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Status and Future Perspectives of Utilizing Big Data in Neurosurgical and Stroke Research

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Abstract

The management, analysis, and integration of Big Data have received increasing attention in healthcare research as well as in medical bioinformatics. The J-ASPECT study is the first nationwide survey in Japan on the real-world setting of stroke care using data obtained from the diagnosis procedure combination-based payment system. The J-ASPECT study demonstrated a significant association between comprehensive stroke care (CSC) capacity and the hospital volume of stroke interventions in Japan; further, it showed that CSC capabilities were associated with reduced in-hospital mortality rates. Our study aims to create new evidence and insight from 'real world' neurosurgical practice and stroke care in Japan using Big Data. The final aim of this study is to develop effective methods to bridge the evidence-practice gap in acute stroke healthcare. In this study, the authors describe the status and future perspectives of the development of a new method of stroke registry as a powerful tool for acute stroke care research.

Key words: Big Data, neurosurgical research, stroke research, Diagnosis Procedure Combination

Introduction

The last decade has seen significant advances in the amount of data routinely generated and collected, as well as in our ability to use technology to analyze and understand this data. The intersection of these trends is called 'Big Data' and it is helping businesses in every industry achieve higher efficiency and productivity. Repeated observations over time and space generate most Big Data; examples include worldwide users' Internet search engine queries (e.g., Google), e-commerce browsing and transactions (e.g., Amazon), and genomic sequencing in biomedical research.[1,2]

In the United States, the advanced bioinformatics technologies have led to the use of Big Data in many fields of healthcare. In stroke care, the use of Big Data has received considerable attention as an important source for creating new evidence.[3–9] Although the use of Big Data for healthcare is considered important in Japan, it is yet to be utilized effectively, including for stroke care research.

The nationwide survey of acute stroke care capacity for proper designation of comprehensive stroke centers in Japan (J-ASPECT study) is the first nationwide survey in Japan on the real-world setting of stroke using Big Data obtained from the diagnosis procedure combination (DPC) based payment system.[10,11] This review discusses the creation and analysis of Big Data using analytics and the current uses that are relevant to stroke and the J-ASPECT study that are challenges to using Big Data in stroke care research.

Big Data Analytics in Healthcare

A simple definition of Big Data is based on the concept of datasets whose sizes are beyond the management capabilities of typical relational database software. A more articulated definition of Big Data is based on the three V paradigm: volume, variety, and velocity.[12,13] The volume of the data requires novel storage scalability techniques and distributed approaches for information query and retrieval. The variety of the data source prevents the straightforward use of neat relational structures. Finally, the velocity, which is the increasing rate at

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which data is generated, follows a similar pattern as the volume.[14] In the domain of healthcare, Big Data sources and techniques include structured electronic health record (EHR) data, unstructured clinical notes, medical imaging data,[15] genetic data,[16] and the other data (epidemiology and behavioral data).[17]

Despite the inherent complexities of healthcare data, there is potential and benefit in developing and implementing Big Data solutions within this realm. A report by McKinsey Global Institute suggests that if the United States healthcare were to use Big Data creatively and effectively, the sector could create more than $300 billion in value every year.[18] Two-thirds of the value would be in the form of reducing the United States healthcare expenditure.[18] Advances in computer and networking technology, patient monitoring systems, and EHR systems have allowed hospitals to collect and store a rapidly increasing volume and variety of patient data.[19,20] Increasing the recognition of the potential utility of Big Data in health outcomes research has created an impetus to collect and pool EHR data in national datasets. These large datasets provide access to information regarding rare conditions and outcomes that are otherwise difficult to study without robust sample sizes. The goal of Big Data analytics in healthcare is to build evidences and insights based on the 'real world,' and furthermore, to use these evidences to lower costs and improve outcomes through smarter decisions.

Bid Data Analyses about Stroke in the United States

An example of health-care-related Big Data efforts in the United States is the nationwide inpatient sample (NIS), which is structured inpatient EHR data. The NIS is one of the major databases compiled and maintained by the healthcare cost and utilization project (HCUP), which is funded by the agency for healthcare research and quality (AHRQ). Federal and state governments along with medical industry fund AHRQ.[21]

The NIS is the largest all-payer database of inpatient discharge data, and hence, it is a useful dataset for outcomes research. Among hospitals participating in the survey, every discharge for the calendar year is included. The database contains discharge-level data instead of patient-level data, and there is no unique patient identifier to identify re-admissions. Several severity measures are also included in the NIS. Researchers can use these measures for risk-adjustment, or to develop their own risk-adjustment models using the diagnosis and procedure codes included in the data. The NIS does not currently identify conditions present on admission. The age, gender, socioeconomic factor and comorbidities index such as Charlson comorbidities index is a typical adjustment factor for risk-adjustment. Propensity score matched analyses or mixed model analyses adjusted for hospital level variability of disease severity are typical statistical methods conducted in claims-based analysis.

NIS contains data on a stratified sample of over 1000 US hospitals with approximately 8 million hospital stays per year; weights are available to convert NIS data into national estimates.[21] Further, specialty hospitals (e.g., orthopedics or obstetrics-gynecology hospitals) are included, as are long-term acute care hospitals (since 2005). The data have been collected on an annual basis since 1988, and resources are available to facilitate the evaluation of time trends.

For the effective use of Big Data in stroke care, analyses using NIS have been reported in the United States since 1999; further, the number of articles increased rapidly after 2006. Chronological change in stroke care in the United States can be analyzed using NIS database as it provides not only overall nationwide data, but also continuous data per annum.

The NIS provides important information such as nationwide epidemiological and health economical information. In 1999, Williams et al. reported the estimation of the occurrence, incidence, and characteristics of total (first-ever and recurrent) stroke using the NIS database that is representative of all 1995 US inpatient discharges.[3] There were 682,000 occurrences of stroke with hospitalization and an estimated 68,000 occurrences of stroke without hospitalization. The overall incidence rate for the occurrence of total stroke (first-ever and recurrent) was 259 per 100,000 population (age- and sex-adjusted to 1995 US population). This new figure emphasized the importance of preventive measures for a disease that has identifiable and modifiable risk factors and of the development of new and improved treatment strategies and infrastructures that can reduce the consequences of stroke. The impact of new treatments for stroke was evaluated by examining the changes between 1990 to 1991 and 2000 to 2001 in in-hospital mortality rates and hospital charges in adult patients with stroke.[4] There had been an increase in the inflation-adjusted hospital charges for all patients with stroke and a reduction in mortality rates for all stroke subtypes, which was probably related to an increase in the proportion of patients with stroke admitted to urban teaching hospitals.

NIS data can provide clinical data such as clinical background or outcome; therefore, a researcher can analyze these data similar to a normal registry. Outcomes in acute stroke patients treated with thrombolysis were examined using the NIS database available in the United States for the years 1999–2002.[5] The thrombolysis cohort had a higher in-hospital mortality rate compared with nonthrombolysis patients (11.4%

vs. 6.8%). The rate of intracerebral hemorrhage was 4.4% for the thrombolysis cohort and 0.4% for nonthrombolysis patients. Multivariate logistic regression showed advanced age, Asian/Pacific Islander race, congestive heart failure, and atrial fibrillation/flutter to be independent predictors of in-hospital mortality after thrombolysis. Trends in therapy for cerebral aneurysms in the US were identified along with outcomes, using NIS data for the period 1993–2003.[6] Endovascular techniques for aneurysm occlusion have been increasingly used, while the use of surgical clipping procedures has remained stable. Toward the end of the study period, better overall outcomes were observed in the treatment of cerebral aneurysms, both ruptured and unruptured. Large academic centers were associated with better results, particularly for surgical clip placement. It was hypothesized that patients with ICH had a higher mortality risk if they were admitted to the hospital on the weekends than if they were admitted during the week.[7]

One advantage of nationwide claim data such as NIS is that they can provide data about rare diseases or special treatments that are difficult to obtain from a single facility. The incidence, mortality, and risk factors for pregnancy-related stroke in the United States from 2000–2001 were estimated.[8] A total of 2,850 pregnancy-related discharges included a diagnosis of stroke for a rate of 34.2 per 100,000 deliveries. There were 117 deaths or 1.4 per 100,000 deliveries. African-American women are at an increased risk, as are women aged 35 years and older. Risk factors, not previously reported, include lupus, blood transfusion, and migraine headaches. The acute stroke hospitalization rates for children and young adults (aged 15–44 years) and the prevalence of stroke risk factors among children and young adults hospitalized for acute stroke[9] has been examined. The prevalence of hospitalizations of acute ischemic stroke increased among all age and gender groups except females aged 5–14 years. Hypertension, diabetes, obesity, lipid disorders, and tobacco use were among the most common coexisting conditions, and their prevalence increased during the period of study among adolescents and young adults hospitalized with acute ischemic stroke.

About 250 articles are published using the NIS database related to stroke. They become an important evidence for epidemiology or health economy about stroke.

Attempt using Big Data about Stroke in Japan—J-ASPECT study

The DPC is a mixed-case patient classification system that was launched in 2002 by the Ministry of Health, Labor, and Welfare of Japan (MHLW) and was linked with a lump-sum payment system.[22] This system collects important data during hospitalization in addition to the characteristics of the unique reimbursement system. Each patient's background information or discharge summary, which includes principal diagnosis, complications, comorbidities, and outcomes are recorded in the administrative database associated with the DPC system. These patient data are coded using the International Classification of Diseases and Injuries 10th Revision (ICD-10) code. The DPC project collects three types of information: Form 1 is a clinical summary that contains information on diagnosis and severity. The E file has information about the bundled charge of the procedure and the F-file indicates the detail of the bundled procedures. Form 1, E-file, and F-file are matched according to the ID number that is unique for each discharged case. Using these data, we can describe the process of each in-patient treatment. From the point of view of Big Data, the DPC is regarded as a large sample of the structured inpatient EHR data in Japan.

The J-ASPECT study was performed to examine the associations between PSC and CSC capabilities and the impact of CSC capabilities on the hospital volume of stroke interventions. This cross-sectional survey used the DPC discharge database from participating institutions in the J-ASPECT study.

Impact of Comprehensive Stroke Care Capacity on the Hospital Volume of Stroke Interventions[10]

In 2000, the brain attack coalition discussed the concept of stroke centers and proposed two types of centers: comprehensive stroke centers (CSCs) and primary stroke centers (PSCs).[23,24] Most patients with stroke can be treated appropriately at a PSC, and the joint commission has established programs for certifying PSCs and evaluating their performance.[25] The concept and recommended key components of CSCs enable intensive care and specialized techniques that are not available at most PSCs. A set of metrics and associated data elements that cover the major types of care distinguishing CSCs from PSCs have been published previously.[23,24]

In the J-ASPECT study, a 49-question survey was developed on hospital characteristics (i.e., number of beds, academic status, geographic location, and participation in the DPC payment system), PSC and CSC capacity, and hospital volume of stroke interventions. The questionnaire was mailed on February 2011 to 1369 certified training institutions of the Japan Neurosurgical Society, Japanese Society of Neurology, and Japan Stroke Society. This survey included 25 items related to the five major components of CSCs (personnel, diagnostic programs, specific expertise, infrastructure, and educational components) and five items related to PSC certification (Table 1). CSC scores were divided with/without the availability of a t-PA protocol into quintiles and analyzed the trend with the Cochran-Armitage trend test and multivariable linear regressions for the hospital volume.

Table 1 Number (percentage) of responding hospitals (n = 749) with the recommended items of comprehensive stroke care capacity

Components	Items	n	%
Personnel	Neurologists	358	47.8
	Neurosurgeons	694	92.7
	Endovascular physicians	272	36.3
	Critical care medicine	162	21.6
	Physical medicine and rehabilitation	113	15.1
	Rehabilitation therapy	742	99.1
	Stroke rehabilitation nurses*	102	13.8
Diagnostic (24/7)	CT*	742	99.2
	MRI with diffusion	647	86.4
	Digital cerebral angiography*	602	80.8
	CT angiography*	627	84
	Carotid duplex ultrasound*	257	34.5
	TCD*	121	16.2
Specific expertise	Carotid endarterectomy*	603	80.6
	Clipping of IA	685	91.5
	Hematoma removal/ draining	689	91.9
	Coiling of IA	360	48.1
	Intra-arterial reperfusion therapy	498	66.5
Infrastructure	Stroke unit*	132	17.6
	Intensive care unit	445	59.4
	Operating room staffed 24/7*	451	60.4
	Interventional services coverage 24/7	279	37.3
	Stroke registry*	235	31.7
Education	Community education*	369	49.4
	Professional education*	436	58.6

CT: computed tomography, IA: intracranial aneurysm, MRI: magnetic resonance imaging, TCD: transcranial Doppler.

Data missing: stroke rehabilitation nurse, 9; CT, 1;digital cerebral angiography, 4; CT angiography, 3; carotid endarterectomy, 1; carotid duplex, 3; TCD, 3; stroke unit, 1; operating room staffed, 2; stroke registry, 7; community education, 2; professional education, 5. Reproduced from Iihara et al.[10] with permission from the publisher.

Approximately 749 hospitals responded to the survey. On performing multivariate analysis adjusted for hospital characteristics, the total CSC score, but not the availability of a t-PA protocol, was associated with the volume of all types of interventions with a clear increasing trend (P for trend < 0.001) (Fig. 1).

This study demonstrated a significant impact of comprehensive stroke care capacity represented by the total CSC score on the hospital volume of stroke interventions and unique aspects of comprehensive stroke care capacity in Japan.

Impact of CSC capabilities on in-hospital mortality in patients with stroke[11]

Among the institutions that responded to the questionnaire on CSC capacity, data on patients hospitalized for stroke between April 1 2010 and March 31 2011 were obtained from the Japanese DPC database. In-hospital mortality was analyzed with hierarchical logistic regression analysis adjusted for age, sex, level of consciousness on admission, comorbidities, and the number of fulfilled CSC items in each component and in total. Hierarchical logistic regression models were used to estimate odds ratios (ORs) for in-hospital mortality adjusting for institutional level difference. Each model had two levels of hierarchy (hospital and patient) while considering the random effects of hospital variation, as well as fixed effects of CSC score and patient effects of age, sex, and level of consciousness. The total score and each subcategory score were analyzed separately. CSC scores were divided into quintiles and analyzed the trend with the Cochran-Armitage trend test.

Data from 265 institutions and 53,170 emergency-hospitalized patients were analyzed (Table 2). Mortality adjusted for age, sex, and level of consciousness was significantly correlated with personnel, infrastructural, educational, and total CSC scores in patients with ischemic stroke. Mortality was significantly correlated with diagnostic, educational, and total CSC scores in patients with ICH and with specific expertise, infrastructural, educational, and total CSC scores in patients with SAH.

CSC capabilities were associated with reduced in-hospital mortality rates, and the relevant aspects of care were found to be dependent on stroke type (Fig. 2).

Problems and future perspectives of utilizing Big Data

There are some problems for the DPC-based clinical study. The most frequent problem is the accuracy of information.[26] As DPC data is closely related to

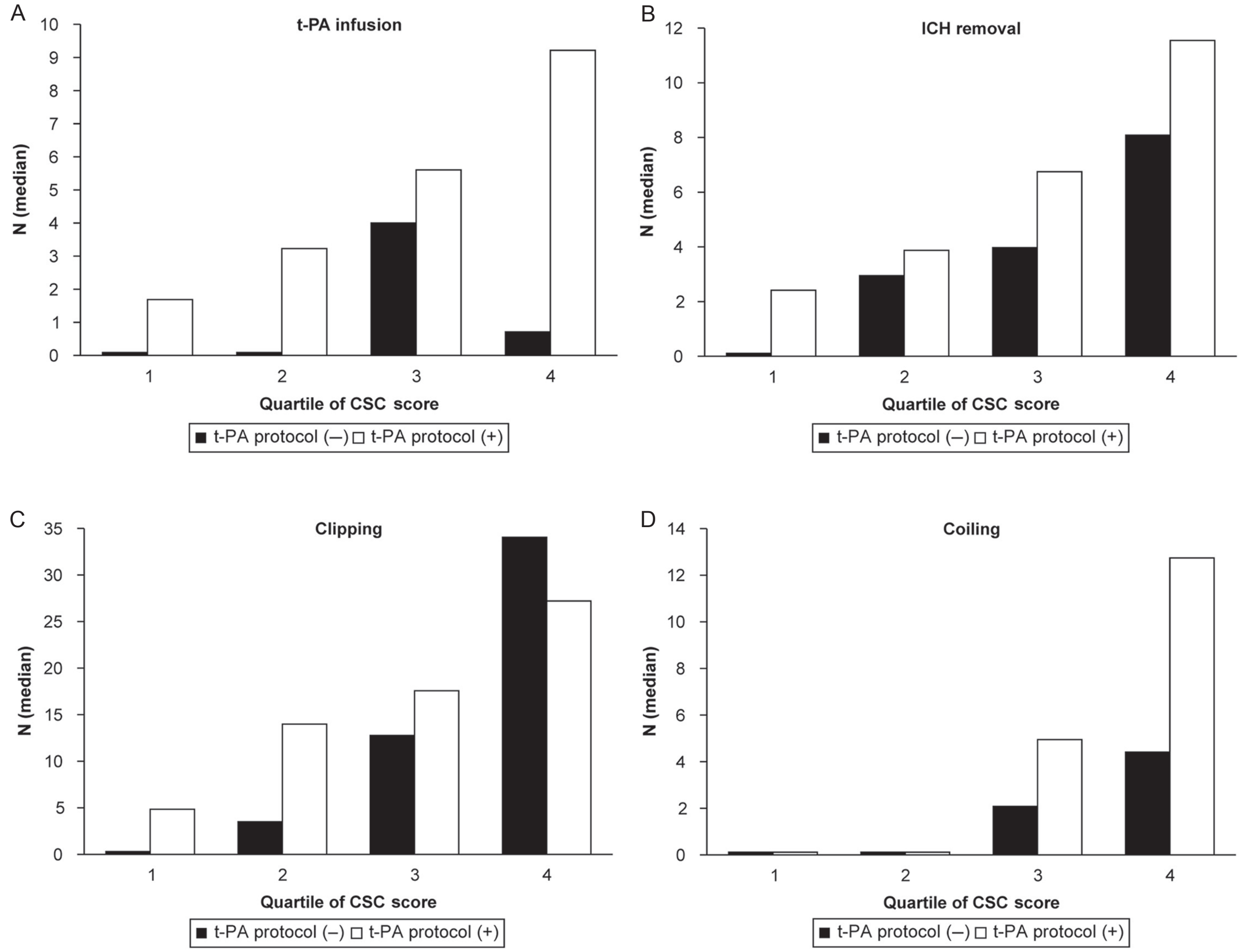

Fig. 1 Associations between primary and comprehensive stroke care capabilities and case volume of stroke treatment in 2009 in Japan. The inclusion of total comprehensive stroke care (CSC) score, availability of a tissue-type plasminogen activator (t-PA) protocol, and other hospital characteristics in the model revealed that the total CSC score, but not the availability of a t-PA protocol, was significantly associated with the hospital volume of stroke interventions. Q, quintile. Reproduced from Iihara et al.[10] with permission from the publisher. Copyright © 2014 National Stroke Association.

the payment, there is a possibility that the medical staff may allocate inappropriate diagnosis in order to obtain more reimbursements. The second problem is the possibility of sampling bias. The current DPC database covers only acute in-patient cases.

Furthermore, DPC data do not provide detailed medical information in comparison with general large-scale cohort studies. Because DPC data are limited to hospitalized data, it can provide information about outcomes such as complications or hospitalized death; however, it cannot provide data such as foreign progress or long-term convalescence.

While DPC data have these limitations, the advantage compared with the other databases is that it can cover all types of diseases treated in acute care facilities. Furthermore, we can obtain data about rare diseases or special treatments, which are difficult to obtain from a single facility.

There have been few academic papers on a large-scale clinical study originating in Japan. One of the reasons is that most Japanese clinical studies are small-scale studies based on close hospital groups, i.e., one university hospital and its associate facilities, and the case registry database is limited to some diseases and domains. Therefore, nationwide statistics about various diseases and treatments are insufficient in Japan. Because nationwide claim data such as DPC data can be obtained from multiple centers with the same format, it is expected as a valid solution to these problems.

