

adjusted for case severity, and these reports included relatively small numbers of hospitals (2 to 28).<sup>14–18</sup> Furthermore, the results of these studies were inconsistent; 2 reported positive relationships between admission hours and outcomes<sup>14,15</sup> and 3 reported negative relationships.<sup>16–18</sup> We examined the relationship between admission time and disabilities/deaths at discharge by adjusting for case severity using data from a nationwide cohort of Japanese hospitals.

## Materials and Methods

### Database

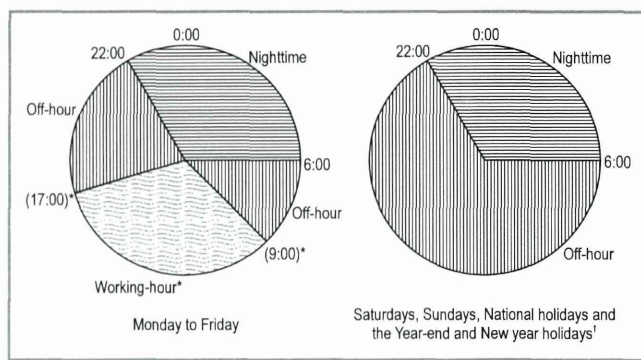
This study included a nationwide retrospective cohort of stroke patients (J-ASPECT study).<sup>19</sup> Among 749 certified training hospitals of the Japan Neurosurgical Society, the Societas Neurologica Japonica, and/or the Japan Stroke Society, 262 participated in this study. We collected Japanese Diagnosis Procedure Combination/Per Diem Payment System (DPC/PDPS) data, which list the lump-sum system of medical expenses evaluated based on diagnostic and procedural costs beginning in 2002.<sup>20</sup> Subject data were extracted from DPC/PDPS data at each hospital using specially developed computer software.

### Inclusion and Exclusion Criteria

We included consecutive patients admitted to 262 hospitals between April 1, 2010 and May 31, 2011 for acute ischemic stroke (IS), non-traumatic intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH) according to the International Classification of Disease 10th revision (ICD-10 codes, I60.0 to I60.9, I61.0 to I61.9, I62.0, I62.1, I62.9, and I63.0 to I63.9). Because of major differences in their typical prognoses, we excluded patients with transient ischemic attack (TIA) (G45). We also excluded patients who experienced in-hospital stroke during treatment for other diseases.

### Variables

The outcome measure was the proportion of severe disability/death (score 5 to 6 on the modified Rankin Scale [mRS]) at discharge.<sup>21</sup> We classified admission into (1) working-hour (professed work hours [usually 8 h] in each hospital from Monday to Friday, except for national holidays), (2) off-hour (hours not included in working-hour or nighttime classifications), or (3) nighttime (22:00 to 6:00 on any day) by using calendar time and additional medical billings in case of admission outside of working hours (Figure 1). We could not count the total hours of each admission-hour category.



**Figure 1.** Classification of hospital admission time. \*Working-hour was defined as working-hours professed by each hospital on consultation day (from Monday to Friday except for national holiday). †The YEAR-end and New Year holidays are from 29th December to 3rd January.

Proportions of total numbers of hours were hypothesized to be 22.2%, 44.5%, and 33.3% for working-hours, off-hours, and nighttime categories, respectively.

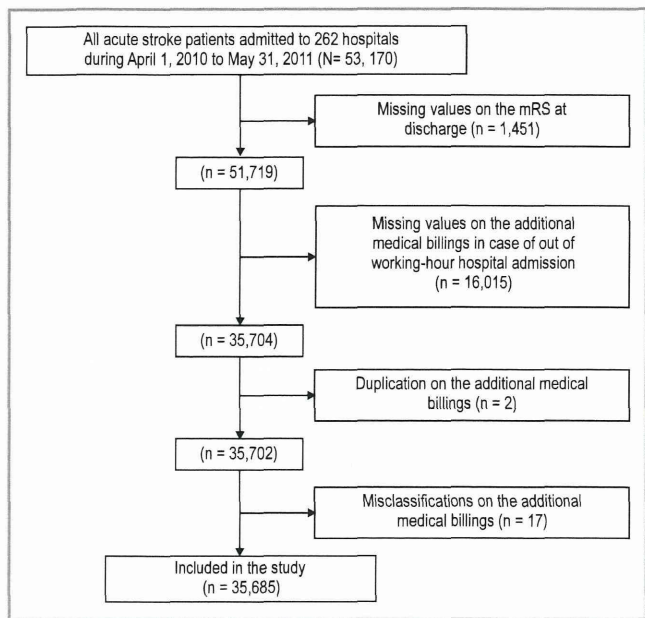
To account for the classical confounding factors for stroke and the capability of stroke care provided by hospitals, we adjusted for the following factors to estimate the effect of admission time: age (categorized as <35 years,

