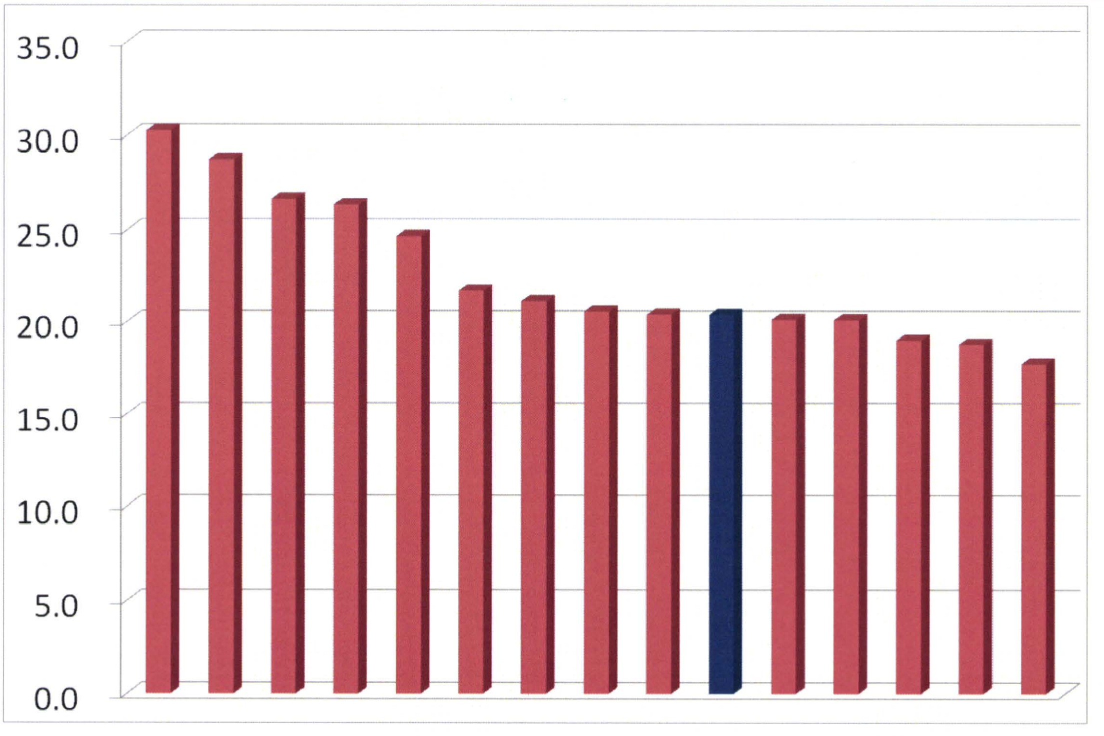
消防本部別　平均搬送時間

範囲：12.6分の地域差



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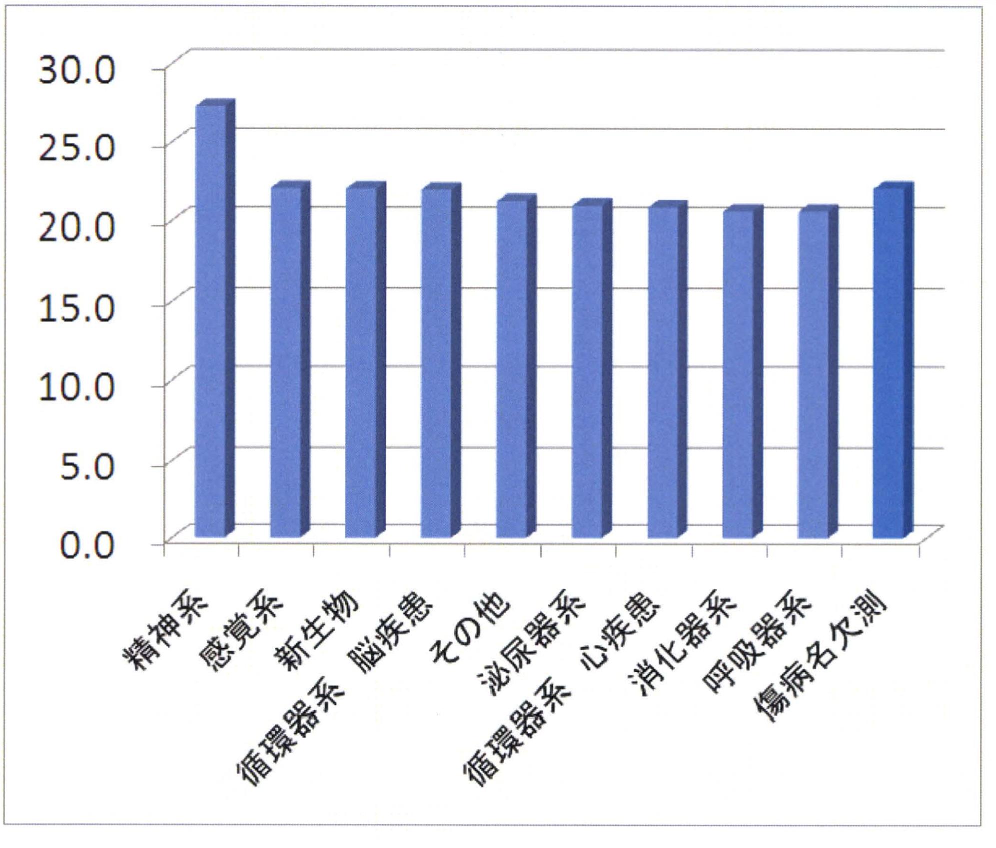
疾患別　平均搬送時間



