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Influence of hospital capabilities and prehospital time on outcomes of thrombectomy for stroke in Japan from 2013 to 2016

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To determine whether increasing thrombectomy-capable hospitals with moderate comprehensive stroke center (CSC) capabilities is a valid alternative to centralization of those with high CSC capabilities. This retrospective, nationwide, observational study used data from the J-ASPECT database linked to national emergency medical service (EMS) records, captured during 2013–2016. We compared the influence of mechanical thrombectomy (MT) use, the CSC score, and the total EMS response time on the modified Rankin Scale score at discharge among patients with acute ischemic stroke transported by ambulance, in phases I (2013–2014, 1461 patients) and II (2015–2016, 3259 patients). We used ordinal logistic regression analyses to analyze outcomes. From phase I to II, MTs increased from 2.7 to 5.5%, and full-time endovascular physicians per hospital decreased. The CSC score and EMS response time remained unchanged. In phase I, higher CSC scores were associated with better outcomes (1-point increase, odds ratio [95% confidence interval]: 0.951 [0.915–0.989]) and longer EMS response time was associated with worse outcomes (1-min increase, 1.007 [1.001–1.013]). In phase II, neither influenced the outcomes. During the transitional shortage of thrombectomy-capable hospitals, increasing hospitals with moderate CSC scores may increase nationwide access to MT, improving outcomes.

Mechanical thrombectomy (MT) is the standard of care for patients with large vessel occlusion (LVO) related to acute ischemic stroke (AIS), but only approximately 3% of patients with AIS underwent MT in the US and Japan in 2016 and 2015, respectively[1,2] patients with AIS and LVO could benefit from direct transportation to intervention centers; however, patients with no LVO need rapid intravenous thrombolysis at the nearest center[3,4]. Patients with AIS admitted directly to comprehensive stroke centers (CSCs) with endovascular treatment capacities may have better outcomes than those receiving drip-and-ship treatment[3], but timely MT may be impeded by the distance that patients need to travel to thrombectomy-capable hospitals. Is there a valid alternative to regional centralization of MT to CSCs with high CSC capabilities to achieve better AIS patient outcomes[5]?

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Item No	Components	Items
1	Personnel*	Neurologists
2		Neurosurgeons
3		Endovascular physicians
4		Emergency medicine
5		Physical medicine and rehabilitation
6		Rehabilitation therapy
7		Stroke nurses
8	Diagnostic (24/7)	Computed tomography
9		Magnetic resonance imaging with diffusion
10		Digital cerebral angiography
11		Computed tomography angiography
12		Carotid duplex ultrasound
13		Transcranial Doppler
14	Specific expertise	Carotid endarterectomy
15		Clipping of intracranial aneurysm
16		Hematoma removal/draining
17		Coiling of intracranial aneurysm
18		Intra-arterial reperfusion therapy
19	Infrastructure	Stroke unit
20		Intensive care unit
21		Operating room staffed 24/7
22		Interventional services coverage 24/7
23		Stroke registry
24	Education	Community education
25		Professional education

Table 1. Comprehensive stroke center score components and items. *Availability of full-time, board-certified personnel.

The existence of a single national emergency medical service (EMS) system in Japan provides a unique opportunity to conduct nationwide studies to examine the influence of prehospital time and hospital characteristics on clinical outcomes using linked data[6].

Using data from the J-ASPECT (Nationwide survey of Acute Stroke care capacity for Proper dEsignation of Comprehensive stroke cenTer in Japan) study—a hospital-based, Japan-wide stroke registry[7,8]—we examined whether increasing thrombectomy-capable hospitals with moderate CSC capabilities[2,9] is a valid alternative for regional centralization of MT to CSCs with high CSC capabilities[3,5]. Accordingly, we compared the influence of CSC capabilities and prehospital time on outcomes of MT for patients with AIS during the transitional phase before and after the pivotal trials[10].

Methods

Ethics statement. To maintain confidentiality, we used deidentified databases, for which it would have been impracticable to obtain informed consent. The study was approved by the National Cerebral and Cardiovascular Center Institutional Review Board (M29-161-4, M29-161-3, and M29-088-3), which waived the requirement for individual informed consent. We reiterate that all methods were performed in accordance with the relevant guidelines and regulations.

J-ASPECT study. Participation of hospitals in the J-ASPECT study was voluntary, and the study was performed in collaboration with the Japan Neurosurgical Society (JNS) and Japan Stroke Society (JSS)[2,7,8,11]. This study consisted of two projects: (1) an institutional survey to assess the CSC capabilities of the hospitals (Table 1)[9,12] and (2) a retrospective cohort study using the nationwide Diagnosis Procedure Combination (DPC) inpatient database[2,7,8,11]. Briefly, the DPC 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. By 2015, the DPC system had been adopted by an estimated 1580 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[7,13]. An increasing number of acute stroke cases in Japan are being registered in the J-ASPECT study each year[14], with approximately 1,090,000 cases registered as of October 2020.

Assessment of facility capabilities using the institutional survey. We sent out questionnaires in 2014 to assess the CSC capabilities of the facilities using 25 items recommended by the Brain Attack Coalition to the training institutions of the JNS and JSS[7,9]. The items are classified into five categories, as follows: personnel, diagnostic, specific expertise, infrastructure, and education (Table 1)[7,9]. A score of 1 point was assigned for each recommended item met by the hospital, yielding a total CSC score of up to 25. The content, development, and predictive validities of this scoring system for measuring CSC capabilities have been reported[7,9]. Our study group previously showed that the CSC score categorized into either quintiles or quartiles is associated with short-term clinical outcomes of patients with ischemic and hemorrhagic stroke including those who received surgical and endovascular treatment for stroke. In this study, we categorized the participating thrombectomy-capable hospitals based on the CSC scores into low (< 17), moderate (17–21) and high (> 21).

Study design. We conducted a retrospective observational study using data from the J-ASPECT stroke database (specifically those that could be linked to the national EMS records) captured between January 2013 and December 2016. Since the JSS, JNS, and Japanese Society for Neuroendovascular Therapy (JSNET) acted quickly to revise the clinical practice guidelines for MT use in response to the publication of the pivotal trials[10], we divided the study period into phases I (2013–2014) and II (2015–2016). After publishing the results of the pivotal trials, the American Heart Association/American Stroke Association (AHA/ASA) updated the clinical guidelines for the endovascular treatment of acute ischemic stroke in 2015[15]. In this guideline, patients should receive endovascular therapy with a stent retriever if they meet all of the criteria. In response to this, the relevant Japanese Society updated guidelines for mechanical thrombectomy[16]. Since the publication of these guidelines[15,16], mechanical thrombectomy has been considered as standard treatment for large-vessel occlusion acute ischemic stroke regardless of geographical locations. Using the J-ASPECT DPC database, we extracted data of 303,719 patients with AIS diagnosed based on the diagnostic criteria of the International Classification of Diseases, 10th Revision (ICD-10) diagnosis code I63. Of those, we included 163,292 records of patients directly transported to facilities by ambulance, in the record linkage analysis. Patients' consciousness level at admission was measured using the Japan Coma Scale (JCS) for stroke severity (Supplementary Table S1)[7,17].

In this study, we defined thrombectomy-capable hospitals as those where MT was performed at least once in each phase. Using government data from 2015, we further categorized hospitals into three classes according to the population density in the regions that they serve, as follows: < 300 persons/km^2, 300–1000 persons/km^2, and > 1000 persons/km^2.[18].

We obtained permission to use all EMS data for 2013 and 2016 from the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications[6]. Almost 99% of 771 EMS departments all over Japan participated in this study, which yielded 21,327,841 patient records. Using this database, we calculated the total EMS response time (i.e., from receipt of the emergency call to arrival at the hospital), which includes EMS response time, on-scene time, and transport time.