**Table 1.** Japan Coma Scale for Grading Impaired Consciousness\*

Grade	Consciousness Level
1-digit code	The patient is awake without any stimuli, and is:
1	Almost fully conscious
2	Unable to recognize time, place, and person
3	Unable to recall name or date of birth
2-digit code	The patient can be aroused (then reverts to previous state after cessation of stimulation):
10	By easily by being spoken to (or is responsive with purposeful movements, phrases, or words) <sup>†</sup>
20	With a loud voice or shaking of shoulders (or is almost always responsive to very simple words like yes or no or to movements)
30	Only by repeated mechanical stimuli
3-digit code	The patient cannot be aroused with any forceful mechanical stimuli, and:
100	Responds with movements to avoid the stimulus
200	Responds with slight movements, including decerebrate and decorticate posture
300	Does not respond at all except for changes in respiratory rhythm

\*"R" and "I" are added to the grade to indicate restlessness and incontinence of urine and feces, respectively; for example; 100-R and 30-RI.

<sup>†</sup>Criteria in parentheses are used in patients who cannot open their eyes for any reason.



**Figure 2.** Flow chart for inclusion criteria.

every 5 years from 35 to 100 years, and  $\geq 100$  years), sex, comorbidities (hypertension, diabetes mellitus, and hyperlipidemia), and number of hospital beds (<100, 100 to 299, 300 to 499, and  $\geq 500$ ). Comorbidities were assessed from recorded disease name and prescription history in patient medical records.

To adjust effects of baseline consciousness level at admission, we used the Japan Coma Scale (JCS).<sup>22–25</sup> The JCS – originally published in 1974 for the assessment of impaired consciousness of head trauma and stroke patients<sup>22</sup> and published in the same year as the Glasgow Coma Scale<sup>26</sup> – remains one of the most popular scales used among health care professionals and personnel for emergency medical services in Japan.<sup>25</sup> Briefly, a normal level of consciousness is graded as 0. Other levels are graded with 1-, 2-, or 3-digit codes depending on status as shown in Table 1. We treated JCS as a categorical variable and classified patients as grade 0, 1 to 3, 10 to 30, or 100 to 300 for analysis. A 3-digit JCS score is roughly equivalent to a GCS score of  $\leq 7$  ( $\leq E1V1M5$ ).

**Table 2.** Demographics and Clinical Characteristics of Patients Included and Excluded in the Analyses

	Total (n=53 170)		
	Excluded Subjects	Included Subjects	P Value
Number, %	n=17 485 (32.9)	n=35 685 (67.1)	
Male, %	58.1	53.8	<0.001
Age mean (SD)	74.0 (12.0)	71.7 (13.6)	<0.001
Stroke subtype, n (%)			
IS	68.1	58.2	<0.001
SAH	5.9	10.9	<0.001
ICH	26.2	31.1	<0.001
Comorbidity, %			
Hypertension	72.7	76.2	<0.001
Diabetes mellitus	28.9	24.3	<0.001
Hyperlipidemia	29.3	27.7	<0.001
Current/past smoking history (n=44 842) (%)	26.7	29.3	<0.001
Japan Coma Scale, %			
0	42.0	34.5	<0.001
1-digit code	34.8	37.2	
2-digit code	11.6	13.8	
3-digit code	11.6	14.6	
Emergency admission by ambulance (%)	51.4	64.5	<0.001
mRS at discharge (n=51 719) (%)			
mRS=6	11.4	12.2	0.014
mRS=5/6	24.1	25.4	0.001
mRS=4 to 6	41.3	44.0	<0.001

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage.

