expected mortality calculating from the COPE model. However in Japan, acute care hospitals have had the role of acute care, sub-acute care, and terminal care. Although functional distinction in each hospital has been developed recently, the length of hospital stay was too long (45.6 days) compared with other advanced countries (18–30% in hospital mortality and 12–17 days in hospital stay.[5,18,19] So we considered that the hospital mortality was very high in Japan. However, ICU mortality and the duration of ICU stay in our study were similar to the values of 10–35% and 7 days found by Vincent *et al.*[2] So we believe that it is acceptable for us to compare ICU examination among advanced countries including Japan.

In the point of multicenter study, administrative data was a useful tool due to comparative accessible collection and uniformity of large population database. In Japan, administrative data introduced in 2004 included records of patient information and daily medical care. From these data, the types of all tests, medications and procedures and the use of intensive or special care and nursing services can be itemized on a daily basis. So we considered that administrative data was a valuable instrument for examination between acute organ dysfunction and ICU mortality in severe sepsis in a multicenter observational study. However, in fact, it was indicated that administrative data was inappropriate for the sole means of conducting surveillance for healthcare-associated infections.[20] So it was expected that administrative coding data further reflected the actual condition.

There are several limitations in the present study. First, our data did not include physiological data and severity scores. Therefore, we could not identify clinical indicators for organ dysfunction such as the ratio of arterial oxygen concentration to the fraction of inspired oxygen (P/F ratio), value of liver enzyme, blood urea nitrogen (BUN), and creatinine, and the severity scores such as SOFA, the Acute Physiology and Chronic Health Evaluation (APACHE), the Mortality Prediction Model (MPM), and the Simplified Acute Physiology Score (SAPS). For the adjustment of severity, we used the Critical care Outcome Prediction Equation (COPE) model using administrative data and simple variables. The COPE model is favored because it has an acceptable area under the ROC curve and relatively few variables, and is currently the only model based on administrative data alone.[10] When the physiological data and general scoring systems were used in the analysis, significant indicators for mortality in severe sepsis[11] were demonstrated. However, administrative data was capable on large population, comparable source among institutions, accuracy of clinical information, and relatively small effort in analysis. Second, the administrative data include information on a “calendar day” basis, rather than an hourly basis, and therefore the first ICU day was defined by a calendar day. So the representative data in patient background was including a small error. But our focus was to determine the hazard ratio of organ dysfunction for ICU death, and we considered that this error could not affect our conclusion.

Conclusions

This study examined the hazard ratio of ICU death for organ dysfunctions in patients with severe septic patients using administrative data. The hazard ratio of ICU death in severe septic patients with multiple organ dysfunctions was average 2.2 times higher than severe septic patients with single organ dysfunction. We demonstrated the ability of large administrative datasets to predict ICU mortality by focusing on acute organ dysfunction in severe septic patients.

Footnotes

Source of Support: Nil

Conflict of Interest: None declared.

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Figures and Tables

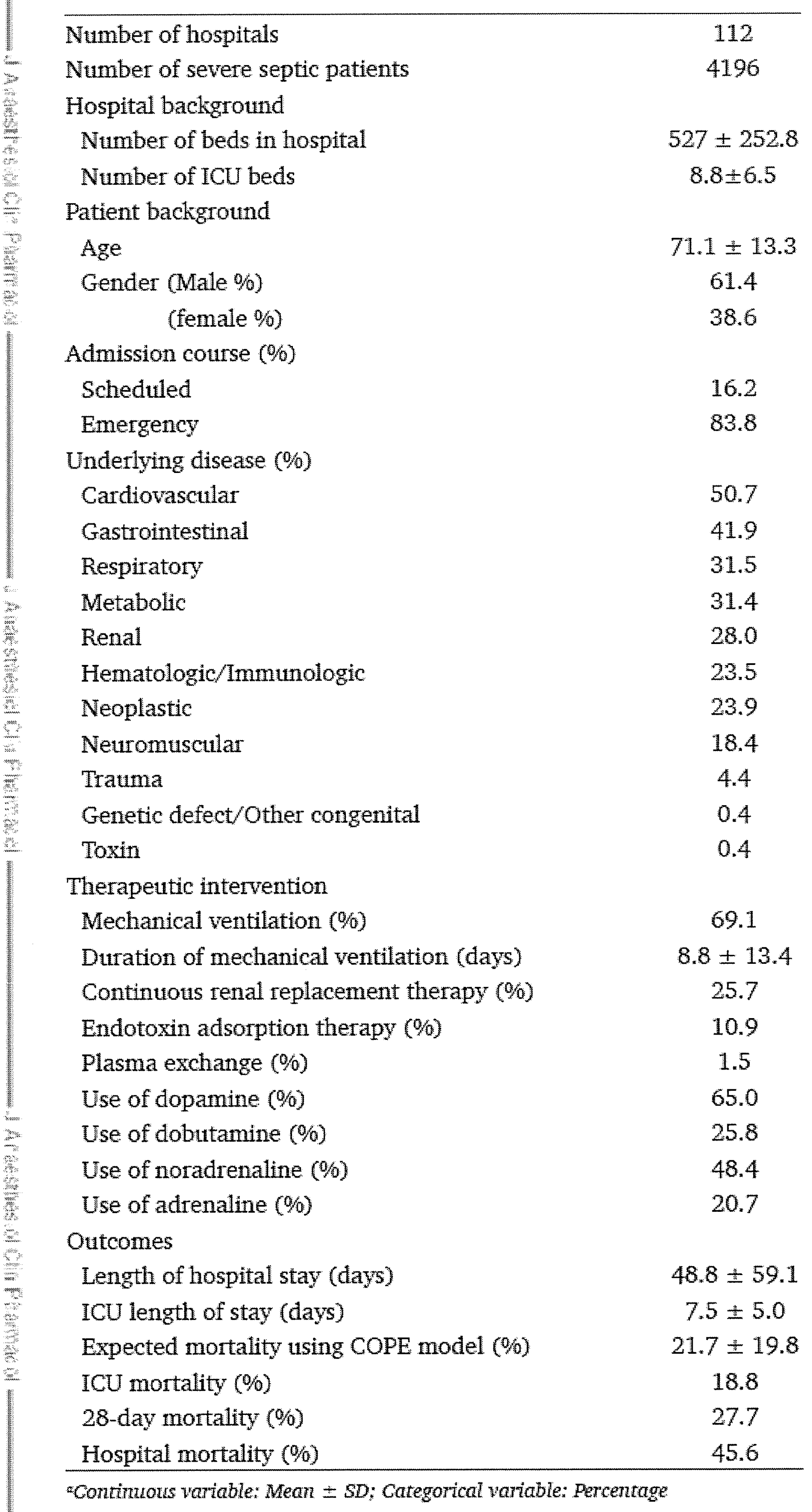
Table 1

Type of organ failure	Description	ICD-9 CM	ICD-10
Respiratory	Acute respiratory failure	518.81	J96.0
	Adult respiratory distress syndrome	518.82	J80
	Respiratory insufficiency	786.09	R06.8
	Respiratory arrest	799.1	R09.2
	Ventilator management	96.7	#
Cardiovascular	Hypotension, postural	458.0	I95.1
	Shock	785.5	E86
	Shock, cardiogenic	785.51	R57.0
	Shock, circulatory or septic	785.59	A41.9
	Hypotension, specified type, not elsewhere classified	458.8	I95.9
Renal	Acute renal failure	584	N17
	Acute glomerulonephritis	580	N00
	Renal shutdown, unspecified	585	N19
	Hemodialysis	39.95	#
Hepatic	Acute hepatic failure or necrosis	570	K72.0
Hematologic	Disseminated intravascular coagulation	286.2	D65
	Thrombocytopenia, primary, secondary, or unspecified	287.3-5	D69
Neurologic	Transient organic psychosis	293	F23
	Anoxic brain injury	348.1	G93.1
	Encephalopathy, acute	348.3	G93.4
	Coma	780.01	R40.2
	Altered consciousness, unspecified	780.09	F51.3