Data linkage and participant selection. We used one-to-one probabilistic linkage using the relink module in Stata 15.1 to match the J-ASPECT study and EMS records using the following five linkage points: date of incident/admission, hospital code, prefectures code, age, and sex[19,20]. A participant was included only if there was a linkage across all these characteristics. After linkage, we identified patients with AIS and excluded those who (1) were younger than 18 years; (2) had been transferred from another facility; or (3) had no valid timestamps, had duplicate cases, or had missing care outcomes. We used information from insurance claims to constitute the MT group by identifying all patients treated with any kind of device, including Merci (Concentric Medical, Mountain View, CA, US), Penumbra (Penumbra, Alameda, CA, US), Trevo ProVue (Stryker, Kalamazoo, MI, US), and Solitaire-FR (Covidien, Irvine, CA, US).

Study outcomes. We assessed outcomes using the modified Rankin Scale (mRS) score at discharge.

Statistical analyses. To compare patient characteristics and outcomes between phases I and II, we used *t*-tests for normally distributed continuous variables and Mann–Whitney U tests for non-normally distributed continuous variables. We compared categorical variables using Fisher's exact or chi-square tests. After linking the records, we used multiple imputations to handle missing data points regarding the CSC scores, body mass index (BMI), and smoking history[21]. We used ordinal logistic regression analyses to investigate the associations of total EMS response time and CSC score with the mRS score at discharge, while adjusting for confounding patient-related (age, sex, stroke severity, comorbidities, BMI, smoking history, and total EMS response time) and hospital-related (CSC score[9] and geographical category[18]) factors. We performed all analyses using JMP Statistical Software version 12 (SAS Institute Inc., Cary, NC, US) and Stata version 15.1 (Stata Corp., College Station, TX, US). A p-value < 0.05 was considered significant.

Results

Probabilistic record linkage. We were able to link 122,457 patients with AIS using the J-ASPECT and EMS data (linkage rate of 75.0%). After implementing the exclusion criteria, we included 113,564 records of patients with AIS in the final analyses (Fig. 1). Among them, 1461 patients with AIS received MT from 170 hospitals in phase I and 3259 patients received MT from 206 hospitals in phase II. From phase I to II, the proportion of patients who received MT according to population density remained unchanged (Table 2).

Comparison of patient characteristics between phases I and II. In the MT group, patients in phase II were significantly older, experienced less severe strokes, had a higher frequency of hyperlipidemia and atrial fibrillation, were treated more frequently with MT (5.5% vs. 2.7%), and had better in-hospital outcomes (30-day mortality 10.5% vs. 14.8%) than those in phase I (Table 2). From phase I to II, the use of stent retrievers significantly increased from 29.6 to 69.8%, whereas the use of aspiration catheters (Penumbra) and Merci retriev-

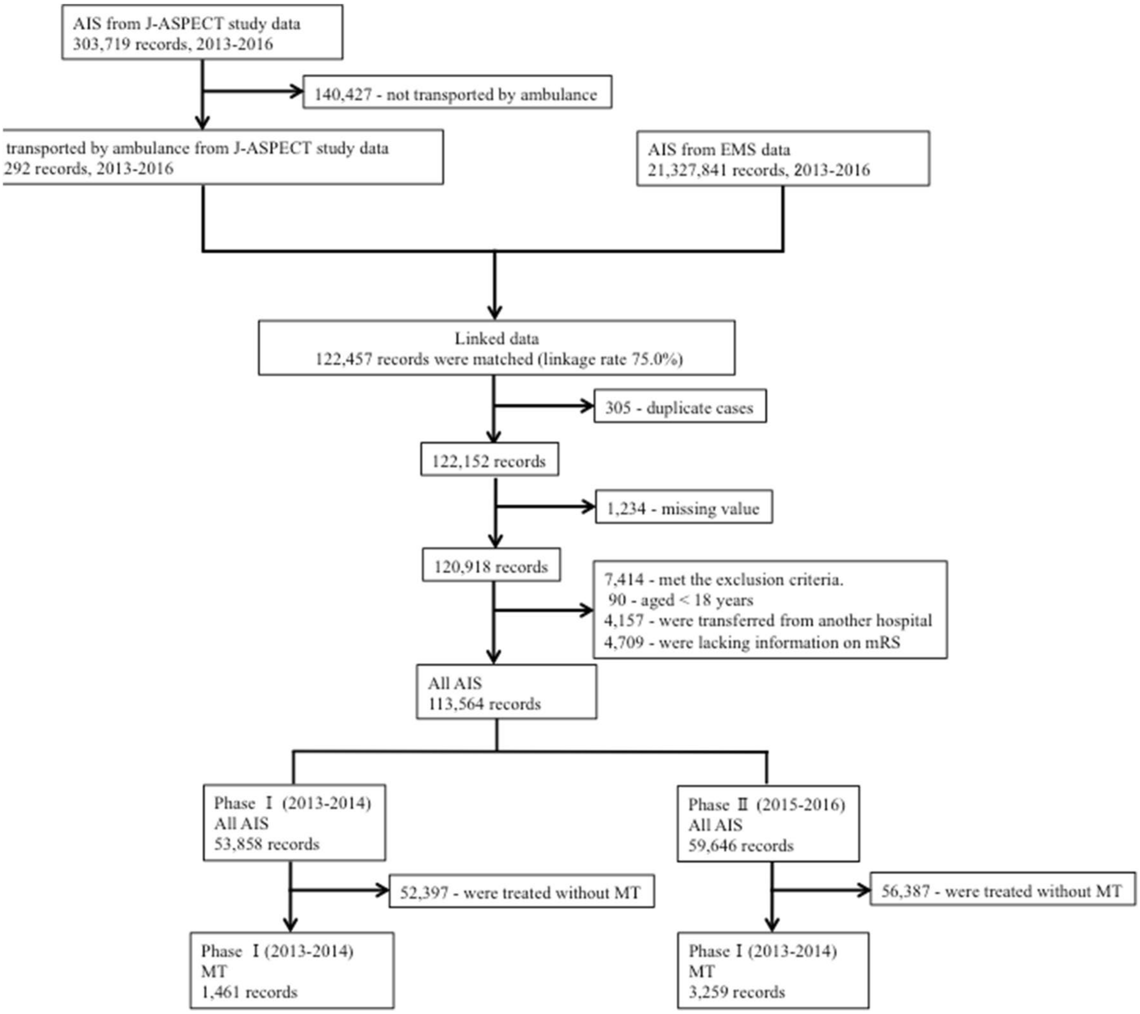

Figure 1. Flow diagram of patients. *AIS* acute ischemic stroke; *EMS* emergency medical services; *mRS* modified Rankin Scale.

ers significantly decreased from 73.9 to 65.2% and from 13.4 to 0.2%, respectively. The proportion of patients who received recombinant tissue-plasminogen activator (rt-PA) administration before MT remained the same between both phases. We observed similar findings for the characteristics of all patients with AIS except for a higher frequency of hypertension, a higher baseline mRS score, and a lower rt-PA administration score in phase I.

Prehospital time of the participating hospitals in each phase. In the MT groups, the total EMS response time remained almost the same between phase I and II, despite a shorter on-scene time in phase II (Table 2). We observed no clinically meaningful differences in prehospital time metrics in all AIS patients between phases. Notably, the transport time in the MT groups remained the same from phase I to II and comparable with those of all patients with AIS in each phase.