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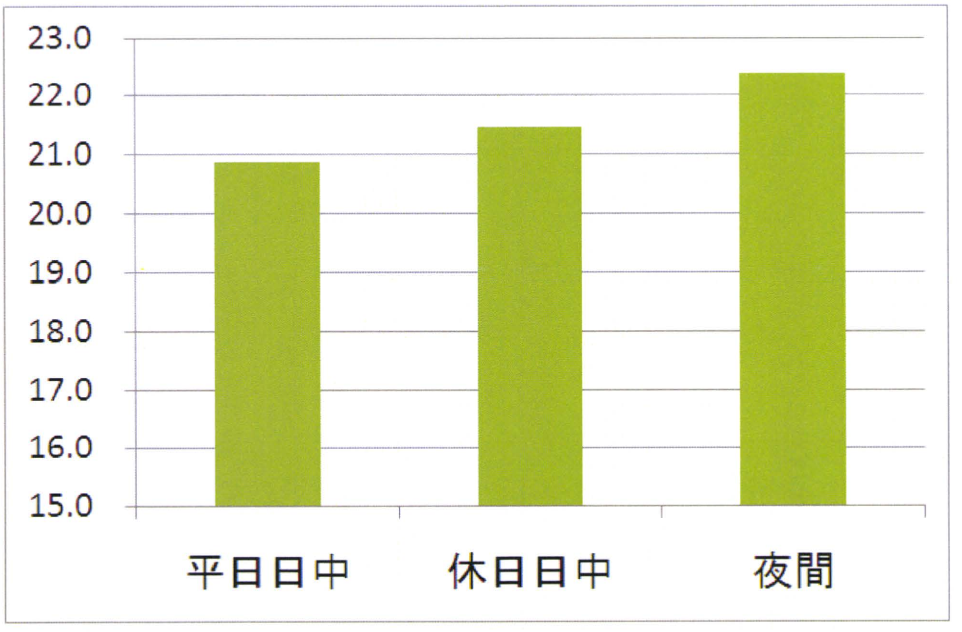
搬送時間帯別　平均搬送時間

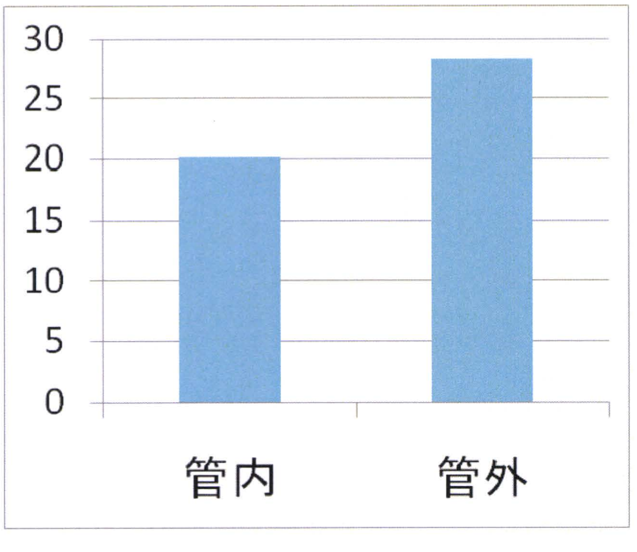
1.5分の時間帯の差

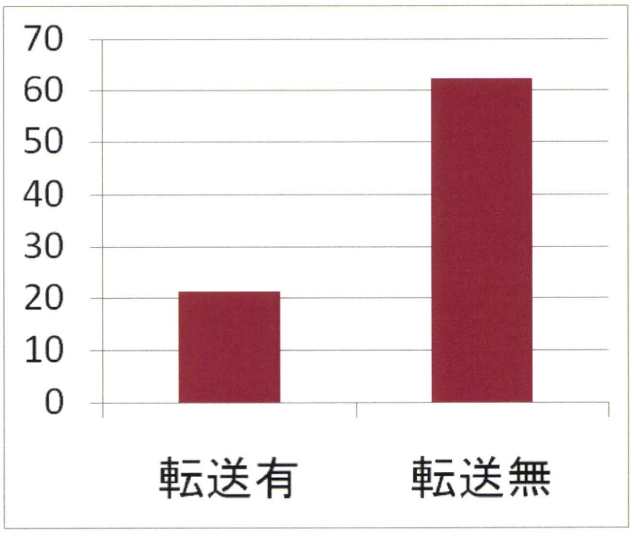


搬送区域別/転送有無別　平均搬送時間

搬送先区域：8.1分の差

転送有無：41分の差





重回帰分析結果　1

いくつかの要因で調整しても地域差が認められた

カテゴリ	変 数	b	β	p-value
消防本部管轄区域	A	6.992	0.119	0.000
	B	6.690	0.160	0.000
	C	4.792	0.081	0.000
	D	1.826	0.030	0.000
	E	0.043	0.001	0.879
	F	-0.517	-0.010	0.020
	G	-1.026	-0.008	0.039
	H	-1.135	-0.023	0.000
	I	-2.340	-0.042	0.000
	J	-2.435	-0.055	0.000
	K	-4.668	-0.114	0.000
	L	-4.712	-0.085	0.000
	M	-5.165	-0.093	0.000
	N	-9.321	-0.087	0.000