**Table 3.** Patient Demographics and Clinical Characteristics by Inclusion in the Analyses for Each Stroke Subtype

	IS (n=32 671)			SAH (n=4934)			ICH (n=15 699)		
	Excluded	Included	P Value*	Excluded	Included	P Value*	Excluded	Included	P Value*
Number, %	11 913 (36.5)	20 758 (63.5)		1035 (21.0)	3899 (79.0)		4588 (29.2)	11 111 (70.8)	
Male, %	59.8	56.3	<0.001	29.1	32.9	0.019	60.4	56.3	<0.001
Age mean (SD)	75.1 (11.4)	74.1 (12.5)	<0.001	67.9 (14.1)	63.8 (14.8)	<0.001	72.5 (12.6)	70.0 (13.8)	<0.001
Comorbidity, %									
Hypertension	69.8	68.5	0.013	82.4	86.6	0.001	78.3	87.2	<0.001
Diabetes mellitus	31.3	27	<0.001	25.6	23.3	0.124	23.6	19.8	<0.001
Hyperlipidemia	34.2	33.9	0.511	26.5	29.2	0.086	17.2	15.7	0.015
Current/past smoking history (n=44 842) (%)	27.6	30.1	<0.001	22.5	28.2	0.001	25.1	28.2	<0.001
Japan Coma Scale, %									
0	48.8	44.4	<0.001	23.4	20.1	<0.001	28.6	20.8	<0.001
1-digit code	35.7	39.2		19.3	23.5		36.2	38.5	
2-digit code	9.9	10.7		14.7	18		15.2	18.1	
3-digit code	5.7	5.7		42.6	38.5		20	22.7	
Emergency admission by ambulance (%)	46.3	57	<0.001	73.8	78.6	0.001	59.7	73.5	<0.001
mRS at discharge (n=51 719) (%)									
mRS=6	7.8	7.2	0.099	29.1	26.8	0.165	17	16.3	0.284
mRS=5/6	19.1	19.5	0.413	46.4	37.8	<0.001	32.1	32.3	0.812
mRS=4 to 6	36.4	37.5	0.061	56.8	47.8	<0.001	50.8	55	<0.001

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage.

\*Off-hour and nighttime were compared with working-hours.

## Statistical Analysis

We performed descriptive analyses for demographic and clinical characteristics for each group using the working-hour group as the control. Chi-square tests and *t* tests were used to compare categorical and continuous variables, respectively. For outcome analysis, we first compared crude outcome proportions among admission times in the total population, and then analyzed for each stroke subtype (IS, ICH, and SAH). For multivariable analysis, we used unique hospital ID in random-intercept hierarchical regression models to assess the relationships between hospital admission times and outcomes, while adjusting for patient characteristics and the hospitals at which patients received stroke care. This modeling adjusts for hospital-level cluster effects on outcome, which arise from various factors such as geographical location and ageing of the local population. We constructed 2 models to assess the impact of case severity. Model 1 included age, sex, hypertension, diabetes mellitus, hyperlipidemia, and number of beds. Baseline consciousness level was included in model 2 in addition to the variables in model 1. Moreover, to examine whether outcomes were

consistent across admission times for patients with the same level of consciousness at admission, we performed subgroup analysis by JCS. To test the sex-specific differences, we performed sex-stratified analysis after the main analysis. Furthermore, to test whether results differ when age is treated as a continuous variable, we performed additional analyses. For sensitivity analyses, we substituted outcomes to death (mRS=6) (sensitivity analysis 1) and moderately severe disability to death (mRS=4 to 6) (sensitivity analysis 2). To confirm the robustness of our results, we also estimated the off-hours effects at admission using the modified Rankin Scale. Unlike JCS, mRS uses 5 categories to assess severity. All statistical analyses were performed using STATA version 12 (StataCorp LP). All tests were 2-tailed, and  $P<0.025$  was considered statistically significant in consideration of multiple comparisons.