CSC capabilities of the participating hospitals in each phase. The CSC capabilities based on hospital characteristics are summarized in Table 3. In phases I and II, the percentages of missing CSC score data in the MT groups were 6.0% and 14.7%, respectively. Among all participating hospitals, the proportion of thrombectomy-capable hospitals increased from 45.6 to 58.2% from phase I to II. The median CSC scores of all participating hospitals and thrombectomy-capable hospitals remained unchanged between phases. Although there were no between-phase differences in the CSC scores for thrombectomy-capable hospitals, the difference in the median CSC scores between all participating and thrombectomy-capable hospitals in phase II became smaller than that in phase I (17 vs. 18 in phase I, 18 vs. 19 in phase II). Among the 25 items used to assess CSC capabilities, we observed no between-phase differences in availability in all participating hospitals; however, in the thrombectomy-capable hospitals, availability of the items related to endovascular treatment such as full-time, board-certified endovascular physicians and intra-arterial reperfusion therapy significantly decreased in phase II ($p=0.05, <0.03$) (Table 3).

	All AIS			MT group		
	Phase I	Phase II		Phase I	Phase II	
	(n = 53,858)	(n = 59,646)	p	(n = 1,461)	(n = 3,259)	p
Age (years), mean (SD)	75.7 (12.1)	76.0 (12.1)	< .001	73.4 (11.3)	74.7 (11.6)	< .001
Men, n (%)	30,850 (57.3)	34,163 (57.3)	0.989	839 (57.4)	1,839 (56.4)	0.522
JCS score at admission, n (%)			< .001			0.010
Alert	18,726 (34.8)	21,070 (35.3)		92 (6.3)	282 (8.7)	
Awake	24,137 (44.8)	26,988 (45.3)		633 (43.3)	1,450 (44.5)	
Arousable	7,021 (13.0)	7,700 (12.9)		485 (33.2)	1,044 (32.0)	
Unarousable	3,974 (7.3)	3,888 (6.5)		251 (17.2)	483 (14.8)	
Baseline mRS, median, (min, max)	1 (0, 3)	0 (0, 2)	< .001	0 (0, 2)	0 (0, 2)	0.552
Comorbidities						
Hypertension, n (%)	32,355 (60.1)	37,437 (62.8)	< .001	1,170 (80.1)	2,642 (81.1)	0.427
Hyperlipidemia, n (%)	17,500 (32.5)	20,370 (34.2)	< .001	364 (24.9)	939 (28.8)	0.006
Diabetes mellitus, n (%)	11,474 (21.3)	12,885 (21.6)	0.222	326 (22.3)	698 (21.4)	0.490
Atrial fibrillation, n (%)	13,746 (25.5)	16,439 (27.6)	< .001	717 (49.1)	1,738 (53.3)	0.007
EMS time in min, median (IQR)						
Response time	7 (6, 9)	7 (6, 10)	< .001	7 (6, 9)	7 (6, 9)	0.168
On-scene time	13 (10, 18)	13 (10, 18)	< .001	14 (10, 18)	13 (10, 17)	0.036
Transport time	10 (6, 16)	10 (7, 16)	< .001	10 (6, 16)	10 (6, 16)	0.858
Total EMS response time	33 (26, 41)	33 (27, 42)	< .001	33 (26, 41)	32 (26, 41)	0.404
Outcome (mRS score)						
0	5,790 (10.8)	6,855 (11.5)	< .001	87 (6.0)	296 (9.1)	< .001
1	10,050 (18.7)	11,339 (19.0)		150 (10.3)	398 (12.2)	
2	7,811 (14.5)	8,851 (14.8)		182 (12.5)	419 (12.9)	
3	6,530 (12.1)	7,463 (12.5)		142 (9.7)	380 (11.7)	
4	11,508 (21.4)	12,840 (21.5)		397 (27.2)	785 (24.1)	
5	7,685 (14.3)	8,154 (13.7)		287 (19.6)	638 (20.0)	
6	4,484 (8.3)	4,144 (6.9)		216 (14.8)	343 (10.5)	
Treatment						
rtPA administration	5,452 (10.1)	6,868 (11.5)	< .001	782 (53.5)	1,763 (54.1)	0.716
MT	1,461 (2.7)	3,529 (5.5)	< .001	1,461 (100)	3,529 (100)	
Device, n (%)						
Stent retriever				433 (29.6)	2,275 (69.8)	< .001
Penumbra				1,079 (73.9)	2,124 (65.2)	< .001
Merci				196 (13.4)	6 (0.2)	< .001
Population density, person/km^2			< .001			0.101
< 300	14,762 (27.9)	15,148 (25.7)		303 (20.7)	702 (21.6)	
300–1000	15,489 (29.3)	18,020 (30.6)		409 (28.0)	988 (30.4)	
> 1000	22,685 (42.9)	15,761 (43.7)		748 (51.2)	1,556 (47.9)	

Table 2. Patient characteristics, EMS time metrics, treatment, and outcomes in all AIS and MT groups. *AIS* acute ischemic stroke; *EMS* emergency medical service; *IQR* interquartile range; *JCS* Japan Coma Scale; *mRS* modified Rankin Scale; *MT* mechanical thrombectomy; *rt-PA* intravenous recombinant tissue-plasminogen activator infusion; *SD* standard deviation.

Associations between total EMS response time and clinical outcomes. No clinically meaningful differences in the median total EMS response time were observed between all patients with AIS and the MT group in each phase (e.g., 33 vs. 32 min in phase II) (Table 2). In the MT group, a longer total EMS response time was associated with worse outcomes in phase I (odds ratio [OR] for each 1-min increase, 1.007 [CI, 1.001–1.013]); however, this association was not observed in phase II (1.003 [0.998–1.007]). The relationships between the total EMS response time and probabilities of an mRS score of 6 at discharge in phases I and II in the MT groups are shown in Fig. 2a, b.

Subgroup analyses demonstrated that the effect of total response time on clinical outcomes in phase I was notable for patients aged ≥ 70 years and those who reside in areas with low and intermediate population density (< 300, 300–1000 persons/km^2; Fig. 3a). This association was only noted for patients aged < 70 years in phase II (Fig. 3b).