$R^2 = 0.230$

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重回帰分析結果　2 (続き)

転送有、管外搬送、精神系疾患が時間延長因子

カテゴリ	変 数	b	β	p-value
疾患分類	循環器系心疾患	-1.241	-0.044	0.000
	消化器系疾患	-1.186	-0.041	0.000
	呼吸器系疾患	-0.936	-0.034	0.000
	精神系疾患	4.555	0.064	0.000
	感覚系疾患	0.357	0.007	0.085
	泌尿器系疾患	-0.926	-0.018	0.000
	新生物	0.043	0.001	0.827
	その他	-0.032	-0.002	0.785
搬送区域	搬送先管内	-9.483	-0.341	0.000
転送有無	転送	36.380	0.198	0.000
年齢層	少年	-2.816	-0.046	0.000
	成人	0.534	0.024	0.000
搬送理由	急病	-2.790	-0.023	0.000
搬送時間帯	休日日中	0.448	0.017	0.000
	夜間	1.245	0.053	0.000
	定数	32.276		

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偏回帰係数の比較　非心肺停止と心肺停止

カテゴリ	変数	非心肺停止症例		心肺停止症例	
		n=52,609		n=2,608	
		b	p-value	b	p-value
消防本部管轄区域	B	6.690	0.000	3.290	0.000
	C	4.792	0.000	0.671	0.350
	G	-1.026	0.039	-3.182	0.259
	H	-1.135	0.000	-0.516	0.402
	J	-2.435	0.000	0.153	0.817
	L	-4.712	0.000	-3.877	0.001
	M	-5.165	0.000	-4.184	0.000
疾患分類	消化器系疾患	-1.186	0.000	-0.661	0.259
	呼吸器系疾患	-0.936	0.000	-0.189	0.817
	新生物	0.043	0.827	-0.073	0.937
	その他	-0.032	0.785	-0.976	0.163
搬送区域	搬送先管内	-9.483	0.000	-6.636	0.000
年齢層	少年	-2.816	0.000	-7.334	0.000
	成人	0.534	0.000	0.411	0.285
搬送時間帯	休日日中	0.448	0.000	0.289	0.459
	夜間	1.245	0.000	1.240	0.000
	定数	32.276		14.743	0.000

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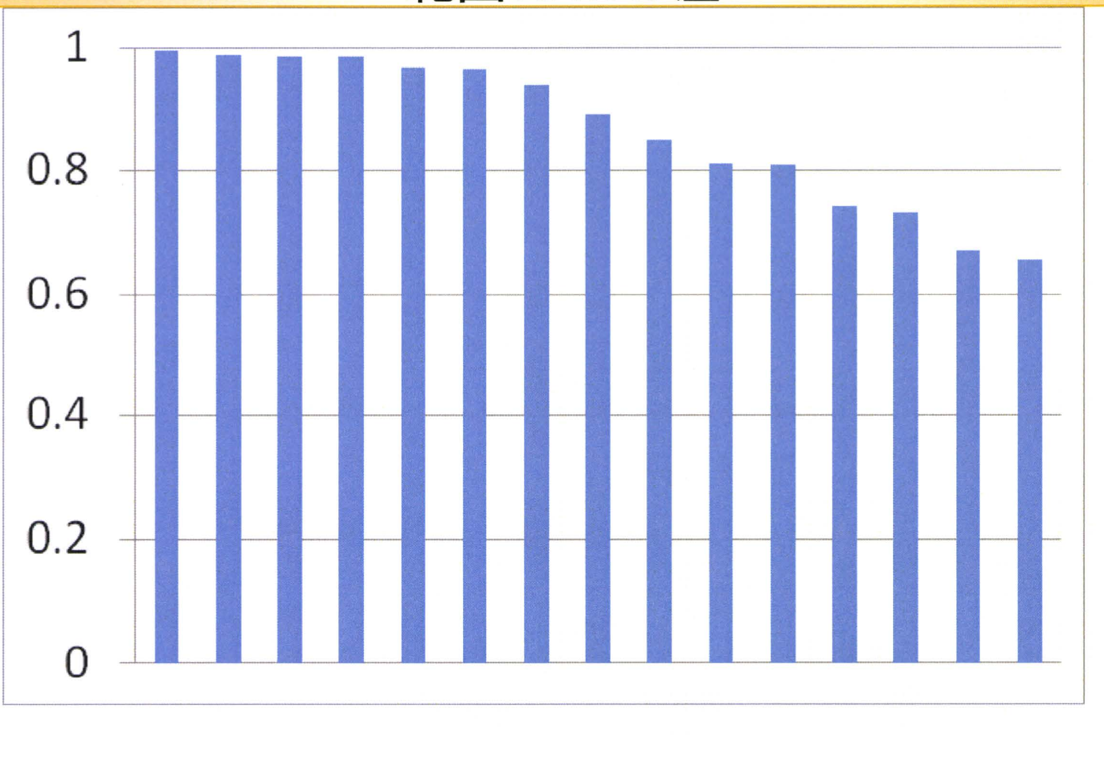
消防本部管轄区域別　人口カバー割合

