinics (without bed allocation) provided treatment more than half of the total hemodialysis population. Approximately 27% ($n=1656$) of patients receiving treatment in medium-sized facilities with less than 200 beds in hospitals. Table 1 summarizes patients' baseline demographic and care facility characteristics.

3.1.2. HAI and 90-day mortality. During the follow-up period, 200 confirmed HAI cases were reported. Tabulation of statistics

Table 1
Patient demographic and hemodialysis care facility characteristics (N=6111).

	N	%	Total (%)		n	%	Total (%)
Sex				<i>m</i> -CCI score*			
Male	3,733	61.09	100	Mild	826	13.52	100
Female	2,378	38.91		Moderate	2,021	32.92	
Age Group				Severe	3,285	53.50	
65–69	1,641	26.85	100	Ownership			
70–74	1432	23.43		Private	5,799	94.89	100
75–79	1303	21.32		Public	312	5.11	
80–84	1036	16.95		Facility Size			
85 ≥	699	11.44		Clinics (no bed)	3,306	54.10	100
Nephritis				20–99 beds	753	12.32	
No	5889	96.37	100	100–199 beds	903	14.78	
Yes	222	3.63		200–299 beds	422	6.91	
Diabetes				300–399 beds	279	4.57	
No	2648	43.33	100	400 ≥ beds	448	7.33	
Yes	3463	56.67					
Hypertension							
No	333	5.45	100				
Yes	5778	94.55					
Malignancy							
No	4692	76.78	100				
Yes	1419	23.22					

m-CCI = Modified Charlson's Comorbidity Index.

* *m*-CCI categories were based on weight assignment of the following values: 1 ≤: Mild; 2–6: Moderate; 7 ≥: Severe.

showed that HAI cases were common among male patients and patients who belonged to the younger age category (65–69 years old). HAI status among patients with diabetes and hypertension were also reported frequently. The number of patients with HAI increased statistically with an increase in *m*-CCI categories (LR $\chi^2_2=6.34$, $P=.042$). Comparing HAI cases with the ownership of care facility, it was obvious that most cases were reported in private facilities, except for only 5 (5) cases reported in public hospitals. The reported HAI cases also decreased proportionately with an increase in the size of care facility (LR $\chi^2_5=11.60$, $P=.041$). Nonetheless, private hemodialysis clinics contributed most to reported HAI cases, followed by small and medium-sized hospitals.

A total of 613 patients died at the end of the follow-up. Of these, 12 patients had previously been diagnosed with HAI and died within 90 days after the onset of infection, accounting for approximately 6% of mortality cases among HAI-diagnosed patients. Table 2 summarizes the statistics regarding HAI and 90-day mortality cases.

3.1.3. Incidence of HAI. The number of patients with hemodialysis and HAI cases were also analyzed according to STMs. A high number of patients receiving hemodialysis treatment was recorded in three STMs, namely *Kitakyushu*, *Fukuoka-Itoshima* and *Kurume* (Fig. 3). Correspondingly, HAI cases were also reported frequently in these 3 STMs (Fig. 4).

HAI incidence represents 3.3% (95% CI 2.9%–3.7%) of the hemodialysis patient population. Incidents varied statistically across the STMs. A high incidence proportion was observed in these STMs: *Yame-Chikugo* (6.10%, 95% CI 2.9%–9.3%), *Kitakyushu* (4.44%, 95% CI 3.4%–5.5%) and *Fukuoka-Itoshima* (3.73%, 95%CI 2.8%–4.7%). Additionally, when the proportions of HAI reported in each STM were compared to the total incidence, a high (and statistically significant) ratio was observed only in *Yame-Chikugo* (1.86%, 95% CI 1.1%–3.2%) and *Kitakyushu* (1.36%, 95% CI 1.0%–1.8%). On the other hand, the 90-day mortality cases represent 6% (95%CI 2.7%–9.3%) of patients diagnosed with HAI. HAI-mortality cases were reported only in some STMs, with *Kitakyushu* reporting 4 cases,

Table 2
Summary of statistics of HAI (n=200) and 90-day fatality cases following HAI (n=12) according to patient demographic and care facility characteristics.