	All participating hospitals		p	Thrombectomy-capable hospitals		p
	Phase I	Phase II		Phase I	Phase II	
	(n = 373)	(n = 354)	p	(n = 170)	(n = 206)	p
Neurologists	210 (56.3)	200 (56.5)	0.976	104 (61.2)	124 (60.2)	0.846
Neurosurgeons	364 (97.6)	347 (98.0)	0.702	168 (98.8)	204 (99.0)	0.847
Endovascular physicians	216 (57.9)	212 (59.9)	0.600	151 (88.8)	168 (81.6)	**0.050**
Emergency medicine	143 (38.3)	140 (39.6)	0.787	73 (42.9)	89 (43.2)	0.959
Physical medicine and rehabilitation	104 (27.9)	95 (26.8)	0.675	43 (25.3)	57 (27.7)	0.604
Rehabilitation therapy	372 (99.7)	353 (99.7)	0.966	169 (99.4)	205 (99.5)	0.892
Stroke rehabilitation nurses	116 (31.1)	111 (31.4)	0.990	68 (40.0)	81 (39.3)	0.893
Computed tomography	371 (99.5)	351 (99.2)	0.605	170 (100.0)	206 (100)	-
Magnetic resonance imaging with diffusion	359 (96.2)	340 (96.1)	0.870	169 (99.4)	203 (98.5)	0.414
Digital cerebral angiography	346 (92.8)	331 (93.5)	0.716	168 (98.8)	203 (98.5)	0.814
Computed tomography angiography	352 (94.4)	334 (94.4)	0.969	166 (97.6)	203 (98.5)	0.522
Carotid duplex ultrasound	156 (41.8)	154 (43.5)	0.631	80 (47.1)	104 (50.5)	0.508
Transcranial Doppler	91 (24.4)	92 (26.0)	0.636	54(31.8)	67 (32.5)	0.875
Carotid endarterectomy	332 (89.0)	316 (89.3)	0.845	163 (95.9)	195 (94.7)	0.581
Clipping of intracranial aneurysm	360 (96.5)	345 (97.5)	0.471	170 (100.0)	205 (99.5)	0.363
Hematoma removal/draining	359 (96.2)	345 (97.5)	0.362	169 (99.4)	205 (99.5)	0.892
Coiling of intracranial aneurysm	248 (66.5)	237 (67.0)	0.895	162 (95.3)	180 (87.4)	**0.008**
Intra-arterial reperfusion therapy	290 (77.7)	281 (79.4)	0.569	167 (98.2)	193 (93.7)	**0.030**
Stroke unit	144 (38.6)	138 (39.0)	0.968	82 (48.2)	97 (47.1)	0.825
Intensive care unit	282 (75.6)	265 (74.9)	0.834	136 (80.0)	168 (81.6)	0.703
Operating room staffed 24/7	250 (67.0)	240 (67.8)	0.823	145 (85.3)	173 (84.0)	0.726
Interventional services coverage 24/7	241 (64.6)	237 (67.0)	0.507	158 (92.9)	180 (87.4)	0.075
Stroke registry	198 (53.1)	195 (55.1)	0.505	102 (60.0)	131 (63.6)	0.475
Community education	107 (28.7)	101 (28.5)	0.953	63 (37.1)	71 (34.5)	0.601
Professional education	231 (62.1)	225 (63.6)	0.656	123 (72.4)	150 (72.8)	0.920
CSC score	17 (14, 20)	18 (14, 20)	0.725	19 (17, 21)	19 (17, 21)	0.447
Population density, person/km^2			0.888			0.887
< 300	108 (29.9)	105 (30.4)		47 (27.8)	54 (26.5)	
300–1000	107 (29.6)	107 (30.9)		50 (29.6)	65 (31.9)	
> 1000	146 (40.4)	134 (38.7)		72 (42.6)	85 (41.7)	

Table 3. CSC capabilities based on hospital characteristics in all groups. *CSC* comprehensive stroke center; * implementation of full-time, board-certified personnel. P-values in bold are significant.

Associations between CSC score and clinical outcomes. In phase I, there was an association between an increase in the CSC score and better outcomes after MT (each 1-point increase, 0.951 [0.915–0.989]). In phase II, however, the association between a higher CSC score and improved outcomes was no longer observed in the MT group (each 1-point increase, 0.987 [0.965–1.010]). The relationships between the CSC score and probabilities of an mRS score of 6 at discharge in phases I and II in the MT groups are shown in Figs. 2c, d.

Subgroup analyses demonstrated that the effect of CSC scores on clinical outcomes in phase I was notable for men, patients aged ≥ 70 years, those who received preceding rt-PA administration, and those who resided in areas with intermediate population density (300–1000 persons/km^2) (Fig. 3c). No influence of the CSC score on clinical outcomes was observed in any subgroup in phase II (Fig. 3d).

Discussion

Linking data from the J-ASPECT stroke database from 2013 to 2016 to the national EMS records, we demonstrated the increased use of MT and better clinical outcomes after MT with less initial stroke severity in an increasing number of thrombectomy-capable hospitals following revisions to the clinical practice guidelines for MT in 2015 by the relevant societies in Japan. Although the availability of endovascular physicians in all participating hospitals remained the same during the study period, fewer endovascular physicians were present in thrombectomy-capable hospitals in phase II, probably because of the rapid nationwide increase of such hospitals in response to the abovementioned revisions.

The influence of the CSC capabilities of the thrombectomy-capable hospitals and prehospital time on the clinical outcomes of patients with AIS who received MT in phase I may support the implementation of regional centralization of thrombectomy-capable hospitals[3,5,22]. No such clinical influence was observed in phase II; however, we posit that, in the current transitional period, while there is a relative shortage of thrombectomy-capable

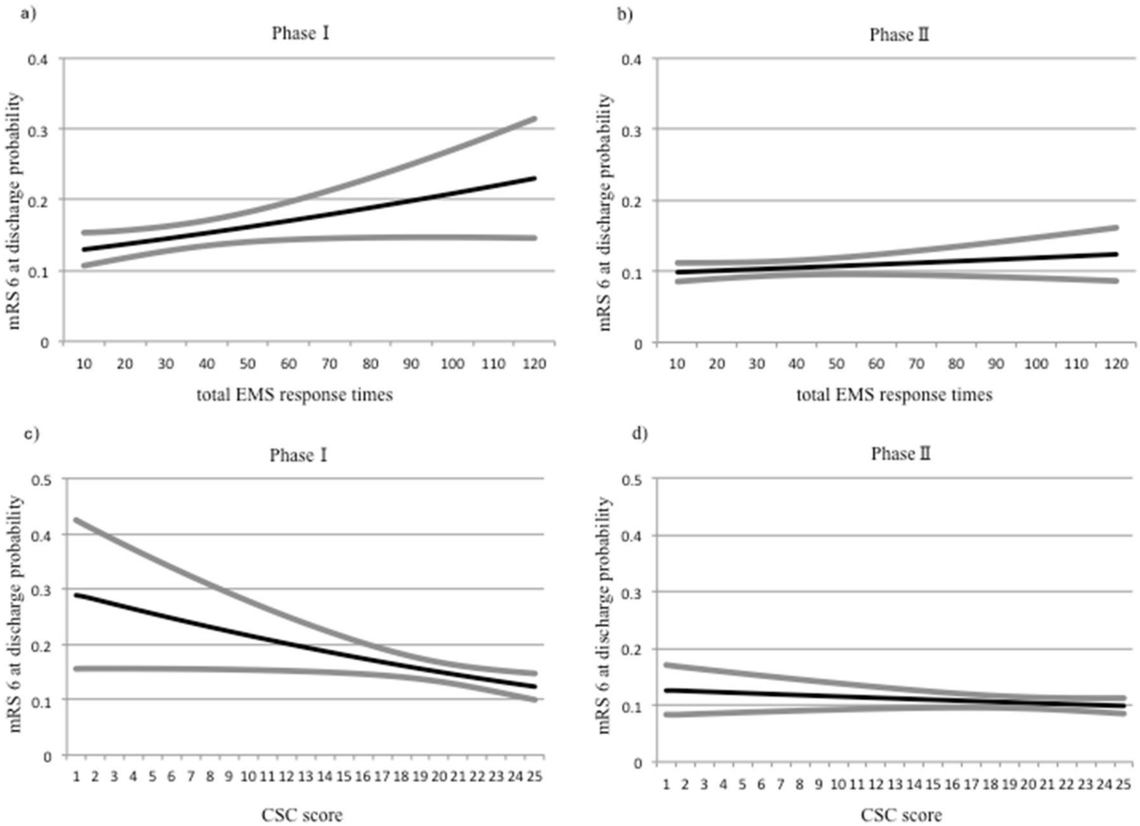

Figure 2. Relationships between the total EMS response time or the CSC scores and probabilities of an mRS score of 6 at discharge (stroke outcomes) in the MT group. Panels (**a**) and (**b**) show the effects of total EMS response time (minutes) on the probabilities of an mRS score of 6 at discharge in phases I and II, respectively, in the MT group. Panels (**c**) and (**d**) show the effects of the CSC scores on the probabilities of an mRS score of 6 at discharge in phases I and II, respectively, in the MT group. *EMS* emergency medical services; *CSC* comprehensive stroke center; *mRS* modified Rankin Scale; *MT* mechanical thrombectomy.

hospitals, increasing the amount of hospitals with moderate CSC scores may benefit the populations of countries with geographical conditions similar to those of Japan.