7区域：19分以内で90%以上をカバー
範囲：34%の差



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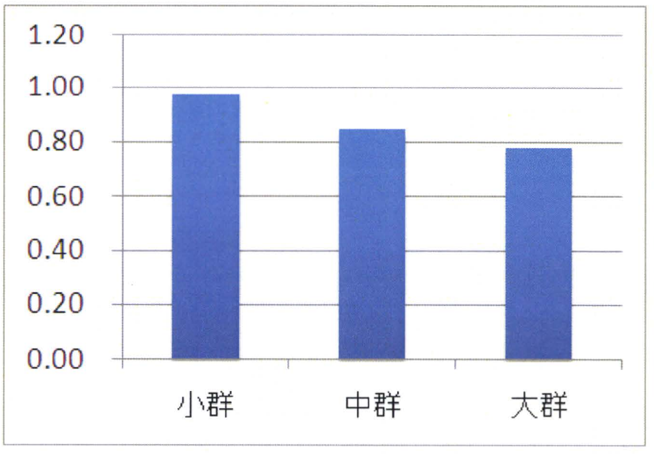
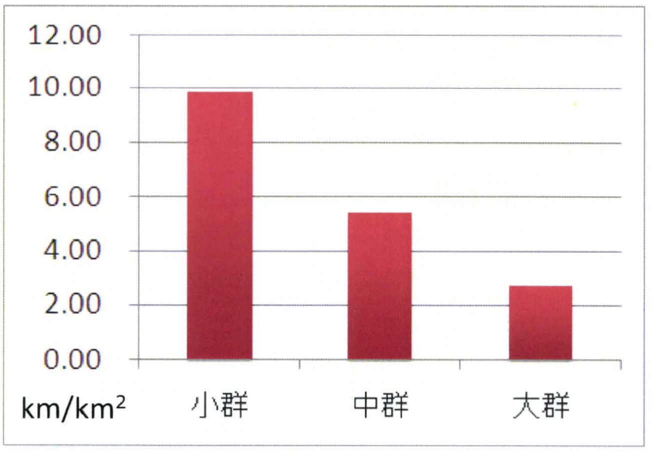
搬送時間群間の地域状況変数の比較

	平均値			有意確率
	小群	中群	大群	
総人口カバー割合	0.97	0.85	0.78	0.027
総面積あたりの道路実延長	9.86	5.45	2.68	0.001
可住地面積人口密度	4,108	2,476	658	0.044
高齢者割合	0.17	0.20	0.26	0.026
昼間夜間人口比	1.02	0.97	0.93	0.858

【総人口カバー割合】



【総面積当たりの道路実延長】



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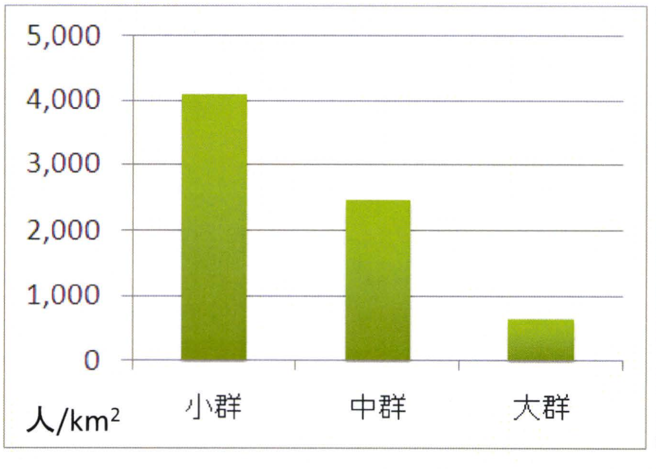
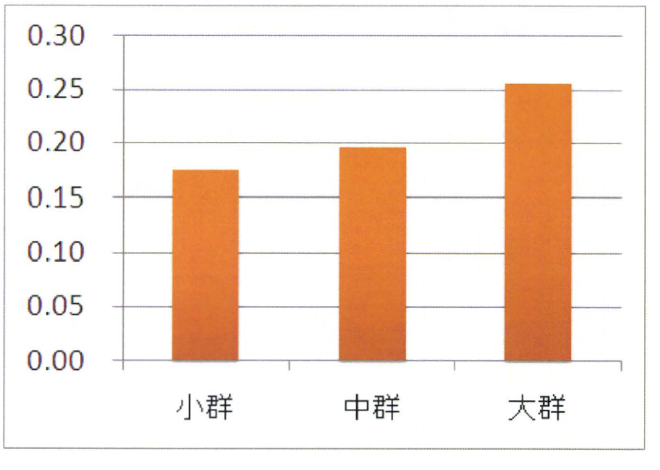
搬送時間群間の地域状況変数の比較

【可住地面積人口密度】



【高齢者割合】



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限界と今後の課題

- 重回帰モデルの説明力について
  - ■地域の区分（消防署などより細かい単位）
  - ■現場の状況（車内収容までに要する活動）
  - ■救急隊の現場活動
  - ■患者・関係者との合意形成（医療機関の探索）
  - ■病状
- 今後の課題
  - ■受入機関の救急医療提供機能の分類とその分布
  - ■救急車搬送・高度緊急手術を要する入院患者の移動距離・時間と医療費や治療成績との関連