Table 2 Demographics of the patient study cohort at the time of diagnosis and hospital characteristics according to stroke type

	Total (n = 53,170)	Ischemic stroke (n = 32,671)	Intracerebral hemorrhage (n = 15,699)	Subarachnoid hemorrhage (n = 4,934)
Male, n (%)	29,353 (55.2)	18,816 (57.6)	9,030 (57.5)	1,584 (32.1)
Age, mean years ± SD	72.5 ± 13.1	74.4 ± 12.2	70.7 ± 13.5	64.7 ± 14.8
Hypertension, n (%)	39,918 (75.1)	22,531 (69.0)	13,281 (84.6)	4,229 (85.7)
Diabetes Mellitus, n (%)	13,725 (25.8)	9,318 (28.5)	3,278 (20.9)	1,174 (23.8)
Hyperlipidemia, n (%)	15,015 (28.2)	11,104 (34.0)	2,529 (16.1)	1,412 (28.6)
Medications during hospitalization				
Anti-renin-angiotensin system agent	34,136 (64.2)	17,694 (54.2)	12,537 (79.9)	4,019 (81.5)
Ca channel antagonist	25,984 (48.9)	10,469 (32.0)	11,719 (74.6)	3,903 (79.1)
Sympathetic antagonist	6,334 (11.9)	3,821 (11.7)	2,172 (13.8)	364 (7.4)
*β-blocker, α,β-blocker	4,357 (8.2)	3,048 (9.3)	1,133 (7.2)	188 (3.8)
α-blocker	2,374 (4.5)	953 (2.9)	1,232 (7.8)	200 (4.1)
Diuretic agent	9,950 (18.7)	5,860 (17.9)	3,074 (19.6)	1,049 (21.3)
Loop diuretic	7,434 (14.0)	4,609 (14.1)	1,912 (12.2)	940 (19.1)
Other diuretic	4,425 (8.3)	2,527 (7.7)	1,653 (10.5)	255 (5.2)
Antidiabetic agent	10,295 (19.4)	6,784 (20.8)	2,473 (15.8)	1,075 (21.8)
Insulin	7,654 (14.4)	4,597 (14.1)	2,044 (13.0)	1,046 (21.2)
Oral antidiabetic agent	5,749 (10.8)	4,459 (13.6)	1,110 (7.1)	197 (4.0)
Antihyperlipidemic agent	12,387 (23.3)	9,264 (28.4)	1,839 (11.7)	1,310 (26.6)
Statin	10,099 (19.0)	7,840 (24.0)	1,366 (8.7)	912 (18.5)
Antiplatelet agent	23,635 (44.5)	21,746 (66.6)	625 (4.0)	1,298 (26.3)
Aspirin	11,929 (22.4)	11,119 (34.0)	378 (2.4)	447 (9.1)
Japan Coma Scale				
0, n (%)	19,635 (36.9)	15,027 (46.0)	3,620 (23.1)	1,024 (20.8)
1-digit code, n (%)	19,371 (36.4)	12,375 (37.9)	5,934 (37.8)	1,117 (22.6)
2-digit code, n (%)	6,937 (13.0)	3,396 (10.4)	2,705 (17.2)	852 (17.3)
3-digit code, n (%)	7,227 (13.6)	1,873 (5.7)	3,440 (21.9)	1,941 (39.3)
Emergency admission by ambulance, n (%)	31,995 (60.2)	17,336 (53.1)	10,909 (69.5)	3,830 (77.6)
Average days in hospital (range)	21 (11–40)	20 (12–38)	22 (10–43)	30 (12–54)
Hospital characteristics (CSC scores)				
Total score (25 items)		16.7 ± 3.8	16.8 ± 3.4	17.1 ± 3.4
Personnel (7 items)		3.7 ± 1.2	3.7 ± 1.2	3.8 ± 1.2
Diagnostic techniques (6 items)		4.4 ± 1.1	4.5 ± 1.0	4.5 ± 1.0
Specific expertise (5 items)		4.4 ± 1.0	4.4 ± 0.9	4.5 ± 0.8
Infrastructure (5 items)		2.8 ± 1.3	2.9 ± 1.3	2.9 ± 1.3
Education (2 items)		1.4 ± 0.8	1.4 ± 0.8	1.4 ± 0.8

CSC: comprehensive stroke center. *A composite variable with a pure beta antagonist and a mixed alpha/beta adrenergic antagonist (e.g., labetalol). Reproduced from Iihara et al.[11] with permission.

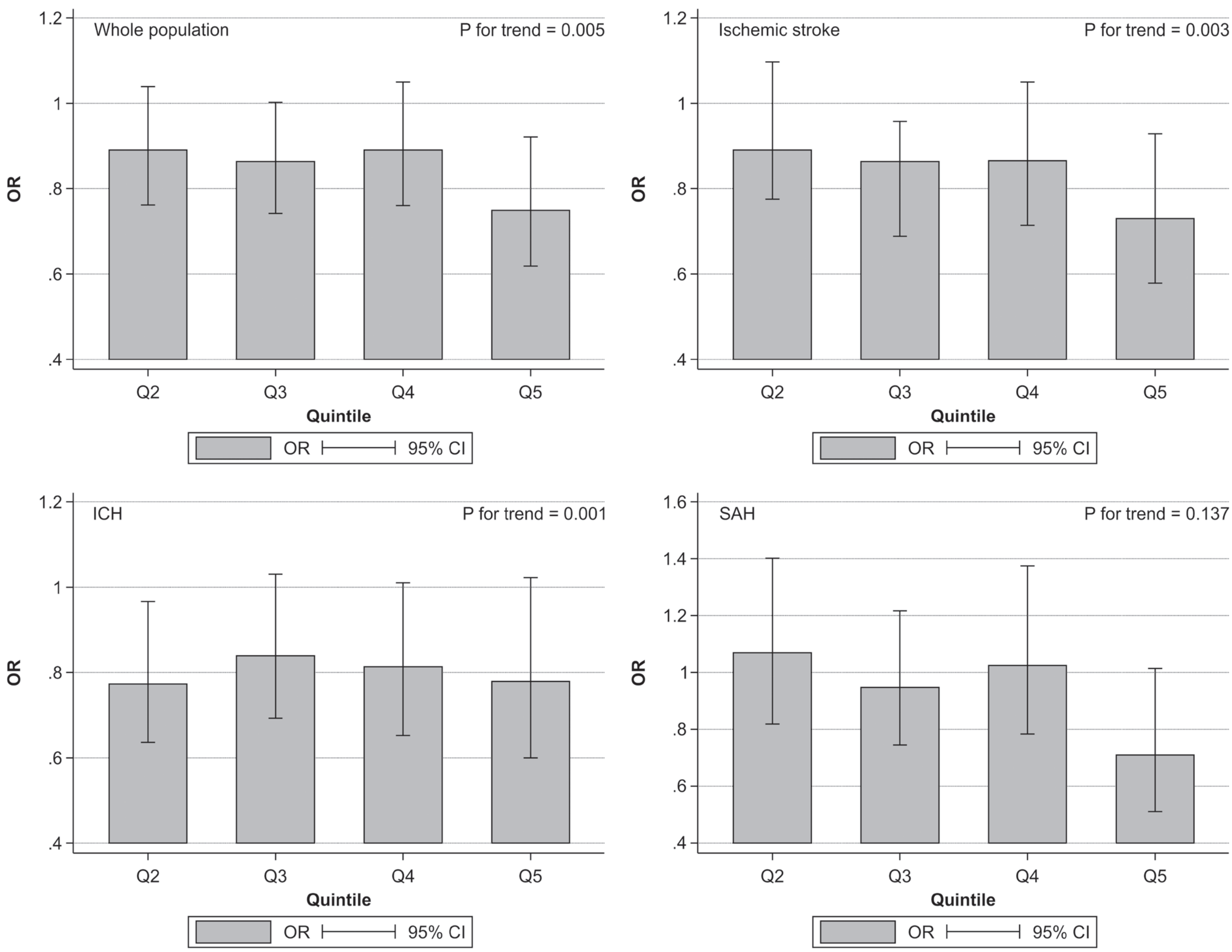

Fig. 2 Associations between total comprehensive stroke care scores separated into quintiles (Q) and in-hospital mortality of patients after all types of stroke. Odds ratios (ORs) and 95% confidence intervals (CIs) of in-hospital mortality for each quintile are depicted compared with that of Q1 as the control (Q1, 4–12 points; Q2, 13–14 points; Q3, 15–17 points; Q4, 18 points; Q5, 19–23 points). Reproduced from Iihara et al.[11] with permission.

As for J-ASPECT study, it is advantage that the overall database about stroke can be established and important information can be provided effectively without bothering stroke physicians. Furthermore, the facilities that participated can feedback their medical treatment process and the outcome of stroke compared to other Japanese hospitals; this benchmark promotes improvements in the quality of the stroke care in each facility.

To make up for the shortcomings of the DPC data and realize a higher quality clinical epidemiologic study, it will be important to link the DPC database with other databases. In the United States, the surveillance, epidemiology, and end results (SEER)-Medicare database is constructed for cancer research. The SEER-Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. The data come from the SEER program of cancer registries that collect clinical, demographic, and the cause of death information for persons with cancer and the Medicare claims for covered health care services from the time of a person's Medicare eligibility until death.[27]

In the field of stroke care, claim data and registry is expected to be linked. In Japan, the construction of the nationwide stroke registry has been planned in order to foresee the development of the basic law for stroke measures. In the future, the linkage of this stroke registry and DPC database can result in a unique population-based source of information that can be used for an array of epidemiological and health services research. Furthermore, it can help discard the manual work required to enter the data in each facility and reduce the burden on prostrate stroke physicians.

Conclusion

The use of Big Data is expected as an effective modality that establishes new evidence about stroke care. The J-ASPECT study demonstrated the importance of the impact of CSC capacity and CSC capabilities on in-hospital mortality in stroke using the DPC database, one of the Big Data databases in Japan. The advantages of applying Big Data such as DPC to stroke care are that the overall database about stroke can be established without bothering stroke physicians and it can become a large-scale clinical study originating in Japan. The development of a new method of stroke registry using Big Data is expected as it would greatly improve future stroke care.

Disclosures

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Current Trends and Healthcare Resource Usage in the Hospital Treatment of Primary Malignant Brain Tumor in Japan: A National Survey Using the Diagnostic Procedure Combination Database (J-ASPECT Study-Brain Tumor)

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Abstract

We conducted this study to clarify the current trends and healthcare resource usage in the treatment of inpatients with primary malignant brain tumors. The Diagnostic Procedure Combination (DPC) data of all inpatients treated between 2013 and 2014 in the 370 core and branch hospitals enrolled in the Japanese Neurosurgical Society training program were collected. DPC is a discharge abstract and administrative claims database of inpatients. We assessed 6,142 primary, malignant brain tumor patients. Patient information, diagnostic information, treatment procedure, and healthcare resource usage were analyzed. Chemotherapy was the most frequent treatment (27% of cases), followed by surgery (13%) and surgery + chemo-radiotherapy (11%). Temozolomide (TMZ), the most frequently used chemotherapeutic drug, was administered to 1,236 patients. Concomitant TMZ and radiotherapy was administered to 816 patients, and was performed according to the Stupp regimen in many cases. The mean length of hospital stay (LOS) was 16 days, and the mean medical cost was 1,077,690 yen. The average medical cost of TMZ-only treatment was 1,138,620 yen whilst it was 4,424,300 yen in concomitant TMZ patients. The LOS was significantly shorter in high-volume than in low-volume hospitals, and the medical cost was higher in hospitals treating 21–50 patients compared to those treating 1–10 patients. However, the direct medical cost of TMZ treatment was the same across different volume hospitals. This is the first report of current trends and healthcare resource usage in the treatment of primary malignant brain tumor inpatients in the TMZ era in Japan.

Key words: malignant brain tumor, DPC, temozolomide, medical cost

Introduction

Malignant brain tumors are amongst the most lethal types of cancer. Its incidence is increasing, and hence, a growing number of patients are being treated in the clinic.[1–4] The current incidence of primary brain tumors is 10–20 cases per 100,000 of the general population. Primary malignant brain tumors can be classified into a number of histological subtypes, but are mostly gliomas with a World Health Organization (WHO) grade between I and IV. Treatment consists of surgery, radiotherapy (RT), and chemotherapy (CTX), either alone or in combination, depending on the tumor histology and the patient's condition. Temozolomide (TMZ) is an oral alkylating agent, and has been widely

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used to treat primary malignant glioma patients in Japan since 2006 when it was first covered by health insurance. After the publication of Stupp et al's influential study, the standard initial treatment strategy for malignant glioma became concomitant RT and TMZ-based CTX.[5] However, as TMZ is an expensive drug compared to carmustine and procarbazine, the economic burden of TMZ usage for the treatment of malignant glioma has been a matter of debate. For example, Wasserfallen et al reported that TMZ usage in concomitant and adjuvant treatment increased medical costs eight fold in a single institution cohort in Switzerland.[6] Nevertheless, several studies demonstrated the cost-effectiveness of TMZ treatment in malignant brain tumor treatment.[7–9] In this context, there is no data as to how many primary brain tumor patients are treated in Japanese hospitals, and how often TMZ is administered overall and in single hospitals. Given that concomitant TMZ treatment after surgery is considered the standard treatment internationally for malignant glioma, the medical economics of TMZ usage should be evaluated in individual countries because the health insurance system is different in each country.

In 2002, the Japanese government introduced a per diem prospective payment system with a Diagnosis-Related Groups (DRG)-like grouping, which is called Diagnostic Procedure Combination (DPC).[10] Data for practices can be obtained from DPC, and an attending physician is responsible for clinical data entry for each patient. Using this database, we have previously reported the discharge outcomes of cerebrovascular disease patients in a nationwide retrospective analysis (the J-ASPECT study).[11–13] In this study, we collected and analyzed all the DPC data for patients treated in 370 core and branch hospitals from a total of 847 hospitals participating in the Japan Neurosurgical Society training program. Brain tumor patients are treated in neurosurgical hospitals in Japan, and this treatment includes CTX and RT. Therefore, this dataset may include the majority of data for patients treated in Japan during the designated period.

The first aim of this study was to reveal what kind of therapeutic modality is administered, and the difference of modality based on patient age, focusing particularly on TMZ usage in the Japanese clinical setting. The second aim was to evaluate healthcare resource usage based on measures such as length of hospital stay (LOS) and direct medical cost using an exhaustive patient administrative claim database. Our findings clarify the current trends in the treatment of primary malignant brain tumor patients, and its associated medical economics in Japan.

Materials and Methods

Data acquisition

Of the 847 hospitals participating in the Japan Neurosurgical Society training program, 392 agreed to participate in this study. We obtained data between April 2013 and Mach 2014 from 392 hospitals, but 22 hospitals were excluded from the analysis because insufficient data are available. In total, the data from 370 hospitals were analyzed, including the DPC data of 501,609 patients admitted to neurosurgical hospitals. This dataset included background patient information such as age, sex, Charlson score, and Japan Coma Scale (JCS) score: 1, 2, 3-digit, and we could acquire information about the treatment procedure and modality, and the administered drug. In addition, we could obtain healthcare resource usage information such as the LOS and direct medical cost. Direct medical costs include hospitalization, medications, imaging examinations, surgery, CTX, and RT. Analysis of indirect medical costs is not included in this study. As mentioned above, the DPC reimbursement system pays for the surgery, RT, and CTX as fee-for-service (FFS), while other costs for hospitalization, medications, blood examination, imaging examination, and physician time are inclusive. As the cost of chemotherapeutic drugs is inclusive, the dose and duration of CTX are not reflected in DPC reimbursement. The medical cost was converted into US dollars based on an exchange rate at 103 Japanese Yen per US dollar.

Patient extraction

In this study, we focused on patients with primary malignant brain tumors of neuroepithelial origin. The DPC database does not include diagnostic histological information. The ICD-10 codes denote different intracranial primary malignant tumors as follows: C71, malignant brain tumor; C70, malignant intracranial tumor originating in the meninges; and C72, malignant intracranial tumor originating in the cranial nerves. In order to extract information on primary malignant brain tumors of neuroepithelial origin, we used C71 as the DPC ICD-10 code. Using this code, we assumed that we could extract data on astrocytic, oligodendroglial, ependymal, pineal, embryonal, germ cell, and other neuroepithelial tumors. Primary central nervous system lymphomas were not included as they are specified by a different code. We also assumed that no malignant meningeal, mesenchymal, or peripheral nerve sheath tumors were included in the analysis. Patients with malignant tumors in the sellar region and pituitary tumors were also excluded. In total, data for 6,142 patients with a primary malignant brain tumor were retrieved using code C71. Data analysis was performed for these patients.

Evaluation of treatment modalities

The DPC database includes sub-codes that specify the surgical procedures and adjuvant therapy used, allowing demographic data to be stratified according to the treatment modalities described below.

Surgery

The type of surgical treatment is specified by a K-code. In this study, we aimed to extract data on surgical procedures related directly to tumor treatment. We used codes K169 (tumor removal by craniotomy), K171 (transsphenoidal tumor removal), and K151-2 (tumor removal by extended skull base craniotomy) to extract data for patients who had a tumor removed by craniotomy. In addition, to extract data on biopsies, we used codes K148 (only craniotomy), K1541 (functional stereotactic surgery [hemilateral]), and K164-4 (stereotactic hematoma evacuation) because stereotactic tumor biopsy was not K-coded as of the end of this study period. We also included codes K1492 (decompressive craniectomy), K145 (extra-ventricle drainage), and K174 (operation for hydrocephalus). Collectively, to extract data for malignant brain tumor patients who underwent surgery, we used codes K-169, K148, K1541, K164-4, K171, K151-2, K1492, K145, and K174 (Table 1).

CTX

In order to evaluate the use of chemotherapeutic drugs, we selected the following agents that are used in the neurosurgical clinic: TMZ, nimustine (ACNU), interferon, bevacizumab, methotrexate, carmustine, ifosfamide, cisplatin, carboplatin, vincristine, cyclophosphamide, and procarbazine. We considered that CTX had been administered when there was a code for CTX and one of these drugs were listed.

Table 1 **Number of extracted patients according to K-code**

K-code	Description	Number of patients (%)
K1691	Tumor removal by craniotomy (pineal region)	18 (0.9)
K1692	Tumor removal by craniotomy	1688 (79.8)
K148	Craniotomy only	34 (1.6)
K1541	Functional stereotactic surgery (hemilateral)	83 (3.9)
K164-4	Stereotactic hematoma evacuation	45 (2.1)
K145	Extraventricular drainage	66 (3.1)
K174	Operation for hydrocephalus	129 (6.1)
K1492	Decompressive craniectomy	22 (1.0)
K151-2	Tumor removal by extended skull base craniotomy	13 (0.6)
K171	Transsphenoidal tumor removal	6 (0.3)
K171-2	Endoscopic transsphenoidal tumor removal	11 (0.5)

RT

In Japan, payments for RT are classified and coded according to the treatment modality. External beam therapy (EBT) is coded as M001, and stereotactic radiosurgery (SRS) and stereotactic RT (SRT) are coded as M001-2 and M001-3, respectively. In this study, we identified patients treated with RT and sub-categorized them by modality using these codes.

Statistical analysis

LOS and medical cost were treated by log transformed value. Geometric means and their 95% confidence intervals were calculated. A general linear mixed model analysis was performed to determine statistically significant differences in mode of therapy on LOS or medical cost adjusted for age, sex, and the Charlson and JCS scores as a fixed effect and the hospital as a random effect. The differences in the number of patients per hospital were also determined. Reference population was set on male, average age (46.28), JCS = 0, and average Charlson score = 4.28, and then estimates and their 95% confidence interval for LOS and medical cost were presented. A value of $p < 0.05$ was considered statistically significant. The reference category for the number of patients per hospital was 1–10, and the JCS score had a value of 0, 1, 2, or 3. The analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical statement

The research plan was designed by the authors and approved by the Institutional Review Board of Kyushu University. The requirement for individual informed consent was waived.

Results

Patient demographics

Of 6,142 primary malignant brain tumor patients, 57% were male and 43% were female. With regard to age, 18% of the patients were children aged 15 years or younger, 65% were adult patients aged between 16 and 70 years, and 17% were elderly patients aged over 71 years. The tumor type was unknown in 3% of the patients; 58% of patients had a primary tumor and 39% of patients had recurrent disease (Table 2). The number of patients treated in a single institution varied between 1 and 277, with a median of 7 (Fig. 1), indicating that many hospitals treated less

Table 2 Demographics and clinical characteristics of patients included in this study

Total, n	6,142
Male, n (%)	3,489 (56.8)
Age	
≤15, n (%)	1,091 (17.8)
16–70, n (%)	3,984 (64.9)
≥71, n (%)	1,067 (17.4)
Primary, n (%)	3,549 (57.8)
Japan Coma scale	
0, n (%)	4,211 (68.6)
1-digit code, n (%)	1,592 (25.9)
2-digit code, n (%)	240 (3.9)
3-digit code, n (%)	99 (1.6)
Charlson score	
2, n (%)	1,948 (31.7)
3, n (%)	733 (11.9)
4, n (%)	757 (12.3)
5, n (%)	962 (15.7)
6–10, n (%)	1643 (26.8)
11–15, n (%)	99 (1.6)

than 20 primary malignant brain tumor patients (small-volume hospitals), and a few hospitals treated more than 100 patients (high-volume hospital).

Surgery

Of 6,142 primary malignant brain tumor patients, 2,236 were assigned a surgical K-code, and of these, 1,963 patients had a K-code related to surgery to treat the tumor (Fig. 2A, Table 1). The remaining 273 patients underwent procedures not directly related to the tumor, such as brain abscess evacuation, tracheostomy, or central venous catheter insertion. According to data from the Japan Neurosurgical Society, there were 25,160 brain tumor surgeries in neurosurgical hospitals in 2013. Therefore, the number of surgical cases analyzed in this study is equivalent to 7.8% of all brain tumor surgeries in Japan for a period of one year.