Temporal changes in patient characteristics. We demonstrated temporal changes in patient characteristics in the MT group, such as a higher age, decreased stroke severity, and better outcomes in phase II, which were consistent with those reported in previous studies of patients with AIS[2,23]. MT use in patients with AIS who were directly transported to a suitable facility via an ambulance in phase I (2.7%) was comparable to the findings from the US hospitals that participated in the Get With The Guidelines-Stroke program (MT use 3.3%)[1]. MT use (5.5%) in patients with AIS in phase II doubled from that in phase I, which may be explained by an increased awareness of the effectiveness of MT and the implementation of thrombectomy-capable hospitals in response to the revised guidelines in Japan[24].

In contrast, MT use in patients with AIS who were directly transported via an ambulance to a suitable facility in phase II was almost twice the proportion (3.0%) of all patients with AIS who were urgently hospitalized in Japan from April 2010 to March 2016[2]. This is consistent with the findings of previous studies showing that only 60% of urgently hospitalized patients with AIS are transported via an ambulance[7,25], suggesting the underuse of ambulances for patients with AIS who are possible candidates of MT in Japan.

Influence of the CSC capabilities and total EMS response time of thrombectomy-capable hospitals on clinical outcomes in phases I and II. The observed influence of CSC capabilities of thrombectomy-capable hospitals on clinical outcomes of patients with AIS who received MT in phase I may support the concept of regional centralization of thrombectomy-capable hospitals[3,5,22]. This is consistent with our previous studies using data before 2015. Therein, we demonstrated that hospitals with higher (vs. lower) CSC capabilities were more likely to have lower in-hospital mortality among patients with AIS and to provide timely rt-PA infusion and MT on a 24-h basis[2,7]. Although the CSC score comprises heterogeneous items of stroke care expertise, it reflects the joint effort of multiple healthcare professionals to manage emergencies[7,9,11,12].

One major finding of this study was the lack of association between the CSC capabilities and clinical outcomes of MT in phase II. This unexpected finding may be explained by several observations. First, and most notably, despite the similar CSC scores in phases I and II in the thrombectomy-capable hospitals in this study,

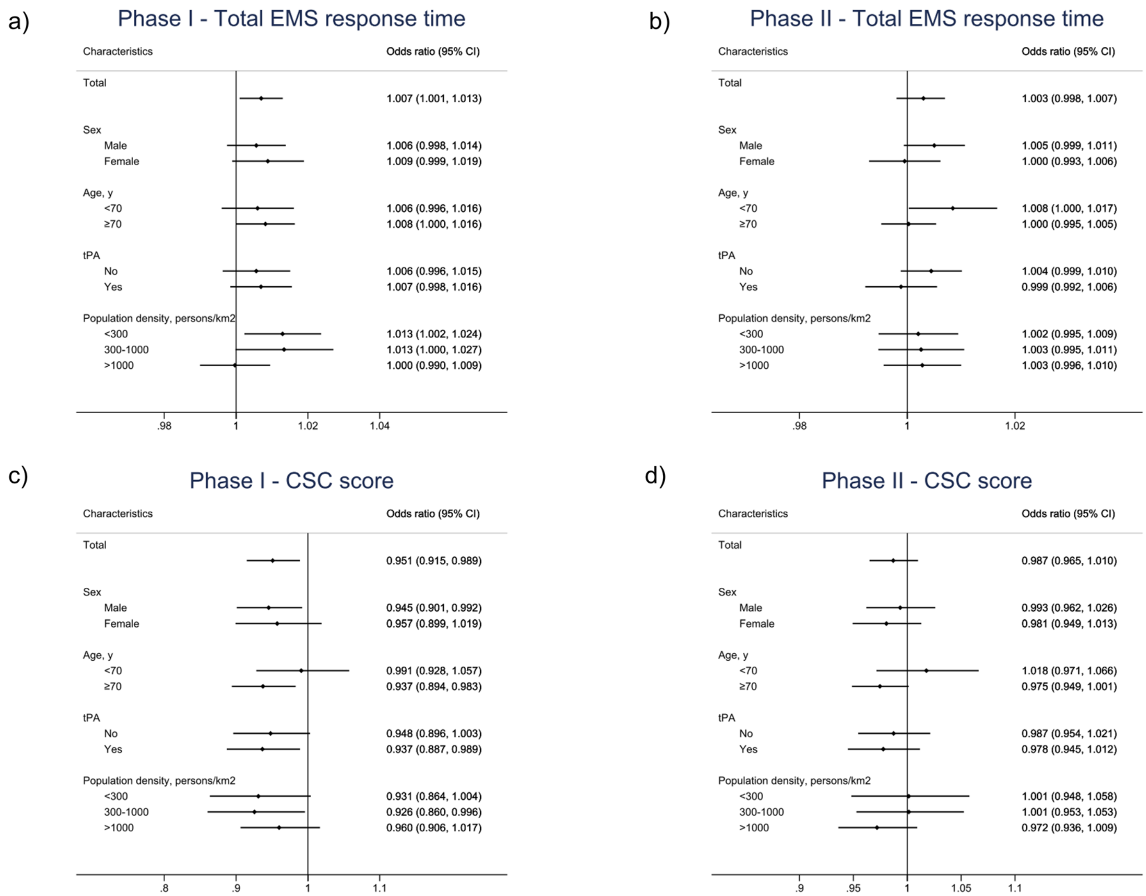

Figure 3. Subgroup analyses of the effect of the total EMS response time and the CSC score on outcomes. The forest plot shows the effect size of a 1-min increase of the total EMS response time on the mRS score at discharge in phases I (panel **a**) and II (panel **b**), respectively, in the MT group, analyzed according to ordinal logistic regression across subgroups. Dots indicate point estimates for the effect of the total EMS response time. The forest plot shows the effect size of a 1-point increase of the CSC score on the mRS score at discharge in phases I (panel **c**) and II (panel **d**), respectively, in the MT group, analyzed according to ordinal logistic regression across subgroups. Dots indicate point estimates for the effect of the CSC score. *EMS* emergency medical services; *CSC* comprehensive stroke center; *mRS* modified Rankin Scale; *MT* mechanical thrombectomy.

the availability of specific items related to endovascular therapy (e.g., full-time availability of board-certified endovascular physicians and intra-arterial reperfusion therapy) decreased. This relative shortage was probably because of the rapid increase in hospitals where MT can be performed. In contrast, in all participating hospitals, the availability of those items remained almost the same from phase I to II, which is consistent with the results in our previous study. Therein, we showed that the implementation of six items, mainly related to endovascular therapy, increased > 20% from 2010 to 2018, especially between 2010 and 2014[12].

Second, even in thrombectomy-capable hospitals with comparable CSC capabilities in phases I and II, there may be a difference in the quality of in-hospital care related to MT, depending on the availability of endovascular physicians[26–29]. For example, thrombectomy-capable hospitals without sufficient in-house endovascular physicians are more likely to make use of those from neighboring hospitals to perform MT, which may increase the onset-to-reperfusion time and worsen the clinical outcomes[26,30].

Another key finding of this study was that the total EMS response time was not associated with clinical outcomes of MT in phase II, regardless of the level of urbanization. The influence of the total EMS response time on clinical outcomes in the MT group in phase I is in line with previous studies evaluating the effect of onset-to-treatment time on outcomes of patients who received MT[10]. The total median EMS response time (phase I, 33 min; phase II, 32 min) in the MT group remained unchanged between phase I and II and was shorter than that in a US study (36 min)[31], suggesting that the total EMS response time may not be an effective target in shortening the onset-to-treatment time. However, this may be characteristic of countries, such as Japan, where a greater proportion of the population lives closer to hospitals than that in more expansive countries[18]. In more expansive countries, driving time exceeding 90 min may be more common. Despite this, we believe that our findings may not be unique to Japan[18] (e.g., 79% of adults in the US reside within 60 min of a hospital that provides acute cardiac therapy[32]).