#Specific code for a universal fee schedule in Japan

Translation of ICD-9 CM to ICD-10 code in the study

Table 2



Number of hospitals	112
Number of severe septic patients	4196
Hospital background	
Number of beds in hospital	527 ± 252.8
Number of ICU beds	8.8±6.5
Patient background	
Age	71.1 ± 13.3
Gender (Male %)	61.4
(female %)	38.6
Admission course (%)	
Scheduled	16.2
Emergency	83.8
Underlying disease (%)	
Cardiovascular	50.7
Gastrointestinal	41.9
Respiratory	31.5
Metabolic	31.4
Renal	28.0
Hematologic/Immunologic	23.5
Neoplastic	23.9
Neuromuscular	18.4
Trauma	4.4
Genetic defect/Other congenital	0.4
Toxin	0.4
Therapeutic intervention	
Mechanical ventilation (%)	69.1
Duration of mechanical ventilation (days)	8.8 ± 13.4
Continuous renal replacement therapy (%)	25.7
Endotoxin adsorption therapy (%)	10.9
Plasma exchange (%)	1.5
Use of dopamine (%)	65.0
Use of dobutamine (%)	25.8
Use of noradrenaline (%)	48.4
Use of adrenaline (%)	20.7
Outcomes	
Length of hospital stay (days)	48.8 ± 59.1
ICU length of stay (days)	7.5 ± 5.0
Expected mortality using COPE model (%)	21.7 ± 19.8
ICU mortality (%)	18.8
28-day mortality (%)	27.7
Hospital mortality (%)	45.6

[a] *Continuous variable: Mean ± SD; Categorical variable: Percentage*

Hospital and patient backgrounds in ICU patients with severe sepsis[a]

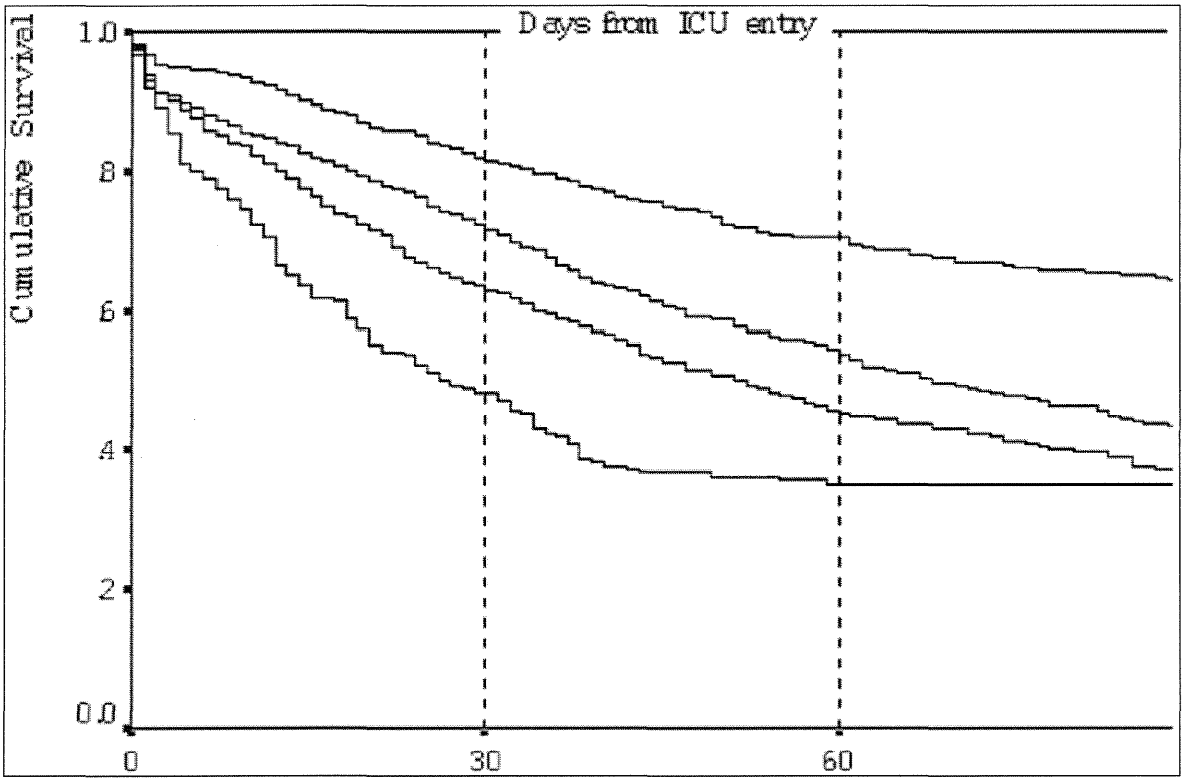
Table 3

Number of organ failure	*n*	Mortality	HR (95% CI) unadjusted	HR (95% CI) adjusted
1	1141	8.9	1	1
2	1582	17.8	1.7 (1.4–1.9)**	1.6 (1.4–1.8)**
3	1077	23.5	2.1 (1.8–2.4)**	2.0 (1.7–2.3)**
≥4	396	38.9	2.8 (2.4–3.3)**	2.7 (2.2–3.2)**

*HR = Hazard ratio; *P < 0.05; **P < 0.01*

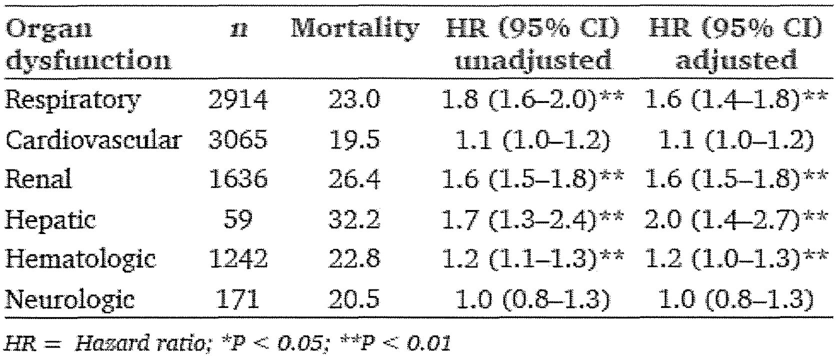
Hazard ratio of multiple organ dysfunctions on ICU mortality

Figure 1



Kaplan– Meier curve of each number of organ dysfunctions: Mortality is calculated from the entry into the ICU. 1; single organ dysfunction, 2; two organ dysfunctions, 3; three organ dysfunctions, ≥4; over four organ dysfunctions

Table 4



Organ dysfunction	*n*	Mortality	HR (95% CI) unadjusted	HR (95% CI) adjusted
Respiratory	2914	23.0	1.8 (1.6–2.0)**	1.6 (1.4–1.8)**
Cardiovascular	3065	19.5	1.1 (1.0–1.2)	1.1 (1.0–1.2)
Renal	1636	26.4	1.6 (1.5–1.8)**	1.6 (1.5–1.8)**
Hepatic	59	32.2	1.7 (1.3–2.4)**	2.0 (1.4–2.7)**
Hematologic	1242	22.8	1.2 (1.1–1.3)**	1.2 (1.0–1.3)**
Neurologic	171	20.5	1.0 (0.8–1.3)	1.0 (0.8–1.3)

*HR = Hazard ratio; *P < 0.05; **P < 0.01*

Hazard ratio of organ dysfunction on ICU mortality

Healthcare-associated infections in acute ischaemic stroke patients from 36 Japanese hospitals: risk-adjusted economic and clinical outcomes

Jason Lee, Yuichi Imanaka*, Miho Sekimoto, Hiroshi Ikai, and Tetsuya Otsubo

Background Healthcare-associated infections are a major cause for worsening in ischaemic stroke patients. In addition to increased morbidity and mortality, healthcare-associated infections also result in a potentially preventable increase in economic costs.

