17. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke 1994;25:2220–2226.
18. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.
19. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. Neurology 2012;78:1916–1922.
20. Strbian D, Meretoja A, Ahlhelm FJ, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology 2012;78:427–432.
21. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The Stroke-Thrombolytic Predictive Instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke 2006;37:2957–2962.
22. Saposnik G, Raptis S, Kapral MK, et al; Investigators of the Registry of the Canadian Stroke Network and the Stroke Outcome Research Canada Working Group. The iScore predicts poor functional outcomes early after hospitalization for an acute ischemic stroke. Stroke 2011;42:3421–3428.
23. Rajajee V, Kidwell C, Starkman S, et al. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. Neurology 2006;67:980–984.
24. Leira EC, Ludwig BR, Gurol ME, Torner JC, Adams HP Jr. The types of neurological deficits might not justify withholding treatment in patients with low total National Institutes of Health Stroke Scale scores. Stroke 2012;43:782–786.
25. Chambers BR, Norris JW, Shurvell BL, Hachinski VC. Prognosis of acute stroke. Neurology 1987;37:221–225.
26. Paolucci S, Antonucci G, Pratesi L, Traballesi M, Lubich S, Grasso MG. Functional outcome in stroke inpatient rehabilitation: predicting no, low and high response patients. Cerebrovasc Dis 1998;8:228–234.
27. Denes G, Semenza C, Stoppa E, Lis A. Unilateral spatial neglect and recovery from hemiplegia: a follow-up study. Brain 1982;105:543–552.
28. Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol 2006;5:603–612.
29. Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36:2121–2125.
30. Greisenegger S, Seyfang L, Kiechl S, Lang W, Ferrari J; Austrian Stroke Unit Registry Collaborators. Thrombolysis in patients with mild stroke: results from the Austrian Stroke Unit Registry. Stroke 2014;45:765–769.
31. Minematsu K, Bang O, Uehara T. Risk factors. In: Kim JS, Caplan LR, Wong KS, editors. Intracranial Atherosclerosis, 1st ed. Philadelphia: Wiley-Blackwell; 2008: 45–54.
32. Guideline Committee of the Japan Stroke Society for IV rt-PA (alteplase) in acute ischemic stroke. Guidelines for IV application of rt-PA (alteplase), October 2005 [in Japanese]. Jpn J Stroke 2005;27:327–354.

Research

Three-dimensional analysis of the left atrial appendage for detecting paroxysmal atrial fibrillation in acute ischemic stroke

Koji Tanaka[1], Masatoshi Koga[2]*, Kazuaki Sato[1], Rieko Suzuki[1], Kazuo Minematsu[1], and Kazunori Toyoda[1]

Background Atrial fibrillation impairs left atrial appendage function and the thrombus formation in the left atrial appendage is a major cause of cardioembolic stroke.

Aims To evaluate the association between the volume of the left atrial appendage measured by real-time three-dimensional transesophageal echocardiography and presence of paroxysmal atrial fibrillation in patients with cerebral infarction or transient ischemic attack.

Methods Real-time three-dimensional transesophageal echocardiography was performed to measure left atrial appendage end-diastolic and end-systolic volumes to calculate left atrial appendage ejection fraction. Patients with normal sinus rhythm at the time of real-time three-dimensional transesophageal echocardiography were divided into groups with and without paroxysmal atrial fibrillation. Volumetric data were corrected with the body surface area.

Results Of 146 patients registered, 102 (29 women, 72·2 ± 10·7 years) were normal sinus rhythm at the examination. In 23 patients with paroxysmal atrial fibrillation, left atrial appendage end-diastolic volume (4·78 ± 3·00 ml/m^2 vs. 3·14 ± 2·04 ml/m^2, $P = 0{\cdot}003$) and end-systolic volume (3·10 ± 2·47 ml/m^2 vs. 1·39 ± 1·56 ml/m^2, $P < 0{\cdot}001$) were larger and left atrial appendage ejection fraction (37·3 ± 19·1% vs. 57·1 ± 17·5%, $P < 0{\cdot}001$) was lower than in the other 79 patients without paroxysmal atrial fibrillation. The optimal cutoff for left atrial appendage peak flow velocity to predict paroxysmal atrial fibrillation was 39·0 cm/s (sensitivity, 54·6%; specificity, 89·7%; c-statistic, 0·762). The cutoffs for left atrial appendage end-diastolic volume, end-systolic volume, and ejection fraction were 4·52 ml/m^2 (sensitivity, 47·8%; specificity, 82·3%; c-statistic, 0·694), 1·26 ml/m^2 (sensitivity, 91·3%; specificity, 60·3%; c-statistic, 0·806), and 47·9% (sensitivity, 78·3%; specificity, 74·7%; c-statistic, 0·774), respectively. In multivariate analysis, all these parameters were independently associated with paroxysmal atrial fibrillation after adjusting for sex, age, diabetes mellitus, and previous stroke.

Conclusions Left atrial appendage volumetric analysis by real-time three-dimensional transesophageal echocardiography is a promising method for detecting paroxysmal atrial fibrillation in acute cerebral infarction or transient ischemic attack.

Correspondence: Masatoshi Koga*, Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan.
E-mail: koga@ncvc.go.jp
[1]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan
[2]Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Osaka, Japan

Received: 17 October 2013; Accepted: 2 February 2014; Published online 13 March 2014

Conflict of interest: None declared.

Funding: This study was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS KAKENHI grant number 24591084).

DOI: 10.1111/ijs.12268

Key words: atrial fibrillation, ejection fraction, ischemic stroke, left atrial appendage, real-time three-dimensional transesophageal echocardiography, volume measurement

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is a major risk factor of ischemic stroke (1). Paroxysmal AF (PAF) has a similar risk of embolism compared with chronic AF (2). Therefore, the identification of hidden AF in acute cerebral infarction or transient ischemic attack (TIA) patients with normal sinus rhythm (NSR) on admission is important for preventing further brain ischemia. In previous reports, left atrial volume index/late diastolic peak tissue Doppler velocity on transthoracic echocardiography (3), or plasma brain natriuretic peptide levels on admission (4) were useful for ruling out or predicting PAF in patients with NSR on admission.

The left atrial appendage (LAA) is an important site of thrombus formation in patients with AF. Two-dimensional (2D) transesophageal echocardiography (TEE) has been widely used for characterizing LAA structure and function. Enlargement of the 2D area of LAA and decreased LAA flow velocity were reported to be associated with AF, spontaneous echo contrast, and thrombus formation (5–7). Moreover, in patients with PAF, LAA flow velocity was significantly decreased even if their electrocardiogram (ECG) showed NSR at the time of TEE (8).

Three-dimensional TEE (3D-TEE) has advantages for volumetric analysis because it allows rotation of heart structures and slicing the images in any plane to enable accurate visualization of the cardiac chambers. Recently, real-time (RT) 3D-TEE was developed to allow real-time acquisition and display of cardiac structures with high quality images (9) that correlate well with cardiac CT (10).

In previous reports on RT 3D-TEE, the volume of LAA was larger (11) and ejection fraction (EF) of LAA was lower in patient with AF (12). However, there is little information on volumetric analysis of the LAA and the utility of volume and function parameters derived from TEE in stroke patients. This study aimed to elucidate the association between volume of the LAA measured by RT 3D-TEE and the presence of PAF in patients with acute cerebral infarction or TIA.

Methods

Study subjects

We retrospectively analyzed data from prospectively collected consecutive acute stroke patients who were admitted to our facility and underwent RT 3D-TEE. Participants referred for RT 3D-TEE were diagnosed with acute cerebral infarction or TIA on admission.

They admitted principally within 14 days of symptom onset. Cerebral infarction was diagnosed by clinical course, neurological examinations, and CT or MRI. TIA was diagnosed based on the Classification of Cerebrovascular Diseases III from the National Institute of Neurological Disorders and Stroke (13). Clinical indication for TEE was made mainly for the detection of embolic sources by an independent attending physician. Two-dimensional and RT 3D-TEE were performed to assess any embolic sources such as intracardiac thrombus, right-to-left shunt, and complicated atherosclerotic changes of the aortic arch. Patients with an evident embolic source such as chronic AF, significant valvular heart disease, a prosthetic heart valve or mitral valve repair, or those with technically inadequate echocardiographic studies were excluded. Informed consent for RT 3D-TEE was obtained from all patients. The following information was obtained from the medical records of each patient: age, sex, vascular risk factors (systemic hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking), extracranial and intracranial large artery atherosclerosis defined as greater than 50% stenosis or occlusion, previous stroke, congestive heart failure, and the left atrial diameter (LAD) measured by transthoracic echocardiography. According to the Oxfordshire Community Stroke Project (OCSP) criteria, patients were classified from their clinical symptoms by two experienced neurologists into four categories, as having total anterior circulation stroke, partial anterior circulation stroke, posterior circulation stroke, or lacunar stroke. The neurologists were blinded to the neuroimaging and vascular imaging results.

The presence of PAF was defined as a history of PAF diagnosed previously or newly diagnosed by continuous ECG monitoring for at least several days after admission or 24-hour Holter ECG monitoring during hospitalization. Patients were allocated to a group with PAF (PAF group) or a group without PAF (non-PAF group). The diagnosis of PAF was based on a history of PAF or recurrent episodes of AF lasting for more than 30 s documented by continuous ECG monitoring or 24-hour Holter ECG monitoring. This study is a retrospective analysis of our prospective stroke registry and was approved by the institutional review committee at the National Cerebral and Cardiovascular Center.

Two- and three-dimensional transesophageal echocardiography

RT 3D-TEE was performed using a commercially available iE 33 Ultrasound machine and fully sampled X7-2t TEE transducer (Philips Medical Systems, Andover, MA, USA). Routine 2D TEE and RT 3D-TEE examinations were performed using the same transducer.

LAA flow velocity was measured by pulsed-wave Doppler echocardiographic interrogation at the orifice of the LAA. The presence of a patent foramen ovale based on the detection using saline contrast technique and atherosclerotic changes of the aorta were assessed with 2D TEE. Atherosclerotic changes of the aorta were defined as ≥4 mm thick, or with mobile components of plaques of the aorta.The scan volume was the wide-angled acquisition mode that included the LAA and surrounding structures acquired at the maximal frame rate. This 3D Full volume mode had high time resolution and provided ECG-gated acquisition of a large 3D volume created from subvolumes stitched together and synchronized to a single cardiac cycle. To avoid stitch artifacts, special care was taken to stabilize the probe during data acquisition. The acquisition was repeated whenever obvious artifacts were found. Images were reviewed online to ensure adequate 3D visualization of the LAA.

Three-dimensional data analysis

Images were digitally stored for subsequent offline analysis using QLAB 7·0 software (Philips Medical Systems). LAA volumes are measured using the multiplanar reconstruction mode of the General Imaging 3D Quantification plug-in to visualize LAA in the three different dimensions. Offline 3D analysis was performed by personnel who were blinded to the clinical information. The image was rotated in order to provide a long-axis view of the LAA (Fig. 1a) and to allow simultaneous visualization of the LAA orifice in the short-axis view (Fig. 1b). The LAA orifice was determined by two lines: one was drawn between the vestibule of the mitral valve annulus near the left coronary artery and the lateral ledge of the left superior pulmonary vein, and the other was drawn between a point near the aortic valve annulus and the left superior pulmonary vein limbus (11,14,15). Using the Stacked Contours mode in the software, a line was drawn from the LAA orifice to the apex, and then 15 short-axis multiplanar slices of the LAA from the orifice to the apex were automatically generated. By manual tracing the LAA contour in each slice (Fig. 1c), a virtual 3D image was automatically created from the stacking of multiple slices, and the volume of the LAA was calculated (Fig. 1d).