	HAI		P	Died		P
	No	Yes		No	Yes	
Patient covariates:						
Sex						
Male	3,613	120	.749	112	8	.623
Female	2,298	80		76	4	
Age category						
65 – 69	1,589	52	.592	51	1	.448
70 – 74	1,392	40		37	3	
75 – 79	1,261	42		40	2	
80 – 84	995	41		38	3	
85 ≥	674	25		22	3	
Nephritis						
No	5,697	192	.781	180	12	.315
Yes	214	8		8	0	
Diabetes						
No	2,561	87	.961	82	5	.895
Yes	3,350	113		106	7	
Hypertension						
No	328	5	.038	5	1	.281
Yes	5,583	192		184	11	
Malignancy						
No	4,549	143	.079	135	8	.706
Yes	1,362	57		53	4	
<i>m</i> -CCI						
Mild	810	16	.042	16	0	.347
Moderate	1,939	67		63	4	
Severe	3,162	117		109	8	
Care facility covariates:						
Ownership						
Private	5,604	195	.061	5	0	.429
Public	307	5		183	12	
Facility Size						
Clinic (no bed)	3,179	127	.041	118	9	.358
20–99 beds	730	23		21	2	
100–199 beds	876	27		27	0	
200–299 beds	411	11		10	1	
300–399 beds	274	5		5	0	
400 ≥ beds	441	7		7	0	

HAI=hemodialysis-associated infection, *m*-CCI=modified Charlson's comorbidity index.

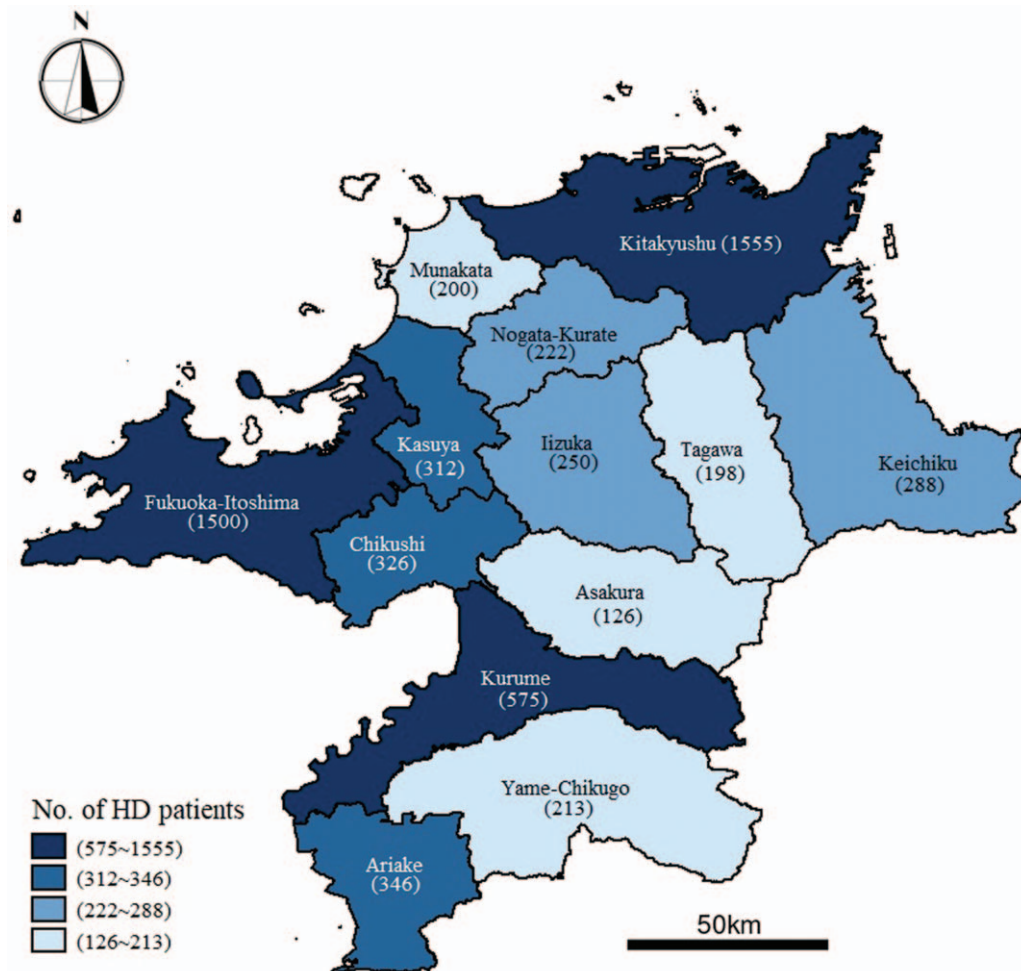


Figure 3. The Number of Hemodialysis Patients according to STM. A total of 6111 hemodialysis patients were treated in 13 STMs. *Kitakyushu* ($n = 1555$), *Fukuoka-Itoshima* ($n = 1500$) and *Kurume* ($n = 575$) reported a high number of treated hemodialysis patients.

followed by *Kasuya* reporting three cases and *Yame-Chikugo* reporting 2 cases. *Fukuoka-Itoshima*, *Kurume* and *Nogata-Kurate* reported one case of mortality each. Detailed result of the analysis is provided in Table 3.