Radiation

A total of 1,510 primary brain tumor patients underwent RT (Fig. 2A), of whom, 1,203 were treated using EBT, 90 using SRS, and 217 using SRT. EBT was the most popular radiation modality followed by SRT and SRS in all age groups (Fig. 2B), and the frequency of these modalities were very similar.

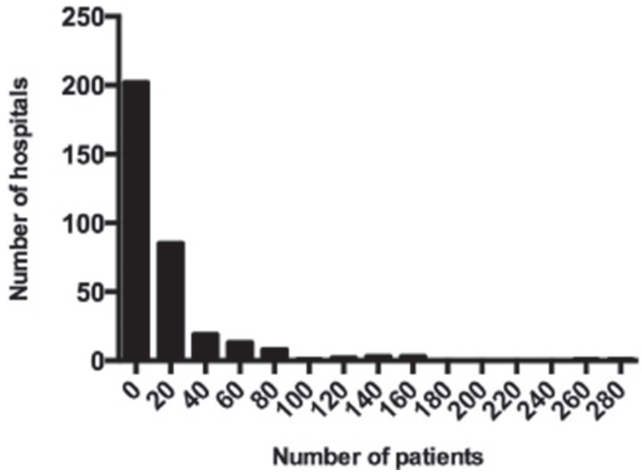

Fig. 1 The distribution of the number of primary malignant brain tumor patients treated at each hospital

CTX

CTX was administered to 3,079 of the 6,142 patients with a primary brain tumor (Fig. 2A), using a total of 4,728 different regimens. As shown in Fig. 3A, the most frequently used drugs were TMZ (41%), followed by etoposide (11%), interferon-β (9%), and carboplatin (9%). Bevacizumab and carmustine were rarely used because they were not covered by health insurance at the start of this study period. With respect to age group, pediatric patients were less frequently administered TMZ compared to adults, but were more frequently treated using etoposide, carboplatin, methotrexate, vincristine, cisplatin, or cyclophosphamide (Fig. 3B). We also investigated the frequency with which combinations of drugs were administered to different age groups (Table 3). In total, combination therapy was used in 871 cases, and combined carboplatin and etoposide (CARE), or combined TMZ and interferon-β, were both commonly used in the adult group. In contrast, combined cisplatin and vincristine was most frequently used for pediatric patients, followed by combinations of carboplatin and etoposide, or ifosfamide, cisplatin, and etoposide (ICE) at a similar frequency. Combined cyclophosphamide, cisplatin, and vincristine therapy (Packer regimen) was also commonly used in the pediatric group.

We focused our analysis on TMZ, as it is the most commonly used chemotherapeutic drug for the treatment of malignant glioma. The most common duration of TMZ administration for initial cases (816 cases) was between 40 and 45 days, which is consistent with the standard concomitant TMZ treatment protocol of 42 days for initial malignant gliomas (Fig. 3C). In addition, in the concomitant TMZ treatment protocol, TMZ therapy and RT were initiated on the same day for most patients (Fig. 3D).

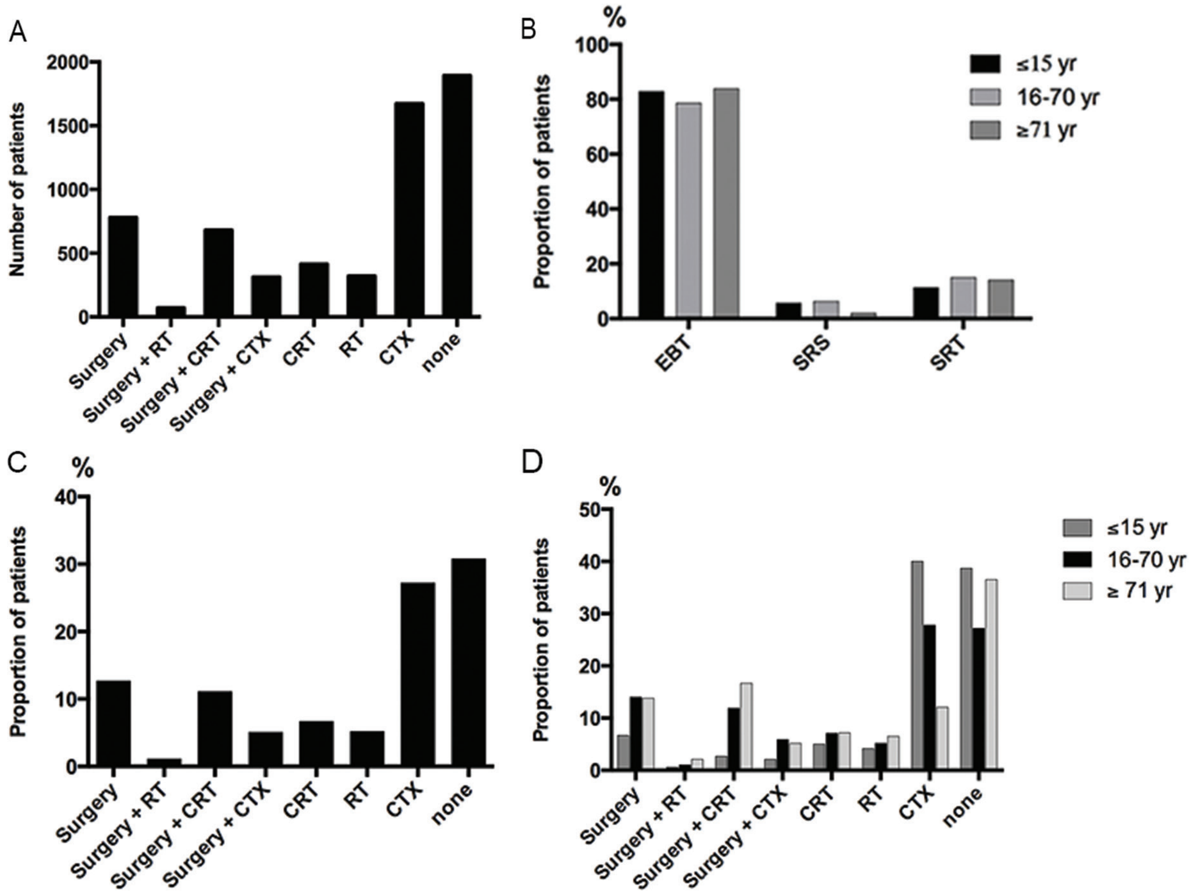

Fig. 2 (A) Frequency of each treatment modality (B) The ratio of different radiotherapy modalities in age groups (C) The distribution of types of therapy for all patients, and (D) by age group

Mode of therapy

The 6,142 primary malignant brain tumor patients were classified into eight groups depending on whether they underwent surgery alone, surgery + RT, surgery + CTX, surgery + chemo-radiotherapy (CRT), RT, CTX, CRT, or none of these (Fig. 2A, C). Patients with primary tumors were most frequently treated using CTX, followed by surgery, and surgery + CRT. Pediatric patients less frequently underwent surgical treatment and were more often treated using CTX compared to adults. Hence, the type of therapy varied between adult and pediatric patients (Fig. 2D).

LOS

We analyzed the LOS with respect to the mode of therapy. The mean LOS of all the patients was 16 days. When we stratified the data according to the mode of therapy, primary tumor patients who underwent surgery had longer hospital stays compared to non-surgically treated patients (Table 4). In the subgroup of primary tumor patients who underwent surgery, the mean LOS was long amongst those who underwent surgery + CRT (73.8 days), followed by surgery + RT (65.5 days), surgery + CTX (38 days), and surgery alone (23.2 days). CRT was the most common treatment administered to patients who did not undergo surgery. When we

Table 3 Combination of chemotherapeutic drug according to the patient age group

Chemotherapeutic drug (n = 871)	≤15 yr (%)	16–70 yr (%)	≥71 yr (%)
Carboplatin + Etoposide	69 (25.7)	253 (43.7)	5 (20.8)
Temozolomide + Interferon-β	22 (8.2)	229 (39.6)	16 (66.7)
Cisplatin + Vincristine	90 (33.6)	19 (3.3)	0
Ifosfamide + Cisplatin + Etoposide	60 (22.4)	46 (7.9)	0
Cyclophosphamide + Cisplatin + Vincristine	27 (10.1)	7 (1.2)	0
Procarbazine + Nimustine + Vincristine	0	25 (4.3)	3 (12.5)

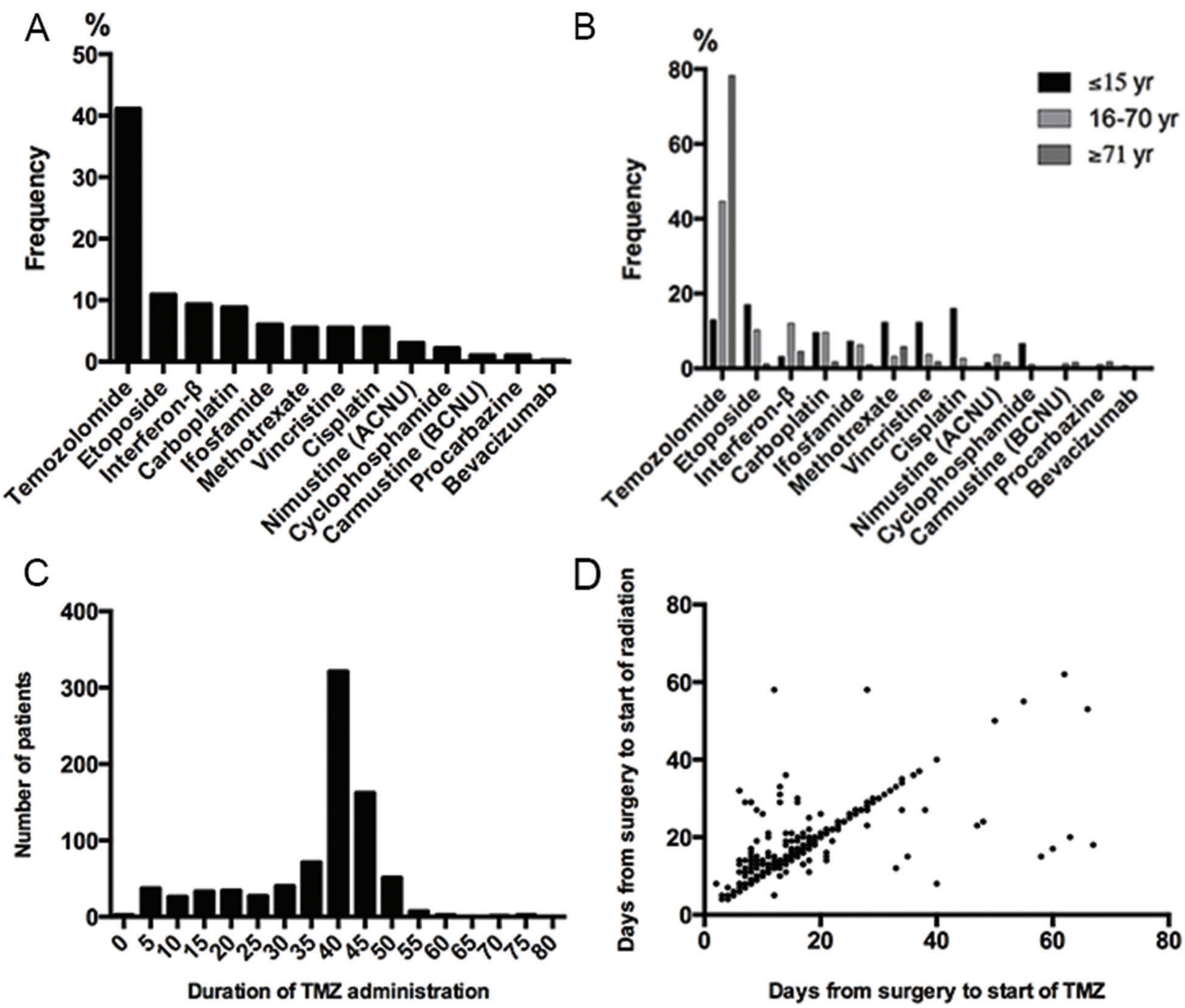

Fig. 3 Frequency with which each type of chemotherapeutic drug was administered for primary malignant brain tumor patients (for a total of 4,728 regimens) in (A) all patients and (B) patients in different age groups (C) The distribution of the duration of temozolomide (TMZ) administration for primary malignant brain tumor patients undergoing initial treatment (D) Relationship between the time between surgery and the start of TMZ or radiotherapy for primary malignant brain tumor patients undergoing initial treatment

stratified the patients according to the number of primary malignant brain tumor patients treated by their hospital, the LOS was significantly shorter in high-volume hospitals than in low-volume hospitals (Table 5).

Direct medical cost

The DPC dataset also lists inpatient direct medical costs including surgery, CTX, RT, hospital stay, and other diagnostic and treatment modalities. The average direct medical cost for treating the patients was 1,077,690 yen. Consistent with the LOS, surgical treatment was much more expensive than non-surgical therapy (Table 4). Surgery + CRT was the most expensive treatment, at 5,926,220 yen, followed by surgery + RT (4,757,000 yen) and surgery + CTX (3,937,540 yen). The mean cost of surgery was 2,752,300 yen. We found that medical cost was higher in hospitals treating 21–50 patients compared to those treating 1–10 patients (Table 6). However, although the medical cost was lower in high-volume hospitals than in small-volume hospitals, this difference was not statistically significant. In the DPC system, days and dose of TMZ administration for the primary patients are not translated in the medical expenditure, which means that medical cost depends on whether TMZ is administered. We analyzed medical expenditure for TMZ only patients (420 cases) and concomitant TMZ patients (816 cases) according to the number of the patients per hospital. In TMZ only patients, the average medical cost was 1,138,620 yen, whilst for concomitant TMZ

Table 4 Length of hospital stay and medical cost depending on therapeutic modalities

		Length of stay (days)			Medical cost (10 thousand yen)	
Modalities	n	Geometric mean	95% CI	n	Geometric mean	95% CI
None	1893	8.0	0.6–101.3	1774	39.1	4.1–369.1
CTX	1672	11.0	1.3–93.7	1640	64.5	11.3–370.1
RT	321	11.9	1.4–98.4	302	97.1	32.8–287.8
CRT	414	37.9	7.8–183.6	408	230.5	69.8–761.4
Surgery	779	23.2	7.4–73.2	763	275.2	132.5–571.5
Surgery + CTX	313	38.0	9.7–148.2	309	393.8	181.3–855.3
Surgery + RT	70	65.5	26.5–162.4	68	475.7	264.3–856.1
Surgery + CRT	680	73.8	35.0–155.7	672	592.6	341.3–1029.0

Table 5 Length of hospital stay according to the patient volume of the hospital

		Length of stay (days)		Analysis of mixed model		
					Estimates for reference population	
Patient volume	n	Geometric mean	95% CI	*p* value	Estimates	95% CI
1–10	998	24.6	2.7–227.5	–	18.1	16.4–20.0
11–20	863	20.8	2.2–194.4	0.256	16.6	14.5–18.9
21–50	1109	18.4	1.5–221.1	0.854	18.4	15.8–21.5
51–100	1480	16.0	1.4–182.9	0.181	15.8	13.2–18.9
≧101	1692	10.0	0.8–124.5	0.001	11.5	8.9–14.9

patients it was 4,424,300 yen, indicating that the direct medical cost increases more than two fold when it includes RT in Japan. In both groups, the medical cost was not statistically different among hospitals with different patient volumes (Table 6).

Discussion

In this study, we analyzed the current status of malignant brain tumor treatment using the DPC database in Japan. The advantage of using DPC data is that patient and hospital information, diagnosis, procedures, and administrative claim data are completely enumerated for all of the patients in the participating hospitals. Another benefit is that all of these data can be collected from the administrative claims database of inpatients without additional effort by medical staff. This study covered 370 hospitals (44%) out of all 847 Japanese Neurosurgical Society training program core and branch hospitals. Thus, we think that our study is a good representation of the current trends in malignant brain tumor treatment in Japan. Approximately 24,000 patients are newly diagnosed with primary malignant brain cancer annually in the United States.[3,4] In this study, 3,562 (58%) of the 6,142 malignant tumor patients had primary disease, which is equivalent to 15% of all the patients in the United States.

Our analysis revealed that many of the hospitals treated less than 20 patients with primary malignant brain tumors in a single year. There are very few high-volume centers treating more than 100 malignant brain tumor patients per year in Japan, in contrast with the USA, Europe, Korea, and China, where malignant brain tumor patients are treated in high-volume core center hospitals. Regarding the use of cytotoxic chemotherapeutic drugs, we found that TMZ was administered to approximately 40% of patients, and that the next most frequently used drug was administered to less than 10% of patients, indicating that TMZ is the most widely prescribed drug for treating primary malignant brain tumors. However, amongst pediatric patients, TMZ was less frequently administered than platinum-based drugs, etoposide, vincristine, and ifosfamide. This may be because TMZ offers no significant benefit in pediatric

Table 6 Direct medical cost according to the patient volume of the hospital

	Medical cost (10 thousand yen)			Analysis of mixed model		
					Estimates for reference population	
Patient volume	n	Geometric mean	95% CI of geometric mean	*p* value	Estimates	95% CI
1–10	977	133.5	13.5–1318.3	–	110.1	99.2–122.1
11–20	795	135.6	13.4–1373.9	0.334	119.3	103.7–137.3
21–50	1063	134.0	11.6–1549.2	0.011	139.7	119.0–163.9
51–100	1472	110.2	8.2–1475.4	0.655	115.2	96.1–138.1
≧101	1629	72.0	5.5–941.0	0.224	92.9	71.7–120.3

TMZ only

		Medical cost (10 thousand yen)	
Patient volume	n	Geometric mean	95% CI
1–10	82	162.2	27.4–958.9
11–20	55	107.6	11.8–984.2
21–50	82	137.1	17.4–1080.5
51–100	105	101.7	11.3–918.6
≧101	93	83.1	12.5–554.3

TMZ + RT (concomitant)

		Medical cost (10 thousand yen)	
Patient volume	n	Geometric mean	95% CI
1–10	149	463.7	160.3–1341.1
11–20	125	460.3	159.3–1329.6
21–50	169	460.2	161.5–1311.3
51–100	226	410.6	116.4–1449.0
≧101	140	437.0	146.9–1300.2

Reference population means male, average age(46.28), JCS = 0, and average Charlson score = 4.28

patients,[14] or, in part, because germ cell and embryonal tumors occur frequently in pediatric patients. Indeed, combination CTX, which is usually administered for germ cell and embryonal tumors, was most frequently used to treat pediatric tumors.

According to the standard protocol, RT consists of fractionated focal irradiation at a dose of 2 Gy per fraction for a total dose of 60 Gy, which is administered once daily 5 days per week over a period of 6 weeks. Concomitant CTX consisted of TMZ at a dose of 75 mg per square meter per day, administered 7 days per week from the first day of RT until the last day of RT. We found that TMZ administration most frequently lasted 40–45 days for many of the initial primary malignant brain tumor patients. In addition, RT and TMZ administration often started at the same time postoperatively, suggesting that concomitant CTX and RT is the current trend for initial primary malignant brain tumors in Japan. Taken together, our findings demonstrate that TMZ treatment for initial primary malignant brain tumor patients was undertaken according to the international standard protocol in Japanese neurosurgical hospitals.

We also evaluated the frequency with which different therapies were used to treat the patients. The most frequent treatment was CTX (27%), followed by surgery (13%), and surgery + CRT (11%). No single treatment type was used for more than 30% of patients. This differs from findings using the Brain Tumor Registry dataset,[15] where surgery + CRT was most frequently used (51%), followed by surgery (18%) and surgery + RT (18%). Observation alone and other treatments accounted for only 2% of patients. There are a number of possible reasons for this discrepancy between the datasets. First, because tumor histology is not included in the DPC dataset, it is possible that this varies significantly between the datasets, which would be reflected in the different therapies used. Second, the TMZ administration for malignant glioma was covered by Japanese health insurance in 2006, which means that Brain Tumor Registry data were collected before the TMZ era between 2001 and 2004. This might explain why CTX (possibly involving TMZ) was used more frequently for patients included in our dataset. Third, actively treated patients in the university and national center (core) hospitals might have been selectively included in the Brain Tumor Registry. Given that our data are collected from all of the patients in registered hospitals including branch hospitals, our results reflect the current situation regarding malignant brain tumor treatment after admission to Japanese neurosurgical hospitals.

Sub-analysis of therapy type for primary tumor patients demonstrated that pediatric patients less frequently underwent surgical treatment, including surgery alone or combined with CRT, compared with adult and elderly patients. However, pediatric patients more frequently underwent CTX. This suggests that pediatric patients are more often treated using CTX than RT, and indeed the prevalence of RT regardless of surgery and CTX was 7.5%, 18%, and 25% in pediatric, adult, and elderly patients, respectively. Regarding the type of RT used, SRS/SRT accounted for a quarter of all RT used to treat primary brain tumors.