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4. 結論

結論

- 救急車搬送時間には
患者状況を調整しても地域格差が存在
  - 地域単位：消防本部の管轄区域
  - 是正を検討するに値する大きさ
- その格差は居住や交通状況と関連
  - 居住状況
    - 人口カバー割合や人口密度が高いほど、短い
    - 高齢者割合が高いほど、長い
    - ベッドタウンかどうかとは、関連が認められない
  - 交通状況
    - 道路整備が行き届いているほど、短い
- 是正にむけた視点
  - 救急車搬送患者を受入れる機関の地理的分布
    - 一定の範囲内にどれだけ高機能機関を配置すべきか

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Research

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

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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 6-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 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 4 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 5 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 $P<0.05$ (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

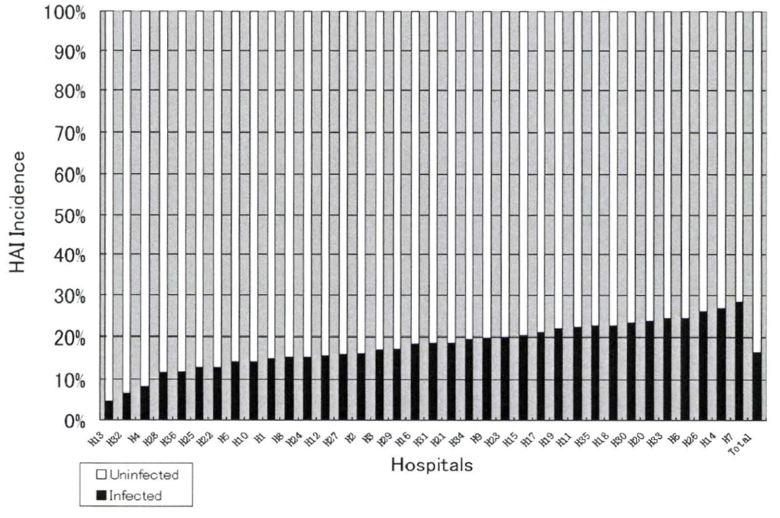

Fig. 1. Healthcare-associated infection (HAI) incidence at hospital level and in total.

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

	Dependent variable: Ln (hospital charges)					Dependent variable: Ln (length of stay)					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
Independent variables	β	SE	β	SE	Independent variables	β	SE	β	SE	Independent variable	*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

Table 2 (Continued)

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)
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.

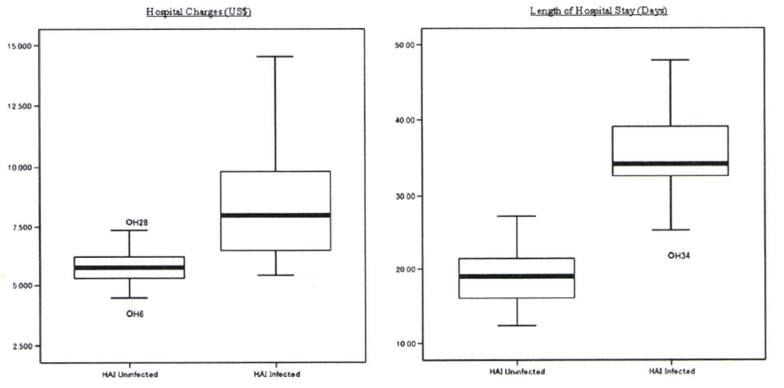

Fig. 2. Box-plot graphs of risk-adjusted hospital charges per admission (in US$) and length of stay (in days) for infected and uninfected patients at the hospital level. HAI, healthcare-associated infection.

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 ($P<0·001$; 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 ($P=0·69$). 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 hotels 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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Review

Variations in analytical methodology for estimating costs of hospital-acquired infections: a systematic review

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SUMMARY

Quantifying the additional costs of hospital-acquired infections (COHAI) is essential for developing cost-effective infection control measures. The methodological approaches to estimate these costs include case reviews, matched comparisons and regression analyses. However, the choice of cost estimation methodologies can affect the accuracy of the resulting estimates, with regression analyses generally able to avoid the bias pitfalls of the other methods. The objective of this study was to elucidate the distributions and trends in cost estimation methodologies in published studies that have produced COHAI estimates. We conducted systematic searches of peer-reviewed publications that produced cost estimates attributable to hospital-acquired infection in MEDLINE from 1980 to 2006. Shifts in methodologies at 10-year intervals were analysed using Fisher's exact test. The most frequent method of COHAI estimation methodology was multiple matched comparisons (59.6%), followed by regression models (25.8%), and case reviews (7.9%). There were significant increases in studies that used regression models and decreases in matched comparisons through the 1980s, 1990s and post-2000 ($P = 0.033$). Whereas regression analyses have become more frequently used for COHAI estimations in recent years, matched comparisons are still used in more than half of COHAI estimation studies. Researchers need to be more discerning in the selection of methodologies for their analyses, and comparative analyses are needed to identify more accurate estimation methods. This review provides a resource for analysts to overview the distribution, trends, advantages and pitfalls of the various existing COHAI estimation methodologies.

Introduction

In 2008, the Centers for Medicare & Medicaid Services adopted a 'no pay for errors' policy in the USA in which hospitals would no longer be reimbursed for preventable adverse events. As an indication of the recognition of their effects, these adverse events included several hospital-acquired infections (HAIs).[1] Accurate estimations of the additional costs associated with HAIs (COHAI) support the decision-making process for infection control measures by making possible the accurate assessments of these measures.