3.1.4. Risk factors for HAI & 90-day mortality. A series of univariate Cox regression analyses were performed to examine the risk factors associated with HAI. The results of the analysis showed an increased risk of HAI in patients with moderate and severe *m*-CCI categories. In particular, patients with severe *m*-CCI were 1.9 times likely to develop HAI when compared to patients with a lower *m*-CCI categorical score (HR 1.86, 95% CI 1.11–3.14, $P = .019$). Similarly, a statistically significant risk of HAI was observed among patients with malignancy (HR 1.36, 95% CI 1.00–1.89, $P = .049$). However, the sex, age and other comorbidity status of the patient (ie, nephritis, diabetes mellitus and hypertension) were not significantly associated with the risk of HAI. Characteristics of the care facilities examined using a similar method indicated that the clinics were statistically and significantly associated with the risk of HAI. The findings suggested that patients receiving treatment in small-sized facilities (clinics) were approximately 2.5 times likely to get HAI (HR 2.493, 95% CI 1.16–5.33, $P = .019$) when large-sized

facility (with 400 beds and more) category was used as a reference.

Separate analyses were also performed on 90-day mortality cases according to patients-baseline characteristics. However, the results failed to detect any statistically significant finding. Similarly, all facility-level covariates did not statistically influence the mortality risk. Table 4 summarizes the results of univariate analyses performed on HAI and mortality risk.

A univariate Cox's regression analysis was also performed on HAI cases according to STMs. When HAI cases in *Fukuoka-Itoshima* were used as a reference, statistically significant HRs were observed only in *Iizuka* (HR 0.207, 95% CI 0.05–0.85, $P = .028$) and *Keichiku* (HR 0.093, 95% CI 0.01–0.67, $P = .019$). Interestingly, patients receiving treatment in these 2 areas were found to have a decreased risk of HAI compared to patients receiving regular hemodialysis treatment in *Fukuoka-Itoshima* (Fig. 5). A similar analysis was conducted in 90-day mortality cases. Only 1 STM was found to be significantly correlated with HAI-mortality. In particular, patients diagnosed with HAI in 90 days of the onset of infection (HR 17.23, 95% CI 1.79–165.74, $P = .014$) compared to HAI-diagnosed patients receiving treatment in *Fukuoka-Itoshima*.