Our analysis also revealed novel findings regarding health care data in Japan. Japan sustains full and equal health insurance coverage with a single reimbursement fee system for all physicians and patients.[16] Under this system, the mean LOS for primary malignant brain tumor patients was 16 days. Hospital stays generally get longer with increasingly complex modes of therapy. According to the 2011 data of the Ministry of Health, Labour and Welfare in Japan, the mean LOS or all cancer patients was 19.5 days.[17] The mean LOS in our dataset was closer to this value (16 days). Accordingly, the mean LOS in the surgically treated groups was 46 days. The Ministry of Health, Labour and Welfare data also reveal that patients who undergo craniotomy have the longest stay in hospital (mean 48.5 days) among all patients undergoing surgery. As data for patients with benign tumors are also included in the Ministry of Health, Labour and Welfare dataset, this study is the first to demonstrate that the LOS of malignant brain tumor patients depends on the mode of therapy. Given that CTX or RT is more likely to be administered as an inpatient treatment in Japan, we need to be careful in comparing healthcare resource usage between countries.

In this study, we first evaluated the direct medical cost for the treatment of inpatient primary malignant brain tumor patients in Japan. The mean medical cost of all 6,142 patients was 1,077,690 yen, which is equivalent to 10,463 US dollars at the exchange rate of 103 Japanese yen per US dollar. A recent publication showed that the total direct cost for surgery and RT ranged from 50,600 to 92,700 US dollars in the United States.[9] We found that the medical cost of patients undergoing both surgery and RT was 4,757,000 yen (46,184 dollars) in this study. Although the direct medical cost cannot be compared between countries with different health insurance systems, it seems clear that the direct medical expenditure for combined surgery and RT is within the same range in both countries. As expected, the medical costs are greater for patients undergoing surgery, RT, and CTX, at 5,926,220 yen (57,536 dollars). Concerning TMZ treatment, the cost of treating patients undergoing concomitant TMZ therapy after surgery was 4,424,300 yen (42,541 dollars). A previous study found that the medical cost of inpatients with concomitant TMZ therapy was 59,121 US dollars in the United States,[18] which indicates that medical costs including TMZ treatment is lower than that in the United States. Furthermore, our results showed that the direct medical cost of patients undergoing surgery with only TMZ and concomitant TMZ is similar among the hospitals regardless of patient volume. This indicates that the same level of treatment is administered for primary malignant brain tumor patients across all hospitals in Japan, which may partly be because TMZ use is included in the DPC system, and thus, the dose and duration of TMZ administration is not reflected in the direct medical cost.

A limitation of this study is that detailed information concerning the tumor site, histology, and extent of resection was not available in the DPC data set. Furthermore, because the DPC dataset only includes mortality data for the corresponding admission period, information on patient outcomes after discharge is not included. Thus, the survival rate cannot be calculated. Moreover, outpatient data are not included. Nevertheless, this study provides a clear picture of the current trend of treatment for malignant brain tumors in Japan. If we can link this population-based dataset to the standard registration database, we could obtain very useful information regarding the treatment of malignant brain tumor patients.

In summary, we have assessed the current treatment and healthcare resource usage of malignant brain tumor patients in Japan using exhaustive claim data from 6,142 patients. This study could act as a road map towards the establishment of a better health care policy.

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Conflict of Interest

The authors declare that there are no potential conflicts of interest in relation to this study.

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RESEARCH ARTICLE

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Development and validation of a score for evaluating comprehensive stroke care capabilities: J-ASPECT Study

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Abstract

Background: Although the Brain Attack Coalition recommended establishing centers of comprehensive care for stroke and cerebrovascular disease patients, a scoring system for such centers was lacking. We created and validated a comprehensive stroke center (CSC) score, adapted to Japanese circumstances.

Methods: Of the selected 1369 certified training institutions in Japan, 749 completed an acute stroke care capabilities survey. Hospital performance was determined using a 25-item score, evaluating 5 subcategories: personnel, diagnostic techniques, specific expertise, infrastructure, and education. Consistency and validity were examined using correlation coefficients and factorial analysis.

Results: The CSC score (median, 14; interquartile range, 11–18) varied according to hospital volume. The five subcategories showed moderate consistency (Cronbach's $\alpha = 0.765$). A strong correlation existed between types of available personnel and specific expertise. Using the 2011 Japanese Diagnosis Procedure Combination database for patients hospitalized with stroke, four constructs were identified by factorial analysis (neurovascular surgery and intervention, vascular neurology, diagnostic neuroradiology, and neurocritical care and rehabilitation) that affected in-hospital mortality from ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. The total CSC score was related to in-hospital mortality from ischemic stroke (odds ratio [OR], 0.973; 95% confidence interval [CI], 0.958–0.989), intracerebral hemorrhage (OR, 0.970; 95% CI, 0.950–0.990), and subarachnoid hemorrhage (OR, 0.951; 95% CI, 0.925–0.977), with varying contributions from the four constructs.

Conclusions: The CSC score is a valid measure for assessing CSC capabilities, based on the availability of neurovascular surgery and intervention, vascular neurology, diagnostic neuroradiology, and critical care and rehabilitation services.

Keywords: Ischemia, Stroke, Hemorrhage, Cerebrovascular circulation, Risk factors

Background

Stroke is the fourth leading cause of mortality and the most common cause of permanent morbidity in Japan, causing an enormous socioeconomic burden. The public health implications of stroke care globally, including in Japan, are profound. Despite accelerating progress in stroke therapy, implementation of appropriate acute treatment remains essential for decreasing the associated mortality and permanent morbidity. In 2000, the Brain Attack Coalition discussed the concept of primary stroke centers and later proposed the design of comprehensive stroke centers (CSCs) [1, 2]. Most stroke patients can be adequately treated at a primary stroke center (PSC), and the Joint Commission established programs for the certification and performance measurement of PSCs [3]. The concept and recommended key components of a CSC enable intensive patient care and the use of specialized techniques that are not available at most PSCs [1, 4]. To continuously monitor the efficiency of care, reliable

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measures of hospital capabilities and performance are needed. Although the Joint Commission and several US states have started certification processes for PSCs and CSCs [5–8], an established, simple scoring system does not exist to evaluate the comprehensive acute stroke care capabilities of CSCs. To this end, a simple tool for assessing CSC capabilities would be useful for monitoring service quality and enabling its improvement [4]. In 2010, we started the J-ASPECT study (Nationwide survey of Acute Stroke care capacity for Proper dEsignation of Comprehensive stroke cenTer in Japan) to establish optimal nationwide implementation of stroke centers to improve acute stroke outcomes. We modified the above recommendations to reflect the specific circumstances in Japan and developed a CSC score; this tool was validated using the nationwide Diagnosis Combination Procedure (DPC) database, created during the first year of this study.

Methods

Content validity

In the first step of the J-ASPECT study, we investigated the current conditions of stroke hospitals in Japan. We created a 49-item questionnaire examining various aspects of stroke care, including medical systems, emergency systems, stroke rehabilitation, education, and medical performance. Some recommended items, such as ventriculostomy availability, were excluded from our questionnaire for the sake of simplicity and to increase the survey response rate since the items seemed identical to the recommendations of board-certified (BC) neurosurgeons in Japan. Other items, such as availability of transesophageal echocardiography, were excluded because of their very low expected usage, which would make an evaluation of their impact on mortality rates difficult. In February 2011, the questionnaire was mailed to 1369 certified training institutions belonging to the Japan Neurosurgical Society, the Japanese Society of Neurology, and the Japan Stroke Society. Based on this questionnaire, the overall organizational and staffing levels of the hospitals, in terms of CSC capacity, were scored following the Brain Attack Coalition recommendations, after reviewing the literature describing CSCs and conducting a thorough discussion with an expert panel [9]. Advanced acute stroke care capabilities were assessed based on 25 items divided into 5 subcategories (listed in Table 1). One point was assigned for each recommended item that the hospital met, resulting in a maximum total score of 25; subcategory scores were also calculated.

Consistency

Cronbach's α was calculated to evaluate the consistency between the 5 CSC score subcategories used for assessing CSC capabilities. To determine the influence of each subcategory, α-values were also calculated for all combinations of the four subcategories. Correlations between the 25 CSC score items were determined using tetrachoric correlation coefficients to evaluate individual items measured with different constructs.

Table 1 The availability of comprehensive stroke center score components

Components	Items	Item No	Number	Percent
Personnel	Neurologists	1	358	47.8
	Neurosurgeons	2	694	92.7
	Endovascular physicians	3	272	36.3
	Critical care medicine	4	162	21.6
	Physical medicine and rehabilitation	5	113	15.1
	Rehabilitation therapy	6	742	99.1
	Stroke rehabilitation nurses	7	102	13.6
Diagnostics (24/7)	CT[a]	8	742	99.1
	MRI[b] with diffusion	9	647	86.4
	Digital cerebral angiography	10	602	80.4
	CT angiography	11	627	83.7
	Carotid duplex ultrasound	12	257	34.3
	TCD[c]	13	121	16.2
Specific expertise	Carotid endarterectomy	14	603	80.5
	Clipping of intracranial aneurysm	15	685	91.5
	Hematoma removal/draining	16	689	92.0
	Coiling of intracranial aneurysm	17	360	48.1
	Intra-arterial reperfusion therapy	18	498	66.5
Infrastructure	Stroke unit	19	132	17.6
	Intensive care unit	20	445	59.4
	Operating room staffed 24/7	21	451	60.2
	Interventional services coverage 24/7	22	279	37.2
	Stroke registry	23	235	31.4
Education	Community education	24	369	49.3
	Professional education	25	436	58.2

[a]computed tomography; [b]magnetic resonance imaging; [c]transcranial Doppler

Construct validity

Factorial analysis, based on tetrachoric correlation coefficients [10], was performed using principal factor analysis to explore possible potential groupings of the 25 items into a more limited number of components. The selection of the number of components was based on the Eigen values. To understand the meaning of the components, promax rotation was used.

Predictive validity

Using the Japanese DPC database for patients hospitalized with strokes during the 2011 fiscal year, we examined the differential effects of the items on mortality and poor outcomes (modified Rankin Scale: 3–6, at discharge) associated with ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). This cross-sectional survey used the DPC discharge database for the institutions participating in the J-ASPECT study. The DPC database is a mixed-case classification system that is linked with the lump-sum payment system, launched in 2002 by the Ministry of Health, Labor and Welfare of Japan [11]. In 2010, approximately 1388 acute care hospitals, representing about 50% of the total hospital beds, had adopted the DPC data system. Data regarding practices were obtained from the DPC database; the attending physician is responsible for each patient's clinical data entry. The details of this database have been described elsewhere [12].

Of the 749 hospitals that responded to the institutional survey of advanced stroke care capabilities, 256 agreed to participate in the DPC discharge database study. Consecutive patients, hospitalized between April 1, 2010 and March 31, 2011, were identified in the annual discharge database using the International Classification of Diseases (ICD)-10 diagnosis codes related to IS (I63.0-9), nontraumatic ICH (I61.0-9, I62.0-1, I62.9), and SAH (I60.0-9). Patients with scheduled admissions were excluded from analysis. This research was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center and, if required, by the participating hospitals.

We used hierarchical logistic regression models to determine relationships between hospital CSC scores, reflecting the capacities they were equipped with, and mortality. Each model had two levels of hierarchy (hospital and patient), and considered the random effects of hospital variables as well as the fixed effects of CSC scores, patient age and sex, and Japan Coma Scale (JCS) scores. Interactions such as those between the JCS and CSC scores were not included in the model. The analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA), and R, version 3.2.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the selected 1369 certified training institutions, 749 (55%) responded to the acute stroke care capability survey. Among the surveyed hospitals, 62% had more than 300 beds, and 51% had more than 200 acute patients (Table 2). Clipping of intracranial aneurysms (IAs) was performed more frequently than any other procedure (median/hospital, 15), followed by craniotomy removal of ICH (6), intravenous infusion of recombinant tissue plasminogen activator (5), and coiling of IAs (3). The availability of each item is shown in Table 1. Even within the same component, the availability of each item varied. Low availability values were noted for IA coiling (48.1%) in the specific expertise component and for stroke units (17.6%) in the infrastructure component.

Table 2 Hospital characteristics

Beds per hospital, n (%)	
20–49	16 (2.1)
50–99	30 (4.0)
100–299	232 (31.0)
300–499	260 (34.7)
> 500	207 (27.6)
Unknown	4 (0.5)
Acute stroke patients per hospital, n (%)	
≤ 49	51 (6.8)
50–99	78 (10.4)
100–199	199 (26.6)
200–299	155 (20.7)
> 300	228 (30.4)
Unknown	38 (5.1)
Treated patients per hospital, median (IQR[a])	
Tissue plasminogen activator	5 (2–10)
Intra-arterial thrombolysis/percutaneous angioplasty	0 (0–2)
Carotid endarterectomy	1 (0–4)
Carotid stenting	1 (0–7)
Extracranial-intracranial bypass surgery	1 (0–5)
Clipping of intracranial aneurysm	15 (6–27)
Coiling of intracranial aneurysm	3 (0–11)
Craniotomy hematoma removal	6 (2–12)
Stereotactic hematoma removal	0 (0–3)
Endoscopic hematoma removal	0 (0–0)

[a]interquartile range

The distribution of CSC score components, by hospital, is shown in Table 3. The median CSC score was 14 (interquartile range, 11–18). These components showed moderate consistency (Cronbach's $\alpha = 0.765$, for the total score). Removal of any one component resulted in Cronbach's α falling in the range of 0.668–0.776, indicating the absence of substantial influence of individual components. High correlations between the survey components pertaining to personnel and specific expertise were observed (Table 4). For example, there were high correlations between neurosurgeon availability and carotid endarterectomy ($r = 0.821$; items 2 and 14), clipping of IAs ($r = 0.936$; items 2 and 15), and hematoma removal/drainage ($r = 0.949$; items 2 and 16). Similarly, endovascular physician availability was strongly correlated with

Table 3 The distribution of comprehensive stroke center score components and their consistency

Components	Mean	SD	Median	IQR[a]	Cronbach's α
Personnel	3.26	1.25	3	2–4	0.724
Diagnostic	4.00	1.28	4	4–5	0.741
Specific expertise	3.79	1.48	4	3–5	0.668
Infrastructure	2.06	1.43	2	1–3	0.674
Education	1.07	0.83	1	0–2	0.776
Total Score	14.18	4.57	14	11–18	0.765

[a]Interquartile range

coiling of IAs (r = 0.932; items 3 and 17) and intra-arterial reperfusion therapy (r = 0.842; items 3 and 18). Other relationships regarding diagnostics, infrastructure, and education did not stand out.

Factorial analysis, based on promax rotation, revealed four constructs (Table 5). The first pattern contained items pertaining to neurovascular surgery and intervention, such as endovascular physician availability, coiling of IAs, intra-arterial reperfusion therapy, 24/7 interventional services coverage, carotid endarterectomy, hematoma removal/drainage, clipping of IAs, neurosurgeon availability, rehabilitation therapy, 24/7 operating room staffing, and stroke rehabilitation nurse availability. The first pattern had the largest explained variance (43% of total variance). The second pattern included imaging modalities mainly associated with diagnostic neuroradiology (e.g., computed tomography, computed tomography angiography, digital cerebral angiography, and diffusion-weighted magnetic resonance imaging) and intensive care units. The third pattern contained items related to vascular neurology: transcranial Doppler, carotid duplex ultrasound, professional education, community education, stroke registry, and available stroke units. The fourth pattern represented neurocritical care and rehabilitation, and included the availability of neurologists, physical medicine and rehabilitation, and critical care medicine.

A total of 53,170 patients in the cohort were analyzed; the in-hospital mortality was 7.8% for IS, 16.8% for ICH, and 28.1% for SAH (Table 6). Table 7 shows the impact of hospital capacity for each of the 25 items on mortality. Among the four constructs obtained using factorial analysis, the availability of neurologists in neurocritical care and rehabilitation was significantly associated with reduced mortality of patients with IS ($P < 0.05$). The 24/7 availability of interventional service coverage in neurovascular surgery and intervention ($P < 0.05$), availability of intensive care units in diagnostic neurology, and physical medicine and rehabilitation in neurocritical care and rehabilitation ($P < 0.05$) were related to SAH mortality. The total CSC score was related to the mortality associated with IS (OR, 0.973; 95% CI, 0.958–0.989), ICH (OR, 0.970; 95% CI, 0.950–0.990), and SAH (OR, 0.951; 95% CI, 0.925–0.977).

The proportions of poor outcomes (modified Rankin Scale, 3–6) were 49.2% for IS, 65.3% for ICH, and 56.4% for SAH (Table 6). In contrast to mortality, the total CSC score was not significantly associated with poor outcomes in patients having any type of stroke (Table 8). The impact of hospital capacity for each of the 25 items on poor outcomes differed from that for mortality in some aspects. For example, among patients with IS, stroke unit availability were significantly associated with a reduced proportion of poor outcomes ($P < 0.05$). Among patients with ICH and SAH, no significant association was observed between the availability of any item and poor outcomes.

Discussion

We evaluated the consistency and validity of the CSC score; based on the Cronbach's α value of 0.765, the five components were moderately consistent [13]. The validity of the score was evaluated using factorial analysis, which revealed four major constructs. Although the four constructs were determined by the five components: personnel, diagnostic techniques, specific expertise, infrastructure, and education, this study showed a high correlation between the survey components pertaining to personnel and specific expertise. The unique fact that BC neurosurgeons comprise more than 95% of BC endovascular physicians, in Japan, may explain why personnel, specific expertise, and infrastructure components closely related to these different treatment aspects were grouped into the same construct (neurovascular surgery and intervention). Considering their influence on the variance of the CSC scores, temporal trends and geographical disparities focused on this construct may provide critical information for proper accreditation and implementation of CSCs.

With regard to the predictive validity of the CSC score, the four constructs had different effects on mortality and poor outcomes in patients with IS, ICH, and SAH. The availability of neurologists involved in neurocritical care and rehabilitation was significantly associated with reduced in-hospital morality in patients with IS. Recently, the treatment paradigm for acute IS has been changing rapidly, such that the critical role of endovascular intervention following tissue plasminogen activator infusion, for acute IS, has been established by several recent randomized controlled trials (MR Clean, ESCAPE, EXTEND-IA) [14–16]. Of note, however, the acute stroke care survey used in this study and the DPC database were both implemented before these evidences were published in 2015. The availability of BC neurosurgeons at more than 90% of the participating hospitals suggests the importance of multidisciplinary acute stroke care [17].

Table 5 Factor analysis

		Factor 1	Factor 2	Factor 3	Factor 4
		Neurovascular surgery and intervention	Diagnostic neuroradiology	Vascular neurology	Neurocritical care and rehabilitation
	Proportion explained	0.43	0.25	0.19	0.14
Item No	Items	Standardized loadings (pattern matrix)			
3	Endovascular physicians	***0.91***[d]	-0.07	-0.04	0.12
17	Coiling of intracranial aneurysm	***0.89***	-0.11	0.04	0.15
18	Intra-arterial reperfusion therapy	***0.88***	0.00	0.10	-0.05
22	Interventional services coverage 24/7	***0.80***	-0.09	0.05	0.23
14	Carotid endarterectomy	***0.76***	0.24	-0.01	-0.10
16	Hematoma removal/draining	***0.75***	**0.37**	0.06	-0.16
15	Clipping of intracranial aneurysm	***0.73***	**0.37**	0.08	-0.16
2	Neurosurgeons	***0.69***	**0.43**	0.02	-0.22
6	Rehabilitation therapy	***0.59***	0.07	-0.63	0.18
21	Operating room staffed 24/7	***0.59***	0.28	0.00	0.18
7	Stroke rehabilitation nurses	***0.34***	-0.36	0.21	0.20
8	CT[a]	-0.03	***0.89***	-0.21	**0.34**
11	CT angiography	0.08	***0.84***	0.06	-0.17
10	Digital cerebral angiography	**0.36**	***0.70***	0.08	-0.10
9	MRI[b] with diffusion	0.03	***0.59***	0.23	-0.06
20	Intensive care unit	-0.06	***0.50***	0.17	0.22
13	TCD[c]	0.02	0.15	***0.71***	0.04
12	Carotid duplex ultrasound	-0.31	0.26	***0.72***	0.16
25	Professional education	0.23	-0.15	***0.63***	-0.23
24	Community education	0.21	-0.17	***0.56***	0.07
23	Stroke registry	0.24	-0.08	***0.52***	0.10
19	Stroke unit	0.23	-0.05	***0.49***	0.06
1	Neurologists	-0.02	-0.02	0.02	***0.85***
5	Physical medicine and rehabilitation	0.10	-0.09	0.00	***0.72***
4	Critical care medicine	-0.09	0.25	0.14	***0.55***

[a]computed tomography; [b]magnetic resonance imaging; [c]transcranial Doppler; [d]values > 0.300 are shown in bold font

The association between the availability of a stroke care unit and the increased proportion of favorable outcomes after IS, observed in this study, is consistent with a 2009 Cochrane review conducted by the Stroke Unit Trialists' Collaboration that showed the benefits of stroke unit care in terms of reducing death, dependency, and institutional care [18].