LAA end-diastolic volume was measured just before the *P* wave in the ECG and the end-systolic volume was measured at the QRS

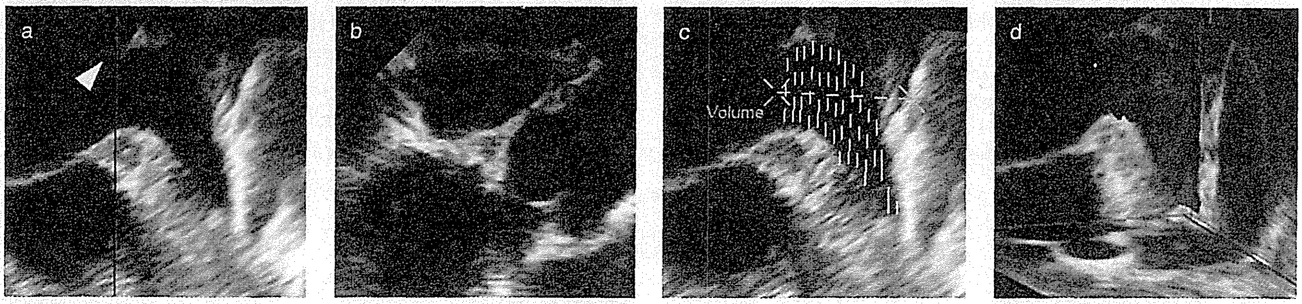

Fig. 1 Offline measurement of the left atrial appendage (LAA). (a) LAA long-axis view at the level of the mitral valve annulus, and lateral ridge of the left superior pulmonary vein (white arrowhead). (b) LAA orifice in the short-axis view. (c) The long-axis view of the LAA that results from the stacking of multiple short-axis segments. (d) By manually tracing the endocardial border of the individual short-axis segments, a virtual three-dimensional image of the LAA is obtained that can be used to calculate the LAA volume.

complex (5). Volumetric data were corrected by area of the body surface based on the Du Bois formula (end-diastolic volume index, end-systolic volume index). LAA-EF was calculated using the following equation: LAA-EF = [(end-diastolic volume – end-systolic volume) * 100]/end-diastolic volume (%).

Statistical analysis

Statistical analysis was performed using JMP 8·0 statistical software (SAS Institute Inc, Cary, NC, USA). Continuous data are expressed as mean ± standard deviation. Categorical data are presented as absolute numbers (percentages). Differences in continuous variables between two groups were assessed using a Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Differences in categorical variables between two groups were assessed using a chi-square test or Fisher's exact test, as appropriate. Observer variability was assessed by the coefficient of variation, and the concordance correlation coefficient for TEE-derived measurements repeating the analysis at least one-month later by the same observer who performed the first analysis and by a second independent blinded observer. Correlations between two variables were evaluated by linear regression analysis. To evaluate the ability of LAA flow velocity, end-diastolic volume index, end-systolic volume index, and LAA-EF to predict PAF, receiver operating characteristic (ROC) curves were constructed. The c-statistic (area under the ROC curve) was used as a scalar measure to assess the performance of each parameter. The c-statistics for different parameters were compared by a nonparametric method (16). To determine whether each TEE parameter was associated with PAF, multivariate logistic regression analysis was performed. The multivariate logistic regression model was adjusted for, age, sex, and variables with a probability value $<0{\cdot}1$ in univariate analysis to assess the independent impact of each cutoffs of TEE parameter on PAF. Probability values $<0{\cdot}05$ were considered significant.

Results

Between July 2010 and November 2012, a total of 150 patients were referred for RT 3D-TEE. Four patients were excluded because we were unable to insert a probe in two patients, and it was difficult to view the LAA in the other two patients. The remaining 146 patients underwent RT 3D-TEE without complications. Among them, 102 patients (73 men, mean age 72·2 ± 10·7 years) were in NSR at the time of TEE and were included in this study. The other 44 patients including 43 with chronic AF and 1 with a prosthetic mitral valve and AF at the TEE examination were excluded. Twenty-three patients were allocated to the PAF group, and 79 to the non-PAF group. The baseline characteristics of each group are listed in Table 1. Diabetes mellitus was less frequent in patients with than without PAF (4% vs. 25%, $P = 0{\cdot}038$). OCSP categories were not different in the groups.

The intraobserver and interobserver correlation coefficients for LAA volume measurement were 0·900 and 0·861, respectively; and the interclass correlation coefficients were 0·891 and 0·847, respectively. The imaging characteristics derived from echocardiography are shown in Table 2. Patients with PAF tended to have larger LAD (39·3 ± 5·9 mm vs. 36·3 ± 7·7 mm, $P = 0{\cdot}086$), lower LAA flow velocity (46·1 ± 27·3 cm/s vs. 66·3 ± 24·2 cm/s, $P < 0{\cdot}001$), larger end-diastolic volume index (4·78 ± 3·00 ml/m^2 vs. 3·14 ± 2·04 ml/m^2, $P = 0{\cdot}003$) and end-systolic volume index (3·10 ± 2·47 ml/m^2 vs. 1·39 ± 1·56 ml/m^2, $P < 0{\cdot}001$), and lower LAA-EF (37·3 ± 19·1% vs. 57·1 ± 17·5%, $P < 0{\cdot}001$) than those without PAF.

The correlations between each TEE parameter are shown in Fig 2. The end-diastolic volume index was strongly correlated with the end-systolic volume index, and was moderately correlated with the LAA flow velocity and LAA-EF.

ROC curve analysis showed that the optimal cutoff value of the LAA flow velocity to predict PAF was 39·0 cm/s, with a c-statistic

Table 1 Baseline clinical characteristics

Characteristics	Total (*n* = 102)	PAF (*n* = 23)	non-PAF (*n* = 79)	*P* value
Sex, men, *n* (%)	73 (72)	15 (65)	58 (73)	0·443
Age (years)	72·2 ± 10·7	73·7 ± 9·0	71·8 ± 11·2	0·654
Body surface area (m^2)	1·59 ± 0·17	1·59 ± 0·21	1·59 ± 0·16	0·935
Hypertension, *n* (%)	72 (71)	14 (61)	58 (73)	0·245
Diabetes mellitus, *n* (%)	21 (21)	1 (4)	20 (25)	0·038
Dyslipidemia, *n* (%)	58 (57)	12 (52)	46 (58)	0·606
Smoking, *n* (%)	20 (20)	3 (13)	17 (22)	0·368
Congestive heart failure, *n* (%)	6 (6)	1 (4)	5 (6)	0·772
Previous stoke, *n* (%)	26 (25)	2 (9)	24 (30)	0·054
Extracranial large artery atherosclerosis, *n* (%)	13 (13)	2 (9)	11 (14)	0·727
Intracranial large artery atherosclerosis, *n* (%)	29 (28)	8 (35)	21 (27)	0·443
Clinical subtypes				
Total anterior circulation stroke, *n* (%)	10 (10)	1 (4)	9 (11)	0·232
Partial anterior circulation stroke, *n* (%)	26 (25)	10 (43)	16 (20)	
Posterior circulation stroke, *n* (%)	27 (26)	5 (22)	22 (28)	
Lacunar stroke, *n* (%)	38 (37)	7 (30)	31 (39)	
Unclassified, *n* (%)	1 (1)	0 (0)	1 (1)	

Continuous values are reported as the mean ± SD. PAF, paroxysmal atrial fibrillation.

Table 2 Echocardiographic parameters

Characteristics	Total (*n* = 102)	PAF (*n* = 23)	non-PAF (*n* = 79)	*P* value
Left atrial diameter (mm)	37·0 ± 7·5	39·3 ± 5·9	36·3 ± 7·7	0·086
*Patent foramen ovale, *n* (%)	36 (41)	3 (23)	33 (44)	0·225
Atherosclerotic changes at the aorta, *n* (%)	37 (36)	6 (26)	31 (39)	0·327
LAA flow velocity (cm/s)	61·8 ± 26·1	46·1 ± 27·3	66·3 ± 24·2	<0·001
End diastolic volume (ml)	5·52 ± 3·68	7·98 ± 5·16	4·90 ± 2·93	0·006
End-diastolic volume index (ml/m^2)	3·51 ± 2·38	4·78 ± 3·00	3·14 ± 2·04	0·003
End-systolic volume (ml)	2·78 ± 2·98	5·00 ± 4·14	2·13 ± 2·18	<0·001
End-systolic volume index (ml/m^2)	1·78 ± 1·93	3·10 ± 2·47	1·39 ± 1·56	<0·001
LAA-EF (%)	52·6 ± 19·6	37·3 ± 19·1	57·1 ± 17·5	<0·001

*Data on patent foramen ovale was available in 13 patients of the PAF group and 75 of the non-PAF group.
Continuous values are reported as the mean ± SD. PAF, paroxysmal atrial fibrillation; LAA, left atrial appendage; EF, ejection fraction.

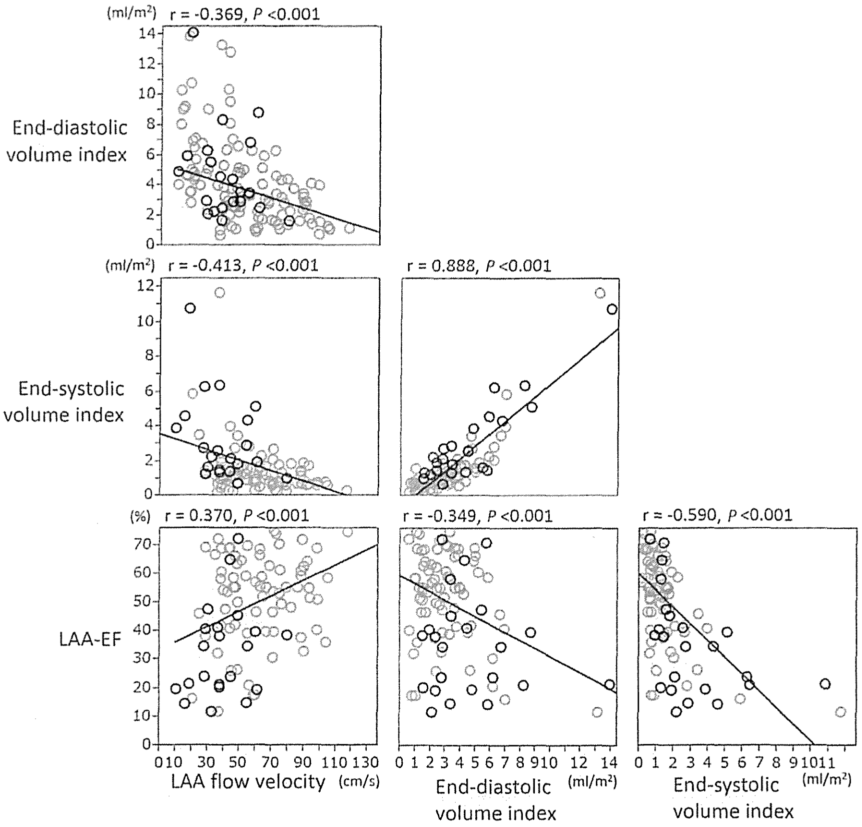

Fig. 2 Relations between transesophageal echocardiographic parameters. Regression lines among all subjects are shown. Black open circles = patients with paroxysmal atrial fibrillation (AF); Gray open circles = patients without AF.

of 0·762. The cutoff values of the end-diastolic volume index and the end-systolic volume index were 4·52 ml/m^2 and 1·26 ml/m^2, with c-statistics of 0·694 and 0·806, respectively. The cutoff of LAA-EF was 47·9%, with a c-statistic of 0·774 (Table 3, Fig. 3). There was a significant difference in the c-statistics among the four TEE-derived parameters ($P = 0{\cdot}007$), and the end-systolic volume index was superior to the end-diastolic volume index for predicting PAF ($P = 0{\cdot}007$).