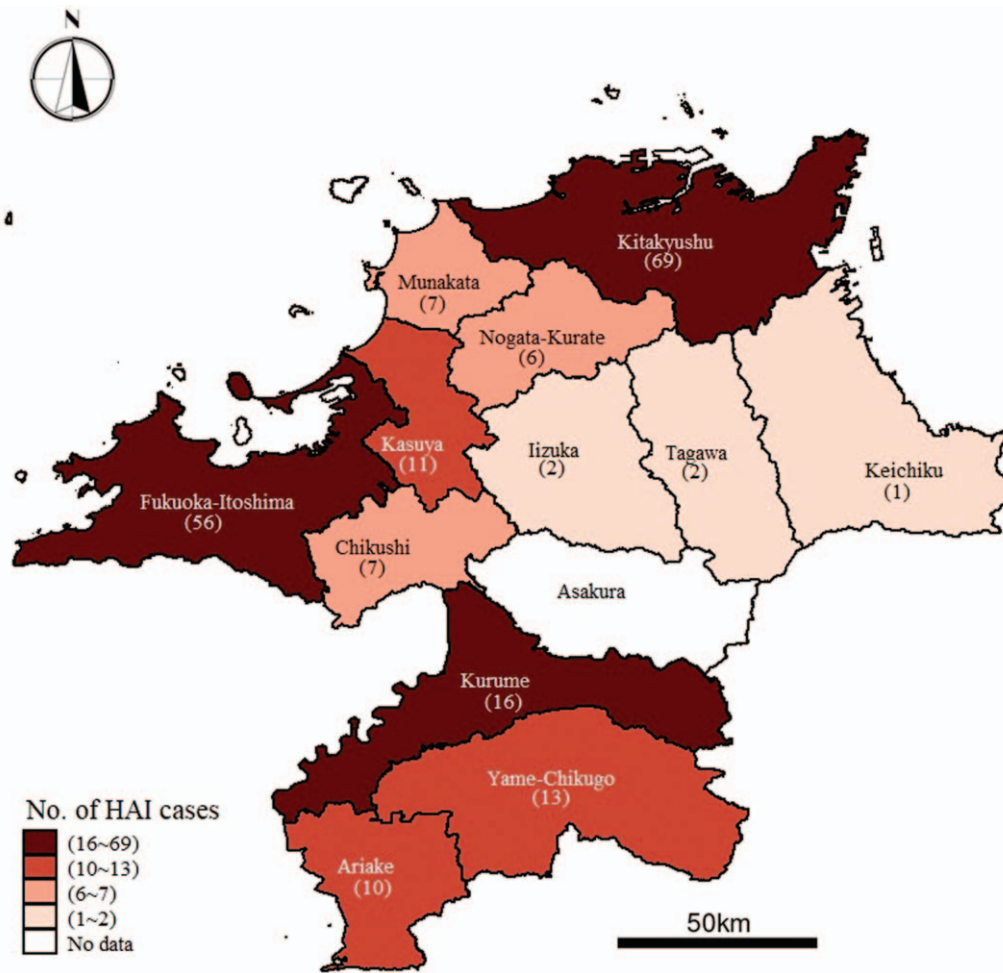


Figure 4. The Reported HAI Cases according to STM. A total of 200 patients with confirmed HAI cases were reported within a one-year follow-up period. HAI cases were frequently reported in *Kitakyushu* (n=69), *Fukuoka-Itoshima* (n=56) and *Kurume* (n=16). The HAI cases reported in these 3 STMs represent 70.5% of the total HAI cases reported in Fukuoka prefecture.

Table 3
Rate (proportion) and the ratio of HAI (n=200) and 90-day mortality (n=12) according to the secondary tier of medical care (STM) of Fukuoka Prefecture.

STM	Patient n	HAI		Rate (%)	95% CI	Ratio	95%CI	Died		Rate (%)	95% CI	Ratio	95% CI
		No	Yes					No	Yes				
Fukuoka-Itoshima	1,500	1,444	56	3.73	(2.8–4.7)	1.14	(0.85–1.53)	55	1	1.79	(-1.7 to 5.3)	0.30	(0.0–2.4)
Kasuya	312	301	11	3.53	(1.5–5.6)	1.08	(0.59–1.96)	8	3	27.2	(0.9–53.6)	4.55	(1.5–13.8)
Munakata	200	193	7	3.50	(0.9–6.1)	1.07	(0.51–2.24)	7	0	–	–	–	–
Chikushi	326	319	7	2.15	(0.6–3.7)	0.66	(0.31–1.38)	7	0	–	–	–	–
Asakura	126	126	0	0.00	–	–	–	0	0	–	–	–	–
Kurume	575	559	16	2.78	(1.4–4.1)	0.85	(0.51–1.40)	15	1	6.25	(-5.6 to 18.1)	1.04	(0.1–7.5)
Yame-Chikugo	213	200	13	6.10	(2.9–9.3)	1.86	(1.08–3.21)	11	2	15.4	(-4.2 to 35.0)	2.56	(0.6–10.3)
Ariake	346	336	10	2.89	(1.1–4.7)	0.88	(0.47–1.65)	10	0	–	–	–	–
Iizuka	250	248	2	0.80	(-0.3 to 1.9)	0.24	(0.06–0.98)	2	0	–	–	–	–
Nogata-Kurate	222	216	6	2.70	(0.6–4.8)	0.83	(0.37–1.84)	5	1	16.7	(-13.2 to 46.5)	2.78	(0.4–18.1)
Tagawa	198	196	2	1.01	(-0.4 to 2.4)	0.31	(0.08–1.23)	2	0	–	–	–	–
Kitakyushu	1,555	1,486	69	4.44	(3.4–5.5)	1.36	(1.04–1.77)	65	4	5.80	(0.3–11.3)	0.97	(0.3–2.9)
Keichiku	288	287	1	0.35	(-0.3 to 1.0)	0.11	(0.01–0.75)	1	0	–	–	–	–
All population (Total)	6,111	5,911	200	3.27	(2.9–3.7)	1.00	–	188	12	6.00	(2.7–9.3)	1.00	–

STM=secondary tier of medical care; HAI=hemodialysis-associated infection; CI=confidence interval.

Table 4
Result of univariate analyses on HAI (n=211), and 90-d mortality following HAI (n=12) according to patient demographic and care facility characteristics.