Aims The aim of this study was to identify healthcare-associated infection incidence in ischaemic stroke patients in Japanese hospitals, and to conduct a risk-adjusted analysis of the associated economic and clinical outcomes.

Methods Healthcare-associated infections were identified in 36 Japanese hospitals using an administrative database. Identification was carried out using a combination of International Classification of Diseases-10 codes and antibiotic utilisation patterns that indicated the presence of an infection. Risk-adjusted hospital charges and length of stay were calculated using multiple linear regression analyses correcting for patient and hospital factors. A logistic regression model was used to analyse the association between healthcare-associated infection infection and mortality.

Results There was an overall healthcare-associated infection incidence of 16·4 %, with an interhospital range of 4·7–28·3%. After risk-adjustment, infected cases paid an additional US$3 067 per admission (interhospital range US$434–US$7 151) and were hospitalised for an additional 16·3-days (interhospital range: 5·1–25·1-days) when compared with uninfected patients. Healthcare-associated infections also had a strongly significant association with increased mortality (odds ratio = 23·2, 95% confidence intervals: 12·5–43·2).

Conclusions We observed a wide range of healthcare-associated infection incidence between the hospitals. Healthcare-associated infections were found to be significantly associated with increased hospital charges, length of stay, and mortality. Furthermore, the use of risk-adjusted multi-institutional comparisons allowed us to analyse individual performance levels in both infection and cost control.

Key words: cost factors, cross infections, health economics, ischaemic stroke, Japan, mortality

Introduction

Healthcare-associated infections (HAIs) have been identified previously as having a significant impact in the worsening of ischaemic stroke patients (1–4). In addition to increased morbidity and mortality, the resulting extension in hospital stay results in increased costs to patients and third party payers, as well as a reduction in potential bed-space for healthcare providers.

The HAIs have been estimated to develop in over one-third of patients with acute stroke, with the most common infections being lung infections and urinary tract infections (1, 2). Studies have reported HAI incidences of 41·5% (5), stroke-associated pneumonia incidences ranging from 10% to 30·9% (3, 4, 6–8), and even incidences of significant bacteriuria alone reaching 39·1% (9). Reported extensions in length of hospital stay ranged from six-days (6) to 23-days (7). Risk factors found to be associated with HAIs in stroke patients have include mechanical ventilation, dysphagia, age, parenteral nutrition, poststroke disability, and urinary catheterisation (6, 10, 11). In addition, the Barthel index has been shown to be significantly associated with infections in acute ischaemic stroke patients (12, 13).

Quantifying the increases in hospital charges and length of stay (LOS) associated with HAIs would be useful for healthcare providers and third party payers when considering the cost-effectiveness of interventions aimed at reducing HAIs. While some studies have attempted to quantify the outcomes

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associated with HAIs in stroke patients at the hospital level (6, 7), a multi-institutional analysis that takes into account patient and hospital-related variations would allow for a more meaningful interpretation of each hospital's results.

There are currently no studies to our knowledge that have analysed HAI incidence in stroke patients in Japanese hospitals, and no studies that have attempted to quantify the economic impact and mortality associated with HAIs at a multiinstitutional level.

Aims

The objective of this study was to utilise an administrative database from multiple Japanese hospitals in order to identify HAI incidence in patients admitted for acute ischaemic stroke, and to quantify risk-adjusted economic and clinical outcomes associated with HAIs.

Methods

Hospital and patient selection

The original sample population consisted of 16 886 ischaemic stroke patients admitted during the period of April 1998 to April 2008 into 40 general hospitals (*designated H1–H40*) enrolled in the Quality Indicator/Improvement Project (QIP), a database of Japanese hospitals that consists of clinical and claims data. Hospitals in the QIP voluntarily join the project and provide claims and administrative data in standardised formats for analysis with the objective of improving the quality and efficiency of healthcare provision. The hospitals included in this study were drawn from this database and represent a variety of public and private, teaching, and non-teaching hospitals with different casemixes and specialties.

Clinical diagnoses were identified using International Classification of Diseases (ICD)-10 codes. Preexisting comorbidity conditions were analysed using the Charlson comorbidity index (Dartmouth–Manitoba version) (14, 15).

Patients who had infections occurring within 48 h were identified as having community-acquired infections and thus excluded from this study. Other exclusion criteria included minors (below 20-years), and cases with missing data in charge information, age, and Japan Coma Scale (JCS) (16) score. For the linear regression models used for hospital charges and LOS, and the logistic regression model used for mortality, cases with standardised residuals > 3 standard deviations from the mean were considered outliers and excluded from analysis. In the regression models for hospital charges and LOS, patients who died during the hospitalisation period were also excluded.

The JCS is the most widely used clinical tool for evaluating consciousness level in Japanese emergency care, and consists of a scale categorised into four levels: (i) alert; (ii) JCS levels 1–3 (disoriented: awake without stimulation); (iii) JCS levels 10–30 (somnolent: arousable only in the presence of stimulation); and (iv) JCS levels 100–300 (comatose: unarousable despite stimulation) (17).

HAI identification

The HAIs were first identified using hospital-reported ICD-10 codes adapted from the Pennsylvania Health Care Cost Containment Council (PHC4) (18). However, previous studies have shown that the use of ICD codes alone is insufficient for HAI identification (18, 19). Therefore, HAIs were also identified through the use of antibiotic utilisation patterns obtained from daily drug claims data, based on a technique adapted from our previous study (20).

Infections were identified where antibiotic utilisation did not conform to surgical prophylaxis patterns in patients who had surgeries performed. Patients were identified as having HAIs if, in addition to reported ICD codes, they fell into any of the following categories: (1) antibiotic utilisation episodes with durations of four or more days that did not overlap a day in which surgery requiring prophylaxis was performed; (2) three or more antibiotic types used within a single episode of antibiotic utilisation; (3) antibiotic types changed or a second antibiotic type added midway during an antibiotic utilisation episode; (4) prophylactic antibiotic utilisation episodes of five or more days in which the start of the episode corresponds to a day where surgery was performed.

Clinical and economic outcome indicators

Total hospital charges and LOS (days) were used as indicators for economic outcome, while mortality was used as the clinical outcome measure.

Statistical analysis

Analyses were performed using spss version II 11.0.1J. Significance for *P*-values was set at $P < 0{\cdot}05$ (two tailed).

Risk adjustment

Total hospital charges and LOS were natural logarithmically transformed before used as dependent variables in multiple linear regression analysis (stepwise). Two models were developed for each dependent variable; one in which hospital stratification was included in the independent variables, and another in which hospital stratification was excluded. The former was used to calculate overall risk-adjusted hospital charges and LOS after taking hospital variations into account. The latter model was used in the calculation of hospital-level risk-adjusted hospital charges and LOS, which enabled inter-hospital comparisons.