In multivariate analysis, the LAA flow velocity ≤39·0 cm/s (odds ratio 12·91, 95% CI 3·70–53·90), the end-diastolic volume index ≥4·52 ml/m^2 (odds ratio 4·03, 95% CI 1·36–12·44), the end-systolic volume index ≥1·26 ml/m^2 (odds ratio 13·37, 95% CI 3·40–89·75), and LAA-EF ≤47·9% (odds ratio 10·02, 95% CI 3·33–35·34) were independently associated with PAF after adjusting for age, sex, and a history of diabetes mellitus, and previous stroke (Table 4).

Discussion

In this study, we determined the association between LAA volumetric parameters assessed by RT 3D-TEE and PAF in patients with acute cerebral infarction or TIA. This is the first report to show the association between LAA volumetric parameters and the presence of PAF in patients with acute stroke, although some 2D

Table 3 Receiver-operating-characteristic curve analysis of 3D-TEE parameters for predicting PAF

Variable	c-Statistic (95% CI)	Optimal cutoff	Sensitivity	Specificity	PPV	NPV
LAA flow velocity (cm/s)	0·762 (0·622–0·862)	≤39·0	54·6	89·7	60·0	87·5
End-diastolic volume index (ml/m^2)	0·694 (0·565–0·798)	≥4·52	47·8	82·3	44·0	84·4
End-systolic volume index (ml/m^2)	0·806 (0·696–0·883)	≥1·26	91·3	60·3	40·4	96·0
LAA-EF (%)	0·774 (0·635–0·871)	≤47·9	78·3	74·7	47·3	92·2

3D-TEE, three dimensional transesophageal echocardiography; CI, confidence interval; EF, ejection fraction; LAA, left atrial appendage; NPV, negative predictive value; PAF, paroxysmal atrial fibrillation; PPV, positive predictive value.

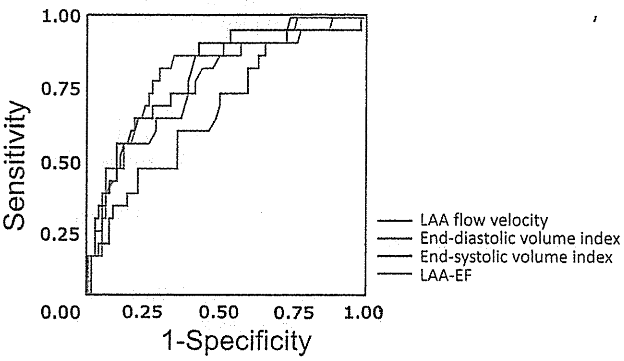

Fig. 3 Receiver operating characteristic curves comparing transesophageal echocardiographic parameters for the prediction of paroxysmal atrial fibrillation. Curves are shown for the left atrial appendage (LAA) flow velocity, end-diastolic volume index, end-systolic volume index, and LAA ejection fraction (EF).

Table 4 Multivariate logistic regression analysis of 3D-TEE parameters for predicting PAF

Variable	Odds ratio (95% CI)	*P* value
LAA flow velocity ≤39·0 cm/s	12·91 (3·70–53·90)	<0·001
End-diastolic volume index ≥4·52 ml/m^2	4·03 (1·36–12·44)	0·010
End-systolic volume index ≥1·26 ml/m^2	13·37 (3·40–89·75)	<0·001
LAA-EF ≤47·9%	10·02 (3·33–35·34)	<0·001

The regression model was adjusted for age, sex, diabetes mellitus, and previous stroke. 3D-TEE, three-dimensional transesophageal echocardiography; CI, confidence interval; EF, ejection fraction; LAA, left atrial appendage; PAF, paroxysmal atrial fibrillation.

parameters on LAA are known predictors for PAF. The first major finding was that LAA volumetric parameters as well as low LAA flow velocity were independently associated with the presence of PAF. The second finding was that not only a large LAA volume but also reduced EF was significantly associated with PAF. Third, the LAA end-systolic volume seems to be superior to the end-diastolic volume for detecting PAF in acute stroke patients. Finally, the intraobserver and interobserver variabilities for LAA volume assessment were excellent.

A large LAA volume, low EF and low flow velocity were independently associated with the presence of PAF in patients with acute cerebral infarction or TIA in the present study. Taguchi *et al.* (8) reported a significant difference in the LAA flow velocity between acute stroke patients with and without PAF (34·7 ± 9·3 cm/s vs. 64·0 ± 12·1 cm/s). In 2D- and 3D-TEE in patients without stroke, a large 2D LAA area (5) and large 3D LAA volume (11) were found to be significantly association with the presence of AF. Nucifora *et al.* (17) reported a progressive increase in LAA orifice size on RT 3D-TEE with an increasing frequency of AF in patients that were candidates for LAA closure endotherapy. Recently, Shimizu *et al.* (18) reported the correlation between LAA-EF derived from 2D-TEE area measurement and PAF in acute stroke patients. In their report, LAA-EF could predict PAF more accurate than the LAA flow velocity. There are several reports regarding LAA volumetric comparison between patients with AF and those with NSR in the absence of stroke (11,19). Chen *et al.* (12) reported lower LAA-EF in 62 patients with AF (24 ± 14%) than that in 34 with NSR (38 ± 17%, $P < 0·01$). Their LAA-EF value in patients with NSR was relatively low compared with ours (57·1 ± 17·5%). This difference is most likely due to the time resolution of 3D image acquisition. Compared with the 3D Zoom mode, the 3D Full volume mode provides higher time resolution and allows more accurate measurements of the end-diastolic and end-systolic volumes, and LAA-EF based on the ECG.

After spontaneous conversion of AF, diminishment of LAA function was reported as LAA 'stunning' (20). The persistence of AF produces changes in atrial function and structure, electrical remodeling, structural remodeling and contractile remodeling as there is reduced contraction and dilatation of the left atrium (21). The end-systolic volume appeared to be most sensitive parameter to detect contractile remodeling, since it reflects systolic dysfunction of a dilated LAA in patients with PAF, even if they return to NSR. Although LAA-EF and the LAA flow velocity are widely used to evaluate contractile function, they might not be appropriate for detecting volume enlargement of LAA. In contrast, the end-diastolic volume directly reflects volume enlargement, but is not useful to evaluate contraction of LAA. The end-systolic volume appears to indicate both volume enlargement and reduced contraction of LAA. However, a direct comparison of these parameters in multivariate analysis is difficult because of the strong correlations.

Our method is feasible for the measurement of LAA volume because of low interobserver and intraobserver variability. In order to analyze LAA volumes precisely based on the ECG, we investigated only patients with NSR at the time of TEE. We used the 3D Full volume mode, and this mode can be used only in patients with a regular cardiac rhythm. This mode provides 3D images with adequate width and depth and has high time resolution. On the other hand, the 3D Zoom mode is commonly used for patients in AF. The time resolution of the routine 3D Zoom mode is reduced by increasing the area of interest. Because ECG gating is not applicable with the 3D Zoom mode, ECG-based analysis with reduced time resolution may be unreliable. LAA flow velocity can be measured easily by 2D-TEE; however, LAA flow velocity was reported to vary about 1·5 times from the measurement site of the LAA orifice or apex (22). In contrast, our LAA volumetric evaluation with high time resolution seems to be consistent and reproducible. Classification of LAA morphology may also enable us to assess the risk of ischemic stroke, but it is still controversial (23,24).

This study had several limitations and our results could not be readily compared with previous reports. First, there was a risk of statistical error because of the small number of patients. Second, this study was not performed for all the consecutive stroke patients, because TEE is an invasive procedure and is not well-tolerated in patients with a poor general condition. Therefore there may be a selection bias. Third, continuous ECG monitoring and 24-hour Holter ECG monitoring during hospitalization might have failed to detect PAF. This leaves the possibility that PAF may be present in some of patients in the non-PAF group. Longer ECG monitoring, such as 7-day Holter ECG monitoring and outpatient telemetry monitoring (25,26), might have improved PAF detection and that may enable for further assessment of the correlations between TEE parameters and duration or frequency of PAF. Fourth, echocardiographic parameters in patients with PAF would not be different from those without PAF if we underwent TEE without recent PAF-attack because of the lack of a recovery effect from LAA stunning. A large prospective cohort study is needed to confirm the association between the LAA volumetric parameters and PAF in patients with acute cerebral infarction or TIA.

Conclusions

LAA function appeared to be impaired in patients with PAF, even though RT 3D-TEE was performed during NSR. Three-dimensional analysis of the LAA is a promising method for detecting PAF in patients with acute cerebral infarction or TIA.

Acknowledgement

The authors thank Dr Yoshifumi Wakata, Medical Information Center, Kyushu University Hospital, for advice on the statistical analyses.

References

1 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22:983–8.

2 Roy D, Marchand E, Gagné P, Chabot M, Cartier R. Usefulness of anticoagulant therapy in the prevention of embolic complications of atrial fibrillation. *Am Heart J* 1986; **112**:1039–43.

3 Stahrenberg R, Edelmann F, Haase B *et al.* Transthoracic echocardiography to rule out paroxysmal atrial fibrillation as a cause of stroke or transient ischemic attack. *Stroke* 2011; 42:3643–5.

4 Okada Y, Shibazaki K, Kimura K, Iguchi Y, Miki T. Brain natriuretic peptide as a predictor of delayed atrial fibrillation after ischaemic stroke and transient ischaemic attack. *Eur J Neurol* 2010; **17**:326–31.

5 Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation* 1991; **84**:223–31.

6 García-Fernández MA, Torrecilla EG, San Román D *et al.* Left atrial appendage Doppler flow patterns: implications on thrombus formation. *Am Heart J* 1992; **124**:955–61.

7 Pozzoli M, Febo O, Torbicki A *et al.* Left atrial appendage dysfunction: a cause of thrombosis? Evidence by transesophageal echocardiography-Doppler studies. *J Am Soc Echocardiogr* 1991; **4**:435–41.

8 Taguchi Y, Takashima S, Hirai T *et al.* Significant impairment of left atrial function in patients with cardioembolic stroke caused by paroxysmal atrial fibrillation. *Intern Med* 2010; **49**:1727–32.

9 Shah SJ, Bardo DM, Sugeng L *et al.* Real-time three-dimensional transesophageal echocardiography of the left atrial appendage: initial experience in the clinical setting. *J Am Soc Echocardiogr* 2008; **21**:1362–8.