The influence of the total EMS response time in phase II may be outweighed by other processes involved in the onset-to-treatment time, such as a delay in EMS activation[33] and the in-hospital workflow before MT[34]. In this study, we did not have information on the time from symptom recognition to the ambulance call or on the in-hospital workflow; therefore, we could not quantify the role of those processes on the outcomes of patients with AIS who received MT[26,35]. A recent study suggested that patients with a lower socioeconomic status may be more likely to delay EMS activation than those with a higher status[33]; however, educational campaigns raising awareness of the signs and symptoms of stroke have had little effect on the actual response to a stroke event[36,37]. In contrast, fast reperfusion is a modifiable factor associated with better clinical outcomes when successful reperfusion is achieved[34,38]. A recent meta-analysis of the pivotal trials that led to the change in guidelines showed that the intermediary outcome, the rate of successful reperfusion, was higher with faster (vs. slower) hospital-arrival-to-groin-puncture time[34]. This nationwide study lends real-world support to the findings of existing literature on the importance of in-hospital workflow to improve clinical outcomes of patients with AIS who receive MT[38,39].

In the US, AIS care and quality may differ between institutions, with CSCs outperforming primary stroke centers (PSCs) in timely acute reperfusion therapy and risk-adjusted mortality[33]. Recently, we developed the Close The Gap-Stroke (CTGS) program, the first nationwide quality improvement program within the J-ASPECT study; it allows prospective evaluation of the quality of acute stroke care in Japan, using the DPC database and electronic medical records[14,29]. Further studies are necessary to examine the influence of CSC capabilities on performance in terms of quality indicators and clinical outcomes of patients with AIS who received MT after the JSS started to certify PSCs who are able to perform MT.

Our study suggests that equal accessibility to MT remains an urgent unmet need in real-world situations, which may justify the nationwide implementation of thrombectomy-capable hospitals with moderate CSC capabilities since 2015[40].

In 2019, in Japan, the JSNET started to certify endovascular physicians who are qualified only to perform MT, and the JSS started to certify PSCs that are encouraged to perform MT. Availability of MT in the PSCs is in line with the increasing availability of endovascular treatment at PSCs in the US[40]. The current findings may lend support to this certification policy, as it may assist in equalizing the accessibility to MT.

Limitations

First, selection bias and unmeasured residual confounders may exist[10]. The participating hospitals in the J-ASPECT study were more likely to commit to quality improvement in stroke care than non-participating hospitals; however, the number of MTs performed in phase I corresponded to approximately 74.4% of those reported in the Japanese Registry of Neuroendovascular Therapy—the official registry of the JSNET[41]. Further, the geographical locations of the thrombectomy-capable and all participating hospitals in this study were comparable with those reported in the previous nationwide study on rt-PA use in Japan[18]. This suggests that the findings may represent the real-world situation in Japan. Second, the DPC database lacks data regarding several important factors, including the National Institutes of Health Stroke Scale (NIHSS) score, time metrics, and imaging results[7,8,13,14]. Thus, we used the JCS score, rather than the NIHSS score, as an index of stroke severity. Nationwide implementation of the CTGS program of the J-ASPECT study may solve this issue. Third, the LVO site was not included in the analysis; however, our recent study showed that approximately 86.4% of patients with AIS underwent MT from January 2013 to December 2015 according to the guidelines[29]. Fourth, we did not examine the effect of CSC capabilities on in-hospital care provision[29,39]. The result of the CTGS, an ongoing nationwide quality improvement initiative in Japan, may answer this question[14,29]. Finally, long-term outcomes (≥ 90 days) after AIS were not evaluated. Further studies are necessary to address these issues.

Conclusion

In the current transitional period, while there is a relative shortage of thrombectomy-capable hospitals, increasing the number of hospitals with moderate CSC scores may benefit the general Japanese population by equalizing access to MT in response to AIS. Certification of endovascular physicians qualified to perform MT may also promote such accessibility in thrombectomy-capable hospitals.

Data availability

We have documented the data, methods, and materials used to conduct the research in this report. The individual patient data are not publicly available owing to the memorandum signed by the directors of the participating hospitals and the principal investigator of the J-ASPECT Study group.