The models for hospital charges included the following independent variables: age, gender, Barthel index, atherothrombotic stroke, cardioembolic stroke; Charlson score, LOS, surgeries performed, central venous catheter (CVC) use, mechanical ventilation, dysphagia, ICU stay, and JCS score upon admission. The models for LOS included the following independent variables: age, gender, Barthel index, atherothrombotic stroke, cardioembolic stroke; Charlson score, surgeries performed, CVC use, mechanical ventilation, dysphagia, ICU stay, and JCS score upon admission. The first model for each dependent variable also included hospital stratification while the second model did not. Apart from atherothrombotic and cardioembolic strokes, patients with other types of stroke were used as a reference for the regression models. The Barthel index used by the hospitals in this sample was the 20-point Collin scoring version (21).

Exponentials of the predicted values from the regression models were calculated in order to obtain expected values in units of Japanese Yen and days, and Duan's smearing coefficient (22, 23) was applied to correct for retransformation bias. Risk adjustment was then conducted by dividing each hospital's mean observed value by the mean expected value, and the result was multiplied by the mean value of the entire dataset. Final estimates of hospital charges were adjusted for inflation using the Japanese consumer price index (adjusting all values to the 2008 yen value) and then converted to US dollars using Purchasing Power Parities (JPN 100 Yen = US$0·80 (21)).

Mortality was used as the dependent variable in the logistic regression model, and adjusted with the following independent variables: HAI status, age, gender, Barthel index, atherothrombotic stroke, cardioembolic stroke; Charlson score, surgeries performed, CVC use, mechanical ventilation, dysphagia, ICU stay, LOS, JCS score upon admission, and hospital stratification. Calibration was evaluated with a Hosmer–Lemeshow statistical analysis (24), while discrimination was evaluated with a receiver operating characteristic (ROC) curve.

Results

Patient and hospital characteristics

After excluding cases that fulfilled the aforementioned exclusion criteria, our final sample for analysis consisted of 8 861 patients from 36 hospitals, with four hospitals excluded due to a lack of patients.

General characteristics of the patients in our sample are shown in Table 1. Elderly patients were heavily represented in the study population, with almost half of the patients older than 75-years of age. There were more men than women at 58·3% vs. 41·7%. Of the patients in our sample, 68% were originally admitted to either neurosurgery or neurology departments, 17·3% were admitted to internal medicine departments, and the remainder in various other departments. The Barthel index showed that upon admission, 20·1% of the patients had no form of disabilities, while 43·3% had relatively severe disabilities. Over 21% of the patients were classified as having an atherothrombotic stroke 10·3% of the patients had a cardioembolic stroke, and 68·5% had strokes that did not fall into either of the above two categories. Almost 70% of the patients were completely lucid upon admission according to the JCS, and more than half were admitted without existing comorbidities. Unadjusted mean hospital charges were US$6 471, with a mean LOS of 21·97-days.

Table 1 Patient characteristics and pre-risk-adjusted total hospital charges and length of stay (N = 8 861)

	N	%
Age		
75-years and below	4 470	50·4
Above 75-years	4 391	49·6
Gender		
Male	5 170	58·3
Barthel index		
0	1 778	20·1
1–10	2 002	22·6
11–15	1 241	14·0
16–20	3 840	43·3
Type of stroke		
Atherothrombotic	1 881	21·2
Embolic	916	10·3
Others	6 064	68·5
Japan Coma Scale		
0	6 022	68·0
1–3	2 102	23·7
10–30	520	5·9
100–300	217	2·4
Charlson score		
0	4 711	53·2
≥1	4 150	46·8
Surgery performed	270	3·0
CVC utilization	189	2·1
Mechanical ventilation	105	1·2
Dysphagia	555	6·3
ICU stay	244	2·8
Total hospital charges (mean)		US$6 471
Length of stay (mean)		21·97-days
Mortality	257	2·9

CVC, central venous catheter.

The hospitals in our sample consisted of general hospitals providing a range of services not limited to stroke care. Of the 36 hospitals, 27 were privately owned and nine were publicly owned. Twenty-nine of the hospitals were teaching hospitals, while seven of the hospitals were not. The hospitals had a mean of 435 beds, with an interhospital range of 98–1 125 beds. More than half of the hospitals had ICUs, but only two of the hospitals had dedicated stroke care units. There was a mean of 98 doctors (range: 9–392) and 337 nurses (range: 45–1 138) in each hospital. Fourteen of the 36 hospitals in our sample had both neurosurgery and neurology departments, 15 hospitals had only one of the two departments, and seven hospitals had neither (in which case stroke patients were warded in internal medicine or other departments).

HAI incidence

The overall HAI incidence in our sample was 16·4%. As seen in Fig. 1, there was a large variation of HAI incidence at the

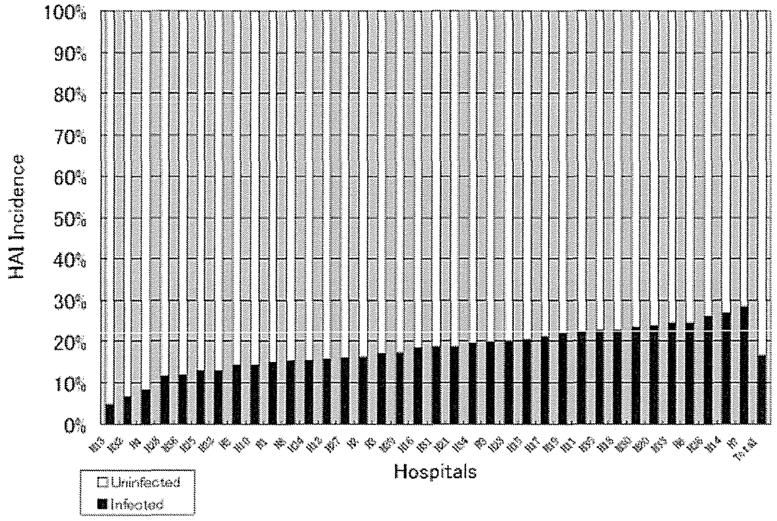

Fig. 1. Healthcare-associated infection (HAI) incidence at hospital level and in total.

hospital level, with a range from 4·7% to 28·3%. Seventeen of the 36 hospitals had HAI incidence proportions lower than the overall mean.

Risk-adjusted hospital charges and LOS

The results of the linear regression analyses are shown in Table 2. The first model for both hospital charges and LOS (as dependent variables) included hospital stratification, while the second model excluded hospitals as independent variables. Tests for multicollinearity were performed and all variance inflation factors values were found to be below 2·1 (data not shown).

With regard to hospital charges, the first model had an R^2 value of 0·764 ($P<0{\cdot}001$). Independent variables which showed significant association with hospital charges included age, gender, Barthel index, both types of stroke, Charlson score, LOS, surgery, CVC use, mechanical ventilation, dysphagia, ICU stay, all JCS levels, and 25 hospitals. Length of stay showed the strongest association with increased hospital charges ($\beta = 0{\cdot}781$; $P<0{\cdot}001$). All independent variables in the second model ($R^2 = 0{\cdot}711$; $P<0{\cdot}001$) except for CVC use and JCS levels 100–300 showed significant associations with hospital charges.

The first model for LOS ($R^2 = 0{\cdot}308$; $P<0{\cdot}001$) showed that gender, Barthel index, both types of stroke, Charlson score, surgery, mechanical ventilation, dysphagia, ICU stay, all JCS levels, and 24 hospitals had significant associations with increased LOS. Mechanical ventilation, CVC use and JCS levels 100–300 had the highest standardised coefficients among the independent variables. In the second model, ($R^2 = 0{\cdot}222$; $P<0{\cdot}001$), gender, atherothrombotic stroke, CVC use, and mechanical ventilation showed no significant association with increased LOS.