10 Kumar V, Nanda NC. Is it time to move on from two-dimensional transesophageal to three-dimensional transthoracic echocardiography for assessment of left atrial appendage? Review of existing literature. *Echocardiography* 2012; **29**:112–6.

11 Nakajima H, Seo Y, Ishizu T *et al.* Analysis of the left atrial appendage by three-dimensional transesophageal echocardiography. *Am J Cardiol* 2010; **106**:885–92.

12 Chen OD, Wu WC, Jiang Y, Xiao MH, Wang H. Assessment of the morphology and mechanical function of the left atrial appendage by real-time three-dimensional transesophageal echocardiography. *Chin Med J* 2012; **125**:3416–20.

13 Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990; **21**:637–76.

14 Budge LP, Shaffer KM, Moorman JR, Lake DE, Ferguson JD, Mangrum JM. Analysis of in vivo left atrial appendage morphology in patients with atrial fibrillation: a direct comparison of transesophageal echocardiography, planar cardiac CT, and segmented three-dimensional cardiac CT. *J Interv Card Electrophysiol* 2008; **23**:87–93.

15 Cabrera JA, Ho SY, Climent V, Sánchez-Quintana D. The architecture of the left lateral atrial wall: a particular anatomic region with implications for ablation of atrial fibrillation. *Eur Heart J* 2008; **29**:356–62.

16 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**:837–45.

17 Nucifora G, Faletra FF, Regoli F *et al.* Evaluation of the left atrial appendage with real-time 3-dimensional transesophageal echocardiography: implications for catheter-based left atrial appendage closure. *Circ Cardiovasc Imaging* 2011; **4**:514–23.

18 Shimizu T, Takada T, Shimode A *et al.* Association between paroxysmal atrial fibrillation and the left atrial appendage ejection fraction during sinus rhythm in the acute stage of stroke: a transesophageal echocardiographic study. *J Stroke Cerebrovasc Dis* 2013; **22**:1370–6.

19 Valocik G, Kamp O, Mihciokur M *et al.* Assessment of the left atrial appendage mechanical function by three-dimensional echocardiography. *Eur J Echocardiogr* 2002; **3**:207–13.

20 Grimm RA, Leung DY, Black IW, Stewart WJ, Thomas JD, Klein AL. Left atrial appendage 'stunning' after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. *Am Heart J* 1995; **130**:174–6.

21 Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002; **54**:230–46.

22 Goldberg YH, Gordon SC, Spevack DM, Gordon GM. Disparities in emptying velocity within the left atrial appendage. *Eur J Echocardiogr* 2010; **11**:290–5.

23 Di Biase L, Santangeli P, Anselmino M *et al.* Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 2012; **60**:531–8.

24 Ren JF, Callans DJ, Marchlinski FE. Letter. What is the natural relationship between left atrial appendage morphology and history of stroke? *J Am Coll Cardiol* 2013; **61**:689–90.
25 Stahrenberg R, Weber-Krüger M, Seegers J *et al.* Enhanced detection of paroxysmal atrial fibrillation by early and prolonged continuous Holter monitoring in patients with cerebral ischemia presenting in sinus rhythm. *Stroke* 2010; **41**:2884–8.
26 Kamel H, Navi BB, Elijovich L *et al.* Pilot randomized trial of outpatient cardiac monitoring after cryptogenic stroke. *Stroke* 2013; **44**:528–30.

OPEN ACCESS Freely available online

PLOS | ONE

Effects of Comprehensive Stroke Care Capabilities on In-Hospital Mortality of Patients with Ischemic and Hemorrhagic Stroke: J-ASPECT Study

Koji Iihara[1]*, Kunihiro Nishimura[2], Akiko Kada[3], Jyoji Nakagawara[4], Kuniaki Ogasawara[5], Junichi Ono[6], Yoshiaki Shiokawa[7], Toru Aruga[8], Shigeru Miyachi[9], Izumi Nagata[10], Kazunori Toyoda[11], Shinya Matsuda[12], Yoshihiro Miyamoto[2], Akifumi Suzuki[13], Koichi B. Ishikawa[14], Hiroharu Kataoka[15], Fumiaki Nakamura[16], Satoru Kamitani[16]

1 Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, **2** Department of Preventive Medicine and Epidemiologic Informatics, National Cerebral and Cardiovascular Center, Suita, Japan, **3** Clinical Research Center, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan, **4** Integrative Stroke Imaging Center, National Cerebral and Cardiovascular Center, Suita, Japan, **5** Department of Neurosurgery, Iwate Medical University, Morioka, Japan, **6** Chiba Cardiovascular Center, Ichihara, Japan, **7** Department of Neurosurgery, Kyorin University, Mitaka, Japan, **8** Showa University Hospital, Tokyo, Japan, **9** Department of Neurosurgery, Nagoya University, Nagoya, Japan, **10** Department of Neurosurgery, Nagasaki University, Nagasaki, Japan, **11** Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan, **12** Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Kita-Kyushu, Japan, **13** Research Institute for Brain and Blood Vessels, Akita, Japan, **14** Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan, **15** Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Japan, **16** Department of Public Health, The University of Tokyo, Tokyo, Japan

Abstract

Background: The effectiveness of comprehensive stroke center (CSC) capabilities on stroke mortality remains uncertain. We performed a nationwide study to examine whether CSC capabilities influenced in-hospital mortality of patients with ischemic and hemorrhagic stroke.

Methods and Results: Of the 1,369 certified training institutions in Japan, 749 hospitals responded to a questionnaire survey regarding CSC capabilities that queried the availability of personnel, diagnostic techniques, specific expertise, infrastructure, and educational components recommended for CSCs. Among the institutions that responded, data on patients hospitalized for stroke between April 1, 2010 and March 31, 2011 were obtained from the Japanese Diagnosis Procedure Combination database. In-hospital mortality was analyzed using 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. Data from 265 institutions and 53,170 emergency-hospitalized patients were analyzed. Mortality rates were 7.8% for patients with ischemic stroke, 16.8% for patients with intracerebral hemorrhage (ICH), and 28.1% for patients with subarachnoid hemorrhage (SAH). 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.

Conclusions: CSC capabilities were associated with reduced in-hospital mortality rates, and relevant aspects of care were found to be dependent on stroke type.

Citation: Iihara K, Nishimura K, Kada A, Nakagawara J, Ogasawara K, et al. (2014) Effects of Comprehensive Stroke Care Capabilities on In-Hospital Mortality of Patients with Ischemic and Hemorrhagic Stroke: J-ASPECT Study. PLoS ONE 9(5): e96819. doi:10.1371/journal.pone.0096819

Editor: Hooman Kamel, Weill Cornell Medical College, United States of America

Received November 4, 2013; **Accepted** April 11, 2014; **Published** May 14, 2014

Funding: This study was supported by Grants-in-Aid from the Ministry of Health, Labour, and Welfare of Japan (Principal Investigator: Koji Iihara). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Ube Industries, Ltd., Central Hospital participated in this study by providing survey data. This does not alter the authors' adherence to PLOS ONE Editorial policies and criteria.

* E-mail: kiihara@ns.med.kyushu-u.ac.jp

Introduction

In Japan, stroke is the third-leading cause of death, as well as a leading cause of long-term disability. Almost 270,000 individuals in Japan have a new or recurrent stroke each year, and nearly 120,000 individuals die following a stroke [1]. In 2000, the Brain Attack Coalition discussed the concept of stroke centers and proposed two types of centers: comprehensive [2] and primary [3]. Most patients with stroke can be appropriately treated at a primary stroke center (PSC), and the Joint Commission has established programs for certifying PSCs and measuring their performance [4]. The concept and recommended key components of comprehensive stroke centers (CSCs) enable intensive care and specialized techniques that are not available at most PSCs [2,5].

Table 1. Number and percentage of participating hospitals (n = 265) with the recommended items of comprehensive stroke care capabilities.

Components	Items	*n*	%
Personnel	Neurologists	143	54.0
	Neurosurgeons	251	94.7
	Endovascular physicians	118	44.5
	Critical care medicine	65	24.5
	Physical medicine and rehabilitation	42	15.8
	Rehabilitation therapy	265	100
	Stroke rehabilitation nurses	38	14.6
Diagnostic techniques	CT	264	99.6
	MRI with diffusion	237	89.4
	Digital cerebral angiography	226	85.6
	CT angiography	234	88.3
	Carotid duplex ultrasound	102	38.5
	TCD	53	20.2
Specific expertise	Carotid endarterectomy	231	87.2
	Clipping of intracranial aneurysm	250	94.3
	Hematoma removal/draining	253	95.5
	Coiling of intracranial aneurysm	153	57.7
	Intra-arterial reperfusion therapy	199	75.1
Infrastructure	Stroke unit	55	20.8
	Intensive care unit	169	63.8
	Operating room staffed 24/7	185	70.0
	Interventional services coverage 24/7	122	46.0
	Stroke registry	109	41.8
Education	Community education	147	55.7
	Professional education	171	64.8

CT, computed tomography; MRI, magnetic resonance imaging; TCD, transcranial Doppler.

doi:10.1371/journal.pone.0096819.t001

Although stroke performance measures have been developed to monitor and improve quality of care, a substantial proportion of patients do not receive effective treatments, and population-based studies have been called for to evaluate the successful translation of evidence-based medicine into clinical practice [4] Organized stroke unit care is a form of in-hospital care provided by nurses, doctors, and therapists who work as a coordinated team specialized in caring for patients with stroke [6]. The effectiveness of organized stroke care has been reported for different ischemic stroke subtypes in the organized care index (OCI) using data from the Registry of the Canadian Stroke Network [7,8]. However, the effectiveness of CSC capabilities on the mortality of patients with ischemic and hemorrhagic stroke remains uncertain. In this study, we examined whether CSC capabilities influence in-hospital mortality for all types of stroke in a real-world setting by using data from the J-ASPECT nationwide stroke registry (obtained from the Japanese Diagnosis Procedure Combination [DPC]-based Payment System) [9].

Methods

Of the 1,369 certified training institutions of the Japan Neurosurgical Society, the Japanese Society of Neurology, and/or the Japan Stroke Society, 749 hospitals responded to a questionnaire survey regarding CSC capabilities. The CSC capabilities were assessed using 25 items specifically recommended for CSCs [2] that were divided into 5 components regarding (1) personnel (seven 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 (six items: 24 hours/day, 7 days/week [24/7] availability of computed tomography [CT], magnetic resonance imaging [MRI] with diffusion-weighted imaging, digital cerebral angiography, CT angiography, carotid duplex ultrasound, and transcranial Doppler), (3) specific expertise (five items: carotid endarterectomy, clipping of intracranial aneurysms [IAs], removal of intracerebral hemorrhage [ICH], coiling of IAs, and intra-arterial reperfusion therapy), (4) infrastructure (five items: stroke unit, intensive care unit, operating room staffed 24/7, interventional services coverage 24/7, and stroke registry), and (5) educational components (two items: community education and professional education). A score of 1 point was assigned if the hospital met each recommended item, yielding a total CSC score of up to 25. The scores were also summed for each component (subcategory CSC score). The impact of specific aspects of acute stroke care (monitoring, early rehabilitation, admission to stroke care unit [SCU], acute stroke team, the organized stroke care index [7], existence of a tissue plasminogen activator [t-PA]

Table 2. Demographics of the study cohort according to the Diagnosis Procedure Combination (DPC) discharge database study in a comparison of hospitals that agreed to participate in the present study and those that did not.