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Competing interests

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Additional information

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General Hospital, Tsuchiura, Japan. [287]Ibaraki Prefectural Central Hospital, Kasama, Japan. [288]JA Toride Medical Center, Toride, Japan. [289]Ushiku Aiwa General Hospital, Ushiku, Japan. [290]University of Tsukuba Hospital, Tsukuba, Japan. [291]Tsukuba Medical Center Hospital, Tsukuba, Japan. [292]Tsuchiura Kyodo Hospital Namegata District Medical Center, Namegata, Japan. [293]Ibaraki Seinan Medical Center Hospital, Sashima, Japan. [295]Saiseikai Ustunomiya Hospital, Utsunomiya, Japan. [296]Shimotsuga General Hospital, Tochigi, Japan. [297]Fujii Neurosurgical Hospital, Utsunomiya, Japan. [298]NHO Tochigi Medical Center, Utsunomiya, Japan. [299]Kurosu Hospital, Sakura, Japan. [300]Kyoto City Hospital, Kyoto, Japan. [301]Takeda Hospital, Kyoto, Japan. [302]Saiseikai Kyoto Hospital, Nagaokakyo, Japan. [303]Kyoto Okamoto Memorial Hospital, Kuse, Japan. [304]Kyoto Yamashiro General Medical Center, Kizugawa, Japan. [305]Kyoto Second Red Cross Hospital, Kyoto, Japan. [306]Ayabe City Hospital, Ayabe, Japan. [307]Kyoto Min-Iren Chuo Hospital, Kyoto, Japan. [308]Kobe University Hospital, Kobe, Japan. [309]Shinsuma General Hospital, Kobe, Japan. [310]Kobe Red Cross Hospital, Kobe, Japan. [311]JCHO Kobe Central Hospital, Kobe, Japan. [312]Nishikobe Medical Center, Kobe, Japan. [313]Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan. [314]Nishinomiya Kyoritsu Neurosurgical Hospital, Nishinomiya, Japan. [315]Takarazuka City Hospital, Takarazuka, Japan. [316]The Veritas Hospital, Kawanishi, Japan. [317]Takarazuka Daiichi Hospital, Takarazuka, Japan. [318]Ohnishi Neurological Center, Akashi, Japan. [321]NHO Himeji Medical Center, Himeji, Japan. [322]Ako City Hospital, Ako, Japan. [323]Toyooka Hospital, Toyooka, Japan. [324]Hyogo Prefectural Awaji Medical Center, Sumoto, Japan. [325]Itami Kousei Neurosurgical Hospital, Itami, Japan. [326]Nara Prefectural Nara Hospital, Nara, Japan. [327]Kouseikai Takai Hospital, Tenri, Japan. [328]Nara Medical University Hospital, Kashihara, Japan. [330]NHO Nara Medical Center, Nara, Japan. [331]Wakayama Medical University Hospital, Wakayama, Japan. [332]Wakayama Rosai Hospital, Wakayama, Japan. [333]NHO Minami Wakayama Medical Center, Tanabe, Japan. [334]Shingu Municipal Medical Center, Shingu, Japan. [335]Wakayama-Seikyo Hospital, Wakayama, Japan. [336]Tottori University Hospital, Yonego, Japan. [337]Hirosaki University Hospital, Hirosaki, Japan. [338]Kurosishi General Hospital, Kuroishi, Japan. [339]Japanese Red Cross Society Hachinohe Hospital, Hachinohe, Japan. [340]Aomori City Hospital, Aomori, Japan. [341]Odate Municipal General Hospital, Odate, Japan. [342]Akita City Hospital, Akita, Japan. [343]Research Institute for Brain and Blood Vessels-Akita, Akita, Japan. [344]Akita University Hospital, Akita, Japan. [345]Kazuno Kosei Hospital, Kazuno, Japan. [346]Fukushima Red Cross Hospital, Fukuchima, Japan. [347]Fukushima Medical University Hospital, Fukuchima, Japan. [348]Fujita General Hospital, Date, Japan. [349]Southern Tohoku Hospital, Koriyama, Japan. [350]Takeda General Hospital, Aizuwakamatsu, Japan. [351]Iwaki Kyoritsu General Hospital, Iwaki, Japan. [352]Minamisoma City General Hospital, Minamisoma, Japan. [353]Yamagata University Hospital, Yamagata, Japan. [354]Yamagata City Hospital Saiseikan, Yamagata, Japan. [355]Shinoda General Hospital, Yamagata, Japan. [356]Kitamurayama Hospital, Higashine, Japan. [357]Yamagata Prefectural Shinjo Hospital, Shinjo, Japan. [358]Okitama Public General Hospital, Higashiokitama, Japan. [359]Yonezawa City Hospital, Yonezawa, Japan. [360]Sanyudo Hospital, Yonezawa, Japan. [361]Tsuruoka Municipal Shonai Hospital, Tsuruoka, Japan. [362]South Miyagi Medical Center, Shibata, Japan. [363]Kohnan Hospital, Sendai, Japan. [364]Sendai City Hospital, Sendai, Japan. [365]Furukawaseiryou Hospital, Osaki, Japan. [366]Omihachiman Community Medical Center, Omihachiman, Japan. [367]Kohka Public Hospital, Koka, Japan. [368]Shiga University of Medical Science Hospital, Otsu, Japan. [369]Otsu City Hospital, Otsu, Japan. [370]Nagahama City Hospital, Nagahama, Japan. [371]Koto Memorial Hospital, Higashiomi, Japan. [373]Mie University Hospital, Tsu, Japan. [374]Saiseikai Matsusaka General Hospital, Matsusaka, Japan. [375]Ise Red Cross Hospital, Ise, Japan. [376]Shizuoka City Shizuoka Hospital, Shizuoka, Japan. [377]Yaizu City Hospital, Yaizu, Japan. [378]Hamamatsu Rosai Hospital, Hamamatsu, Japan. [379]Hamamatsu Medical Center, Hamamatsu, Japan. [380]Seirei Mikatahara General Hospital, Hamamatsu, Japan. [381]Iwata Municipal General Hospital, Iwata, Japan. [382]NHO Shizuoka Medical Center, Shimizu, Japan. [383]Fuji City General Hospital, Fuji, Japan. [384]Shizuoka Childrens Hospital, Shizuoka, Japan. [385]Gifu Municipal Hospital, Gihu, Japan. [386]Gifu University Hospital, Gihu, Japan. [387]Gifu Prefectural Tajimi Hospital, Tajimi, Japan. [388]Toki General Hospital, Toki, Japan. [389]Saku Central Hospital, Saku, Japan. [390]Aizawa Hospital, Matsumoto, Japan. [391]Nagano Municipal Hospital, Nagano, Japan. [392]Shinonoi General Hospital, Nagano, Japan. [393]Suwa Central Hospital, Chino, Japan. [394]Iida Municipal Hospital, Iida, Japan. [395]Showa Inan General Hospital, Komagane, Japan. [396]Japanese Red Cross Society Azumino Hospital, Azumino, Japan. [397]Azumi General Hospital, Kitaazumi, Japan. [398]NHO Shinshu Ueda Medical Center, Ueda, Japan. [399]Shimane Prefectural Central Hospital, Izumo, Japan. [400]Yasugi Municipal Hospital, Yasugi, Japan. [401]NHO Hamada Medical Center, Hamada, Japan. [402]NHO Okayama Medical Center, Okayama, Japan. [403]Okayama Kyokuto Hospital, Okayama, Japan. [404]Okayama City Hospital, Okayama, Japan. [405]Okayama University Hospital, Okayama, Japan. [406]Kawasaki Medical School Hospital, Kurashiki, Japan. [407]Kurashiki Central Hospital, Kurashiki, Japan. [408]Kurashiki Heisei Hospital, Kurashiki, Japan. [409]Tsuyama Chuo Hospital, Tsuyama, Japan. [411]Kasaoka Daiichi Hospital, Kasaoka, Japan. [412]JCHO Tokuyama Central Hospital, Shunan, Japan. [413]Yamaguchi Prefectural Grand Medical Center, Hofu, Japan. [414]Yamaguchi Red Cross Hospital, Yamaguchi, Japan. [415]Yamaguchi University Hospital, Ube, Japan. [416]Ube-Kohsan Central Hospital, Ube, Japan. [417]NHO Kanmon Medical Center, Shimonoseki, Japan. [418]Shimonoseki City Hospital, Shimonoseki, Japan. [419]Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima, Japan. [420]Suiseikai Kajikawa Hospital, Hiroshima, Japan. [421]Hiroshima University Hospital, Hiroshima, Japan. [422]Hiroshima Prefectural Hospital, Hiroshima, Japan. [423]Araki Neurosurgical Hospital, Hiroshima, Japan. [424]Mazda Hospital, Aki, Japan. [425]Chugoku Rosai Hospital, Kure, Japan. [426]Kohsei General Hospital, Mihara, Japan. [427]Mitsugi General Hospital, Onomichi, Japan. [428]Miyoshi Central Hospital, Miyoshi, Japan. [429]Tokushima University Hospital, Tokushima, Japan. [430]Tokushima Prefecture Naruto Hospital, Naruto, Japan. [431]Tokushima Prefectural Kaifu Hospital, Kaifu, Japan. [432]Kansai Medical University Hospital, Hirakata, Japan. [433]Kyushu Rosai Hospital, Kitakyushu, Japan. [434]Teinekeijinkai Hospital, Sapporo, Japan. [435]Sapporo Azabu Neurosurgical