Most studies in the existing literature that produce COHAI estimates have used case reviews, matched comparison analyses or regression analyses as their estimation methodologies. In case reviews, researchers are able to accurately distinguish between resources used in the treatment of the primary diagnosis of patients, and the additional resources used for HAIs. Recent development of methods such as appropriateness evaluation protocols have allowed for more rigorous evaluations.[2] The accuracy of the case review approach is dependent on the quality of information recorded in patient charts, and hampered by the associated labour intensiveness.

The main advantage of the matched comparisons methods is its relative simplicity, which eschews the need for overly complicated statistical knowledge on the part of analysts. However, variations in patient attributes make it extremely difficult to find a corresponding uninfected patient for every infected case. Selection bias may consequently arise due to the exclusion of unmatched cases and controls.

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The regression analysis approach enables the inclusion of almost all infected and uninfected patients in analysis, and therefore provides a means to avoid selection bias. Though vulnerable to the influence of endogenous variables, methods such as instrumental variable models have been developed in order to minimise the effects.[3]

Other biases may arise from the failure to account for the influence of confounding factors such as disease severity or patient time at risk.[3–5] The occurrence of an HAI generally extends the hospital length of stay (LOS) of a patient, and therefore contributes to increased healthcare costs.[6] Longer LOS prior to infection may also represent a risk factor for infections, and this presents a potential endogeneity problem in COHAI estimates.[3,7,8]

Graves *et al.* have recently highlighted the importance of accurate HAI cost estimations, and the need for more stringent measurement methodologies.[9] Over the years, pioneering researchers have developed new strategies to minimise the aforementioned issues and produce more accurate COHAI estimates for downstream use.[3,10] There has been an increase in the number of published studies that have conducted COHAI estimates, and it is entirely plausible that these estimates have been used in downstream research such as the assessments of infection control measures. However, the trends and distribution of methodologies that have been used in COHAI estimation studies remain unknown. Furthermore, researchers who intend to conduct COHAI estimates, as well as third parties who use the published estimates may benefit from a review of the trends, advantages and pitfalls of the various methodologies. Therefore, the first objective of this study was to conduct a systematic review of the analytic methodologies used in published studies that produced COHAI estimates, and observe the distribution of approaches employed to deal with the issues as described above. The second objective was to observe changes in trends, if any, of methodologies over time.

Methods

Data sources and search strategies

This systematic review was conducted according to the general principles of the Cochrane Collaboration framework.[11] We conducted a systematic review of studies published in the English language from 1980 to 2006 that had produced original COHAI estimates. Candidate studies were identified using a MEDLINE search using the following keywords: 'economics'[Subheading] OR 'Hospital Costs'[MeSH]) AND ('Cross Infection'[MeSH] OR 'Surgical Wound Infection'[MeSH] OR 'Bacteremia'[MeSH] OR 'Bacterial Infections'[MeSH] OR 'Sepsis'[MeSH] OR 'Staphylococcal Infections'[MeSH] OR 'Pseudomonas Infections'[MeSH] OR 'Pneumonia'[MeSH] OR 'Urinary Tract Infections'[MeSH].

Study selection

Studies that corresponded to the abovementioned search keywords were subjected to a two-step review process consisting of an abstract review and a full literature review. The abstract review was conducted in order to identify studies that had produced original cost estimates for the treatment of HAIs and exclude (1) studies that had utilised existing cost estimates obtained from other published studies, (2) studies that had included community-acquired infections in their sample, and (3) studies that had included infected patients in the reference comparison group. The subsequent full literature review stage included studies identified as having produced original COHAI estimates, and studies that could not be fully evaluated from the abstract review stage. In the full literature review stage we confirmed the suitability of the studies for inclusion in analysis, and through the use of data collection forms we evaluated the analytic methodologies used for COHAI estimation.

Additionally, we conducted a hand-search of the references cited in the studies obtained in the MEDLINE search, and identified other publications that had also produced original COHAI estimates using the same two-step review method as outlined above.

All reviews were conducted independently by two evaluators (H.F. and J.L.), and non-congruent evaluations were discussed before decisions were made.[11]

Analytic methodologies

There are three major analytic approaches used in COHAI estimation research: (1) case reviews, (2) matched comparisons, and (3) regression analysis.[2,4,5] We evaluated the distribution of analytic methodologies categorised by infection type, and analysed the matching variables in matched comparisons and independent variables used in regression analysis. COHAI estimates were also reported for reference purposes.

Trends in methodology

Several treatises regarding novel methodologies have been published, and these studies may have influenced shifts in trends in COHAI estimation approaches: of particular importance are those developed by McGowan in 1981, Haley in 1991, and Howard *et al.* in 2001.[3–5] Taking into account the year of publication of these studies, we analysed the methodology of COHAI estimates by categorising the papers according to whether they were published in the 1980s, 1990s or post 2000. Statistical analysis of the shifts in trends over the years was conducted using Fisher's exact test.