	Participating hp	Non-participating hp	P value[#]
	(n = 265)	(n = 484)	
Hospital characteristics (CSC scores)			
Total score (25 items)	15.4±4.2	13.5±4.6	<0.001
Personnel (7 items)	3.5±1.2	3.1±1.3	<0.001
Diagnostic techniques (6 items)	4.2±1.2	3.9±1.3	0.002
Specific expertise (5 items)	4.0±1.4	3.6±1.6	<0.001
Infrastructure (5 items)	2.4±1.4	1.9±1.4	<0.001
Education (2 items)	1.2±0.8	1.0±0.8	0.002
Number of beds, n (%)			
20–49	3 (1.1)	13 (2.7)	<0.001
50–99	9 (3.4)	21 (4.3)	
100–299	66 (24.9)	166 (34.3)	
300–499	97 (36.6)	163 (33.7)	
500–	90 (34.0)	117 (24.2)	
Annual stroke cases, n (%)			
0–49	8 (3.0)	43 (8.9)	0.003
50–99	31 (11.7)	47 (9.7)	
100–199	56 (21.1)	143 (29.5)	
200–299	67 (25.3)	88 (18.2)	
300–	92 (34.7)	136 (28.1)	
Annual volume of t-PA infusion	8.3	6.4	0.002

[#] Wilcoxon rank-sum test.
CSC, comprehensive stroke center.
Hp, hospital.
doi:10.1371/journal.pone.0096819.t002

protocol, number of t-PA cases/year, and number of acute stroke cases/year) on stroke mortality was also examined. This survey was completed by neurosurgeons or neurologists in the responding hospitals and returned by mail. Any incomplete answers were completed in follow-up phone interviews with the neurosurgeons or neurologists of the study group. The English version of the survey is shown in File S1.

This cross-sectional survey used the DPC discharge database from participating institutions in the 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 and was linked with a lump-sum payment system [9]. Of the 749 hospitals that responded to the institutional survey regarding CSC capabilities, 265 agreed to participate in the DPC discharge database study (File S2). Computer software was developed to identify patients hospitalized because of acute stroke from the annual de-identified discharge database by using the International Classification of Diseases (ICD)-10 diagnosis codes related to ischemic stroke (I63.0-9), nontraumatic ICH (ICH: I61.0-9, I62.0-1, and I62.9), and subarachnoid hemorrhage (SAH: I60.0-9). Because of major differences in their typical prognosis, patients with transient ischemic attack were excluded. Patients hospitalized because of ischemic and hemorrhagic stroke between April 1, 2010 and March 31, 2011 were included; however, patients with scheduled admissions were excluded from analysis. The following data were collected from the database: unique identifiers of hospitals, patients' age and sex, diagnoses, comorbidities at admission, in-hospital use of medications (antihypertensive agents, oral hypoglycemic agents, insulin, antihyperlipidemic agents, statins, anticoagulant agents, or antiplatelet agents), smoking, arrival by ambulance or not, level of consciousness at admission according to the Japan Coma Scale [10], and discharge status. The Japan Coma Scale [11] was originally published in 1974, the same year as the Glasgow Coma Scale (GCS) [12], and it remains one of the most popular grading scales for assessing impaired consciousness among health care professionals and personnel for emergency medical services in Japan. Grading with the 1-, 2-, and 3-digit codes corresponds to the following statuses: 1) the patient is awake in the absence of any stimulation, 2) the patient can be aroused but reverts to the previous state after the cessation of stimulation, and 3) the patient cannot be aroused even by forceful mechanical stimulation. Each specific digit status is further subdivided into three levels: 1-digit code into 1, 2, and 3; 2-digit code into 10, 20, and 30; and 3-digit code into 100, 200, and 300 (Table S1). In addition to these nine grades, a normal level of consciousness is graded as zero. Consciousness level on admission was determined by the physician and data on all medication use was collected electronically from the claim data. Comorbidity was determined primarily from the ICD-10 code, but was also checked against what medications and procedures the patient was receiving/undergoing, to see if these were compatible with the code data. Smoking was defined by the physician's record, which rated patients as active or inactive smokers. In-hospital mortality, defined as death by the time of discharge from the hospital, was analyzed with the total and subcategory CSC scores using hierarchical logistic regression analysis adjusted for age, sex,

Table 3. Demographics of the patient study cohort at the time of diagnosis and hospital characteristics according to stroke type.

	Total	Ischemic Stroke	Intracerebral hemorrhage	Subarachnoid hemorrhage
	(n = 53,170)	(n = 32,671)	(n = 15,699)	(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)
Smoking (n = 4,4842)	12,761 (24.0)	8,188 (25.1)	3,540 (22.5)	1,074 (21.8)
Medications during hospitalization				
Antihypertensive agent	34,136 (64.2)	17,694 (54.2)	12,537 (79.9)	4,019 (81.5)
Anti-renin-angiotensin system agent	19,881 (37.4)	10,262 (31.4)	8,280 (52.7)	1,410 (28.6)
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).

doi:10.1371/journal.pone.0096819.t003

Japan Coma Scale score, comorbidities, and institutional difference.

Ethics Statement

This research plan was designed by the authors and approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, which waived the requirement for individual informed consent.

Statistical Analysis

We used hierarchical logistic regression models [13,14] to estimate odds ratios (ORs) for in-hospital mortality. 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. We also divided CSC score into quintiles and analyzed the trend with the Cochran-Armitage trend test. The

Table 4. The impact of total comprehensive stroke care (CSC) score on in-hospital mortality after ischemic stroke, adjusted by age, sex, and level of consciousness at admission according to the Japan Coma Scale (JCS).

Factor	OR	95% CI	P value
Male	1.23	1.12–1.35	<0.001
Age	1.40	1.34–1.47	<0.001
CSC total score	0.97	0.96–0.99	0.001
JCS			
normal	1		
one-digit code	2.40	2.11–2.74	<0.001
two-digit code	7.46	6.47–8.60	<0.001
three-digit code	21.62	18.69–25.02	<0.001

CI, confidence interval; CSC, comprehensive stroke care; JCS, Japan Coma Scale; OR, odds ratio.

doi:10.1371/journal.pone.0096819.t004

difference between participating and non-participating hospitals in the DPC discharge study was determined by Wilcoxon rank-sum test. The analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and STATA version 12 (STATA Corp, College Station, TX, USA).

Results

A total of 265 hospitals participated in this study. The number and percentage of the participating hospitals with the recommended items of CSC capabilities are shown in Table 1. The distribution of total CSC scores ranged from 1 to 23 (mean: 15.4, median: 14 standard deviation [SD]: 4.2, interquartile range [IQR]: 11–18). Because we initially sent the CSC questionnaire to 749 hospitals, we sought to determine whether there was a selection bias in stroke care capabilities that could have impacted which hospitals returned the questionnaire. We found that such a bias did exist; in fact, the total CSC scores, subcategory CSC scores and annual volume of t-PA infusion, with the exception of the diagnostic techniques and education/research subcategories, were significantly higher for the participating hospitals than for the non-participating hospitals (Table 2).

Data from 265 institutions and 53,170 emergency-hospitalized patients (age in years, mean ±SD: 72.5±13.1; male: 55.2%) were analyzed. Patient demographics according to stroke type at the time of diagnosis are shown in Table 3. The study cohort included 32,671 patients with ischemic stroke (age: 74.4±12.2 years; male: 57.6%), 15,699 with ICH (age: 70.7±13.5 years; male: 57.5%), and 4,934 with SAH (age: 64.7±14.8 years; male: 32.1%). Use of antihypertensive agents, antidiabetic agents, antihyperlipidemic agents, and antiplatelet agents is also shown in Table 3. Almost 60% of the patients arrived by ambulance, with the incidence ranging from 77.6% for SAH to 53.1% for ischemic stroke. These rates of arrival by ambulance based on stroke type were in accordance with different degrees of stroke severity, as reflected by level of consciousness. Hospital characteristics shown by total and subcategory CSC scores did not reveal any significant differences with respect to stroke type.

Overall, mortality rates were 7.8% for ischemic stroke, 16.8% for ICH, and 28.1% for SAH. Table 4–6 show the results of a hierarchical logistic regression analysis of these data. Mortality of patients with ischemic stroke was significantly correlated with male sex (OR = 1.23), age (10 incremental years, OR = 1.4), and level of consciousness (1-digit code: OR = 2.4, 2-digit code: OR = 7.46, 3-digit code: OR = 21.62, versus zero [normal consciousness {control}]) as patient characteristics, and total CSC score (OR = 0.97) adjusted for age, sex, and level of consciousness as a hospital characteristic (Table 4). Mortality of patients with ICH was also significantly correlated with male sex (OR = 1.72), age (10 incremental years, OR = 1.36), and level of consciousness (1-digit code: OR = 1.45, 2-digit code: OR = 4.22, 3-digit code: OR = 49.59, versus zero as control) as patient characteristics and total CSC score (OR = 0.97) adjusted for age, sex, and level of consciousness as a hospital characteristic (Table 5). Mortality of

Table 5. The impact of total comprehensive stroke care (CSC) score on in-hospital mortality after intracerebral hemorrhage, adjusted by age, sex, and level of consciousness at admission according to the Japan Coma Scale (JCS).

Factor	OR	95% CI	P value
Male	1.72	1.54–1.92	<0.001
Age	1.36	1.30–1.42	<0.001
CSC total score	0.97	0.95–0.99	0.003
JCS			
normal	1		
one-digit code	1.45	1.14–1.83	0.002
two-digit code	4.22	3.34–5.33	<0.001
three-digit code	49.59	40.12–61.27	<0.001

CI, confidence interval; CSC, comprehensive stroke care; JCS, Japan Coma Scale; OR, odds ratio.

doi:10.1371/journal.pone.0096819.t005

Table 6. The impact of total comprehensive stroke care (CSC) score on in-hospital mortality after subarachnoid hemorrhage, adjusted by age, sex, and level of consciousness at admission according to the Japan Coma Scale (JCS).

Factor	OR	95%CI	P value
Male	1.39	1.17–1.65	<0.001
Age	1.37	1.29–1.45	<0.001
CSC total score	0.95	0.93–0.98	<0.001
JCS			
normal	1		
one-digit code	1.05	0.75–1.46	0.785
two-digit code	2.01	1.46–2.77	<0.001
three-digit code	17.13	13.14–22.35	<0.001

CI, confidence interval; CSC, comprehensive stroke care; JCS, Japan Coma Scale; OR, odds ratio.

doi:10.1371/journal.pone.0096819.t006

patients with SAH was likewise significantly correlated with male sex (OR = 1.39), age (10 incremental years, OR = 1.37), and level of consciousness (2-digit code: OR = 2.01, 3-digit code: OR = 17.12, versus zero as control) as patient characteristics and total CSC score (OR = 0.95) adjusted for age, sex, and level of consciousness as a hospital characteristic. Therefore, total CSC score was independently associated with in-hospital mortality for all stroke types after adjusting for age, sex, and stroke severity (Table 6). The impact of total CSC score on in-hospital mortality for ischemic stroke and ICH remained significant after adjustment for age, sex, severity of stroke, and existence of comorbid conditions (hypertension, diabetes mellitus, and hyperlipidemia) (Table S2–S4).