	HAI			90-day mortality*		
	HR	95% CI	P	HR	95% CI	P
Patient covariate:						
Sex						
Male	(Ref.)			(Ref.)		
Female	1.037	0.78–1.38	.799	0.686	0.21–2.27	.538
Age category						
65 – 69	(Ref.)			(Ref.)		
70 – 74	0.887	0.59–1.34	.568	4.033	0.42–38.8	.227
75 – 79	1.030	0.69–1.55	.887	2.380	0.22–26.2	.479
80 – 84	1.294	0.86–1.95	.217	3.698	0.38–35.6	.257
85 ≥	1.214	0.75–1.96	.425	6.072	0.63–58.4	.118
Nephritis						
No	(Ref.)					
Yes	1.107	0.55–2.25	.778			
Diabetes						
No	(Ref.)			(Ref.)		
Yes	0.996	0.75–1.32	.975	1.068	0.34–3.37	.911
Hypertension						
No	(Ref.)			(Ref.)		
Yes	2.093	0.86–5.09	.103	0.276	0.04–2.14	.217
Malignancy						
No	(Ref.)			(Ref.)		
Yes	1.360	1.00–1.85	.049	1.273	0.38–4.23	.693
m-CCI						
Mild	(Ref.)			(Ref.)		
Moderate	1.728	1.00–2.98	.049			
Severe	1.865	1.11–3.14	.019	1.159	0.35–3.85	.809
Care facility covariate:						
Ownership						
Private	(Ref.)					
Public	0.474	0.19–1.15	.099			
Facility Size						
Clinic (no bed)	2.493	1.16–5.33	.019	0.820	0.10–6.48	.851
20~99 beds	1.965	0.84–4.58	.117	0.948	0.09–10.5	.965
100~199 beds	1.948	0.85–4.47	.116			
200~299 beds	1.687	0.65–4.35	.279	(Ref.)		
300~399 beds	1.142	0.36–3.60	.820			
400 beds	(Ref.)					

HAI = hemodialysis-associated infection, HR = hazard ratio, m-CCI = modified Charlson's comorbidity index, CI = confidence interval.

* Categories without a mortality case were excluded from the estimation.

3.1.5. Multilevel Analysis. To assess the magnitude of regional and care facility variations and contextual effects on HAI risk, multilevel analyses were performed. Survival data were fitted into multilevel Poisson's regression using the *meqrpoisson* stata module. Four models were developed and adapted into multilevel Poisson's regression model in stages.

The empty model (with no explanatory variables) fitted of the whole sample indicated significant variations only at the level of care facility (σ^2 1.93, 95% CI 1.22–3.04). Similarly, random effect estimates suggested a significantly high between-cluster variability and strong healthcare level differences (ICC 0.985). In particular, the MHR calculated at care facility-level indicated an increased risk of up to 3.8 times for HAI development, which was attributed to variations in the care facility-level alone.

Subsequent analyses performed by adding patient-level covariates in Model 1 did not seem to address this variability issue as the change in variance was negligibly small. Nonetheless,

both moderate and severe *m*-CCI categories as well as malignancy status were found to have a statistical effect on HAI risk in univariate analysis, were no longer statistically significant when the clustering effects of care facilities and STM were statistically controlled.

In model 2, approximately 3% of the variability was explained by the inclusion of care facility level covariates (PCV 3.0%), resulting in a slight decrease in both ICC (0.983) and MHR (3.68) values. Results, however, did not show any significant impact of care facility-level covariates on the risk of HAI based on fixed-effect estimation. Combining both patient-level and care facility-level covariates in the final model (model 3), a further reduction of between-cluster variability, albeit small, was observed in ICC (0.982) and MHR (3.65) values, with a small increase in the value of the PCV 4.42%. Examining the results of fixed-effect estimation in the final model, all patient and care facility covariates were found to be unrelated to the risk of HAI.