The SAH-associated mortality was higher than that associated with IS or ICH, and the condition of the patients with SAH was also more severe and required more urgent intervention. Accordingly, the availability of items representing SAH treatment, such as 24/7 interventional service coverage, intensive care unit, and BC physical medicine and rehabilitation, showed the greatest effects on mortality. The critical role of endovascular coil embolization for ruptured IAs was previously established by the International Subarachnoid Aneurysms Trial [19]. Using Nationwide Inpatient Survey data, Qureshi et al. reported a significant increase in endovascular treatment as well as a decrease in in-hospital mortality (2000–2002, 27%; 2004–2006, 24%) in patients with SAH after publication of the International Subarachnoid Trial (ISAT) in 2002 [20]. However, whether the ISAT results can be generalized to all patients with SAH is questionable because most of the patients enrolled in the study were patients with good clinical grades, having small, anterior circulation aneurysms.

The second common cause of SAH-related death and poor functional outcome is rebleeding [21], and early treatment of the ruptured aneurysm is known to lower the incidence of rebleeding. Intensive care unit and 24/7

Table 4 Correlation coefficients between the 25 survey items

Item No[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1	1.000																								
2	-0.071	1.000																							
3	0.201	0.671	1.000																						
4	0.282	0.243	0.244	1.000																					
5	0.520	0.063	0.259	0.476	1.000																				
6	0.334	0.282	0.239	-0.190	0.140	1.000																			
7	0.171	0.072	0.248	0.054	0.117	0.125	1.000																		
8	0.300	0.451	0.265	0.202	0.037	0.392	0.007	1.000																	
9	-0.018	0.500	0.325	0.054	-0.025	0.043	0.047	0.636	1.000																
10	-0.027	0.827	0.490	0.255	0.058	0.132	-0.005	0.616	0.594	1.000															
11	-0.132	0.701	0.264	0.201	-0.050	0.017	0.055	0.632	0.614	0.830	1.000														
12	0.120	0.215	0.118	0.198	0.016	-0.196	0.158	0.306	0.357	0.332	0.295	1.000													
13	0.155	0.435	0.361	0.156	0.036	-0.142	0.102	0.194	0.287	0.492	0.372	0.713	1.000												
14	0.095	0.821	0.639	0.238	0.155	0.234	0.138	0.281	0.363	0.694	0.492	0.196	0.305	1.000											
15	0.029	0.936	0.669	0.208	0.073	0.253	0.123	0.414	0.405	0.840	0.675	0.253	0.521	0.885	1.000										
16	0.010	0.949	0.709	0.227	0.053	0.263	0.105	0.431	0.429	0.831	0.663	0.256	0.512	0.865	0.987	1.000									
17	0.215	0.648	0.932	0.283	0.270	0.228	0.373	0.262	0.288	0.486	0.243	0.220	0.386	0.648	0.695	0.729	1.000								
18	0.092	0.784	0.842	0.209	0.226	0.215	0.289	0.234	0.407	0.646	0.391	0.247	0.418	0.754	0.793	0.821	0.874	1.000							
19	0.185	0.378	0.277	0.109	0.045	0.049	0.373	0.197	0.333	0.340	0.193	0.206	0.260	0.345	0.408	0.395	0.307	0.357	1.000						
20	0.154	0.358	0.256	0.237	0.086	-0.230	0.012	0.451	0.197	0.416	0.374	0.187	0.229	0.325	0.403	0.416	0.265	0.243	0.291	1.000					
21	0.291	0.599	0.603	0.205	0.155	0.314	0.180	0.484	0.287	0.583	0.429	0.193	0.386	0.714	0.756	0.718	0.564	0.515	0.443	0.382	1.000				
22	0.273	0.515	0.912	0.226	0.218	0.229	0.376	0.347	0.277	0.464	0.224	0.217	0.400	0.538	0.594	0.626	0.895	0.762	0.321	0.283	0.697	1.000			
23	0.203	0.314	0.360	0.145	0.210	0.014	0.213	0.059	0.342	0.357	0.253	0.287	0.406	0.373	0.425	0.451	0.385	0.405	0.381	0.165	0.369	0.362	1.000		
24	0.193	0.346	0.298	0.080	0.134	0.188	0.104	0.179	0.219	0.234	0.079	0.249	0.414	0.266	0.337	0.334	0.293	0.314	0.408	0.174	0.303	0.344	0.315	1.000	
25	0.038	0.425	0.230	0.025	0.073	-0.114	0.055	0.012	0.312	0.292	0.260	0.193	0.289	0.373	0.422	0.395	0.267	0.359	0.417	0.101	0.282	0.221	0.311	0.576	1.000

[a]Item No in Table 1

Table 6 Demographics of the patient cohort at diagnosis, mortality, and severe disability at discharge

	Total		IS[a]		ICH[b]		SAH[c]	
	(n = 53170)		(n = 32671)		(n = 15699)		(n = 4934)	
	N	%	N	%	N	%	N	%
Male	29353	55.2	18816	57.6	9030	57.5	1584	32.1
Age (years)								
18–50	3515	6.6	1328	4.1	1271	8.1	927	18.8
51–60	5824	11.0	2742	8.4	2171	13.8	934	18.9
61–70	11744	22.1	6894	21.1	3640	23.2	1242	25.2
71–80	15825	29.8	10342	31.7	4466	28.4	1048	21.2
81–106	16262	30.6	11365	34.8	4151	26.4	783	15.9
Hypertension	39918	75.1	22531	69.0	13281	84.6	4229	85.7
Diabetes mellitus	13725	25.8	9318	28.5	3278	20.9	1174	23.8
Hyperlipidemia	15015	28.2	11104	34.0	2529	16.1	1412	28.6
Smoking (n = 44842)	12761	24.0	8188	25.1	3540	22.5	1074	21.8
Japan Coma Scale								
0	19635	36.9	15027	46.0	3620	23.1	1024	20.8
1-digit code	19371	36.4	12375	37.9	5934	37.8	1117	22.6
2-digit code	6937	13.0	3396	10.4	2705	17.2	852	17.3
3 digit code	7227	13.6	1873	5.7	3440	21.9	1941	39.3
Emergency admission by ambulance	31995	60.2	17336	53.1	10909	69.5	3830	77.6
Mortality	6522	12.3	2535	7.8	2630	16.8	1384	28.1
Poor outcome (modified Rankin Scale 3–6) at discharge. (N = 51719)	28238	54.6	15566	49.2	10044	65.3	2721	56.4

[a]ischemic stroke; [b]intracerebral hemorrhage; [c]subarachnoid hemorrhage

interventional coverage availability were significant factors associated with decreasing in-hospital mortality after SAH. These findings are explained by the importance of early obliteration of ruptured aneurysms for preventing rebleeding and by the early detection and appropriate treatment of vasospasms, another important cause of morbidity and mortality in patients with SAH. The study provided additional evidence that the availability of endovascular treatment and surgical clipping may reduce in-hospital mortality in patients with SAH [22]. Another recent study also showed that an early mobilization program for patients with aneurysmal SAH is feasible and safe [23]. In addition, appropriate nutritional care from the acute stage is reported to be essential for improving functional outcomes and reducing post-SAH mortality [24]. Taken together, the significant association between the availability of BC physical medicine and rehabilitation and reduced mortality observed in our study reinforces the importance of comprehensive care capabilities, including early rehabilitation and nutritional care for patients with SAH, to prevent complications. Further investigation is required to understand the role of BC physical medicine and rehabilitation in reducing SAH-associated mortality.

Finally, the total CSC score correlated with reduced mortality for all types of stroke, supporting the usefulness of this score as a comprehensive measure of acute stroke care capabilities. Another study showed that hemorrhagic stroke patients admitted to CSCs were more likely to receive neurosurgical and endovascular treatments and to be alive at 90 days than patients admitted to other hospitals. The authors used certification by the New Jersey Department of Health and Senior Services to identify CSCs. The impacts of CSCs on mortality determined in that study are similar to the results obtained using our simple scoring system [25].

In contrast to its impact on in-hospital mortality, the total CSC score did not show a significant impact on poor functional outcomes in patients with any type of stroke. Similarly, no specific item had a significant impact on poor outcomes in patients with hemorrhagic stroke. In patients with IS, the significant role of the presence of a stroke unit in reducing poor outcomes, observed in the present study, was consistent with the results of a previous report [26]. A validation study investigating functional outcomes using the DPC database may be necessary to explain the disparities between the total CSC scores (and specific items) on mortality and poor functional outcomes.

Table 7 The effect of items on mortality

Item No	Items	IS[a] (n = 32671)			ICH[b] (n = 15699)			SAH[c] (n = 4934)		
		OR[d]	95% CI[e]		OR	95% CI		OR	95% CI	
3	Endovascular physicians	0.832	0.653	1.060	0.896	0.671	1.198	1.309	0.906	1.891
17	Coiling of intracranial aneurysm	1.062	0.832	1.355	1.075	0.797	1.451	0.982	0.667	1.444
18	Intra-arterial reperfusion therapy	1.155	0.931	1.434	0.919	0.706	1.194	0.854	0.608	1.201
22	Interventional services coverage 24/7	1.071	0.831	1.379	1.145	0.844	1.555	0.674[j]	0.458	0.992
14	Carotid endarterectomy	0.945	0.708	1.262	0.833	0.595	1.165	0.789	0.503	1.237
15 and 16	Clipping of intracranial aneurysm and hematoma removal/draining	0.798	0.465	1.368	0.537	0.266	1.088	0.359	0.082	1.564
2	Neurosurgeons	0.905	0.530	1.546	1.513	0.744	3.077	0.840	0.230	3.071
6	Rehabilitation therapy	1.000			1.000			1.000		
21	Operating room staffed 24/7	0.986	0.826	1.176	0.956	0.769	1.187	1.217	0.921	1.610
7	Stroke rehabilitation nurses	1.021	0.831	1.253	1.019	0.803	1.293	1.074	0.803	1.436
8	CT[f]	0.963	0.208	4.462	0.515	0.035	7.590	1.000		
11	CT angiography	1.127	0.877	1.449	0.820	0.608	1.107	0.978	0.662	1.446
10	Digital cerebral angiography	0.840	0.652	1.082	1.243	0.917	1.684	1.068	0.722	1.580
9	MRI[g] with diffusion	1.117	0.849	1.471	0.844	0.605	1.176	0.897	0.581	1.383
20	Intensive care unit	1.032	0.897	1.188	0.964	0.813	1.144	0.795[j]	0.640	0.988
13	TCD[h]	0.852	0.699	1.038	0.879	0.700	1.105	1.222	0.930	
12	Carotid duplex ultrasound	1.039	0.889	1.215	1.021	0.849	1.228	1.119	0.891	1.406
25	Professional education	0.907	0.765	1.076	1.061	0.868	1.296	0.954	0.751	1.212
24	Community education	0.948	0.810	1.109	0.908	0.753	1.094	0.800	0.636	1.006
23	Stroke registry	0.895	0.781	1.026	0.861	0.732	1.013	0.915	0.749	1.118
19	Stroke unit	0.993	0.838	1.177	0.887	0.724	1.086	0.871	0.679	1.118
1	Neurologists	0.854[j]	0.742	0.982	1.043	0.881	1.234	1.110	0.901	1.367
5	Physical medicine and rehabilitation	1.025	0.844	1.245	0.976	0.777	1.225	0.746[j]	0.562	0.991
4	Critical care medicine	0.967	0.825	1.134	0.993	0.823	1.200	0.895	0.712	1.126
	Total CSC[i] score	0.973[j]	0.958	0.989	0.970[j]	0.950	0.990	0.951[j]	0.925	0.977

[a]ischemic stroke; [b]intracerebral hemorrhage; [c]subarachnoid hemorrhage; [d]*OR* odds ratio adjusted by hierarchical logistic model including patient age, sex, Japan Coma Scale scores, and hospital variables; [e]*CI* confidence interval; [f]computed tomography; [g]magnetic resonance imaging; [h]transcranial Doppler; [i]comprehensive stroke center; [j]$P < 0.05$ (hierarchical logistic model)

Strengths and limitations of the present study

First, this study is limited by a possible selection bias because hospitals actively working to improve stroke care were more likely to respond to the questionnaire. However, the coverage of the J-ASPECT Study group, which collaborates with the Japan Neurosurgical Society and the Japanese Congress of Neurological Surgeons, was broad enough to provide a reliable study sample. Second, information bias might have existed (self-reporting, recall, and nonresponse). Third, the CSC score mainly evaluated structural measures and did not consider their utilization, supported with real data. To assess clinical practice quality, the use of process measures is preferred [27], but process measures, such as electrocardiogram monitoring and pulse oximetry, were not considered in this scoring system [4, 28]. However, strong correlations between survey components pertaining to personnel and specific expertise (e.g., availability of neurosurgeons and carotid endarterectomy) were observed in this study, suggesting that these items may not be considered as purely structural, but may have characteristics of both structural and process measures. We are planning to develop a new registry system in the J-ASPECT Study to include key metrics required for certification of CSCs in the US, in addition to the DPC database, to study and monitor the association of such quality metrics on mortality and morbidity of acute stroke patients, in Japan. Fourth, in-hospital mortality was selected as an outcome measure to test the validity of the CSC score. A recent systematic review showed that hospital mortality does not necessarily reflect the quality of clinical practice because mortality is affected

Table 8 The effect of items on poor outcome (modified Rankin Scale 3–6)

Item No	Items	IS[a] (n = 31640) OR[d]	95% CI[e]		ICH[b] (n = 15391) OR	95% CI		SAH[c] (n = 4821) OR	95% CI	
3	Endovascular physicians	1.180	0.890	1.563	0.896	0.671	1.198	1.267	0.856	1.875
17	Coiling of intracranial aneurysm	0.838	0.634	1.106	1.075	0.797	1.451	0.933	0.618	1.407
18	Intra-arterial reperfusion therapy	0.990	0.777	1.261	0.919	0.706	1.194	0.704	0.487	1.017
22	Interventional services coverage 24/7	0.969	0.725	1.295	1.145	0.844	1.555	0.928	0.615	1.400
14	Carotid endarterectomy	1.293	0.946	1.768	0.833	0.595	1.165	0.838	0.511	1.376
15 and 16	Clipping of intracranial aneurysm and hematoma removal/draining	0.763	0.427	1.364	0.537	0.266	1.088	0.553	0.065	4.693
2	Neurosurgeons	1.026	0.582	1.807	1.513	0.744	3.077	4.449	0.987	20.041
6	Rehabilitation therapy	1.000	.	.	1.000	.	.	1.000	.	.
21	Operating room staffed 24/7	0.883	0.723	1.078	0.956	0.769	1.187	0.959	0.712	1.290
7	Stroke rehabilitation nurses	0.874	0.693	1.101	1.019	0.803	1.293	0.877	0.641	1.200
8	CT[f]	1.328	0.296	5.956	0.515	0.035	7.590	1.000	.	.
11	CT angiography	1.227	0.931	1.617	0.820	0.608	1.107	0.877	0.579	1.329
10	Digital cerebral angiography	0.912	0.685	1.213	1.243	0.917	1.684	1.274	0.842	1.928
9	MRI[g] with diffusion	0.940	0.706	1.252	0.844	0.605	1.176	0.793	0.490	1.284
20	Intensive care unit	0.987	0.842	1.156	0.964	0.813	1.144	1.000	0.795	1.259
13	TCD[h]	0.966	0.773	1.208	0.879	0.700	1.105	1.152	0.858	1.547
12	Carotid duplex ultrasound	1.183	0.988	1.415	1.021	0.849	1.228	1.206	0.945	1.538
25	Professional education	0.892	0.737	1.079	1.061	0.868	1.296	1.015	0.782	1.317
24	Community education	1.144	0.957	1.368	0.908	0.753	1.094	0.871	0.680	1.116
23	Stroke registry	0.981	0.840	1.146	0.861	0.732	1.013	0.860	0.695	1.065
19	Stroke unit	0.783[j]	0.645	0.952	0.887	0.724	1.086	0.878	0.676	1.141
1	Neurologists	1.137	0.969	1.335	1.043	0.881	1.234	1.096	0.877	1.370
5	Physical medicine and rehabilitation	1.163	0.934	1.449	0.976	0.777	1.225	0.979	0.725	1.322
4	Critical care medicine	1.113	0.929	1.334	0.993	0.823	1.200	1.062	0.830	1.360
	Total CSC[i] score	0.995	0.977	1.014	1.007	0.984	1.030	0.978	0.950	1.008

[a]ischemic stroke; [b]intracerebral hemorrhage; [c]subarachnoid hemorrhage; [d]OR odds ratio adjusted by hierarchical logistic model including patient age, sex, Japan Coma Scale scores, and hospital variables; [e]CI: confidence interval; [f]computed tomography; [g]magnetic resonance imaging; [h]transcranial Doppler; [i]comprehensive stroke center; [j]$P < 0.05$ (hierarchical logistic model)

to a greater extent by the patients' condition rather than by the quality of practice [29]. Possible correlations between specific items and mortality in patients with IS may have been missed because of the relatively low in-hospital mortality associated with these patients; a larger study is necessary to resolve this issue. Fifth, the DPC-based payment system contains limited information regarding patient condition severity beyond post-discharge data and the National Institute of Health Stroke (NIHSS) Scale, Glasgow Coma Scale (GCS), ICH-, or Hunt-Hess severity scores, upon admission. Nevertheless, the JCS is a useful tool for evaluating stroke severity. Notably, the importance of the JCS, published in 1974, for predicting stroke outcomes has been recently reconfirmed [9, 30]. Further study is necessary to validate the results of the present study with other patient-level measurements, such as the NIHSS, GCS, etc. Despite the above limitations, clear correlations were revealed between the CSC score and in-hospital mortality in patients with all types of strokes. In future work, the score's components should be weighted according to stroke type, based on their influence on patient outcomes.

Conclusions

The CSC score is a valid measure for assessing the capabilities of CSCs with regard to the availability of neurovascular surgery and intervention, vascular neurology, diagnostic neuroradiology, and neurocritical care and rehabilitation. The total CSC score was associated with mortality in patients with IS, ICH, and SAH, with varying contributions from the four abovementioned constructs.

Abbreviations

BC: Board-certified; CI: Confidence interval; CSC: Comprehensive stroke center; DPC: Diagnosis combination procedure; GCS: Glasgow coma scale; IA: Intracranial aneurysm; ICH: Intracerebral hemorrhage; IS: Ischemic stroke; ISAT: International subarachnoid trial; JCS: Japan coma scale; NIHSS: National institute of health stroke; OR: Odds ratio; PSC: Primary stroke center; SAH: Subarachnoid hemorrhage

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Availability of data and materials

The datasets for this manuscript will not be shared, based on agreements between the principal investigator and the presidents of the participating hospitals.

Authors' contributions

KI initiated the collaborative project. AK, KN, SK, and KI designed the study, drafted and revised the article. AK, KN, SK monitored data collection and analyzed the data. JN, KO, JO, YS, TA, SM, IN, KT, SM, AS, HK, FN designed the study, and validated the survey questions from the views of physicians and experts. All authors read and approved the final manuscript.

Competing interests

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Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethical approval was provided by National Cerebral and Cardiovascular Center in Japan.

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JNS

CLINICAL ARTICLE

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Effect of treatment modality on in-hospital outcome in patients with subarachnoid hemorrhage: a nationwide study in Japan (J-ASPECT Study)

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OBJECTIVE Although heterogeneity in patient outcomes following subarachnoid hemorrhage (SAH) has been observed across different centers, the relative merits of clipping and coiling for SAH remain unknown. The authors sought to compare the patient outcomes between these therapeutic modalities using a large nationwide discharge database encompassing hospitals with different comprehensive stroke center (CSC) capabilities.

METHODS They analyzed data from 5214 patients with SAH (clipping 3624, coiling 1590) who had been urgently hospitalized at 393 institutions in Japan in the period from April 2012 to March 2013. In-hospital mortality, modified Rankin Scale (mRS) score, cerebral infarction, complications, hospital length of stay, and medical costs were compared between the clipping and coiling groups after adjustment for patient-level and hospital-level characteristics by using mixed-model analysis.

RESULTS Patients who had undergone coiling had significantly higher in-hospital mortality (12.4% vs 8.7%, OR 1.3) and a shorter median hospital stay (32.0 vs 37.0 days, $p < 0.001$) than those who had undergone clipping. The respective proportions of patients discharged with mRS scores of 3–6 (46.4% and 42.9%) and median medical costs (thousands US$, 35.7 and 36.7) were not significantly different between the groups. These results remained robust after further adjustment for CSC capabilities as a hospital-related covariate.

ABBREVIATIONS BRAT = Barrow Ruptured Aneurysm Trial; CCI = Charlson Comorbidity Index; CSC = comprehensive stroke center; DPC = Diagnosis Procedure Combination; HAC = hospital-acquired condition; ISAT = International Subarachnoid Aneurysm Trial; JCS = Japan Coma Scale; mRS = modified Rankin Scale; PPV = positive predictive value; PSI = patient safety indicator; RCT = randomized controlled trial; SAH = subarachnoid hemorrhage.