Table 7–9 show the correlations between CSC subcategory scores and in-hospital mortality adjusted for age, sex, and level of consciousness depending on the different stroke types: mortality of patients with ischemic stroke was significantly correlated with subcategory scores in personnel (OR = 0.93), infrastructure (OR = 0.94), and education (OR = 0.89) (Table 7). Mortality of patients with ICH was significantly correlated with subcategory scores in diagnostic technique (OR = 0.91), infrastructure (OR = 0.92), and education (OR = 0.91) (Table 8). Mortality of patients with SAH was significantly associated with subcategory scores in personnel (OR = 0.91) specific expertise (OR = 0.83), infrastructure (OR = 0.89), and education (OR = 0.84) (Table 9). We found that while infrastructure and education subcategory CSC scores significantly impacted outcomes for all types of stroke, other subcategory CSC scores were differentially associated with in-hospital mortality depending on stroke type.

Figure 1 shows the impact of total CSC score classified into quintiles (Q1: 4–12, Q2: 13–14, Q3: 15–17, Q4: 18, Q5: 19–23) on the in-hospital mortality of patients with all types of stroke (a), ischemic stroke (b), ICH (c), and SAH (d) after adjusting for age, sex and level of consciousness. There was a significant association between total CSC score and in-hospital mortality in all types of stroke (all $P<0.001$) (Table 4–6). Figure 2 illustrates the impact of total CSC score on the in-hospital mortality of patients with all types of stroke (a), ischemic stroke (b), ICH (c), and SAH (d) after adjustment for age; sex; level of consciousness; and incidence of hypertension, hyperlipidemia, and diabetes mellitus. The association between total CSC score and in-hospital mortality in patients after all types of stroke (a), ischemic stroke (b), and ICH (c) remained significant after adjustment for age; sex; level of consciousness; and incidence of hypertension, hyperlipidemia, and diabetes mellitus. This same association was not evident in patients with SAH ($P = 0.601$) (Table 10).

Hospitals with higher CSC scores were also more likely to provide early rehabilitation, improved monitoring, the possibility of admission to an SCU, presence of an acute stroke care team, existence of a t-PA protocol, greater numbers of t-PA cases/year, and higher scores on the organized stroke care index. In addition to the CSC score, the processes of acute stroke care, such as admission to SCU, presence of an acute stroke team, the organized stroke care index [7], and number of acute stroke cases/staff physician significantly impacted in-hospital mortality after all types of acute stroke, although in some cases, to a greater or lesser degree for the different types of stroke (Table 11–14).

Discussion

Using the nationwide discharge data obtained from the Japanese DPC-based Payment System, we evaluated the effect of

Table 7. The impact of subcategory CSC score on in-hospital mortality after ischemic stroke adjusted by age, sex and JCS.

Component	OR	95% CI	P value
Personnel	0.93	0.88–0.98	0.008
Diagnostic techniques	0.95	0.90–1.01	0.090
Specific expertise	0.96	0.90–1.01	0.136
Infrastructure	0.94	0.90–0.99	0.014
Education/research	0.89	0.83–0.96	0.003

CI, confidence interval; CSC, comprehensive stroke care; JCS, Japan Coma Scale; OR, odds ratio.

doi:10.1371/journal.pone.0096819.t007

Table 8. The impact of subcategory CSC score on in-hospital mortality after intracerebral hemorrhage adjusted by age, sex and JCS.

Component	OR	95% CI	P value
Personnel	0.98	0.92–1.04	0.523
Diagnostic techniques	0.91	0.85–0.98	0.012
Specific expertise	0.93	0.86–1.00	0.055
Infrastructure	0.92	0.87–0.98	0.005
Education/research	0.91	0.83–1.00	0.047

CI, confidence interval; CSC, comprehensive stroke care; JCS, Japan Coma Scale; OR, odds ratio.
doi:10.1371/journal.pone.0096819.t008

hospital characteristics based on the recommended components of CSCs [2] on the in-hospital mortality of patients with acute ischemic and hemorrhagic stroke treated between April 1, 2010 and March 31, 2011. We found that the total CSC score was significantly associated with in-hospital mortality rates irrespective of stroke type after adjustment for age, sex, and initial level of consciousness according to the Japan Coma Scale. However, the subcategory scores that were significantly associated with in-hospital mortality differed among stroke type. Importantly, the association between total CSC scores and in-hospital mortality remained significant after adjustment for age; sex; initial level of consciousness according to the Japan Coma Scale; and incidence of hypertension, diabetes mellitus and hyperlipidemia for all types of stroke except SAH. These findings highlight the importance of CSC capabilities for optimal treatment of ischemic and hemorrhagic stroke and will enable health care professionals and policy makers to focus their efforts on improving specific aspects of CSC capabilities for different types of stroke.

Increasing attention has been given to defining the quality and value of health care through the reporting of process and outcome measures. Following the original proposal to establish CSCs [2], detailed metrics for measuring quality of care in CSCs have been reported [5]. The so-called "drip-and-ship" model has emerged as a paradigm for emergency departments that are able to diagnose acute ischemic stroke and administer intravenous (IV) recombinant t-PA (rt-PA) but lack the infrastructure to provide intensive monitoring for patients after rt-PA administration [15,16]. A recent study demonstrated that despite having more severe strokes on arrival at the CSC, transfer-in patients with acute ischemic stroke had in-hospital mortality similar to that of front door patients and were more likely to be discharged to rehabilitation. These findings lend support to the concept of regionalized stroke care and directing patients with greater disability to more advanced stroke centers [17]. At present, no official certification of stroke centers in Japan has been launched, and the current study indicates that patients with acute ischemic stroke or hemorrhagic stroke are being admitted on an emergent basis to hospitals with similar CSC total and subcategory scores.

In the present study, stroke severity was adjusted by baseline level of consciousness according to the Japan Coma Scale [10,11]. The Get With the Guidelines-Stroke (GWTG-Stroke) risk model was recently developed to predict in-hospital ischemic stroke mortality, suggesting that the National Institutes of Health Stroke Scale (NIHSS) score provides substantial incremental information on a patient's mortality risk [18], emphasizing the importance of adjustment of stroke severity to develop a hospital risk model for mortality [19]. Previous prospective multicenter study has demonstrated that the development of a decreased level of consciousness within the initial hours after stroke onset, as evaluated by a simple six-point scale, is a powerful independent predictor of mortality after a major ischemic stroke of the anterior vasculature [20]. In hemorrhagic stroke, the degree of impaired consciousness at admission was also included in the various proposed ICH scores to predict functional outcome and mortality [21,22]. This study demonstrated that the level of consciousness at admission, as measured by the Japan Coma Scale, is a powerful independent predictor of mortality after ischemic and hemorrhagic stroke. Determining an individual patient's risk of mortality at admission could improve clinical care by providing valuable information to patients and their family members and by identifying those at high risk for poor outcomes who may require more intensive resources.

Health care quality of CSCs in the present study was scored on the basis of the results of a questionnaire referring to 25 items originally recommended by the Brain Attack Coalition. Although there is now increasingly good evidence from initiatives like GWTG-Stroke [23] that a process based on the systematic collection and evaluation of stroke performance measures can

Table 9. The impact of subcategory CSC score on in-hospital mortality after subarachnoid hemorrhage adjusted by age, sex and JCS.

Component	OR	95% CI	P value
Personnel	0.91	0.84–0.98	0.016
Diagnostic techniques	1.01	0.92–1.11	0.896
Specific expertise	0.83	0.75–0.93	<0.001
Infrastructure	0.89	0.83–0.96	0.002
Education/research	0.84	0.75–0.95	0.005

CI, confidence interval; CSC, comprehensive stroke care; JCS, Japan Coma Scale; OR, odds ratio.
doi:10.1371/journal.pone.0096819.t009

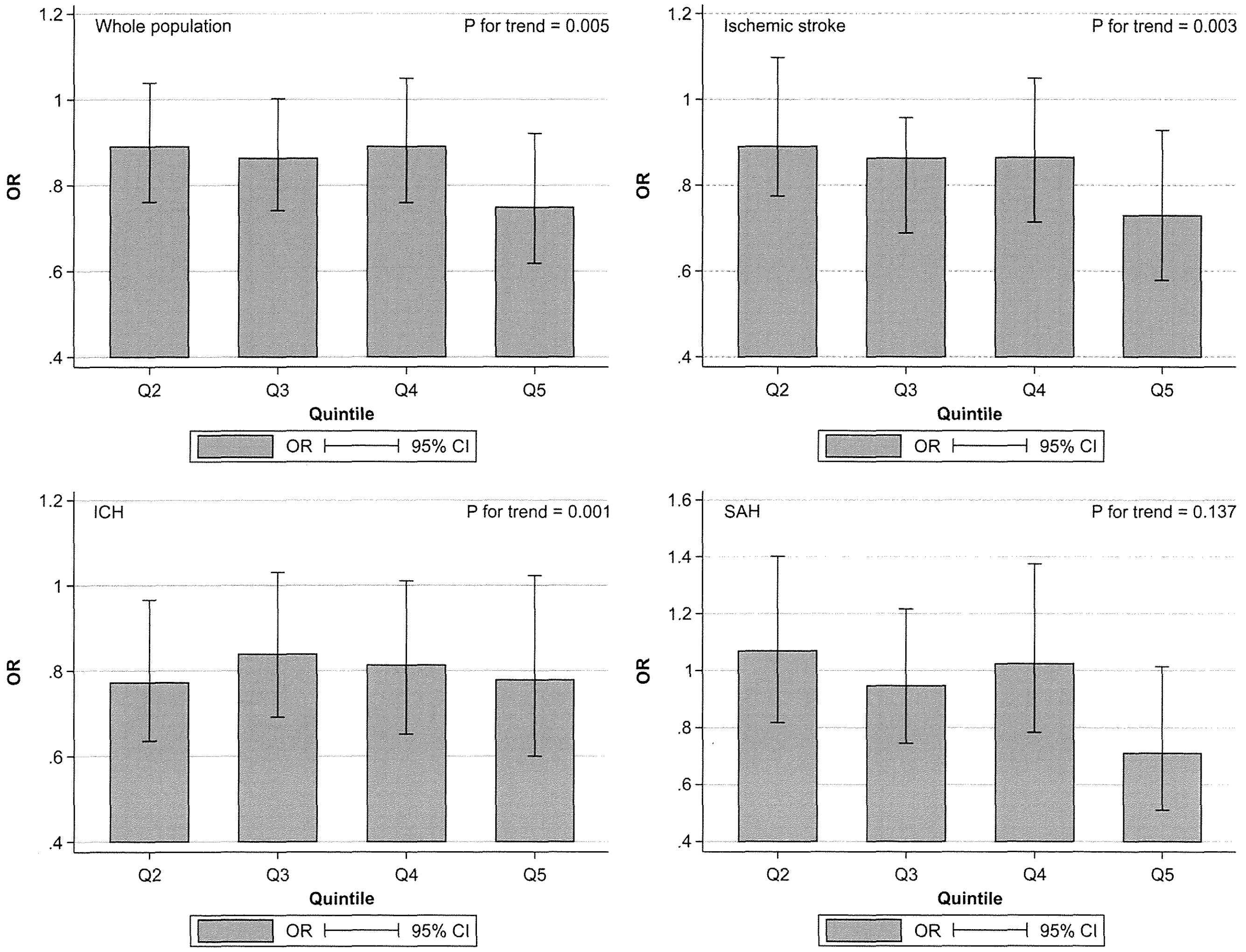

Figure 1. Associations between total comprehensive stroke care (CSC) scores separated into quintiles (Q1: 4–12, Q2: 13–14, Q3: 15–17, Q4: 18, Q5: 19–23) and in-hospital mortality of patients after all types of stroke (a), ischemic stroke (b), intracerebral hemorrhage (ICH) (c), and subarachnoid hemorrhage (SAH) (d), after adjustment for age and sex. Odds ratios (ORs) and 95% confidence intervals (CIs) of in-hospital mortality of each total CSC score quintile are depicted compared with that of Q1 as control.
doi:10.1371/journal.pone.0096819.g001

rapidly improve the quality of stroke care delivered by hospitals, current metrics are mostly limited to process measures that address the care of patients with ischemic stroke in acute hospital-based settings [4]. In addition, there is a pressing need to demonstrate a direct link between better adherence to stroke performance measures and improved patient-oriented outcomes [4,24].