After conducting risk-adjustment based on data from the first model, the overall mean hospital charges were US$6 009 for uninfected patients and US$9 076 for infected patients, resulting in an additional US$3 067 associated with HAIs. Length of stay after risk-adjustment was 19·0-days in uninfected patients and 35·3-days in infected patients, with an additional 16·3-day increase associated with HAIs. Mean hospital charges per day for uninfected and infected patients were thus US$317 and US$257, respectively.

Using data from the second model for both hospital charges and LOS, risk-adjustment was calculated at the hospital level. Figure 2 shows box-plot graphs of the risk-adjusted hospital charges and LOS for uninfected patients and infected patients by hospital.

After risk-adjustment, there was a hospital-level range of US$3 824 (Hospital H6) to US$7 710 (Hospital H28) for hospital charges in uninfected patients. For infected patients, this range was US$5 438 (Hospital H6) and US$14 505 (Hospital H24). Therefore, additional charges associated with HAIs ranged from US$434 to as high as US$7 151 at the hospital level. The 25th, 50th, and 75th percentile hospital charges for the uninfected patients were US$5 305, US$5 764, and US$6 232, respectively. The 25th, 50th, and 75th percentile hospital charges for infected patients were US$6 379, US$7 983, and US$9 865, respectively. Hospitals H6 and H28 were identified as outliers with inordinately low and high hospital charges, respectively, for uninfected patients.

At the hospital level, the minimum risk-adjusted LOS for uninfected patients was 12·3-days (Hospital H34) and the maximum LOS was 27·2-days (Hospital H1). The 25th, 50th, and 75th percentiles for the uninfected patients were 15·9, 19·0, and 21·4-days, respectively. For patients who had an HAI, the risk-adjusted LOS ranged from 21·8-days (Hospital H34) to 47·9-days (Hospital H8). The 25th, 50th, and 75th

Table 2 Results of multiple linear regression models with hospital charges and length of stay as dependent variables, and a logistic regression model using mortality as the dependent variable

Independent variables	Dependent variable: Ln (hospital charges)				Independent variables	Dependent variable: Ln (length of stay)				Independent variable	Dependent variable: mortality		
											Hosmer–Lemeshow Statistic		5·6 ($P = 0·690$)
	R^2	0·764***	R^2	0·711***		R^2	0·308***	R^2	0·222***		AUROC		0·995
	β	SE	β	SE		β	SE	β	SE		*B*	SE	Exp(*B*)
Constant		0·018***		0·015***	Constant		0·031***		0·025***	Constant	−7·785	0·787	0·000***
Age >75-years	−0·049	0·007***	−0·050	0·007***	Age >75-years	0·015	0·012	0·037	0·013**	Infection	3·145	0·316	23·228***
Gender	−0·023	0·006***	−0·019	0·007**	Gender	0·020	0·012*	0·014	0·012	Age > 75-years	1·620	0·345	5·051***
Barthel index	−0·070	0·001***	−0·111	0·001***	Barthel index	−0·291	0·001***	−0·252	0·001***	Gender	0·087	0·258	1·091
Atherothrombotic stroke	0·049	0·009***	0·028	0·008***	Atherothrombotic stroke	0·039	0·017**	−0·003	0·015	Barthel index	−0·025	0·023	0·975
Cardioembolic stroke	0·063	0·011***	0·070	0·011***	Cardioembolic stroke	0·060	0·020***	0·020	0·020*	Atherothrombotic stroke	−0·342	0·470	0·710
Charlson score	0·058	0·003***	0·088	0·003***	Charlson score	0·100	0·006***	0·094	0·006***	Cerebroembolic stroke	0·464	0·347	1·591
Length of stay	0·781	0·000***	0·748	0·000***	Surgery	0·096	0·034***	0·099	0·035***	Charlson score	0·419	0·114	1·520***
Surgery	0·030	0·019***	0·026	0·021***	CVC use	0·011	0·054	0·026	0·057	Length of stay	−0·063	0·008	0·939***
CVC use	0·021	0·029**	0·006	0·032	Mechanical ventilation	−0·022	0·055*	−0·012	0·058	Surgery	−2·572	0·529	0·076***
Mechanical ventilation	0·035	0·029***	0·033	0·032***	Dysphagia	0·106	0·025***	0·079	0·025***	CVC use	6·349	0·438	572·181***
Dysphagia	0·035	0·014***	0·053	0·014***	ICU stay	0·086	0·036***	0·051	0·036***	Mechanical ventilation	7·958	0·581	2857·695***
ICU stay	0·076	0·020***	0·066	0·020***	JCS Level 1–3 (Grade I)	0·111	0·017***	0·104	0·017***	Dysphagia	−0·640	0·490	0·527
JCS level 1–3 (Grade I)	0·033	0·009***	0·048	0·010***	JCS Level 10–30 (Grade II)	0·129	0·020***	0·137	0·020***	ICU stay	2·820	0·629	16·773***
JCS level 10–30 (Grade II)	0·017	0·011*	0·028	0·011***	JCS Level 100–300 (Grade III)	0·046	0·041***	0·050	0·043***	JCS level 1–3 (Grade I)	1·082	0·483	2·949*
JCS level 100–300 (Grade III)	−0·013	0·021*	−0·011	0·023	H1	0·121	0·035***			JCS level 10–30 (Grade II)	2·421	0·408	11·257***
H1	−0·024	0·019***			H2	0·072	0·045***			JCS level 100–300 (Grade III)	6·021	0·523	412·089***
H2	−0·016	0·024**			H3	0·062	0·050***			H1	1·166	0·624	3·208
H3	0·005	0·028			H4	0·038	0·041***			H2	0·085	0·758	1·089
H4	−0·042	0·021***			H5	0·074	0·039***			H3	−3·833	3·526	0·022
H5	−0·083	0·021***			H6	0·017	0·087			H4	−2·402	0·942	0·091
H6	0·011	0·049*			H7	0·013	0·041			H5	−0·300	0·690	0·741
H7	0·040	0·023***			H8	0·034	0·059**			H6	−16·585	5653·229	0·000
H8	−0·023	0·031***			H9	0·030	0·045**			H7	−0·021	0·757	0·979
H9	−0·007	0·025			H10	0·025	0·076**			H8	0·698	0·615	2·009
H10	−0·002	0·037			H11	0·013	0·081			H9	−0·805	1·164	0·447