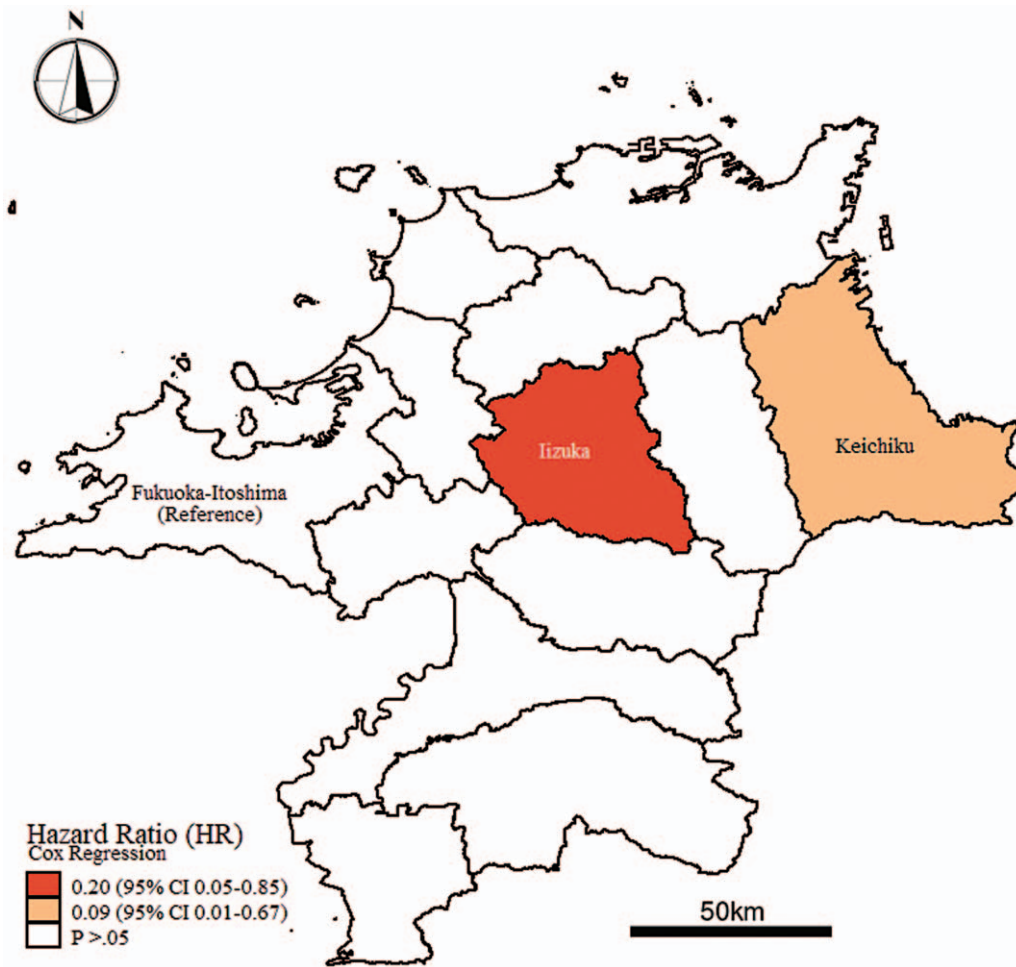


Figure 5. The statistically significant association of HAI risk in two STMs according to the results of Cox's regression analysis. The survival analysis performed using Cox's regression identified a statistically significant decrease of HAI risk among hemodialysis patients treated in *Iizuka* (HR 0.20, 95% CI: 0.05–0.85, $P = .028$) and *Keichiku* (HR 0.09, 95% CI 0.01–0.67, $P = .019$) when compared to patients treated in *Fukuoka-Itoshima*. No statistically significant association between HAI risk and other STMs was observed.

Attempts to analyze HAI-mortality data using a multilevel model was not made due to data requirements and sparsity issues. The results of multilevel analyses detailing fixed-effect and random-effect estimations for HAI are summarized in Table 5.

4. Discussion

The objective of this study was twofold: to examine the incidence of HAI and its associated factors and to quantify the magnitude of care-facility and regional variations in the context of HAI risk. Descriptive analyses performed identified a total of 200 HAI cases and 12 patients died within 90 days following the onset of infection. In general, HAI cases were proportionate to the number of patients receiving hemodialysis treatment in each STM. Cox's regression analyses identified two STMs with reduced risks for HAI, namely *Iizuka* and *Keichiku*. A similar analysis of mortality cases identified by one particular STM was statistically associated with a 17-fold increase in the mortality risk among HAI-diagnosed patients. However, given the small number of reported cases of mortality, this result must be interpreted with caution.

Assessed demographic variables that include sex and age categories were not significantly correlated with the risk of HAI. In the past, the association of age and HAI has been rigorously studied with mixed findings. In particular, 5 out of nine studies found in our literature search did not show any significant association.^[22–25] Likewise, sex was consistently found to be irrelevant to HAI cases.^[22–24,26–28] Comorbidity was often assumed to be an important determinant for HAI. However, the findings of this study were consistent with previous studies that no association was found between HAI and diabetes mellitus,^[22,25,26] hypertension,^[22,25] and nephritis.^[25] Interestingly, a significant increase in HAI risk was seen in this study among patients with malignancy, despite the fact that one study conducted in the past had not seen such association.^[25] The severity of co-morbid conditions, when measured by *m*-CCI, indicated that patients with severe *m*-CCI category had an increased risk of developing HAI. In agreement, one study found a 3-fold increase in the risk of developing a bloodstream infection.^[26]

In this study, an increased risk was observed as much as 2.5 times among patients who received hemodialysis treatment in clinics. One plausible explanation is that these small-sized

Table 5
Results of multivariate (multilevel) analyses examining the contextual effects of HAI.