One potential issue with the interpretation of this study could be the lack of a control group. Although there is currently no clear consensus regarding the recommended criteria for CSCs in Japan, the present study distinctly shows that the CSC scores widely distributed in Figure 1 and classified into quintiles were significantly associated with in-hospital mortality for all types of stroke; in fact, mortality after all types of stroke markedly decreased, for example, in ischemic stroke cases by about 40% in hospitals in the highest quintile compared with those in the lowest quintile.

In the present study, our questionnaire was primarily based on the American definition of CSCs. However, according to the definitions derived from a European survey of experts in the field [25], facilities that meet the criteria for CSCs should include the capability to conduct sophisticated monitoring, such as automated electrocardiography (ECG) monitoring at bedside and automated monitoring of pulse oximetry, in addition to the numerous aspects of care capability indexed by the American definition of CSCs used in this study. According to the European approach, to meet the criteria for CSCs, hospitals should have the availability of at least 80% of the components rated as absolutely necessary by at least 50% of experts who participated in the previous expert survey; moreover, these components must be present in each of 6 categories and include the 19 components rated as absolutely necessary by >75% of experts. Based on the present results and an additional ongoing study using a validation cohort in Japan, the criteria for the designation of CSCs in Japan should be determined after further thorough discussion among Japanese stroke experts.

The present study demonstrated the feasibility and impact of using nationwide discharge data with hierarchical logistic regression analysis to examine the random effects that vary among hospitals, as well as the fixed effects of CSC score and patient effects of age, sex, and level of consciousness. We used unique hospital ID in random-intercept hierarchical regression models to assess the association between CSC score and mortality, adjusting

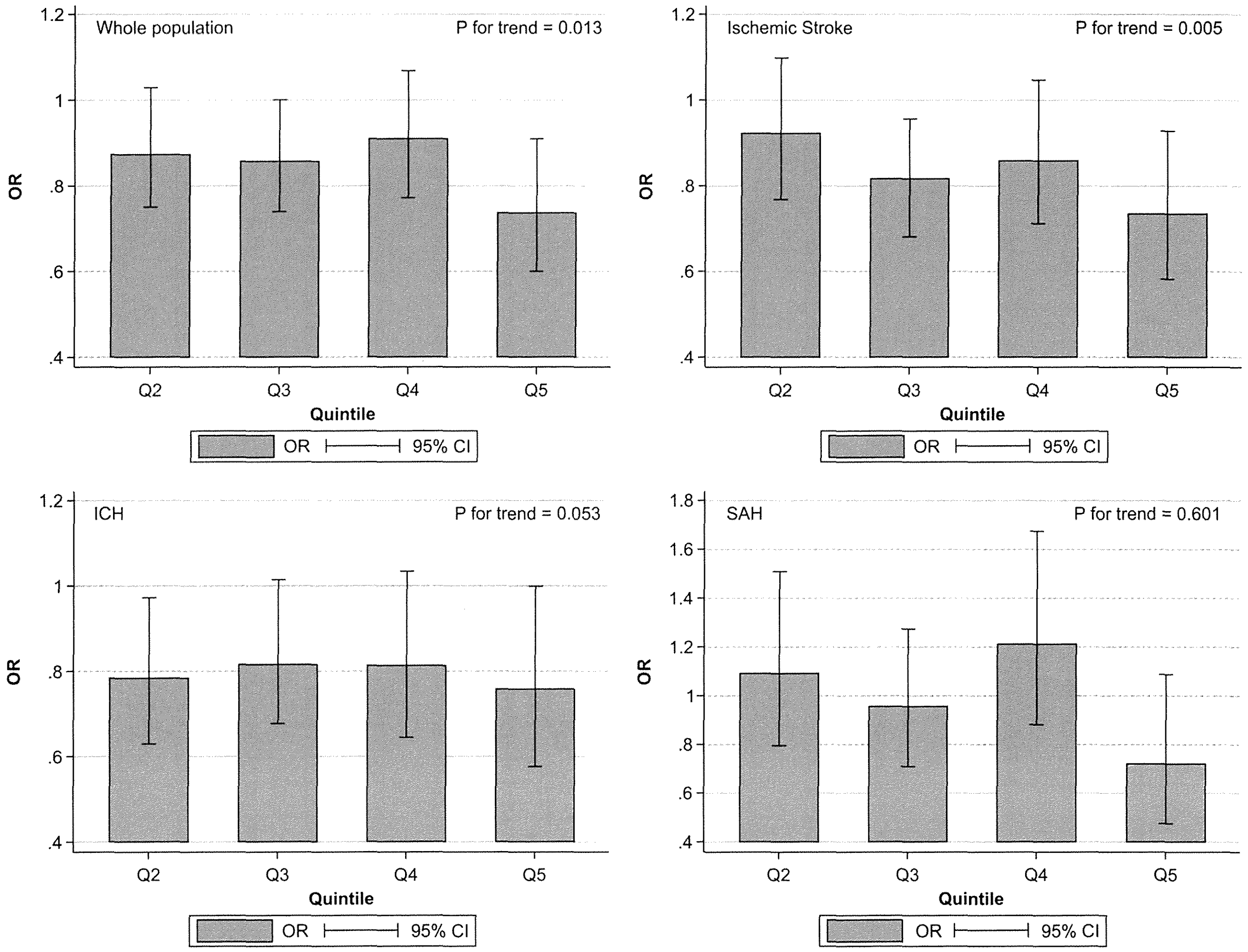

Figure 2. Associations between total comprehensive stroke care (CSC) scores separated into quintiles (Q1: 4–12, Q2: 13–14, Q3: 15–17, Q4: 18, Q5: 19–23) and in-hospital mortality of patients after all types of stroke (a), ischemic stroke (b), intracerebral hemorrhage (ICH) (c), and subarachnoid hemorrhage (SAH) (d), after adjustment for age; sex; initial level of consciousness; and incidence of hypertension, hyperlipidemia, and diabetes mellitus. Odds ratios (ORs) and 95% confidence intervals (CIs) of the in-hospital mortality of each total CSC score quintile are depicted compared with that of Q1 as control.
doi:10.1371/journal.pone.0096819.g002

for patient characteristics and the hospital where a patient was treated.

This model adjusts for hospital-level effects that arise from factors such as geographical location and ageing of the local population. After adjustment, we can isolate the pure CSC score effects on mortality by hospital, as discussed by Localio et al. [26]. If the CSC score is no longer significant after accounting for hospital-level variation, the differences in mortality can be assumed to arise from differences among hospitals. This approach enabled us to elucidate the impact of various CSC metrics on in-hospital mortality of patients with different stroke types. By expanding the scope of performance measures to include all types of stroke, the present study was able to direct links between specific recommended items of CSC capacities and in-hospital mortality after both hemorrhagic and ischemic stroke. While previous reports [7] showed that aspects of acute stroke care, such as admission to an SCU, the presence of an acute stroke team, and the organized stroke care index, were significantly associated with effects on in-hospital mortality after acute stroke, the present study clearly shows that the same is true for the CSC score based on the items recommended by the American Stroke Association.

Finally, one could argue that there really is no concept of 3/4 CSCs, but rather only CSCs or PSCs. In light of the existing evidence regarding the impact of the recommended CSC items on stroke outcomes, we advocate a CSC scoring system to examine the impact of availability of the recommended items on in-hospital mortality for all types of stroke. Considering the marked impact of the CSC score on outcome after all types of stroke, the differential impacts of CSC subcategory scores for different stroke types may make a single simple and effective CSC criterion unrealistic as a tool to produce a nationwide reduction in stroke mortality. In our opinion, it may be a more viable option to employ CSC scores in a more limited fashion, that is, to benchmark the state of care currently provided by medical centers treating stroke patients.

Limitations

First, the questionnaire used in this study is new and has not undergone pilot testing or systematic analysis; thus, its validity and reliability are uncertain. The current set of CSC score items does

Table 10. Associations between total comprehensive stroke care (CSC) scores separated into quintiles (Q1: 4–12, Q2: 13–14, Q3: 15–17, Q4: 18, Q5: 19–23) and in-hospital mortality of patients after all types of stroke (a), ischemic stroke (b), intracerebral hemorrhage (ICH) (c), and subarachnoid hemorrhage (SAH) (d), model 1: after adjustment for age, sex, and initial level of consciousness; and model 2: after adjustment for age, sex, initial level of consciousness, and incidence of hypertension, hyperlipidemia, and diabetes mellitus.

		Model 1					Model 2				
Type of Stroke	**Quintile**	**OR**	**P value**	**95% CI**		**P for trend**	**OR**	**P value**	**95% CI**		**P for trend**
Whole Population (n = 53,170)	Q2	0.87	0.077	0.74	1.02	0.005	0.88	0.119	0.75	1.03	0.013
	Q3	0.84	0.023	0.72	0.98		0.86	0.045	0.74	1.00	
	Q4	0.87	0.115	0.74	1.03		0.91	0.254	0.77	1.07	
	Q5	0.73	0.003	0.60	0.90		0.74	0.004	0.60	0.91	
Ischemic Stroke (n = 32,671)	Q2	0.90	0.278	0.75	1.08	0.003	0.92	0.356	0.77	1.10	0.005
	Q3	0.79	0.008	0.66	0.94		0.81	0.015	0.68	0.96	
	Q4	0.84	0.097	0.69	1.03		0.86	0.131	0.71	1.05	
	Q5	0.71	0.006	0.56	0.91		0.73	0.01	0.58	0.93	
ICH (n = 15,699)	Q2	0.76	0.015	0.62	0.95	<0.001	0.79	0.034	0.63	0.98	0.053
	Q3	0.82	0.058	0.67	1.01		0.83	0.083	0.68	1.02	
	Q4	0.79	0.039	0.63	0.99		0.82	0.099	0.65	1.04	
	Q5	0.76	0.050	0.58	1.00		0.76	0.051	0.58	1.00	
SAH (n = 4,934)	Q2	1.04	0.814	0.78	1.38	0.137	1.10	0.568	0.80	1.51	0.601
	Q3	0.92	0.524	0.71	1.19		0.96	0.767	0.71	1.28	
	Q4	1.00	0.975	0.75	1.34		1.22	0.232	0.88	1.68	
	Q5	0.68	0.043	0.47	0.99		0.73	0.126	0.48	1.09	

ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

doi:10.1371/journal.pone.0096819.t010

not include all worthwhile items related to CSC. These items were appropriately modified from the original American version [2] in consideration of the medical, social, and logistical differences between the U.S. and Japan. For example, most cerebrovascular surgeries, including carotid endarterectomy and neurointervention, are performed by neurosurgeons rather than vascular surgeons or neuroradiologists. At the beginning of this project, a survey including the 25 components recommended by the Brain Attack Coalition in 2005 was created after a review of the literature on comprehensive stroke centers and a thorough discussion by an expert panel. Some recommended items such as availability of ventriculostomy were excluded from our questionnaire merely for simplicity, and thus to increase the response rate of the survey, since they seemed to be identical to recommendations of the board-certified neurosurgeons of Japan. On the other hand, some items such as transesophageal echocardiography were excluded because of the expected very low usage of this examination. According to the Japanese Stroke Databank 2009, for example, transesophageal echocardiography was performed for only 5.4% of the 34,417 acute ischemic stroke

Table 11. Impact of processes of stroke care on in-hospital mortality after all types of stroke.