Hospital, Sapporo, Japan. [436]Hakodate Central General Hospital, Hakodate, Japan. [437]Otaru Chuo Hospital, Otaru, Japan. [438]NHO Hokkaido Medical Center, Sapporo, Japan. [439]Sapporo Medical University Hospital, Sapporo, Japan. [440]Hakodate Municipal Hospital, Hakodate, Japan. [441]Sapporoteishinkai Hospital, Sapporo, Japan. [442]Shinsapporo Neurosurgical Hospital, Sapporo, Japan. [443]Sapporo Shiroishi Memorial Hospital, Sapporo, Japan. [444]Sendai East Neurosurgical Hospital, Sendai, Japan. [445]JA Akita Kouseiren Oomagarikousei Medical Center, Daisen, Japan. [446]Noshiro Kosei Medical Center, Noshiro, Japan. [447]Iwate Prefectural Kuji Hospital, Kuji, Japan. [448]Tohoku University Hospital, Sendai, Japan. [449]Aomori Prefectural Central Hospital, Aomori, Japan. [450]Iwate Prefectural Central Hospital, Morioka, Japan. [451]NHO Sendai Medical Center, Sendai, Japan. [452]Saitama Red Cross Hospital, Saitama, Japan. [453]Ishinomaki Red Cross Hospital, Ishinomaki, Japan. [454]Osaki Citizen Hospital, Osaki, Japan. [455]Yamagata Saisei Hospital, Yamagata, Japan. [456]Ohta Nishinouchi Hospital, Koriyama, Japan. [457]Tokyo Metropolitan Childrens Medical Center, Fuchu, Japan. [458]Mito Kyodo General Hospital, Mito, Japan. [459]Chiba Rosai Hospital, Ichihara, Japan. [460]Chiba Cancer Center, Chiba, Japan. [461]Chiba Childrens Hospital, Chiba, Japan. [462]Secomedic Hospital, Funabashi, Japan. [463]Saiseikai Kawaguchi General Hospital, Kawaguchi, Japan. [464]Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan. [465]Keio University Hospital, Tokyo, Japan. [466]Jinmeikai Akiyama Neurosurgical Hospital, Yokohama, Japan. [467]Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan. [468]Mitsuwadai General Hospital, Chiba, Japan. [469]Ebina General Hospital, Ebina, Japan. [470]Tokyo Metropolitan Health and Medical Treatment Corporation Ohkubo Hospital, Tokyo, Japan. [471]Itabashi Chuo Medical Center, Tokyo, Japan. [472]Ome Municipal General Hospital, Ome, Japan. [473]Tokyo Metropolitan Tama Medical Center, Fuchu, Japan. [474]Teraoka Memorial Hospital, Fukuyama, Japan. [475]Kitasato University Hospital, Sagamihara, Japan. [476]Yokohama Asahi Chuo General Hospital, Yokohama, Japan. [477]Yamagata Prefectural Central Hospital, Yamagata, Japan. [478]Japanese Red Cross Akita Hospital, Akita, Japan. [479]Shinshu University Hospital, Matsumoto, Japan. [480]Kobayashi Neurosurgical Neurological Hospital, Ueda, Japan. [481]Komoro Kosei General Hospital, Komoro, Japan. [482]Nagano Childrens Hospital, Azumino, Japan. [483]Ina Central Hospital, Ina, Japan. [484]Toyama University Hospital, Toyama, Japan. [485]Noto General Hospital, Nanao, Japan. [486]Keiju Medical Center, Nanao, Japan. [487]Toyohashi Municipal Hospital, Toyohashi, Japan. [488]Chubu Rousai Hospital, Nagoya, Japan. [489]Kamiiida Daiichi General Hospital, Nagoya, Japan. [490]Nagoya Central Hospital, Nagoya, Japan. [491]Nagoya City University Hospital, Nagoya, Japan. [492]Nagoya City East Medical Center, Nagoya, Japan. [493]Chutoen General Medical Center, Kakegawa, Japan. [494]Japanese Red Cross Takayama Hospital, Takayama, Japan. [495]Daiyukai General Hospital, Ichinomiya, Japan. [496]Seikeikai Hospital, Sakai, Japan. [497]Higashiosaka City Medical Center, Higashiosaka, Japan. [498]Kyoto University Hospital, Kyoto, Japan. [499]Tenri Hospital, Tenri, Japan. [500]Kishiwada City Hospital, Kishiwada, Japan. [501]Otsu Red Cross Hospital, Otsu, Japan. [502]Rakuwakai Otowa Hospital, Kyoto, Japan. [503]Higashisumiyoshi Morimoto Hospital, Osaka, Japan. [504]Daiichitowakai Hospital, Takatsuki, Japan. [505]Kano Hospital, Osaka, Japan. [506]Moriguchi-Ikuno Memorial Hospital, Moriguchi, Japan. [507]Ishikiriseiki Hospital, Higashiosaka, Japan. [508]Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan. [510]Hyogo College of Medicine, Nishinomiya, Japan. [511]Akashi City Hospital, Akashi, Japan. [512]Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Japan. [513]Tokushima Red Cross Hospital, Komatsushima, Japan. [514]NHO Shikoku Medical Center for Children and Adults, Zentsuji, Japan. [515]NHO Iwakuni Clinical Center, Iwakuni, Japan. [516]Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan. [517]Okayama Saiseikai General Hospital, Okayama, Japan. [518]Fukuyama City Hospital, Fukuyama, Japan. [519]Onomichi Municipal Hospital, Onomichi, Japan. [520]Kaneda Hospital, Maniwa, Japan. [521]Higashihiroshima Medical Center, Higashihiroshima, Japan. [522]Tottori Municipal Hospital, Tottori, Japan. [523]Shuto General Hospital, Yanai, Japan. [524]Hospital of the University of Occupational and Environmental Health, Kitakyushu, Japan. [525]Munakata Suikokai General Hospital, Fukutsu, Japan. [526]JCHO Kyushu Hospital, Kitakyushu, Japan. [527]Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka, Japan. [528]Harasanshin Hospital, Fukuoka, Japan. [529]Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan. [530]Hakujyuji Hospital, Fukuoka, Japan. [531]Saga University Hospital, Saga, Japan. [532]St. Marys Hospital, Kurume, Japan. [533]Tobata Kyoritsu Hospital, Kitakyushu, Japan. [534]JCHO Hitoyoshi Medical Center, Hitoyoshi, Japan. [535]Oitaken Koseiren Tsurumi Hospital, Beppu, Japan. [536]Sanseikai Kanemaru Neurosurgery Hospitai, Miyazaki, Japan. [537]Atsuchi Neurosurgical Hospital, Kagoshima, Japan. [538]NHO Kagoshima Medical Center, Kagoshima, Japan. [539]Okinawa Red Cross Hospital, Naha, Japan. [540]Asahi General Hospital, Asahi, Japan. [541]Kobe City Medical Center General Hospital, Kobe, Japan. [542]Yoshida Hospital, Kobe, Japan. [543]Wakkanai Teishinkai Hospital, Wakkanai, Japan. [544]Southern Tohoku General Hospital, Iwanuma, Japan. [545]Tokyo General Hospital, Tokyo, Japan. [546]St.Lukes International Hospital, Tokyo, Japan. [547]Chiba Tokushukai Hospital, Funabashi, Japan. [548]Nozaki Tokushukai Hospital, Daito, Japan. [549]Fukuoka University Chikushi Hospital, Chikushino, Japan. [550]Fukuoka Wajiro Hospital, Fukuoka, Japan. [551]Shintakeo Hospital, Takeo, Japan. [552]Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan. [553]Kansai Electric Power Hospital, Osaka, Japan. [554]Tomakomaihigashi Hospital, Tomakomai, Japan. [555]Date Red Cross Hospital, Date, Japan. [556]Hirosaki Stroke and Rehabilitation Center, Hirosaki, Japan. [557]Kitakami Saiseikai Hospital, Kitakami, Japan. [558]Izumi Hospital, Sendai, Japan. [559]Shin-Oyama City Hospital, Oyama, Japan. [560]Kamagaya General Hospital, Kamagaya, Japan. [561]Nissan Tamagawa Hospital, Tokyo, Japan. [562]Higashitotsuka Memorial Hospital, Yokohama, Japan. [563]Kaetsu Hospital, Niigata, Japan. [564]NHO Niigata Hospital, Kashiwazaki, Japan. [565]Toyama Red Cross Hospital, Toyama, Japan. [566]Maruko Central Hospital, Ueda, Japan. [567]Okaya City Hospital, Okaya, Japan. [568]Kenwakai Hospital, Iida, Japan. [569]Suwa Red Cross Hospital, Suwa, Japan. [570]Kyoto Katsura Hospital, Kyoto, Japan. [571]Shimizu Hospital, Kyoto, Japan. [572]Mimihara General Hospital, Sakai, Japan. [573]Osaka Saiseikai Ibaraki Hospital, Ibaraki, Japan. [574]Kobe Ekisaikai Hospital, Kobe, Japan. [575]Kita-Harima Medical Center, Ono, Japan. [576]Fujii Masao Memorial Hospital, Kurayoshi, Japan. [577]HITO Medical Center, Shikokuchuo, Japan. [578]Chidoribashi Hospital, Fukuoka, Japan. [579]Souseikai Shin Yoshizuka Hospital, Fukuoka, Japan. 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[599]Kyoritsu Hospital, Kawanishi, Japan.