H11	−0·016	0·044**	H12	0·056	0·048***	H10	0·674	0·759	1·962
H12	−0·012	0·026*	H13	0·010	0·083	H11	1·433	1·383	4·193
H13	−0·041	0·045***	H14	0·030	0·035**	H12	0·205	3·862	1·228
H14	−0·003	0·019	H15	0·013	0·075	H13	−1·707	1·038	0·181
H15	−0·021	0·041***	H16	−0·006	0·126	H14	−5·484	2·619	0·004*
H16	−0·008	0·069	H17	0·009	0·082	H15	−4·454	1·697	0·012**
H17	−0·003	0·042	H18	−0·038	0·081***	H16	−14·915	9644·678	0·000
H18	0·010	0·045	H19	0·058	0·032***	H17	0·486	1·380	1·625
H19	0·022	0·017**	H20	−0·059	0·034***	H18	−2·686	1·420	0·068
H20	−0·079	0·019***	H21	0·018	0·044	H19	1·137	0·529	3·118*
H21	0·018	0·024**	H22	−0·063	0·035***	H20	−2·344	1·344	0·096
H22	0·004	0·019	H23	−0·020	0·046*	H21	−4·978	0·980	0·007***
H23	−0·027	0·025***	H24	0·043	0·045***	H22	−1·622	1·281	0·197
H24	−0·006	0·024	H25	0·023	0·043*	H23	0·288	0·773	1·334
H25	−0·020	0·024**	H26	0·043	0·044***	H24	−4·834	1·240	0·008***
H26	−0·025	0·024***	H27	−0·005	0·047	H25	−2·156	0·951	0·116*
H27	0·010	0·027	H28	−0·096	0·029***	H26	−0·547	1·213	0·579
H28	0·044	0·016***	H29	−0·110	0·025***	H27	−2·819	0·712	0·060***
H29	0·130	0·014***	H30	−0·061	0·030***	H28	−1·058	0·510	0·347*
H30	−0·021	0·017**	H31	0·004	0·032	H29	−13·243	5·127	0·000**
H31	0·059	0·017***	H32	−0·026	0·043**	H30	−3·545	0·766	0·029***
H32	0·014	0·024*	H33	0·005	0·045	H31	−5·162	1·721	0·006**
H33	0·060	0·024***	H34	−0·084	0·034***	H32	−1·827	1·304	0·161
H34	−0·065	0·019***	H35	0·023	0·052*	H33	−1·575	0·926	0·207
H35	−0·021	0·027				H34	−1·329	0·933	0·265

*Significance at $P<0.05$;**Significance at $P<0.01$;***Significance at $P<0.001$.Two multiple linear regression models for each dependent variable are shown, in which the first model included hospital stratification and the second model did not.AUROC, area under receiver operating characteristic curve; CVC, central venous catheter; JCS, Japan Coma Scale.

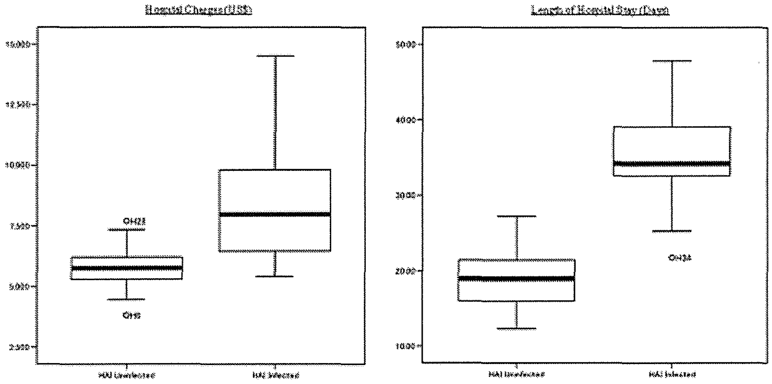

Fig. 2. Box-plot graphs of risk-adjusted hospital charges per admission (in US$) and length of stay (in days) for infected and uninfected patients at the hospital level. HAI, healthcare-associated infection.

percentiles for infected patients were 32·6, 34·2, and 41·7-days, respectively. Additional LOS associated with HAIs ranged from 5·1-days (Hospital H4) to 25·1-days (Hospital H8). Hospital H34 was identified as an outlier with exceptionally low LOS in infected patients.

Risk-adjusted mortality

After adjusting for patient and hospital variations, the adjusted odds ratio for the association of HAIs and mortality was 23·2 ($P<0{\cdot}001$; 95% confidence interval: 12·5–43·2). The area under the ROC was calculated to be 0·995, while the Hosmer–Lemeshow statistic had a χ^2-value of 5·6 ($P=0{\cdot}69$). Healthcare-associated infection status, age, Charlson score, LOS, surgery, CVC use, mechanical ventilation, ICU stay, JCS levels 1–3, and JCS levels 10–30 were all positively associated with increased mortality.

Discussion

In this study, we identified HAI incidence in ischaemic stroke patients from 36 Japanese hospitals, and conducted a multi-institutional analysis of the risk-adjusted economic and clinical outcomes associated with HAIs. Our data showed that 68% of the patients were alert upon admission, which was slightly less than the 74·8% reported in 2004 by Kimura *et al.* (25).

The HAI incidence observed in our study (16·4%; range: 4·7–28·3%) was fairly similar to infection rates reported in other studies (3–9). We also found significant increases in both overall hospital charges and LOS associated with HAIs. In order to verify the accuracy of our HAI identification method (20), we conducted a validation study using gastrectomy patients. Healthcare-associated infections identified by our method were compared with those identified by chart review. At the current sample size ($n=425$), there is an 89% level of agreement of between the two methods, and Cohen's κ coefficient is 0·73, which is generally considered as having a 'substantial agreement' (26). Sensitivity and specificity are 0·86 and 0·91, respectively, showing a high level of accuracy in identification (unpublished data).

At the hospital level, we observed wide variation between healthcare institutions in both hospital charges and LOS. Hospitals such as H4 maintained a relatively low HAI incidence (8·3%), and also managed to control mean hospital charges for both uninfected and infected patients (US$5 304 and US$6 250, respectively). Hospital H4 also showed the lowest increase in LOS associated with HAIs at 5·1-days.

Hospital H32, on the other hand, had a low HAI incidence at 6·7%. Furthermore, HAIs were associated with an increase of only 13·6-days in LOS in this hospital. Despite this, mean hospital charges, while relatively low for uninfected patients (US$4 922), was one of the most expensive for infected patients at US$11 908. In comparison, Hospital H6 had a lengthy 21·2-days increase in LOS associated with HAI, but had the lowest hospital charges for both uninfected and infected patients (US$3 824 and US$5 438, respectively). Therefore, while the regression models show that LOS had the largest association with hospital charges, it is evident that other factors are also important.

Furthermore, in addition to having a high odds ratio associated with increased mortality, Hospital H28 was one of the most expensive hospitals for both infected and uninfected patients, at US$7 710 and US$12 387, respectively. The mean age of the infected patients was 77-years in this hospital, while that of the uninfected was 70-years, and in general it was the older patients (aged >85-years) that resulted in the longer LOS. This high representation of the elderly may explain the high values observed.

The mean hospital charges per day were found to be slightly higher in uninfected patients (US$317 vs. US$217). This could represent a possible loss of income to hospitals, as infected patients occupy bed-space that could potentially be offered to new patients. With an already lengthy LOS in Japanese acute care hospitals (27), the reduction of unnecessarily protracted LOS would be beneficial to an already strained healthcare system.

The LOS has been an issue with Japanese acute care hospitals, and Japan has the longest mean LOS among the OECD countries (28). However, this may be due in part to acute care hospitals in Japan frequently including rehabilitation and palliative care among the provided services. This mixture of acute, subacute, and chronic healthcare provision may also explain the wide variations that we observed between hospitals in hospital charges, LOS, and mortality.

Dedicated stroke units are a rarity in Japan, despite strong recommendations for the use of such units in the treatment of acute stroke patients published in guidelines in 2004 (29). Most hospitals in Japan manage acute stroke patients in general medical wards, and when intensive care was required, these patients were treated in standard ICUs. Because the patients who have had a stint in the ICU would represent more severe cases who required ICU treatment in addition to baseline stroke treatment, it would therefore be unsurprising for ICU stay to have significant and strong associations with hospital charges, LOS, and mortality, as shown in our regression models.