Results

Of the 3069 studies that matched our search terms on MEDLINE, we identified 79 studies that produced estimates on incremental COHAI using the abstract review and full literature review. The subsequent hand-search identified a further 110 non-duplicate candidate publications from the references in the original 79 studies, 10 of which were evaluated as suitable for our analysis. Therefore, the final analysis consisted of 89 studies.[A1–A89]

Analytic methodologies

The characteristics of the studies used in our analysis are presented in Table I. Of the 89 studies, 28 studies produced estimates on surgical site infections (SSI), 20 bloodstream infection (BSI) studies, 12 pneumonia/ventilator-associated pneumonia (VAP) studies, 10 urinary tract infection (UTI) studies, 5 respiratory tract infection (RTI) studies, and 40 studies with unspecified infections. There was an observed increase in studies producing COHAI estimates over the years, with 10 of the studies published in the 1980s, 21 in the 1990s, and 58 from 2000 to 2006. With regard to the distribution of analytical approaches used in producing COHAI estimates, the most frequent method used was multiple matched comparisons (53 studies, 59.6%), followed by regression models (23 studies, 25.8%), case reviews (7 studies, 7.9%), unmatched comparisons (3 studies, 3.4%) and unspecified methods (3 studies, 3.4%).

Forty of the studies that used matched comparisons employed a 1:1 matching method in which each case (infected) patient was matched to a single reference patient. An approximately equal number of studies assumed a normal distribution for regression models (10 studies), or used a logarithm transformation for the dependent variable of healthcare costs (9 studies). While there

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Table I
Characteristics of published studies that had produced estimates of additional healthcare costs due to hospital-acquired infections ($N = 89$)

Study characteristics	No. (%) of studies
Type of infection	
Surgical	28 (31.5%)
Bloodstream	20 (22.5%)
Pneumonia/ventilator-associated pneumonia	12 (13.5%)
Urinary tract	10 (11.2%)
Respiratory tract	5 (5.6%)
General	40 (44.9%)
Country/region	
USA	41 (46.1%)
Europe	26 (29.2%)
Asia	13 (14.6%)
Other	9 (10.1%)
Year of publication	
1980–1984	7 (7.9%)
1985–1989	3 (3.4%)
1990–1994	9 (10.1%)
1995–1999	12 (13.5%)
2000–2004	35 (39.3%)
2005–2006	23 (25.8%)
Methods for estimating cost of hospital-acquired infection	
Case review	7
Standardised case review (AEP)	3 (3.4%)
Standardised case review	1 (1.1%)
Case review	3 (3.4%)
Unmatched comparison (1:*x*)	3 (3.4%)
Matched comparison	53
Multiple matched comparison (1:1)	40 (44.9%)
Multiple matched comparison (1:*x*)	8 (9.0%)
Multiple matched comparison (1:2)	4 (4.5%)
Multiple matched comparison (1:all)	1 (1.1%)
Regression analysis	23
Multiple linear regression (normal distribution)	10 (11.2%)
Multiple linear regression (logarithmic transformation)	9 (10.1%)
Multiple linear regression (gamma model)	1 (1.1%)
Generalised estimating equation	1 (1.1%)
Heckman's two-stage model	1 (1.1%)
Multiple regression (unknown)	1 (1.1%)
Unknown	3 (3.4%)

AEP, acute eosinophilic pneumonia.
Europe includes UK (5), France (5), Belgium (4), Germany (3), Spain (3), Netherlands (2), Ireland (1), Italy (1), Scotland (1), and Switzerland (1). Asia includes Turkey (6), Taiwan (4), India (1), Thailand (1), and China (1). Others include Canada (2), Argentina (2), Mexico (1), Trinidad and Tobago (1), Australia (1), New Zealand (1), and multi-country study (1).

were no studies that addressed the endogeneity problem by employing an instrumental variables model, there was one publication that used Heckman's two-stage model in order to reduce bias. There was also one study that used matched comparisons as the primary approach with regression analysis as the secondary approach, and five studies that used regression analysis as the primary approach with matched comparisons as the secondary approach.

The details of the studies used in analysis, including year of publication, country of origin, types of healthcare institution, patient sample, analytic methodologies, COHAI estimates and matching variables or independent variables are presented in Table II.

We observed that 18 of the 53 publications that used matched comparison analyses, and 8 out of the 23 publications that used regression analyses, had included time at risk in the estimation of COHAI. In matched comparisons, the selection of control reference patients with an LOS of at least the same duration as infected cases was the most frequently used method of taking into account time at risk. However, none of the studies had used the methods proposed by Schulgen.[7] In studies that employed regression analysis, time at risk was taken into account by the inclusion of LOS before surgery, ventilator duration, or intensive care unit duration in the independent variables.

Trends in methodology

Table III shows the changes in methodologies by publication year. Regression analyses had not been used for COHAI estimations in the 1980s. In the 1990s, there were three studies that had used regression analyses, and this number rose to 20 (34.5%) in studies published after 2000. While matched comparisons accounted for the majority of studies in our sample in the 1980s and the 1990s, this method was less popular in studies published post 2000. Also, the proportion of studies using case reviews has also decreased greatly in recent years. These changes in COHAI estimation methodologies were found to be statistically significant ($P = 0.033$).

There was a transition in the number of studies that accounted for LOS relating to both HAI rates and resource use for patients: in the 1980s, there were no studies that had included LOS as a variable, but this has increased in recent years. These studies have accounted for about one-third of all COHAI estimate publications since 2000, showing a marginally statistically significant change over the years ($P = 0.058$).