	OR	**P value**	**95% CI**
Monitoring (%)	1.04	0.53	0.92–1.17
Early rehabilitation (%)	1.15	0.352	0.86–1.52
Admission to SCU (%)	0.87	0.039	0.76–0.99
Acute stroke team	0.88	0.029	0.79–0.99
Organized care index*	0.93	0.031	0.86–0.99
Existence of t-PA protocol (%)	0.88	0.295	0.69–1.12
Number of t-PA cases/year (mean)	1.00	0.203	0.99–1.00
Number of acute stroke patients/staff physician (mean)	0.999	0.012	0.998–1.000

*The organized stroke care index was created to represent different levels of access to organized stroke care ranging from 0 to 3 as determined by the presence of early rehabilitation, acute stroke team assessment, and admission to a stroke unit based on the report of Saposnik et al. (2009).

SCU, stroke care unit; t-PA, tissue plasminogen activator.

doi:10.1371/journal.pone.0096819.t011

Table 12. Impact of processes of stroke care on in-hospital mortality after ischemic stroke.

	OR	P value	95% CI
Monitoring (%)	0.98	0.738	0.85–1.12
Early rehabilitation (%)	1.09	0.615	0.78–1.52
Admission to SCU (%)	0.91	0.218	0.78–1.06
Acute stroke team	0.85	0.016	0.74–0.97
Organized care index*	0.92	0.055	0.85–1.00
Existence of t-PA protocol (%)	0.82	0.158	0.61–1.08
Number of t-PA cases/year (mean)	0.99	0.132	0.98–1.00
Number of acute stroke patients/staff physician (mean)	0.999	0.047	0.998–1.000

*The organized stroke care index was created to represent different levels of access to organized stroke care ranging from 0 to 3 as determined by the presence of early rehabilitation, acute stroke team assessment, and admission to a stroke unit based on the report of Saposnik et al. (2009).
SCU, stroke care unit; t-PA, tissue plasminogen activator.
doi:10.1371/journal.pone.0096819.t012

Table 13. Impact of processes of stroke care on in-hospital mortality after intracerebral hemorrhage.

	OR	P value	95% CI
Monitoring (%)	1.12	0.177	0.95–1.32
Early rehabilitation (%)	1.39	0.091	0.95–2.03
Hospitalization for SCU (%)	0.84	0.048	0.70–1.00
Acute stroke team	0.90	0.194	0.77–1.05
Organized care index*	0.93	0.163	0.85–1.03
Existence of t-PA protocol (%)	0.84	0.314	0.60–1.18
Number of t-PA cases/year (mean)	1.00	0.313	0.99–1.00
Number of acute stroke patients/staff physician (mean)	0.999	0.043	0.998–1.000

*The organized stroke care index was created to represent different levels of access to organized stroke care ranging from 0 to 3 as determined by the presence of early rehabilitation, acute stroke team assessment, and admission to a stroke unit based on the report of Saposnik et al. (2009).
SCU, stroke care unit; t-PA, tissue plasminogen activator.
doi:10.1371/journal.pone.0096819.t013

Table 14. Impact of processes of stroke care on in-hospital mortality after subarachnoid hemorrhage.

	OR	P value	95% CI
Monitoring (%)	1.04	0.737	0.84–1.28
Early rehabilitation (%)	1.02	0.945	0.63–1.64
Admission to SCU (%)	0.79	0.039	0.63–0.99
Acute stroke team	0.85	0.101	0.69–1.03
Organized care index*	0.88	0.034	0.78–0.99
Existence of t-PA protocol (%)	1.09	0.732	0.66–1.81
Number of t-PA cases/year (mean)	1.00	0.456	0.98–1.01
Number of acute stroke patients/staff physician (mean)	0.998	0.006	0.997–1.000

*The organized stroke care index was created to represent different levels of access to organized stroke care ranging from 0 to 3 as determined by the presence of early rehabilitation, acute stroke team assessment, and admission to a stroke unit based on the report of Saposnik et al. (2009).
SCU, stroke care unit; t-PA, tissue plasminogen activator.
doi:10.1371/journal.pone.0096819.t014

patients in a real-world situation. The impact of this examination on the mortality rates of this study would be difficult to evaluate because of low usage. All 25 components of the questionnaire are shown in the appendix. Second, discharge data obtained from the Japanese DPC-based Payment System lacks important information, such as post-discharge data and an NIHSS or GCS score as an index of stroke severity at admission. Although the Japan Coma Scale proved to be a powerful independent predictor of mortality after all types of stroke, further study is necessary to validate the results of the present study with another indicator of stroke severity, such as the NIHSS or GCS. This can be done separately or in combination with a validation data set (the estimated data volume in the J-ASPECT 2013 is more than 80,000 cases that will be available in 2013). Third, there is an inherent risk of information bias when evaluating data obtained by self-assessment. Moreover, hospitals actively working to improve stroke care may have been more likely to respond to the questionnaire. Admittedly, the participation rate of DPC data collection of the J-ASPECT study was relatively low. The participation rates were 19.4% of the 1,369 certified training institutions of the Japan Neurosurgical Society, and 35.4% of the 749 hospitals that responded to the institutional survey. However, the institutes that participated in the present study tended to have more beds and more stroke cases than average. This suggests that the hospitals that were more active in stroke care and potentially eligible for CSC participated in this study. Therefore, the present results may not generalize to non-participating hospitals. External validation greatly increases the reliability of self-assessment data. Accordingly, we plan to validate the information regarding hospital characteristics and outcomes by using a small sample set from the 2010 validation cohort of the present study. Since the number of participating hospitals in this study is increasing every year, we are planning to evaluate how the validity and reliability of the CSC score in predicting stroke patient mortality changes when weighting factors are applied to the recommended items, stroke type, and severity. Through annual evaluations, we aim to achieve higher predictive validity and responsiveness to establish the usefulness of the CSC score. Fourth, we assigned 1 point if the hospital met each recommended item for CSC. However, this equal weight assumption is probably not valid since some components were not significant on subgroup analysis. Although some associations between individual CSC components and mortality achieved significance, several did not but were very close to significant, based on the confidence intervals. These non-significant trends are telling and suggest that the subgroup component analyses were underpowered and thus prone to type 2 error. In addition, we performed multiple comparisons for each stroke type, and therefore, some of the secondary analyses, particularly those that evaluated the impact of stroke care procedures on in-hospital mortality, are prone to type 1 error. We need a larger sample size to validate each recommended item and appropriately weight the subscores.

Conclusions

Although patient demographics and stroke severity are important predictors of in-hospital mortality of patients with all types of stroke, CSC capacities were associated with reduced in-hospital mortality rates, with relevant aspects of care dependent on stroke type.

Supporting Information

File S1 English translation of the survey.
(DOCX)

File S2 List of the participating hospitals (J-ASPECT Study).
(DOCX)

Table S1 Japan Coma Scale for grading impaired consciousness.
(DOCX)

Table S2 The impact of total comprehensive stroke care (CSC) score on in-hospital mortality after ischemic stroke adjusted by age, sex, level of consciousness at admission, and incidence of hypertension (HTN), diabetes mellitus(DM), and hyperlipidemia(HPL).
(DOCX)

Table S3 The impact of total comprehensive stroke care (CSC) score on in-hospital mortality after intracerebral hemorrhage adjusted by age, sex, level of consciousness at admission, and incidence of hypertension (HTN), diabetes mellitus(DM), and hyperlipidemia(HPL).
(DOCX)

Table S4 The impact of total comprehensive stroke care (CSC) score on in-hospital mortality after subarachnoid hemorrhage adjusted by age, sex, level of consciousness at admission, and incidence of hypertension (HTN), diabetes mellitus(DM), and hyperlipidemia(HPL).
(DOCX)

Acknowledgments

The names of the participating 265 hospitals are listed in the File S2. We thank Drs. Manabu Hasegawa, Shunichi Fukuhara, Hisae Mori, Takuro Nakae, and Noriaki Iwata for their helpful discussions and Ms. Arisa Ishitoko and Ai Shigemura for secretarial assistance.

Author Contributions

Conceived and designed the experiments: KI KN AK. Analyzed the data: KI KN AK. Wrote the paper: KI KN AK. Collection of data: JN KO JO YS TA S. Miyachi IN KT S. Matsuda YM AS KBI HK FN SK.

References

1. The vital statistics of Japan (2011). Available: http://www.e-stat.go.jp/SG1/estat/ListE.do?lid=000001101881. Accessed 2013 Nov 22.
2. Alberts MJ, Latchaw RE, Selman WR, Shephard T, Hadley MN, et al. (2005) Recommendations for comprehensive stroke centers: A consensus statement from the Brain Attack Coalition. Stroke 36: 1597–1616.
3. Alberts MJ, Hademenos G, Latchaw RE, Jagoda A, Marler JR, et al. (2000) Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. JAMA. 283: 3102–3109.
4. Reeves MJ, Parker C, Fonarow GC, Smith EE, Schwamm LH (2010) Development of stroke performance measures: Definitions, methods, and current measures. Stroke 41: 1573–1578.
5. Leifer D, Bravata DM, Connors JJ 3rd, Hinchey JA, Jauch EC, et al. (2011) Metrics for measuring quality of care in comprehensive stroke centers: Detailed follow-up to Brain Attack Coalition comprehensive stroke center recommendations: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 42: 849–877.
6. Stroke Unit Trialists' Collaboration (2007) Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 4: CD000197.
7. Saposnik G, Kapral MK, Coutts SB, Fang J, Demchuk AM, et al. (2009) Do all age groups benefit from organized inpatient stroke care? Stroke 40: 3321–3327.
8. Smith EE, Hassan KA, Fang J, Selchen D, Kapral MK, et al. (2010) Do all ischemic stroke subtypes benefit from organized inpatient stroke care? Neurology 75: 456–462.
9. Yasunaga H, Ide H, Imamura T, Ohe K (2005) Impact of the Japanese Diagnosis Procedure Combination-based Payment System on cardiovascular medicine-related costs. Int Heart J 46: 855–866.
10. Ohta T, Kikuchi H, Hashi K, Kudo Y (1986) Nizofenone administration in the acute stage following subarachnoid hemorrhage. Results of a multi-center controlled double-blind clinical study. J Neurosurg 64: 420–426.