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CONCLUSIONS Despite the increasing use of coiling, clipping remains the mainstay treatment for SAH. Regardless of CSC capabilities, clipping was associated with reduced in-hospital mortality, similar unfavorable functional outcomes and medical costs, and a longer hospital stay as compared with coiling in 2012 in Japan. Further study is required to determine the influence of unmeasured confounders.

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KEY WORDS subarachnoid hemorrhage; clipping; coiling; nationwide database study; comprehensive stroke center; vascular disorders

Numerous studies have compared outcomes between clipping and coiling procedures for patients with subarachnoid hemorrhage (SAH).[7,17–21,26,28,30,31] The International Subarachnoid Aneurysm Trial (ISAT), a large randomized controlled trial (RCT) that compared neurosurgical clipping with endovascular coiling in patients with SAH, demonstrated the superiority of coiling.[20] This finding of the ISAT led to a prominent shift in the pattern of treatment for SAH, with the number of coiling procedures steadily increasing following publication.[28] However, it remains questionable whether the results of the ISAT can be generalized to all patients with SAH because most participants enrolled in the study were high-clinical-grade patients with small anterior circulation aneurysms.[23] While patient demographics and SAH severity remain the strongest predictors of outcome following treatment, interhospital, interregional, and cross-national disparities may also contribute to differences in patient outcomes. For example, fatality rates in patients with SAH in Japan are substantially lower than those in other regions.[24] Such differences may be explained by the varied expertise of the treating physician, the SAH case volumes at different institutions, and a hospital's propensity to use endovascular therapy.[3,11,13] Recently, using the Japanese Diagnosis Procedure Combination (DPC) database, we established that high comprehensive stroke center (CSC) capability scores were associated with reduced in-hospital mortality in patients with ischemia and hemorrhage.[15]

Researchers have increasingly relied on the use of administrative databases of hospital admissions to assess clinical outcomes. Despite several limitations, studies using nationwide databases produce more generalizable results than those of RCTs because of the elimination of potential selection and referral biases.[7,17,26] Previous large database studies that have compared outcomes following clipping and coiling in patients with SAH have been conducted in the US, yielding mixed results.[7,17]

To address these discrepancies, we used the nationwide DPC database (JASPECT Study) to identify patients urgently hospitalized for SAH between April 1, 2012, and March 31, 2013. We then performed a mixed-model analysis adjusted with patient-level and hospital-level covariates to compare outcomes for patients with SAH who had undergone clipping and coiling procedures.

Methods

The DPC Database

The DPC database is a mixed-case classification system linked with a lump-sum payment system that was launched in 2002 by the Ministry of Health, Labor, and Welfare of Japan.[34] In 2010, an estimated 1388 acute care hospitals, representing about 50% of all hospital beds, adopted the DPC system. Data on practices can be obtained from the DPC database, and the attending physician is responsible for clinical data entry for each patient. The DPC system includes all patients admitted to participating hospitals. Compared with other registry databases, the DPC database has strength in enabling researchers to conduct nationwide studies of descriptive or analytical epidemiology in the real-world setting of clinical practice. The Japanese DPC database includes data on the following elements: each patient's profile (that is, age, sex, height, weight, smoking index); principal diagnoses (coded according to the *International Classification of Diseases and Injuries, 10th revision*); comorbidities at admission (coded similarly); complications after admission (coded similarly); and procedures, including surgery, medications, and devices used during hospitalization; length of stay; discharge status; and medical expense.[22,34,35] Institutions using the DPC system encompass a wide variety of centers, including academic, large, urban, and rural hospitals.[15] Of the 847 certified training institutions of the Japan Neurosurgical Society, 393 agreed to participate in the J-ASPECT Study. This cross-sectional survey used DPC discharge data from the participating institutions.

Assessment of CSC Capabilities

We investigated whether the effect of treatment modality on outcomes in patients with SAH was influenced by CSC capabilities. The CSC capabilities questionnaire was completed by 266 of the 393 participating institutions. This institutional survey has been described in detail elsewhere.[15] The CSC capabilities were assessed using 25 items specifically recommended for CSC,[1] which were divided into 5 categories: 1) personnel (7 items: board-certified neurologists, board-certified neurosurgeons, board-certified endovascular physicians, board-certified physicians in critical care medicine, board-certified physicians in physical medicine and rehabilitation, personnel in rehabilitation therapy, and stroke rehabilitation nurses); 2) diagnostic techniques (6 items: 24 hours/day, 7 days/week [24/7] availability of CT, MRI with diffusion-weighted imaging, digital cerebral angiography, CT angiography, carotid duplex ultrasound, and transcranial Doppler ultrasonography); 3) specific expertise (5 items: carotid endarterectomy, clipping of intracranial aneurysms [IAs], removal of intracerebral hemorrhage, coiling of IAs, and intraarterial reperfusion therapy); 4) infrastructure (5 items: stroke unit, intensive care unit, operating room staffed 24/7, interventional services coverage 24/7, and stroke registry); and 5) educational components (2 items: community education and professional education). One point was assigned for each recommended item, with a maximum possible CSC score of 25.

Sampling Strategy

Computer software was developed to identify patients hospitalized for SAH from the de-identified discharge database using the ICD-10 diagnosis codes related to SAH (I60.0–9). We extracted data from the Japanese DPC database for patients who had been urgently hospitalized for SAH in the period from April 1, 2012, to March 31, 2013. Patients with a scheduled admission were excluded from our study.

The DPC database includes the following data: hospitals' unique identifiers and CSC scores; patients' age, sex, height, and weight; diagnoses; comorbidities on admission, including those based on the Charlson Comorbidity Index (CCI);[6] Brinkman Index;[4] level of consciousness on admission according to the Japan Coma Scale (JCS); admission source; days between admission and treatment; in-hospital mortality; modified Rankin Scale (mRS) score at discharge; cerebral infarction after admission; complications after admission according to patient safety indicators (PSIs) and hospital-acquired conditions (HACs);[10] length of hospital stay; medical costs; and procedures coded with Japanese original K-codes. The extent of smoking was assessed based on the Brinkman Index (daily number of cigarettes × years).[4] The JCS is the most widely used grading scale for assessing impaired consciousness in Japan (Supplementary Table S1).[14,29] This scale represented levels of consciousness upon admission regardless of whether patients had subsequently undergone ventriculostomy or CSF shunt placement.

Validation Study

We collected a 1% representative sample from among 501,609 patients at the 393 institutions included in the DPC discharge database from April 1, 2012, to March 31, 2013, by using 2-stage random sampling. Admissions were randomly drawn from among the 393 included institutions, after which patients with SAH were randomly selected using ICD-10 codes. The primary diagnosis, treatment modality, in-hospital mortality, mRS score at discharge, and JCS score on admission were verified based on the discharge summary, hospital records of the clinical presentation according to neurosurgeons or neurologists, and CT or MRI evidence. Validation of the attending physician's contemporary assessment was equivalent to that of a retrospective chart review. The sensitivity, specificity, and positive predictive value (PPV) of SAH as the primary diagnosis were calculated using the sample set. The sensitivities, specificities, and PPVs of treatment modality, in-hospital mortality, mRS score at discharge, and JCS score on admission were calculated using the ICD-10 diagnosis codes related to SAH (I60.0–9) in the sample set.

Statistical Analysis

For statistical analysis, the mRS score at discharge was dichotomized into score groups 0–2 and 3–6. The JCS score was treated as a categorical variable of 0, 1, 2, or 3. Differences in patient demographics between the clipping and coiling groups were analyzed using the Wilcoxon rank-sum and chi-square tests. We used mixed-model analysis to estimate odds ratios for in-hospital mortality, mRS score at discharge, cerebral infarction, and complications and to estimate differences in length of hospital stay and medical costs. Odds ratios and differences were adjusted using a mixed model with sex, age, JCS score, and CCI score as fixed effects and hospital as a random effect (full cohort). To examine whether patient outcomes were affected by the CSC capabilities of each institution, the CSC score was applied as a fixed effect in addition to the aforementioned variables (subgroup with CSC scores). After conducting stratified analysis by JCS 0, 1-digit, 2-digit, and 3-digit codes, odds ratios and differences were adjusted using a mixed model with sex, age, CCI scores, and treatment modalities (clipping or coiling) as fixed effects and hospital as a random effect. We estimated odds ratios and differences for outcomes after 1:1 propensity score matching to account for differences in baseline characteristics between groups. Propensity scores for coiling were estimated using a probit model with age, sex, JCS score, and CCI score. To match patients, we used an automated matching procedure in the STATA software package that randomly selected a patient with clipping and a patient with coiling from the pool of potential patients within a propensity score caliper of ± 0.001. Successfully matched pairs were removed, and the procedure was repeated until all patients were matched to one comparator or until no further patients that could be matched were available within the caliper. Analyses were performed using SAS version 9.3 (SAS Institute Inc.), STATA version 12 (STATA Corp.), and SPSS version 12 (SPSS Inc.). A p value < 0.05 was considered statistically significant.

Ethics Statement

This research was designed by us and approved by the institutional review board of Kyushu University, which waived the requirement for individual informed consent.

Results

Patient Demographics

A total of 5214 patients with SAH (clipping 3624, coiling 1590) at 393 institutions were identified based on ICD-10 codes (full cohort). Of the 4327 patients (83%) with SAH who were hospitalized at the 266 institutions that participated in the CSC capabilities survey and assigned a CSC score (subgroup with CSC scores), 2996 had undergone clipping and 1331 had undergone coiling. Table 1 shows the demographics of the full cohort and the subgroup with CSC scores.

In the full cohort, significant differences in some characteristics were observed between patients who had undergone clipping and those who had undergone coiling. Specifically, patients who underwent coiling were significantly older (mean age: clipping 62.0 years, coiling 63.5

TABLE 1. Demographics of the full cohort and the subgroup with CSC scores

Parameter	Full Cohort			Subgroup w/ CSC Scores		
	Clipping	Coiling	p Value	Clipping	Coiling	p Value
Total	3624	1590		2996	1331	
Patients						
Male	1147 (31.6)	480 (30.2)	0.294	955 (31.9)	388 (29.2)	0.074
Age in yrs	62.0 ± 13.9	63.5 ± 15.3	0.003	62.1 ± 13.9	63.3 ± 15.3	0.025
Height in cm	157.9 ± 9.2	157.4 ± 9.6	0.080	157.9 ± 9.2	157.3 ± 9.6	0.066
Weight in kg	57 ± 12.4	56.2 ± 13.3	0.005	57.0 ± 12.5	56.1 ± 13.3	0.004
Brinkman Index	215.4 ± 376.7	164.9 ± 387.4	<0.001	220.5 ± 384.7	158.4 ± 351.5	<0.001
Comorbidities						
CCI score	4.0 ± 1.0	4.1 ± 1.6	0.034	4.0 ± 1.5	4.1 ± 1.6	0.166
Hypertension	1993 (55.0)	852 (53.6)	0.347	1658 (55.3)	709 (53.3)	0.206
Diabetes mellitus	352 (9.7)	133 (8.4)	0.123	278 (9.3)	109 (8.2)	0.246
Hyperlipidemia	565 (15.6)	236 (14.8)	0.491	455 (15.2)	190 (14.3)	0.437
Hyperuricemia	12 (0.3)	9 (0.6)	0.218	11 (0.4)	8 (0.6)	0.283
JCS score on admission			<0.001			<0.001
0	834 (23.0)	285 (17.9)		663 (22.1)	245 (18.4)	
1-digit code	1120 (30.9)	450 (28.3)		951 (31.7)	371 (27.9)	
2-digit code	811 (22.4)	363 (22.8)		673 (22.5)	320 (24.0)	
3-digit code	859 (23.7)	492 (30.9)		709 (23.7)	395 (29.7)	
Admission source						
Ambulance	2837 (78.3)	1244 (78.2)	0.971	2369 (79.1)	1045 (78.5)	0.671
Days btwn admission & treatment	2.0 ± 3.3	2.0 ± 4.1	0.141	2.0 ± 3.4	2.0 ± 3.7	0.076
Surgery for hydrocephalus						
Ventriculostomy	182 (5.0)	322 (20.3)	<0.001	160 (5.3)	267 (20.1)	<0.001
CSF shunt	802 (22.1)	270 (17.0)	<0.001	682 (22.8)	225 (16.9)	<0.001
Hospital characteristics (CSC scores)						
Total score	NA	NA	NA	16.8 ± 3.6	17.9 ± 2.8	<0.001
Personnel	NA	NA	NA	3.9 ± 1.3	4.2 ± 1.1	<0.001
Diagnostic techniques	NA	NA	NA	4.4 ± 1.0	4.4 ± 1.0	0.286
Specific expertise	NA	NA	NA	4.3 ± 0.9	4.8 ± 0.6	<0.001
Infrastructure	NA	NA	NA	2.8 ± 1.4	3.2 ± 1.3	<0.001
Educational components	NA	NA	NA	1.3 ± 0.8	1.3 ± 0.8	0.971

NA = not applicable.
Values expressed as the mean ± standard deviation or number (%).

years, p = 0.003). The proportion of patients with impaired consciousness was significantly higher in the coiling group (for example, comatose patients: clipping 23.7%, coiling 30.9%, p < 0.001). The mean CCI score was also significantly higher in the coiling group (clipping 4.0 ± 1.0, coiling 4.1 ± 1.6 , p = 0.034). No significant differences in other comorbidities, such as hypertension, diabetes mellitus, hyperlipidemia, and hyperuricemia, were noted between the groups. The mean weight (clipping 57.0 ± 12.4 kg, coiling 56.2 ± 13.3 kg, p = 0.005) and mean Brinkman Index (clipping 215.4 ± 376.7, coiling 164.9 ± 387.4, p < 0.001) were significantly lower in the coiling group.

In the subgroup with CSC scores, the corresponding differences between the 2 treatment groups were also significant except in the mean CCI score (clipping 4.0 ± 1.5, coiling 4.1 ± 1.6, p = 0.166). Regarding hospital characteristics, the mean CSC total (clipping 16.8 ± 3.6, coiling 17.9 ± 2.8, p < 0.001), personnel (clipping 3.9 ± 1.3, coiling 4.2 ± 1.1 , p < 0.001), specific expertise (clipping 4.3 ± 0.9, coiling 4.8 ± 0.6, p < 0.001), and infrastructure subgroup scores (clipping 2.8 ± 1.4, coiling 3.2 ± 1.3, p < 0.001) were significantly higher in the coiling group.

Mixed-Model Analysis

Table 2 shows outcomes in the full cohort and the subgroup with CSC scores. In the full cohort, rates of in-hospital mortality (clipping 8.7%, coiling 12.4%), cerebral infarction (clipping 16.7%, coiling 18.1%), mRS score of 3–6 at discharge (clipping 42.9%, coiling 46.4%), and PSIs ≥ 1 (clipping 48.5%, coiling 63.1%) were higher in the coiling group. However, the proportion of HACs ≥ 1 was higher in the clipping group (7.9% vs 7.0%). The median hospital

TABLE 2. Outcomes in the full cohort and the subgroup with CSC scores

Parameter	Full Cohort		Subgroup w/ CSC Scores	
	Clipping	Coiling	Clipping	Coiling
Total	3624	1590	2996	1331
In-hospital mortality	315 (8.7)	198 (12.4)	257 (8.6)	152 (11.4)
Discharge mRS Scores 3–6	1555 (42.9)	738 (46.4)	1307 (43.6)	618 (46.4)
Cerebral infarction	607 (16.7)	288 (18.1)	500 (16.7)	237 (17.8)
PSIs ≥1	1757 (48.5)	1003 (63.1)	1442 (48.1)	856 (64.3)
HACs ≥1	288 (7.9)	111 (7.0)	240 (8.0)	97 (7.3)
Length of hospital stay in days	37.0 ± 33.7	32.0 ± 30.7	38.0 ± 33.9	32.0 ± 30.7
Medical costs in thousands US$	36.7 ± 14.1	35.7 ± 14.9	36.7 ± 14.1	36.0 ± 14.5

Values expressed as the median ± standard deviation or number (%).

stay was longer in the clipping group (median days: clipping 37.0, coiling 32.0), whereas the median medical costs were similar between the groups (thousands US$: clipping 36.7, coiling 35.7). Similar results were obtained for the subgroup with CSC scores.

Table 3 shows patient outcomes in the full cohort and the subgroup with CSC scores according to the mixed-model analysis. In the full cohort, after adjusting for sex, age, JCS and CCI scores as fixed effects and hospital as a random effect, in-hospital mortality was significantly higher in the coiling group (OR 1.30, p = 0.013). Rates of cerebral infarction (OR 1.19, p = 0.066) and mRS scores of 3–6 at discharge (OR 0.98, p = 0.761) were not significantly different between the treatment groups. The proportion of PSIs ≥ 1 was significantly higher in the coiling group (OR 1.3, p = 0.003), whereas that of HACs ≥ 1 was significantly higher in the clipping group (OR 0.73, p = 0.021). The median hospital stay was significantly longer in the clipping group (β = −7.18, p < 0.001), whereas the medical costs were not significantly different between the groups (β = −144.64, p = 0.742). Analysis of the subgroup with CSC scores revealed similar results regarding in-hospital mortality (OR 1.27, p = 0.046), cerebral infarction (OR 1.18, p = 0.124), mRS scores of 3–6 at discharge (OR 0.96, p = 0.657), PSIs ≥ 1 (OR 1.33, p = 0.003), length of hospital stay (β = −6.98, p < 0.001), and medical costs (β = −603.15, p = 0.210). Although the proportion of HACs ≥ 1 was no longer significantly different between the groups, the odds ratio exhibited a similar tendency to that in the full cohort (OR 0.78, p = 0.105).

Because we suspected the JCS score to be the most important confounder, we also conducted stratified analyses by JCS 0, 1-digit, 2-digit, and 3-digit codes (Supplementary Tables S2 and 3). Although coiling did not have a significant effect on discharge mRS scores of 3–6 in patients with JCS 0, 1-digit, and 2-digit codes, rates of discharge mRS scores of 3–6 in the coiling group were significantly lower in patients with 3-digit codes in both the full cohort (OR 0.74, p = 0.038) and the subgroup with CSC scores (OR 0.70, p = 0.024). Although coiling did not have a significant effect on cerebral infarction in patients with JCS 0, 1-digit, and 2-digit codes, rates of cerebral infarction in the coiling group were significantly higher in patients with 3-digit codes in both the full cohort (OR 1.57, p = 0.008) and the subgroup with CSC scores (OR 1.69, p = 0.006). Regarding in-hospital mortality, PSIs ≥ 1, HACs ≥ 1, hospital stay, and medical costs, the influence of treatment modality seemed similar between the clipping and coiling groups in patients with each JCS score.

Propensity Score Analysis

Following 1:1 matching, 1556 patients who had undergone clipping and 1556 who had undergone coiling fol-

TABLE 3. Outcomes of patients with SAH according to mixed-model analysis

Parameter	Full Cohort			Subgroup w/ CSC Scores		
	OR*	95% CI	p Value	OR*	95% CI	p Value
In-hospital mortality	1.3	1.06–1.59	0.013	1.27	1.01–1.60	0.046
Discharge mRS Scores 3–6	0.98	0.85–1.14	0.761	0.96	0.81–1.14	0.657
Cerebral infarction	1.19	0.99–1.43	0.066	1.18	0.96–1.45	0.124
PSIs ≥1	1.3	1.10–1.53	0.003	1.33	1.10–1.60	0.003
HACs ≥1	0.73	0.55–0.95	0.021	0.78	0.58–1.05	0.105
Length of hospital stay	−7.18*†	−9.14 to −5.21	<0.001	−6.98*†	−9.15 to −4.80	<0.001
Medical costs	−144.64*†	−1008.17 to 718.88	0.742	−603.15*†	−1546.05 to 339.75	0.21

* Odds ratios and differences were adjusted by a mixed model with sex, age, JCS scores, and CCI scores as fixed effects and hospital as a random effect. Clipping was used as the reference.

† Number represents the β value.

lowing aneurysm rupture were matched based on demographic similarities. All covariates between the clipping and coiling groups were statistically indistinguishable after matching. Outcomes for patients with SAH after matching according to propensity score are shown in Table 4. In-hospital mortality was significantly higher in the coiling group (OR 1.25, p = 0.047). Rates of cerebral infarction (OR 0.97, p = 0.745) and mRS scores of 3–6 at discharge (OR 0.94, p = 0.409) were not significantly different between the groups. The proportion of PSIs ≥ 1 was significantly higher in the coiling group (OR 1.77, p < 0.001), whereas that of HACs ≥ 1 was not significantly different between the groups (OR 0.83, p = 0.16). The median hospital stay was significantly longer in the clipping group (β = −6.71, p < 0.001), whereas the medical costs were not significantly different between the groups (β = 754.04, p = 0.086). Compared with the results of the mixed-model analysis, except for the proportion of HACs ≥ 1, a similar tendency was observed for the odds ratios and differences for the other factors.