The HAIs have been previously shown to have positive associations with mortality (30). Our data corroborate these findings, although we observed a stronger association between HAIs and increased mortality. While the clinical complications associated with stroke have been looked previously at (2, 6), most of these studies focused on single-institution databases. The use of a multiinstitutional database in this study helps to increase the generalisability of our results, as well as allow for the interpretation of the results from each individual hospital within the context of other hospitals. Downstream studies could include qualitative studies in which particular characteristics in hospitals with low HAI incidences are identified, as well as elucidating problem areas in hospitals with higher HAI incidences. In this way, the quality of HAI control measures may be increased. Furthermore, the approximate cost-effectiveness of subsequent interventions to reduce infections may benefit from the estimations provided in this study.

The limitations of this study are that the identification method used is unable to specify the types of infections that occurred; therefore, the infections identified in this study would potentially include cases of severe pneumonia together with relatively milder infections. As there were no standard stroke severity scales like the Japan Stroke Scale or the NIH Stroke Scale, we were unable to adjust for severity directly, but instead had to use the Barthel index and JCS as approximate proxies. Also, our database did not include the duration after onset at the time of admission, which may have an effect on the results. A multicentre study in Japan conducted by Kimura *et al.* (25) has shown that almost 37% of patients were admitted within 3 h of onset, and 73% within 24 h. However, due to database limitations, we were unable to include this variable in our analysis. Finally, the hospitals used in this study are voluntarily part of a programme known as the QIP, in which participating hospitals voluntarily provide data for analysis for the purpose of improving healthcare outcomes. As such, there may be some selection bias involved and the hospitals used in this study may not be indicative of all hospitals in Japan.

Summary

In this study, the use of risk adjustment allows for a more meaningful interpretation of the economic and clinical outcomes from a multicentre database. Quantification of the increases in resource utilisation associated with HAIs allows for more precise policy making and planning for interventions.

Owing to the use of hospital charges, the economic outcomes here may be interpreted as cost estimation from a third party payer perspective, which in an insurance-centric healthcare payment system such as the one existing in Japan, may be highly useful.

With a rapidly ageing population in Japan, diseases such as ischaemic stroke that are usually associated with the aged will become more prominent. This study analyses the incidence and impact of HAIs in stroke patients, and highlights the salient need for interventions for their reduction in Japanese hospitals. Possible interventions could include further hand hygiene practice, dedicated infection control staff, high-risk patient identification, and promoting antimicrobial stewardship protocols.

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Risk-adjusted increases in medical resource utilization associated with health care-associated infections in gastrectomy patients

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Abstract

Rationale, aims and objectives Quantifying the impact of health care-associated infections (HAIs) on medical resource utilization is necessary for payers and providers to appropriately allocate limited resources for interventions. However, previous studies tend to involve single institutions and do not take into account patient and practice variations between several hospitals. The objective of this study was to conduct a multi-institutional risk-adjusted comparison of HAI-associated impact on medical resources in gastrectomy patients in Japan.

Methods Health care-associated infections were identified using a combination of International Classification of Diseases-10 codes and antibiotic utilization patterns in 1058 gastrectomy patients from 10 Japanese hospitals. Multiple linear regression models and risk adjustment were used to analyse the impact of HAIs on: (1) total hospital costs; (2) antibiotic costs; and (3) post-surgical length of stay (LOS).

Results Overall HAI incidence for the database was 20.3%, with a range of 8.8–29.6% among the 10 hospitals. Regression models showed that HAIs were significantly associated with increases in all three indicators. Risk-adjusted comparisons revealed that HAIs were associated with an increase of US$2767 (range: US$1035–6513) in overall hospital cost, US$202 (US$98.8–764.6) antibiotic costs and 10.6 (4.7–24 days) post-surgical LOS days.

Conclusions Even after adjusting for patient characteristics and other variables, there was still a high degree of variation observed in the impact of HAIs on total hospital costs and antibiotic costs from a third-party payer's perspective and post-surgical LOS among the 10 hospitals. This information can increase the efficiency of allocation of resources for interventions to reduce HAIs.

Introduction

The control of health care-associated infections (HAIs) is a particularly important yet elusive goal for increasing the quality of health care. In addition to decreased quality of life [1,2] and increased morbidity and mortality [3], HAIs represent potentially preventable increases in medical resource utilization [4–7]. These increases in resource utilization must first be quantified in order for providers and payers to decide how to appropriately allocate limited resources for preventive measures.

While studies that estimate the impact of HAIs on resource utilization generally involve data from one or two hospitals [8–12], a multi-institutional comparison would provide a wider contextual backdrop in which to interpret the results of each hospital. However, risk adjustments must first be conducted in order to account for practice variations and patient characteristics before meaningful comparisons can be made. To the best of our knowledge, there is no current risk-adjusted multi-institutional comparison of the impact of HAIs on medical resource utilization in a Japanese setting.

The aforementioned studies generally involved chart reviews [8,9] or prospective studies [10–12]. However, these methods are extremely labour-intensive and tend to be self-limiting in terms of population sample size and study period duration. An alternative approach is the use of reimbursement data or administrative data, which provides a standardized and detailed database that can be used for multi-institution comparative studies. The hospital payment system in Japan uses an identical reimbursement schedule for all acute-care hospitals, and it is required for hospitals to produce data in similar formats. Therefore, these data are easily obtained, analysed and used to compare multiple institutions in a Japanese setting.

Infection identification using administrative data can be conducted by the use of International Classification of Diseases (ICD) codes. However, the use of these codes alone to identify HAIs has been found to have poor identification capability [13,14]. In order to improve identification capability, we chose to complement ICD code-based identification with the use of antibiotic utilization patterns as a clinically relevant indicator of infection incidence.

The objective of this study was to quantify increases in medical resource utilization associated with infections in gastrectomy patients from several Japanese hospitals, and to conduct a risk-adjusted comparison of performance between the hospitals.

Methods

Patient selection

Patient information was obtained from hospitals enrolled in the Quality Indicator/Improvement Project (QIP), a database of 16 Japanese hospitals (at the time of study) that consists of clinical and claims data on discharged patients. We selected patients with gastric cancer who were hospitalized for the purpose of gastrectomy as our target population as gastric cancer occurs with very high incidence in Japan [15]. By focusing on patients who had only undergone gastrectomies, we reduced the intrinsic variation associated with procedural differences.

Data were obtained on patients who were admitted from April 2004 to January 2007. Total and subtotal gastrectomies for gastric cancer performed were identified using the Diagnostic Procedure Combination coding system for reimbursement, a national fee schedule introduced into Japan in 2003. The sampled hospitals had a bed size ranging from 280 to 1106 beds, with a mean of 561 beds.

Patients were excluded if they fulfilled any of the following criteria: (1) patients who had died during admission; (2) patients who were given antibiotics before the day when gastrectomy was performed; (3) patients who had other surgeries before gastrectomy; (4) patients admitted directly from the emergency ward; and (5) patients with missing data with regards to antibiotic payments and anaesthesia time. Finally, hospitals with fewer than 30 cases were excluded from analysis.

Clinical diagnoses were conducted using ICD-10 (10th revision of ICD codes). Pre-existing co-morbidity conditions were analysed using the Charlson co-morbidity index (Dartmouth–Manitoba version) [16,17].