	Multivariate											
	Null Model			Model 1			Model 2			Model 3 (Full model)		
	AHR	95% CI	P	AHR	95% CI	P	AHR	95% CI	P	AHR	95% CI	P
Patient-level												
Sex												
Male			(Ref.)							(Ref.)		
Female			1.045	0.78–1.40	.768					1.047	0.78–1.41	.762
Age category												
65–69			(Ref.)							(Ref.)		
70–74			0.893	0.59–1.36	.594					0.889	0.58–1.35	.583
75–79			1.041	0.69–1.36	.847					1.035	0.68–1.57	.871
80–84			1.256	0.83–1.91	.286					1.257	0.83–1.91	.283
≥85			1.192	0.73–1.95	.485					1.183	0.72–1.94	.502
Nephritis status												
No			(Ref.)							(Ref.)		
Yes			0.881	0.42–1.83	.734					0.886	0.43–1.84	.746
Diabetes status												
No			(Ref.)							(Ref.)		
Yes			0.918	0.67–1.25	.591					0.926	0.79–1.26	.627
Hypertension status												
No			(Ref.)							(Ref.)		
Yes			1.945	0.79–4.81	.150					1.952	0.79–4.83	.148
Malignancy status												
No			(Ref.)							(Ref.)		
Yes			1.117	0.78–1.61	.551					1.116	0.78–1.60	.553
m-CCI												
Mild			(Ref.)							(Ref.)		
Moderate			1.555	0.89–2.73	.124					1.561	0.89–2.74	.121
Severe			1.745	0.98–3.12	.061					1.759	0.98–3.15	.057
Care facility Level												
Ownership												
Private						(Ref.)				(Ref.)		
Public						0.735	0.19–2.77	.649		0.720	0.19–2.70	.627
Facility size												
0–19 beds						1.863	0.59–5.85	.286		1.915	0.61–5.99	.264
20–99 beds						1.648	0.41–6.59	.480		1.727	0.43–6.88	.439
100–199 beds						1.378	0.39–4.91	.621		1.412	0.39–5.01	.594
200–299 beds						1.935	0.48–7.85	.356		1.905	0.47–7.71	.366
300–399 beds						0.827	0.15–4.60	.828		0.847	0.15–4.69	.849
>400 beds						(Ref.)				(Ref.)		
Intercept	0.000045			0.0000146			0.0000288				0.0000091	
Variation												
Level 3	<0.001			<0.001			<0.001				<0.001	
Level 2	1.9272	1.22–3.04		1.9080	1.21–3.01		1.8693	1.18–2.97		1.8421	1.16–2.93	
ICC												
Level 3	<0.001			<0.001			<0.001				<0.001	
Level 2	0.9846			0.9840			0.9828			0.9819		
PCV (%)												
Level 3	(Ref.)			-			-			-		
Level 2	(Ref.)			0.996			3.004			4.416		
MHR												
Level 3	1.000			1.000			1.000			1.000		
Level 2	3.7591			3.7344			3.6845			3.6497		
Log-Likelihood	-1804.9			-1799.3			-1803.1			-1797.4		
AIC	3623.72			3634.52			3632.23			3642.84		
BIC	3704.90			3843.27			3782.99			3921.18		

HAI = hemodialysis-associated infection, AHR = adjusted hazard ratio, CI = confidence interval, m-CCI = modified Charlson's comorbidity index.

HAI = hemodialysis-associated infection, AHR = adjusted hazards ratio, CI = confidence interval, ICC = inter-class correlation coefficient, PCV = proportion change in variance, MHR = median hazards ratio AIC = akaike information criterion, BIC = Bayesian information criterion.

hemodialysis facilities (ie, clinics) may have limited capacity (eg, dialysis equipment, trained full-time physicians and nurses) to treat large volumes of hemodialysis patients. Descriptive analysis performed earlier also found that approximately 54% of hemodialysis patients received treatment in such facilities. Further reference made to other databases revealed that most clinics employed a very limited number of physicians and most employees often work on a part-time basis.

On the contrary, a statistically significant increase in HAI risk was not observed in the facility categories with 20 to 99 beds and 100 to 199 beds, despite the fact that hemodialysis services were provided for a large number of patients. Compared to clinics, these facilities may have better services to handle large volumes of hemodialysis patients and well-trained health professionals to provide quality hemodialysis treatment. Similar effects could also be observed in medium-sized facilities with 200 to 299 beds. In general, facilities with 200 to 299 beds could be operated either as a general hospital or as a regional medical support hospital (*chiiki iryou shienbyouin*) which acts as a coordinator to support local hospitals and clinics. In reviewing HAI cases occurring in these facilities, one or a maximum of 2 cases were reported in nine out of 18 hospitals. This number is quite small given the fact that these facilities have provided care to a number of hemodialysis patients across Fukuoka prefecture. Fewer cases of HAI were reported in large-sized facilities. This might be due to the fact that some of these facilities are special function hospitals (*tokutei kinou byouin*) that are well-equipped to provide high-quality hemodialysis care and are housed by highly trained medical professionals. Therefore, even with 12 HAI cases reported in facilities with 300 beds and more, a significant increase in risk was not statistically observed in these large-sized facilities.