Validation of Diagnosis, Treatment Modality, and Outcomes

Our sample, selected using 2-stage random sampling, consisted of 495 patients at 68 institutions. The sensitivity, specificity, and PPV of SAH as the primary diagnosis were 100%, 99.0%, and 95.1%, respectively. Among the 495 patients, 82 were identified using the ICD-10 diagnosis codes related to SAH (I60.0–9). The sensitivities, specificities, and PPVs of treatment modality and in-hospital mortality were all 100%. The sensitivity, specificity, and PPV of mRS Scores 3–6 at discharge were 97.2%, 87.0%, and 85.4%, respectively. The κ coefficient of the JCS score on admission was 0.683. The results of the validation study are summarized in Table 5.

Discussion

In Japan, the incidence of SAH is higher,[8] and the associated mortality is lower,[24] than in other countries, possibly because of differences in genetic backgrounds, socioeconomic indicators,[13] and national medical systems, including centralization of neurosurgical and acute stroke care capabilities. Therefore, international, national, and longitudinal comparisons of outcomes for patients with SAH treated using different therapeutic modalities should be discussed in light of socioeconomic indicators, acute stroke care capabilities at the specific time,[13,14,26,28,31] and patient-level characteristics such as SAH severity.[27] The present study is the first to compare outcomes for SAH patients treated with clipping and coiling via a mixed-model analysis of a large nationwide discharge database (DPC database) after adjustment for patient-level characteristics including age, sex, level of consciousness (JCS score), CCI score, and hospital-level CSC capabilities (CSC score).[14,15] Our results revealed that patients who had undergone coiling exhibited significantly higher in-hospital mortality (12.4% vs 8.7%) and shorter hospital stays (32.0 vs 37.0 days) than those in patients who had undergone clipping. The proportion of patients discharged with mRS scores of 3–6 (coiling 46.4%, clipping 42.9%) and median medical costs (thousands US$: coiling 35.7, clipping 36.7) were not significantly different between the groups. Furthermore, the high accuracy of diagnoses, treatment modalities, and outcomes of the DPC cohort in the present study were confirmed using a 2-stage sampling method.

TABLE 4. Outcomes of patients with SAH according to propensity score analysis

Parameter	OR*	95% CI	p Value
In-hospital mortality	1.25	1.00–1.57	0.047
Discharge mRS Scores 3–6	0.94	0.82–1.08	0.409
Cerebral infarction	0.97	0.81–1.16	0.745
PSIs ≥1	1.77	1.53–2.04	<0.001
HACs ≥1	0.83	0.64–1.08	0.16
Length of hospital stay	−6.70*†	−8.64 to −4.77	<0.001
Medical costs	754.04*†	−106.89 to 1614.96	0.086

* Odds ratios and differences were estimated for outcomes after 1:1 propensity score matching to account for differences in baseline characteristics between groups. Clipping was used as the reference.
† Number represents the β value.

TABLE 5. Results of the validation study

Parameter	Sensitivity	Specificity	PPV
SAH as primary diagnosis	100%	99.0%	95.1%
Treatment modality	100%	100%	100%
In-hospital mortality	100%	100%	100%
Discharge mRS Scores 3–6	97.2%	87.0%	85.4%

Discrepancies in the Results of Comparative Studies

Our results were partly consistent with those of 2 previous RCTs—the ISAT and the Barrow Ruptured Aneurysm Trial (BRAT)—with regard to functional outcomes, although rates of in-hospital mortality differed significantly.[18,20] One possible explanation for this discrepancy is that almost 80% of all eligible aneurysms were excluded from the ISAT cohort, calling into question the general applicability of the results. In the BRAT, a relatively small number of patients were randomized and treated by highly experienced surgeons and endovascular physicians at a single high-volume center. The merits of using an electronic hospital claim database are associated with decreases in the risk of selection biases. Such biases may largely account for the differences between results of the present study and those of previous RCTs.

Researchers have increasingly relied on administrative databases of hospital admissions to assess clinical outcomes in patients with SAH. Three nationwide database studies were conducted to compare outcomes for patients with SAH who had undergone clipping or coiling, yielding mixed results.[7,17,26] Using administrative claim data from Canada entered between 1995 and 2004, authors of one study found that endovascular coiling was associated with a significantly increased risk of death or SAH readmission.[26] The results were confirmed by propensity score–matched analysis. Authors of another study, who used the National (Nationwide) Inpatient Sample from 1998 to 2003 in the US, reported higher in-hospital mortality after coiling than after clipping (16.6% vs 12.7%).[7] These 2 studies, both conducted relatively soon after the publication of the ISAT, produced results similar to ours in terms of the case volume ratio, mortality, and functional outcomes of clipping and coiling.[7,26] Qureshi et al. revealed that, after the publication of the ISAT in 2002, there was a significant increase in endovascular treatment as well as a decrease in in-hospital mortality in patients with SAH.[28] A third nationwide database study used the Premier database, which is a voluntary, fee-supported collection of data developed to assess the quality and resource utilization of health care delivery in the US.[17] In contrast to findings in the present and aforementioned studies, the Premier database study revealed no significant differences in mortality between the groups (clipping 12%, coiling 13%, OR 0.94, 95% CI 0.73–1.21), though functional outcomes were significantly better in the coiling group (discharge to long-term care: clipping 42%, coiling 36%).[17] Except for the present study, the only other study to use an administrative database in the analysis of patients treated relatively late after the publication of the ISAT was a US study in which patients admitted from 2006 to 2011 demonstrated higher in-hospital mortality after clipping (11.9% vs 8.7%) and similar in-hospital mortality after coiling (12.6% vs 12.5%), relative to patients in the present study.[17] Since age is a predictor of a poor outcome,[7,24] it is important to note that the patients with SAH who had undergone clipping (mean age 62.0 years) and coiling (63.5 years) in our Japanese cohort were almost 10 years older than those in the US and Canadian studies.[7,17,26] Nonetheless, in-hospital mortality rates after clipping were much lower in Japan than the corresponding rates in the other countries, whereas rates after coiling remained similar.

Unmeasured Confounders

Discrepancies between findings of the present and previous large-scale database studies may be explained by the influence of unmeasured confounders. In general, the most common cause of death and poor functional outcomes following SAH is the initial bleeding.[5,16] In fact, we revealed that the influence of treatment modalities on rates of discharge mRS scores of 3–6 and cerebral infarction differs between patients with 0 to 2-digit JCS scores and those with 3-digit JCS scores. Although McDonald et al. performed propensity score analysis to minimize potential selection bias, SAH severity was not included in the patient variables used to generate propensity scores, making interpretation of the results difficult.[17] On the other hand, SAH severity was adjusted by the JCS score[14,25,29] in the present study, minimizing its confounding effects. Notably, the importance of the JCS, first developed in 1974 for the prediction of stroke outcomes, has recently been validated.[29] The second most common cause of SAH-related death and poor functional outcome is rebleeding.[5,16] Earlier treatment of ruptured aneurysms reduces the incidence of rebleeding.[33] However, no significant difference in the mean preoperative period (2 days) between clipping and coiling was observed in the present study. Intracranial aneurysm size and location are also important clinical variables used to guide treatment decisions. However, details regarding these variables are unavailable in administrative databases and represent potentially important unmeasured confounders. In this regard, the Prospective Registry of Subarachnoid Aneurysms Treatment (PRESAT) trial provided reasonable estimates of the differences in ruptured aneurysm size and location in patients treated with clipping versus coiling.[31] The PRESAT trial was undertaken from 2006 to 2007 at 29 tertiary care referral centers in Japan where both clipping and coiling were available for ruptured cerebral aneurysms, and the treatment choice was based on both patient and aneurysm characteristics.[31] Clipping was mostly performed for small aneurysms with wide necks and for middle cerebral artery aneurysms, whereas coiling was preferred for larger, internal carotid artery and posterior circulation aneurysms. Authors of the study concluded that treatment modality, aneurysm size, and aneurysm location did not influence outcomes at tertiary care referral hospitals with high CSC capabilities.

Ideally, ruptured cerebral aneurysms should be treated at centers offering high-quality treatment with open surgical procedures as well as endovascular techniques. Our study demonstrated that high-quality surgical clipping remains available as both a first-line and a complementary treatment option for ruptured cerebral aneurysms in Japan: Our results were similar regardless of whether total CSC scores were adjusted in the mixed-model analysis. The optimal balance between clipping and coiling to maximize the overall proportion of favorable outcomes in patients with SAH will vary somewhat among centers, regions, and countries, depending on local expertise and CSC capabilities.

After CSC capabilities (total CSC scores) were adjusted in the mixed model, the odds ratios of in-hospital mortality and unfavorable outcomes of coiling compared with clipping remained almost unchanged. Although coiling was performed in hospitals with significantly higher CSC scores, the effect of treatment modality on outcomes in patients with SAH was unaffected by CSC capabilities. This finding is unexpected since higher CSC capabilities were found to be significantly associated with reduced in-hospital mortality in patients with SAH in our previous analysis of the J-ASPECT study.[14] Rather than the CSC capabilities, surgeon-related factors such as technical skill and patient-related factors such as aneurysm location, size, and morphology may primarily influence the association between treatment modality and outcome. Further study is required to assess the influence of surgical skill and aneurysm characteristics.

In Japan, the official designation of primary stroke centers or CSCs has not yet begun, although the clear correlation between comprehensive stroke care capabilities and in-hospital mortality for all types of stroke revealed using the J-ASPECT Study database has had a significant impact on national policy. Given recently established evidence for the efficacy of mechanical thrombectomy in patients with acute ischemic stroke, a task force headed by the Japan Stroke Society and the Japan Neurosurgical Society has initiated an active discussion regarding the recommended items and criteria for the designation of primary stroke centers and CSCs in Japan, such as the CSC score.[14]

Study Strengths and Limitations

In light of the possible selection bias, the present study can be considered a snapshot of the state of ruptured aneurysm treatment in Japan rather than a direct comparison between the safety and efficacy of both treatments. Given that heterogeneity in patient outcomes following stroke has been observed across different hospitals in the same country,[14] considering the patients within each hospital as a cluster in a mixed model may be superior to conventional regression, which views all participants as independent. The present study is the first in which outcomes in patients with SAH treated with clipping and coiling have been compared using a mixed-model analysis of a large nationwide discharge database (DPC database), after adjustment for important patient and hospital characteristics.[14,15] In addition, we added a propensity score analysis to verify the results of the mixed-model analysis. Findings of the propensity score analysis were mostly consistent with those of the mixed-model analysis. Therefore, we consider the results of our study to be highly reliable.

Our study has several limitations. First, the DPC database lacks several types of data such as cause of death and aneurysm characteristics. As previously mentioned, such confounders peculiar to Japan may underlie the differences in outcomes compared with other countries. Second, as a measure of SAH severity, we used the JCS score rather than the Hunt and Hess grade or the World Federation of Neurological Surgeons (WFNS) grade. The JCS is widely used for the assessment of impaired consciousness in patients with SAH in Japan.[2,12,14,25,32] Although the JCS cannot assess neurological impairment other than diminished consciousness, the JCS score on admission had the greatest impact on the outcomes of patients with SAH.[9] In addition, JCS scores have been reported to correlate with stroke outcomes.[29] Therefore, we believe that the JCS is sufficient for clinical grade assessment in patients with SAH. However, as an increasing number of stroke researchers have used JCS scores in recent Japanese DPC database studies,[2,9,12,14,25,30,33] it may be necessary to compare the JCS scoring system with more typical grading scales. Third, the DPC database includes information collected only during hospitalization; thus, we were unable to evaluate long-term outcomes. However, the ISAT reported that the probability of death or dependency at 2 months, 1 year, and 10 years after treatment were higher in the clipping group.[19,20] Results of the ISAT suggest that short-term outcomes regarding mRS scores and mortality may serve as reasonable predictive markers for long-term outcomes. Fourth, the external validity of the CSC grading system has not been confirmed. External validation is necessary to increase the reliability of self-assessment; therefore, we aim to validate information regarding hospital characteristics and outcomes using a small sample set from the validation cohort of the present study.

Conclusions

Clipping remains the standard treatment for SAH in Japan. Compared with coiling, clipping was associated with reduced in-hospital mortality, longer hospital stay, and similar unfavorable functional outcomes and medical costs in Japan in 2012. These findings were independent of CSC capabilities. Further study is required to determine the effects of unmeasured confounders on the outcomes of clipping and coiling.

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Author Contributions

Conception and design: Iihara. Acquisition of data: Iihara, Nakagawara, Toyoda, Ogasawara, Ono, Shiokawa, Aruga, Miyachi, Nagata, Matsuda, Yoshimura, Okuchi, Suzuki, Nakamura. Analysis and interpretation of data: all authors. Drafting the article: Kurogi. Critically revising the article: Iihara. Reviewed submitted version of manuscript: Kurogi, A Nishimura, Sayama, Nakagawara, Toyoda, Ogasawara, Ono, Shiokawa, Aruga, Miyachi, Nagata, Matsuda, Yoshimura, Okuchi, Suzuki, Nakamura, Onozuka, Hagihara. Statistical analysis: K Nishimura, Kamitani, Nakamura, Onozuka, Hagihara. Administrative/technical/material support: K Nishimura, Kamitani. Study supervision: Iihara.

Supplemental Information

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ARTICLE OPEN ACCESS

Comparing intracerebral hemorrhages associated with direct oral anticoagulants or warfarin

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Abstract

Objectives

This cross-sectional survey explored the characteristics and outcomes of direct oral anticoagulant (DOAC)–associated nontraumatic intracerebral hemorrhages (ICHs) by analyzing a large nationwide Japanese discharge database.

Methods

We analyzed data from 2,245 patients who experienced ICHs while taking anticoagulants (DOAC: 227; warfarin: 2,018) and were urgently hospitalized at 621 institutions in Japan between April 2010 and March 2015. We compared the DOAC- and warfarin-treated patients based on their backgrounds, ICH severities, antiplatelet therapies at admission, hematoma removal surgeries, reversal agents, mortality rates, and modified Rankin Scale scores at discharge.

Results

DOAC-associated ICHs were less likely to cause moderately or severely impaired consciousness (DOAC-associated ICHs: 31.3%; warfarin-associated ICHs: 39.4%; $p = 0.002$) or require surgical removal (DOAC-associated ICHs: 5.3%; warfarin-associated ICHs: 9.9%; $p = 0.024$) in the univariate analysis. Propensity score analysis revealed that patients with DOAC-associated ICHs also exhibited lower mortality rates within 1 day (odds ratio [OR] 4.96, $p = 0.005$), within 7 days (OR 2.29, $p = 0.037$), and during hospitalization (OR 1.96, $p = 0.039$).

Conclusions

This nationwide study revealed that DOAC-treated patients had less severe ICHs and lower mortality rates than did warfarin-treated patients, probably due to milder hemorrhages at admission and lower hematoma expansion frequencies.

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Glossary

AF = atrial fibrillation; **DOAC** = direct oral anticoagulant; **DPC** = Diagnosis Procedure Combination; **FFP** = fresh frozen plasma; **ICD-10** = *International Classification of Diseases–10*; **ICH** = intracerebral hemorrhage; **JCS** = Japan Coma Scale; **mRS** = modified Rankin Scale; **OR** = odds ratio; **PCC** = prothrombin complex; **PT-INR** = prothrombin time–international normalized ratio.

Clinical trials have shown that 4 direct oral anticoagulants (DOACs)—dabigatran, rivaroxaban, apixaban, and edoxaban—are as efficacious and safe as warfarin for stroke prevention in patients with atrial fibrillation (AF).[1] In randomized clinical trials with strict indication criteria, DOAC-treated patients are reportedly at lower risk for hemorrhagic strokes than are warfarin-treated patients.[1] Mortality rates were similar among patients randomly prescribed either DOAC or warfarin according to a secondary analysis of intracerebral hemorrhages (ICHs) occurring in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial[2] and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.[3] However, because those trials featured very strict inclusion criteria, these results cannot be generalized to all patients with DOAC- or warfarin-associated ICHs. Notably, in clinical practice of stroke prevention in AF, stroke outcomes can depend on various patient baseline characteristics, suboptimal dosage, and oral anticoagulant therapy adherence.[4] However, few studies have compared the characteristics and outcomes of DOAC- and warfarin-associated ICHs in clinical practice. Because DOACs are used liberally in clinical practice, we expect that the incidence of DOAC-associated ICHs will increase in coming years.[5] We therefore aimed to compare the characteristics and outcomes of patients with DOAC- and warfarin-associated ICHs in clinical practice in Japan using a nationwide Diagnosis Procedure Combination (DPC) database.

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the Kyushu University Institutional Review Board, which waived the requirement for individual informed consent.

The DPC database

The DPC is a mixed-case patient classification system that was launched in 2002 by the Japanese Ministry of Health, Labour and Welfare and is linked with a hospital financing system.[6] By 2015, the DPC system had been adopted by an estimated 1,580 acute care hospitals, representing approximately half of all Japanese hospital beds and encompassing a wide variety of centers, including rural and urban, academic and non-academic, and small and large hospitals.[7] The DPC database includes data about all patients admitted to participating hospitals, including each patient's profile (e.g., age, sex); principal diagnoses and comorbidities at admission (both coded by the International Classification of Diseases and Injuries, 10th revision); complications after admission (coded similarly); procedures including surgeries, medications, and devices used during hospitalization; length of stay; discharge status; and medical expense.[8] The J-ASPECT study group has analyzed the DPC database to gain new clinical insights,[7,9–11] an approach we applied again for this cross-sectional survey.

Sampling strategy

Of the 1,369 training institutions certified by the Japan Neurosurgical Society, the Japanese Society of Neurology, and the Japan Stroke Society, 621 agreed to participate in the J-ASPECT study. We identified patients hospitalized for nontraumatic ICH in the deidentified discharge database using the ICD-10 diagnosis codes related to nontraumatic ICH (I61.0-9, I62.0-1, and I62.9). We further selected those patients who had been urgently hospitalized between April 1, 2010, and March 31, 2015, and were receiving a DOAC or warfarin before admission. We then extracted data about age and sex; comorbidities on admission, including those based on Charlson scores[12]; level of consciousness on admission according to the Japan Coma Scale (JCS), the most widely used grading scale for impaired consciousness in Japan (table e-1, links.lww.com/WNL/A284)[7,9,13]; concurrent pre-admission use of antiplatelet drugs including aspirin, clopidogrel, ticlopidine, cilostazol, sarpogrelate, and prasugrel; hematoma removal with craniotomy, endoscopic surgery, or stereotactic aspiration; CSF drainage coded with Japanese original K-codes; use of reversal agents including vitamin K, prothrombin complex (PCC) concentrate, and fresh frozen plasma (FFP); length of hospital stay; mortality; and modified Rankin Scale (mRS) score at discharge. Patients with missing data were excluded from this survey.

Statistical analysis

We compared the characteristics of DOAC- and warfarin-associated ICHs using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables. Multivariable analysis was undertaken to estimate the 2 groups' odds ratios (ORs) for mortality rates within 1 day, within 7 days, and during hospitalization and for discharge mRS scores in the 0–3 (good functional outcome) or 4–6 (poor functional outcome) ranges. The ORs were adjusted for sex, age, comorbidities, admission JCS scores, concurrent antiplatelet therapies, and treatment with surgery or reversal agents. We also estimated ORs for outcomes after 1:1 propensity score matching to account for between-group differences in baseline characteristics. To match patients, we used an automated matching procedure in STATA (STATA Corp., College Station, TX) that randomly selected a DOAC-treated patient and a warfarin-treated patient within a propensity score caliper of ±0.01. Successfully matched pairs were removed, and the procedure was repeated until all patients were matched or until no further matches were available within the caliper. Propensity scores for warfarin-associated outcomes were estimated using a probit model in which the independent variables were sex, age, comorbidities, admission JCS scores, concurrent antiplatelet therapy, and treatment with surgery or reversal agents. The interaction between usage of DOAC and usage of reversal agents for ICH removal surgeries was examined. The analyses were performed using JMP 11.0 (SAS Institute, Cary, NC), SAS 9.3 (SAS Institute), STATA 12, and SPSS 12 (IBM, Armonk, NY). We defined statistical significance as $p < 0.05$.

Results

Patient demographics

We identified 2,245 patients with DOAC- or warfarin-associated ICHs (DOAC: 227; warfarin: 2,018). The percentages of DOAC-treated patients in each year from 2010 to 2014 were 0%, 0.4%, 3.8%, 9.6%, and 21.4%, respectively. The proportions of dabigatran, rivaroxaban, apixaban, and edoxaban among DOAC-associated cases were 23.8%, 57.8%, 18.5%, and 0%, respectively.