Identification of post-surgical HAI

Antibiotic utilization patterns were discerned using daily drug claims data, which allowed us to identify antibiotic administration, type of antibiotic and dosage on a day-to-day basis. We used antibiotic utilization patterns that would not occur in the simple pre-surgical prophylaxis observed in uninfected patients. Patients were deemed to have HAIs if they fell into any of the following categories: (1) post-admission complications with ICD-10 codes indicating HAI, adapted from the Pennsylvania Health Care Cost Containment Council (PHC4) [13]; (2) the use of three or more different types of antibiotics during their hospital stay; (3) the use of two types of antibiotics in which a second antibiotic type was added or changed midway through the course; (4) more than 1 day of antibiotics given in a separate time frame in which no surgery was conducted; and (5) the use of more than 3 days of antibiotics starting from the day of surgery. The final sample size (*N*) used for analysis was 1058 patients from 10 hospitals.

Resource utilization indicators

Total hospital costs and antibiotic costs from a third-party payer's perspective, as well as post-surgical length of stay (LOS), were used as indicators of medical resource utilization.

Statistical analysis

Analyses were performed using Dr. SPSS VER. II 11.0.1J (SPSS Inc., Chicago, IL, USA); *P*-values reported were two-tailed and the level of significance was set at $P < 0.05$.

Multiple linear regression models were developed to estimate the impact of HAIs on medical resource utilization. Total hospital costs, antibiotic costs and post-surgical LOS were natural logarithm transformed before being used as dependent variables in the regression models. The independent variables used were age (equal to and above 70 years), gender, post-surgical infection, co-morbidities, pre-surgical LOS, type of gastrectomy (total or partial), number of surgeries, surgery duration and hospital stratification. The age of 70 years was selected as preliminary analysis showed that the proportions of patients above and below this age were approximately equal, and univariate analysis showed highly significant association with HAI presence/absence (data not shown). Anaesthesia time (minutes) was used as a proxy indicator for surgery duration.

Hierarchal regression models were developed, with covariates grouped into patient characteristics, co-morbidities and surgery-associated factors. The first model for each dependent variable excluded the use of hospitals as dummy variables, while the second model included hospital stratification.

Risk-adjusted values were obtained using the first regression models as described previously, but with hospital stratification and post-surgical infection status excluded as variables. These regression models were then used to produce predicted values for each of the three medical resource utilization indicators. As the dependent variables were logarithmic transformed before analysis, the exponentials of the predicted values were calculated in order to obtain expected values with units of Japanese Yen and days. Duan's smearing coefficient was applied to correct for retransformation bias [18,19]. Risk adjustment was conducted by dividing each hospital's mean observed value (O) by the mean expected value (E), and multiplying the result by the mean value of the entire data set.

Final estimates were adjusted for inflation using the Japanese consumer price index (to adjust all values to the 2007 Yen value) and then converted to US dollars using Purchasing Power Parities (Japanese 100 Yen = US\$0.85; April 2007) [20].

Results

The distribution of patient characteristics and gastrectomy type are presented in Table 1. The population was skewed towards an older patient population, with 47.9% of the subjects equal to or more than 70 years of age. In all, 9.7% of the study population suffered from diabetes, and 9.5% exhibited metastatic cancer. There were more patients (64.2%) who underwent subtotal gastrectomies than those who underwent total gastrectomies.

Figure 1 shows HAI incidence in total and at the hospital level. In general, there was an infection incidence of 20.3% (215 cases) in our sample population, and a range from 8.8% (Hospital A) to 29.6% (Hospital E). A breakdown of infection cases by identification method shows that the use of ICD-10 codes resulted in 85 cases (8.03%) identified. In all, 72 of these cases were also identified by antibiotic utilization. Of the cases identified by ICD codes, 70% were 'unspecified infections following a procedure', 20% were specified as 'surgical site infections' (SSIs), and the remaining 10% consisted of unspecified pneumonia, septicaemia and urinary tract infections. There were an additional 130 patients identified by antibiotic utilization alone.

Furthermore, while 'the use of >3 days of antibiotics starting from the day of surgery' was included as a criterion for infection identification, all of the cases that were identified as infected patients by this particular criterion were also identified by at least one of the other four criteria.

The regression models used are shown in Table 2. Cases with post-surgical HAIs showed highly significant association in all three indicators of increased medical resource utilization ($P < 0.001$) in all of the six models constructed.

The first regression model constructed was able to account for 60.7% of variation observed in total hospital costs. With hospital stratification, the model accounted for 64.3% of variation. Age and all surgery-associated factors were significantly associated with total hospital costs, while gender was not. Congestive heart failure was the only co-morbid condition that was consistently significant in both models for total hospital costs, and diabetes showed significance when hospital stratification was included in analysis.

Hospital	A	B	C	D	E	F	G	H	I	J	Total	%
N	57	31	85	222	81	37	93	220	159	73	1058	100
Patient characteristics												
Female	16	8	30	61	28	12	31	74	59	24	343	32.4
Age (≥70 years)	24	16	52	102	41	15	30	102	92	33	507	47.9
Acute myocardial infarction	2	0	1	0	4	0	1	2	5	0	15	1.4
Congestive heart failure	0	1	0	0	1	1	0	0	4	0	7	0.7
Peripheral vascular disease	1	0	0	1	0	0	0	1	0	1	4	0.4
Cerebral vascular disease	3	1	3	7	7	0	3	3	6	2	35	3.3
Pulmonary disease	2	1	4	13	3	1	1	6	8	1	40	3.8
Peptic ulcer	3	2	8	7	2	1	0	9	13	9	54	5.1
Liver disease	0	0	0	3	1	0	0	1	1	0	6	0.6
Diabetes	10	4	10	30	3	2	4	16	21	3	103	9.7
Diabetes w/complications	0	1	0	1	7	0	0	1	2	0	12	1.1
Renal disease	2	0	0	2	1	0	2	1	7	1	16	1.5
Metastatic cancer	8	3	5	15	1	13	1	38	12	4	100	9.5
Gastrectomy type												
Subtotal	37	19	42	153	54	23	69	148	99	35	679	64.2

Table 1 Distribution of patients, patient characteristics and type of gastrectomy by hospital and in total

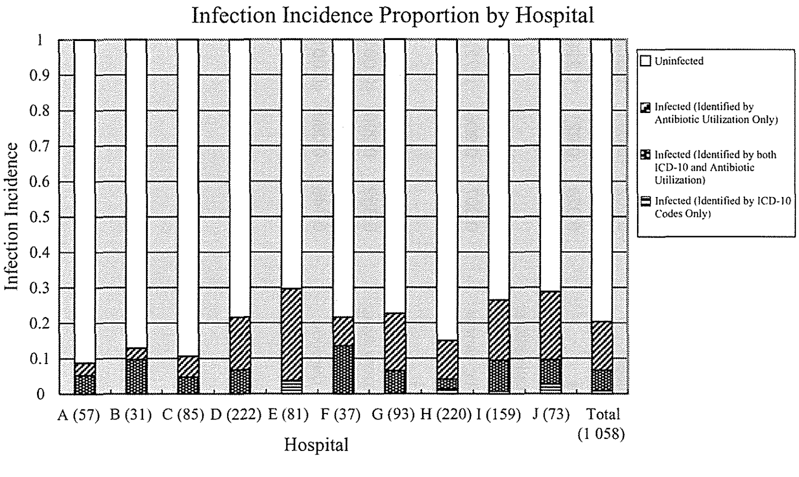

Figure 1 Infection incidence proportion by hospital and in total. White sections represent patients uninfected with HAIs; sections with diagonal lines represent infected patients identified by antibiotic utilization only; sections with dots represent infected patients identified by both International Classification of Diseases (ICD)-10 codes and antibiotic utilization; sections with horizontal lines represent infected patients identified by ICD-10 codes only (only in Hospitals E, H, I and J).