Relating to HAI cases and facility size, the findings revealed that most HAI cases occurred in facilities with a small number of full-time physicians. As the size of facility increases along with the number of full-time physicians employed, the number of reported HAI cases reduces proportionately. This initial observation, despite not being statistically assessed in this study, might suggest a possible connection between physician density and HAI, and facilities with low physician density might need to employ more full-time physicians to control the risk of HAI.

In the case of HAI-associated mortality, the findings did not show a statistically significant influence on the patient characteristics and facility-level characteristics. This lack of association could be explained by the small number of patients who died after 90 days of infection. Nevertheless, the results were not consistent with one study which reported that gender was associated with post-infection mortality,^[29] and other studies that reported a significant increase in mortality risk in older age categories.^[29,30]

The influence of care facility on the risk of HAI was further enhanced by the results of multilevel analyses where significant variations were observed only at the care facility-level. Demonstrated in the earlier results, the patient covariates did not explain any variability, whereas the random effect estimates of facility-level showed that at least 3% of variability was explained following the inclusion of care facility covariates. Fitting care facility covariates as fixed-effect components, statistics suggested that hemodialysis patients had an MHR of 3.68, indicating a 3.65-fold incidence of HAI with variations or clustering effects at the care-facility level being statistically controlled.

The findings highlight a number of policy implications. To address significant variations in clinical outcomes at the care

facility level, it is important to look beyond individual patient-level characteristics. While there were almost no variations at the regional (STM) level — justifying spatial equity in the distribution and use of health care, significant variations exist at the care facility level. Therefore, the development of specific policies to reduce the incidence of hospital-induced infection and improve the survival of hemodialysis patients is urgently needed to address this issue. A task force that composes of various specialties must be set up and must work together to identify the best strategies for improving the current outcome and the quality of healthcare delivery.

It is important to properly implement infection control and prevention protocols at every health facility providing hemodialysis care. A few collaborative studies have documented the positive impact of such a program on reducing access-related bloodstream infection rates, and hospitalization rates due to bloodstream infection, leading to improved hemodialysis care delivery and overall patient survival outcome.^[31–33] A significant reduction in infection rate could also translate to a substantial amount of potential savings from avoidable medical costs. In a Canadian study, for example, an estimated Can \$14.52 million (US \$10.79 million) in medical cost savings was projected following the implementation of infection control and prevention programs in hemodialysis centers throughout the country.^[34]

Policies aiming at addressing healthcare-associated infection must also cover aspects of workforce management. As heavy reliance on non-permanent healthcare workers was found to have a negative impact on the quality of health care delivery,^[35,36] a review of existing employment practices might be needed. At the care facility level, standardized, evidence-based clinical guidelines must be made available and communicated to all healthcare employees. Constant monitoring of the adherence of these guidelines together with the provision of continuous professional training must be incorporated into the quality improvement initiatives. Evidence demonstrating the effectiveness of introducing evidence-based practices and continuous training for health professionals is readily available.^[37–39] Along with education and training, other strategies such as audit and feedback process of dialysis procedures are significantly proven to reduce the infection rates.^[40]

The study has several limitations. First, the analyzed data were obtained from insurance claim records. The accuracy of statistical analyses, therefore, depends heavily on both accuracy and specificity of coded data processed at the hospital level for reimbursement purposes. Dealing with regard to big data, it is reasonable to assume that some information may be missing and subject to errors and misclassifications. The identification of HAI cases was also based on billing codes, and the confirmation of those cases could not be pathologically confirmed due to the limitation of records. Similarly, the billing codes also did not distinguish between patients who underwent hemodiafiltration procedure. Since hemodiafiltration procedure produces better clinical outcomes,^[41] the inclusion of hemodiafiltration patients may reduce the estimates of HAI risk and mortality, although the evidence suggesting a reduced risk remains inconclusive.^[42]

Despite these limitations, the results of the study provide better population-based estimates because the study used a large sample size. Insurance claim data were obtained from an electronic database with a wide population coverage. Few studies using the same database cited that the penetration rate was as high as 98.6% in April 2015.^[43,44] Nonetheless, the results of multilevel analyses provided meaningful ways to quantify the contextual

and clustering effects of care facilities and STM variations. Researchers who are interested to conduct similar studies in the future are encouraged to adopt similar techniques when performing multilevel analyses, allowing the comparison of results between studies. Researchers may also consider the inclusion of hemodialysis access (eg, arteriovenous graft vs arteriovenous fistula) and the capacity of hemodialysis facility (eg, ratio of trained nursing staff per dialysis machine) as study covariates when assessing risk factors for HAI development and associated mortality.

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