Discussion

Quantifying the additional costs associated with HAIs supports the decision-making process in infection control measures, and is therefore essential to healthcare policy development and hospital management. There are many potential biases that can affect the validity of these estimates, and methods have been developed to minimise their effect. In this study, we have conducted a systematic review of the methodologies used in studies that produced COHAI estimates published from 1980 to 2006. It was found that studies that had used measures to minimise biases and deal with confounding factors were in the minority, and there is a strong possibility that many of the published COHAI estimates are biased to varying extents. Furthermore, we observed a gradual shift from matched comparisons to regression analyses in recent years. This is a desirable trend as regression analyses are generally preferable to the matched comparisons method in order to obtain estimates with reduced bias. Within regression analyses, it has also been suggested that instrumental variable models can address the issues of endogenous variables.[3,8]

Haley *et al.* analysed the differences in COHAI estimates produced by clinicians' assessments, unmatched comparisons and matched comparisons. It was found that the lowest estimate arose from the clinicians' assessments, followed by matched comparisons and unmatched comparisons.[12] In the case of clinicians' assessments, the distinction between healthcare costs for the primary diagnosis at admission and the additional treatment costs for HAIs are based on subjective opinions, and therefore vulnerable to the effects of bias.[2,4,5] Another study has conducted a comparative analysis of the additional LOS due to surgical site infections (SSI) as calculated by two different methodological approaches. In the case of general SSIs, the standardised case reviews method produced shorter LOS extensions, but with no statistically significant difference.[13] To the best of our knowledge there are no reports of comparisons between standardised case reviews and regression analyses. Furthermore, standardised case reviews have the disadvantage of requiring high labour intensiveness. The current evidence therefore provides little incentive to conduct standardised case reviews for the purpose of COHAI estimates.

By contrast, there have been several studies comparing matched comparisons and regression analyses, with results ranging from no significant difference between the two methods, higher estimates in regression analysis, and higher estimates in matched comparisons.[14–17] Warren *et al.* found that a matched comparison using a propensity score produced COHAI estimates more than twice

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Table II
Analytical methodology, estimates of additional costs of hospital-acquired infections, matching variables and regression analysis covariates used in the studies cited in the systematic review

First author	Year	Country	Type of setting	Type of patients	Analytical methodology	Additional cost to HAI (SSI), if stated [infected vs uninfected]	Matching variables or regression analysis covariates
Surgical site infection							
Herwaldt[A1]	2006	USA	Mixed: 2 hospitals	Surgical	Linear regression (log)	<Non-fatal> + US$1,574 [3,473 vs 1,899] ($P < 0.001$) <Fetal> + US$2,005 [3,904 vs 1,899] ($P < 0.001$)	(1) Karnofsky score*, (2) NNIS risk index*, (3) No.of comorbid illnesses*, (4) Obesity*, (5) Preoperative LOS*, (6) Age*, (7) Interaction of type of surgery and the McCabe and Jackson classification*
Vogel[A2]	2006	USA	University hospital	Surgical	Regression	+US$94,331 [264,778 vs 170,447] ($P < 0.001$)	Not specified
Gavalda[A3]	2006	Spain	Teaching hospital	Mixed	Standardized case review (AEP): mean	+€3,816	NA
Wilson[A4]	2006	UK	University hospital	Surgical	Unknown: mean	+£4,018 [7,718 vs 3,700]	Not specified
Kasatpibal[A5]	2005	Thailand	University hospital	Surgical	Matched comparison (1:1): mean & median	Mean: +TB43,658 [75,544 vs 31,886] ($P < 0.001$) Median: +TB31,140 [50,951 vs 24,568] ($P < 0.001$)	(1) Surgical operation, (2) Diagnosis, (3) ASA
Sheng[A6]	2005	Taiwan	University hospital	Admissions	Matched comparison (1:1): median	+T$117,802 [357,013 vs 126,519] ($P < 0.001$)	(1) Age, (2) Sex, (3) Underlying medical illness, (4) Types of surgery, (5) Diagnosis at admission, (6) Admission date, (7) Types of wards and disease severity
Coskun[A7]	2005	Turkey	University hospital	Surgical	Matched comparison (1:1): mean	<Deep sternal> + US$6,851 <Superficial sternal> + US$3,741	(1) Operation year, (2) Sex, (3) Age
McGarry[A8]	2004	USA	Mixed: 2 hospitals	Surgical	Linear regression (log)	+US$41,117 ($P < 0.001$)	(1) Diabetes*, (2) Renal disease*, (3) ASA score*, (4) Duration of surgery*, (5) Preoperative LOS*, (6) Rheumatological disorder*, (7) Malignancy*, (8) Hospital*
Hollenbeak[A9]	2003	USA	Mixed: 3 hospitals	Surgical (children)	Linear regression (normal)	+US$132,507 ($P < 0.05$)	(1) Race*, (2) Ventilator support*, (3) Age, (4) Packed red blood cells, (5) Cold ischaemia time, (6) HLA-A and -B mismatches, (7) Sex
Engemann[A10]	2003	USA	Mixed: 2 hospitals	Surgical	Matched comparison (1:x): median	<MSSA> + US$23,336 [52,791 vs 29,455] ($P < 0.001$) <MRSA> + US$62,908 [92,363 vs 29,455] ($P < 0.001$)	(1) Type of surgical procedure, (2) Calendar years of surgery
Apisarnthanarak[A11]	2003	USA	Community hospital	Surgical	Matched comparison (1:x): mean	+US$12,477	(1) Surgery, (2) Time period
Whitehouse[A12]	2002	USA	University hospital	Surgical	Matched comparison (1:1): median	+US$27,969 [38,640 vs 10,671] ($P < 0.001$)	(1) Operative procedure, (2) NNIS risk index, (3) Age, (4) Date of surgery within the same year, (5) Surgeon

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