Table 1 shows the characteristics of patients with DOAC- and warfarin-associated ICHs. No significant between-group differences were noted for age (mean age in years: DOAC, 74.4; warfarin, 74.2); comorbidities such as Charlson scores (mean: 4.9, 5.0), hypertension (56.4%, 53.0%), diabetes mellitus (22.5%, 22.0%), or hyperlipidemia (12.3%, 12.0%); or median lengths of hospital stays (median days: 18.0, 18.0). The DOAC-treated group had a greater proportion of men (75.3%, 65.1%; $p = 0.002$) and smaller proportion of JCS 2- and 3-digit codes (moderately or severely impaired consciousness, respectively) (31.3%, 39.4%; $p = 0.002$). Concurrent use of antiplatelet drugs was more frequent among warfarin-treated patients (25.1%, 40.1%; $p < 0.001$). Overall usage rates for reversal agents, especially PCC, were quite low for both warfarin- and DOAC-treated patients. The DOAC-treated patients were less likely to be given vitamin K (2.6%, 63.1%; $p < 0.001$) or FFP (4.9%, 11.7%; $p < 0.001$); tended to be given PCC (3.1%, 5.8%; $p = 0.094$), the most effective early reversal agent for warfarin; and were less likely to require ICH removal surgeries (5.3%, 9.9%; $p = 0.024$).

Considering the lack of specific antidotes for DOACs during the study period, we further analyzed the relationships between the frequency of ICH removal surgeries and the use of vitamin K, FFP, or PCC in warfarin- and DOAC-treated patients. We found that surgical ICH removal was associated with the use of vitamin K (presence, 13.6%; absence, 3.6%; $p < 0.001$), FFP (presence, 47.9%; absence, 4.9%; $p < 0.001$), or PCC (presence, 31.0%; absence, 8.6%; $p < 0.001$) in patients with warfarin-associated ICHs, whereas no significant associations were observed for the use of vitamin K (presence, 0%; absence, 5.3%; $p = 0.558$), FFP (presence, 9.1%; absence, 5.1%; $p = 0.563$), or PCC (presence, 14.3%; absence, 5.0%; $p = 0.280$) in patients with DOAC-associated ICHs. After adjusting for the use of vitamin K, PCC, or FFP, the DOAC- and warfarin-treated groups exhibited no significant difference in ORs for ICH removal surgeries (OR 1.21, $p = 0.608$), but the interaction between usage of DOAC and usage of reversal agents for ICH removal surgeries was marginally significant ($p = 0.062$) (table e-2, links.lww.com/WNL/A284). This suggested that warfarin vs DOAC tends to show different effect on ICH removal surgeries within the group based on usage of reversal agents. Table e-3 shows the hemorrhage locations of DOAC- and warfarin-associated ICHs obtained from DPC data representing 68.9% of the study cases. These

Table 1 Characteristics of direct oral anticoagulant (DOAC) and warfarin-associated intracerebral hemorrhage (ICH) patients

	DOAC, n = 227	Warfarin, n = 2,018	*p* Value
Patients			
Male, n (%)	171 (75.3)	1,314 (65.1)	0.002
Age, y, mean ± SD	74.4 ± 8.5	74.2 ± 10.5	0.737
Comorbidities			
Charlson score, mean, n ± SD	4.9 ± 1.4	5.0 ± 1.6	0.172
Hypertension, n (%)	128 (56.4)	1,070 (53.0)	0.335
Diabetes mellitus, n (%)	51 (22.5)	443 (22.0)	0.859
Hyperlipidemia, n (%)	28 (12.3)	242 (12.0)	0.880
JCS score on admission			0.002
0- or 1-digit code, n (%)	156 (68.7)	1,224 (60.7)	
2- or 3-digit code, n (%)	71 (31.3)	794 (39.4)	
Concurrent antiplatelet therapy, n (%)	57 (25.1)	810 (40.1)	<0.001
Treatment/surgery			
ICH removal, n (%)	12 (5.3)	200 (9.9)	0.024
External CSF drainage, n (%)	7 (3.1)	77 (3.8)	0.582
Treatment/reversal agent			
Vitamin K, n (%)	6 (2.6)	1,273 (63.1)	<0.001
PCC, n (%)	7 (3.1)	116 (5.8)	0.094
FFP, n (%)	11 (4.9)	236 (11.7)	0.002
Length of hospital stay, d, median ± SD	18 ± 26.1	18 ± 27.6	0.684

Abbreviations: FFP = fresh frozen plasma; PCC = prothrombin complex concentrate.

Table 2 Outcomes of direct oral anticoagulant (DOAC) and warfarin-associated intracerebral hemorrhage patients

	DOAC, n = 227	Warfarin, n = 2,018	*p* Value
Mortality within 1 day, n (%)	6 (2.6)	131 (6.5)	0.022
Mortality within 7 days, n (%)	27 (11.9)	368 (18.2)	0.017
In-hospital mortality, n (%)	40 (17.6)	510 (25.3)	0.011
Discharge mRS, mean ± SD	3.30 ± 1.95	3.50 ± 2.04	0.158
Discharge mRS 4–6, n (%)	119 (52.4)	1111 (55.1)	0.45

Abbreviation: mRS = modified Rankin Scale.

data suggest no significant between-group differences in hematoma locations.

Table 2 shows mortality rates and discharge mRS scores for the DOAC- and warfarin-treated patients. The warfarin-treated patients exhibited higher mortality rates within 1 day (2.6%, 6.5%; $p = 0.022$), within 7 days (11.9%, 18.2%; $p = 0.017$), and during hospitalization (17.6%, 25.3%; $p = 0.011$). There were no significant differences in mean discharge mRS scores (3.30, 3.50) or the proportion of discharge mRS scores of 4–6 (52.4%, 55.1%).

Table 3 shows the 2 groups' ORs for mortality within 1 day, within 7 days, and during hospitalization and for discharge mRS scores of 4–6 after adjusting for sex, age, comorbidities, admission JCS scores, concurrent antiplatelet therapy, and treatment with surgery or reversal agents. The warfarin-treated patients exhibited higher ORs for mortality within 1 day (OR 4.06, $p < 0.001$), within 7 days (OR 1.96, $p = 0.012$), and during hospitalization (OR 1.60, $p = 0.041$). The 2 groups' ORs for discharge mRS scores of 4–6 were not significantly different.

Table 3 Odds ratios (ORs) of mortality within 1 day, 7 days, and during hospitalization, and modified Rankin Scale (mRS) 4–6 at discharge in warfarin-associated intracerebral hemorrhage patients compared with direct oral anticoagulant–associated patients after adjusting for sex, age, comorbidities, Japan Coma Scale on admission, concurrent antiplatelet therapy, and treatment (surgery and reversal agent)

	OR	95% CI	*p* Value
Mortality within 1 day	4.06	1.78–10.99	<0.001
Mortality within 7 days	1.96	1.15–3.39	0.012
In-hospital mortality	1.6	1.02–2.56	0.041
Discharge mRS 4–6	0.79	0.56–1.12	0.181

Abbreviation: CI = confidence interval.

Table 4 Odds ratios (ORs) of mortality within 1 day, 7 days, and during hospitalization, and modified Rankin Scale (mRS) 4–6 at discharge in warfarin-associated intracerebral hemorrhage patients compared with direct oral anticoagulant–associated patients after matching by propensity score

	OR	95% CI	*p* Value
Mortality within 1 day	4.96	1.61–15.25	0.005
Mortality within 7 days	2.29	1.05–5.00	0.037
In-hospital mortality	1.96	1.03–3.72	0.039
Discharge mRS 4–6	0.76	0.48–1.20	0.246

Abbreviation: CI = confidence interval.

Propensity score analysis

Table 4 shows the 2 groups' ORs for mortality within 1 day, within 7 days, and during hospitalization and for discharge mRS score of 4–6 after matching patients by propensity scores (n = 221 vs n = 221). Table e-4 (links.lww.com/WNL/A284) shows the propensity score–adjusted data for sex, age, comorbidities, admission JCS scores, concurrent antiplatelet therapies, and treatment with surgery or reversal agents. The warfarin-treated patients exhibited higher ORs for mortality within 1 day (OR 4.96, $p = 0.005$), within 7 days (OR 2.29, $p = 0.037$), and during hospitalization (OR 1.96, $p = 0.039$). The 2 groups did not significantly differ in ORs for discharge mRS scores of 4–6.

We also applied propensity score analysis to the outcomes for DOAC- and warfarin-treated patients. The propensity score–matched patients tended to have similar characteristics. Compared to the warfarin-treated patients, the dabigatran- (n = 51 vs n = 51) and apixaban-treated patients (n = 42 vs n = 42) did not exhibit significantly different mortality rates or likelihoods of discharge mRS scores of 4–6 (table e-5 and e-6). The rivaroxaban-treated patients (n = 127 vs n = 127), however, exhibited lower mortality rates within 1 day (OR = 11.22, $p = 0.023$), though this was not the case for mortality rates within 7 days or during hospitalization or for the likelihood of discharge mRS scores of 4–6 (table e-7).

Discussion

Our objective in this study was to compare the characteristics and outcomes of DOAC- and warfarin-associated ICHs in clinical practice. Administrative databases of hospital admissions are increasingly used for clinical outcome studies. Despite several limitations, using nationwide databases provides large sample sizes and produces more generalizable results than randomized trials because it eliminates potential selection and referral biases.[10] The J-ASPECT study is the first nationwide survey on the clinical practice of stroke care in Japan that uses data obtained from hospitals subject to the DPC-based payment system.[10] This study had a larger sample of clinical patients than did previous reports comparing DOAC- and warfarin-associated ICHs.[5,14–16] Furthermore, we added a propensity score analysis and a multivariable analysis to compare the clinical outcomes from warfarin-associated ICHs to DOAC-associated ICHs collectively and the ICHs associated with each individual DOAC separately, with adjustments for key variables such as concurrent antiplatelet therapies[17–19] and reversal agents.[17,20,21] Compared to the warfarin-associated ICHs, the DOAC-associated ICHs were of lesser severity in the univariate analysis and were associated with lower in-hospital mortality after matching with propensity scores derived from clinical data. Our results are therefore robust and provide important clinical insights into optimizing oral anticoagulation therapy for stroke prevention in patients with AF.

Few studies have compared the clinical and radiologic characteristics and outcomes of DOAC- and warfarin-associated ICHs,[5,15,16] and they have featured small sample sizes of DOAC-associated ICHs.[5,15,16] These studies found that patients with DOAC-associated ICHs had lower mortality rates,[15] smaller hematomas,[5,15,16] and less hematoma expansion.[5,15] In a case series study of DOAC-associated ICHs,[22,23] none showed small hematoma expansion. In animal model studies, dabigatran treatment results in lower ICH volumes and less hematoma expansion than does warfarin treatment.[24,25] These reports support our observation that DOAC-associated ICHs were less severe and were associated with lower mortality rates.

Several reports have explored the mechanisms behind DOAC-associated ICHs having smaller volumes and less hematoma expansion than warfarin-associated ICHs.[5,22,23,26] Complexes of tissue factor VII are essential for the first reaction in the extrinsic coagulation cascade.[27] Warfarin inhibits vitamin K–dependent coagulation proteins II, VII, IX, and X, while DOAC never inhibits factor VII function.[28] Furthermore, DOAC half-lives are shorter than warfarin's half-life.[28]

Our univariate analysis showed that warfarin-treated patients were more likely to undergo ICH removal surgeries, but this difference did not survive adjustments for the use of reversal agents. However, it is difficult to interpret these contradictory results, because the interaction between ICH removal surgeries and reversal agent usage was marginally significant. The appropriateness of surgery for most patients with spontaneous ICHs remains controversial, but it is recommended for patients with cerebellar hemorrhages who are deteriorating neurologically or who have brainstem compression or hydrocephalus from ventricular obstruction.[29] Initial hematoma volume is the most powerful predictor of neurologic deterioration, functional outcome, and mortality in both spontaneous and oral anticoagulant–associated ICHs, whereas the level of consciousness is highly predictive in infratentorial ICHs.[30,31] The proportion of cerebellar hemorrhages in this study is notably similar to that of a previous Japanese study that showed that prior treatment with antiplatelets, warfarin, or both is predictive of cerebellar hemorrhages, hematoma enlargement, and early death in Japanese patients with ICHs.[32] In line with previous studies comparing patients with DOAC- and warfarin-associated ICHs,[5,16,33] we found no significant between-group difference in ICH locations. However, the DPC data excluded information about the eloquence of the ICH lesions and the size and expansion of hematomas. In terms of lesion eloquence, our study revealed that DOAC-associated ICHs were associated with similar functional outcomes. Given the strong effect of initial hemorrhage locations on functional outcomes following DOAC- and warfarin-associated ICHs regardless of hematoma size or expansion,[34] we doubt there were any between-group differences in the proportions of eloquent area ICHs in our sample. Therefore, the localization and eloquence of the lesions does not seem to explain the different rates of ICH removal surgeries for our warfarin- and DOAC-treated groups. Regarding the size and expansion of hematomas, past studies[5,15–20] have shown that DOAC-associated ICHs have smaller hemorrhage volumes and lower chances of hematoma expansion, which may explain our observation. A previous study comparing the effects of different reversal agents on hematoma growth and outcomes in patients with warfarin-related ICHs found that PCC was associated with a reduced incidence and extent of hematoma growth relative to FFP and vitamin K.[35] The present study, however, revealed that reversal strategies are not as widely applied in clinical practice in Japan as they are in Western countries,[16,33] with PCC being used less frequently for warfarin-treated patients and specific reversal agents for DOACs such as idarucizumab being unavailable during the study period.[17,20,21] Despite such overall low usage, more frequent usage in specific scenarios, especially PCC for patients who underwent removal surgeries for warfarin-associated ICHs, suggests that such strategies are mainly indicated for patients with large initial hematoma volumes and a high risk of neurologic deterioration. Furthermore, our study revealed that patients with warfarin-associated ICHs who were treated with reversal agents were more likely to require removal surgeries. This suggests that among patients with warfarin-associated ICHs, those who require surgical removal of large ICHs are more likely to use reversal agents.

Despite the release of DOACs, issues with warfarin such as overuse for low-risk patients and underuse for high-risk patients persist, as does discordance between guidelines and clinical practice. Our results are inconsistent with those of comparative studies of DOAC- or warfarin-associated ICHs in clinical settings in Western countries.[5,14,33] Alonso et al.[14] found no significant medication-related differences in mortality for any type of intracranial hemorrhage (intracerebral, subdural, or subarachnoid). However, the results of subtype analyses should be interpreted cautiously because of imprecise estimates and small numbers.[14] Considering the prognosis differences between ICH subtypes, we focused on 227 DOAC-associated ICHs while excluding other hemorrhage subtypes. In contrast, the Registry of Acute Stroke Under New Oral Anticoagulants[33] showed that DOAC-associated ICHs were associated with higher mortality rates, more unfavorable outcomes, and greater hematoma expansion frequencies. However, these conclusions were derived from comparisons with both warfarin-associated ICHs in that study and those in previously published retrospective observational studies. Another comparative study showed slightly higher mortality rates in patients with DOAC-associated ICHs but did not adjust for confounding factors with multivariate analyses or propensity score matching.[5] Another explanation for the disparity between our study and that of those 3 studies[5,14,33] may be the differences in patient ethnicity. The median case-fatality at 1 month for patients with ICHs is lower in Japan than in other countries,[36] and there are slight differences in the efficacy and safety of DOACs and warfarin between Asian and non-Asian populations.[37,38] Resolving these discrepancies will require multinational observational collaborative studies and randomized controlled trials comparing DOACs and warfarin.

Each DOAC exhibits a unique dose-dependent efficacy and safety profile.[1] We therefore used propensity score analysis to separately compare the outcomes for each DOAC to those of warfarin. Compared to warfarin-treated patients, rivaroxaban-treated patients exhibited significantly lower 1-day mortality rates, while dabigatran- and apixaban-treated patients did not. These differences may be explained by the sample sizes for each DOAC. In Japan, dabigatran, rivaroxaban, and apixaban were launched in March 2011, April 2012, and February 2013, respectively, and edoxaban was approved for additional indications in September 2014. The timing of these launches may account for the proportions of each DOAC in this study. Larger sample sizes are needed to compare the characteristics and outcomes of each DOAC with those of warfarin.

The DPC database lacks several types of data. First, the database does not include laboratory data. The prothrombin time–international normalized ratio (PT-INR) is a particularly important factor in assessing the influence of hemorrhagic stroke.[17] In this respect, it is interesting to note that the Japanese Fushimi AF Registry reported that over 90% of patients had PT-INR values within the optimal range.[39] Given this observation, it is unlikely that high PT-INR values alone could account for our observation of warfarin-associated ICHs being more severe, requiring removal more often, and being associated with higher mortality rates. Second, it does not contain vital signs data. Notably, a meta-analysis of 5 randomized controlled trials also showed that early intensive blood pressure reduction did not significantly reduce the mortality rate.[40] Admittedly, these missing data are unmeasured confounders for this study, so there is a need for further research that combines DPC database information with laboratory and radiologic data.

Although end-of-life decisions are an important factor in mortality, we had no information about such decisions. Previous studies comparing patients with DOAC- and warfarin-associated ICHs revealed no between-group differences in end-of-life decisions and found that mortality due to end-of-life decisions was low (i.e., 6%).[5] In Japan, the proportion of end-of-life decisions is reportedly much lower than in other countries.[41] Collectively, these facts lead us to suspect a minor effect of end-of-life decision on mortality in our patients.

This is the largest Japan-wide study of DOAC-associated ICHs in clinical practice, and it revealed that DOAC-associated ICHs were less lethal than warfarin-associated ICHs, probably due to lower hemorrhage severity at admission and lower hematoma expansion frequencies.

Author contributions

Ryota Kurogi drafted the manuscript. Koji Iihara was involved in conceptualizing and designing the study and in obtaining funding. Jyoji Nakagawara, Kazunori Toyoda, Kuniaki Ogasawara, Junichi Ono, Yoshiaki Shiokawa, Toru Aruga, Shigeru Miyachi, Izumi Nagata, Shinya Matsuda, Shinichi Yoshimura, Kazuo Okuchi, and Akifumi Suzuki were involved in data acquisition. Ryota Kurogi, Kunihiro Nishimura, Michikazu Nakai, Akiko Kada, Satoru Kamitani, Daisuke Onozuka, Keisuke Ido, Ai Kurogi, Nobutaka Mukae, Ataru Nishimura, Koichi Arimura, Akihito Hagihara, and Koji Iihara were involved in analyzing and interpreting the data. Jyoji Nakagawara, Kazunori Toyoda, Kuniaki Ogasawara, Junichi Ono, Yoshiaki Shiokawa, Toru Aruga, Shigeru Miyachi, Izumi Nagata, Shinya Matsuda, Shinichi Yoshimura, Kazuo Okuchi, Akifumi Suzuki, Takanari Kitazono, and Koji Iihara were involved in study supervision.

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Comparing intracerebral hemorrhages associated with direct oral anticoagulants or warfarin

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Study question

How do outcomes for direct oral anticoagulant (DOAC)-associated intracerebral hemorrhages (ICHs) compare to those for warfarin-associated ICHs?

Summary answer

DOAC-associated ICHs are less severe and are associated with lower mortality rates.

What is known and what this paper adds

Past studies reported that patients with DOAC-associated ICHs have lower mortality rates than patients with warfarin-associated ICHs do, but strict inclusion criteria limited the generalizability of their results. This study provides corroborating evidence obtained by analyzing the nationwide Japanese Diagnosis Procedure Combination (DPC) clinical practice database.

Participants and setting

This study examined 2,245 patients who experienced non-traumatic ICHs while taking anticoagulants (DOAC, 227; warfarin, 2,018) and were urgently hospitalized at 621 Japanese institutions between 1 April 2010 and 31 March 2015.

Design, size, and duration

This study accessed the DPC database to obtain clinical data including consciousness impairment levels upon admission (as measured with the Japan Coma Scale), surgical removal rates, at-discharge modified Rankin Scale (mRS) scores, and mortality rates.

Primary outcomes

The primary outcomes were ICH severities, which were assessed based on consciousness impairments or the need for surgical removal, and mortality rates within 1 day, within 7 days, or during hospitalization.

Timeframe	Odds ratio for mortality	*p* Value	95% confidence intervals
1 d	4.06	<0.001	1.78–10.99
7 d	1.96	0.012	1.15–3.39
During hospitalization	1.60	0.041	1.02–2.56

Main results and the role of chance

Compared to warfarin-associated ICHs, DOAC-associated ICHs were less likely to cause moderate or severe consciousness impairments at admission (39.4% vs 31.3%; $p = 0.002$) or to necessitate surgical removal (9.9% vs 5.3%; $p = 0.024$) but were not associated with a lower mean at-discharge mRS score (3.50 vs 3.30; $p = 0.158$). Furthermore, the patients with DOAC-associated ICHs had lower mortality rates within 1 day (6.5% vs 2.6%; $p = 0.022$), within 7 days (18.2% vs 11.9%; $p = 0.017$), and during hospitalization (25.3% vs 17.6%; $p = 0.011$).

Bias, confounding, and other reasons for caution

The DPC database lacks some potentially relevant data, including laboratory data, vital signs data, and end-of-life decisions data.

Generalizability to other populations

The use of a nationwide database makes this study's results more generalizable than those of previous reports.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