## Ethical Approval

The Institutional Review Board of the National Cerebral and Cardiovascular Center and the University of Tokyo approved this research.

**Table 4.** Patient Demographic and Clinical Characteristics by Admission Time

	Total (n=35 685)				
	Working-Hour	Off-Hour	P Value*	Nighttime	P Value*
Number, %	15 084 (42.3)	16 908 (47.4)		3693 (10.4)	
Male, %	54.7	52.8	0.001	54.6	0.957
Age mean (SD)	72.4 (13.3)	71.8 (13.5)	<0.001	68.3 (14.3)	<0.001
Comorbidity, %					
Hypertension	74.8	77.2	<0.001	77.8	<0.001
Diabetes mellitus	24.9	23.8	0.015	24.2	0.329
Hyperlipidemia	29.5	26.5	<0.001	26.1	<0.001
Current/past smoking history (n=30 179) (%)	30	28.3	0.001	31.3	0.191
Japan Coma Scale, %					
0	38.4	32.1	<0.001	29.2	<0.001
1-digit code	37.7	37.6		33.9	
2-digit code	12.4	14.6		15.7	
3-digit code	11.6	15.8		21.3	
Emergency admission by ambulance (%)	54.2	69.9	<0.001	81.4	<0.001

\*Off-hour and nighttime were compared with working-hours.

## Results

### Demographic and Clinical Characteristics

Out of 53 170 patients, we analyzed 35 685 patients. The inclusion criteria are shown in Figure 2. Demographics and clinical characteristics of excluded and included subjects for each stroke subtype are shown in Tables 2 and 3. IS, SAH, and ICH patients accounted for 58.2% (n=20 758), 10.9% (n=3899), and 31.1% (n=11 111), respectively. Overall, 42.3% (n=15 084), 47.4% (n=16 908), and 10.4% (n=3693) of patients were admitted during working hours, off hours, and nighttime, respectively. Patient demographics and clinical characteristics categorized according to admission time are shown in Table 4. Patients admitted during off hours and nighttime had lower baseline consciousness levels, and the percentage of these patients transferred to hospitals by ambulance was higher than that of patients admitted by ambulance during working hours. Patient demographics and clinical characteristics for each stroke subtype are shown in Table 5. The trends for age, baseline consciousness levels, and ambulance use by admission time were the same for each stroke subtype as observed for the total population.

Table 6 shows differences in primary outcomes among the 3 admission times for each stroke subtype. In the total population, increasing proportions of severe disability/death (mRS=5 to 6) at discharge were observed (22.8%, 27.2% and 28.2% for working-hour, off-hour, and nighttime, respectively). This remained the case when results were stratified by stroke subtype, although nighttime IS and off-hour and nighttime

SAH patients did not have statistically significant higher disabilities/death at discharge compared with patients admitted during working hours.

Figure 3 shows adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for severe disability/death at discharge depending on stroke subtype and admission time. In model 1, which was adjusted for age, sex, comorbidities, and number of beds, off-hour and nighttime admitted patients had higher risks of severe disability/death than working-hour admitted patients irrespective of stroke subtype (adjusted OR, 1.23; 95% CI, 1.17 to 1.30 for off-hour and adjusted OR, 1.45; 95% CI, 1.33 to 1.58 for nighttime). When we further adjusted for consciousness level at admission (model 2), the effects of admission time were no longer significant (adjusted OR, 1.06; 95% CI, 1.00 to 1.13;  $P=0.067$  for off-hour and adjusted OR, 0.99; 95% CI, 0.89 to 1.10;  $P=0.851$  for nighttime compared with working-hour). The same trends were observed when we stratified by stroke subtype: off-hour and nighttime admission times were associated with significantly higher risks of severe disability/death at discharge in each stroke subtype except for off-hour SAH (adjusted OR, 1.12; 95% CI, 0.95 to 1.32,  $P=0.168$ ) in model 1, and these effects were no longer significant in model 2 (Figure 3). Table 7 shows the effects of consciousness level at admission using Model 2.

In the subgroup analysis by using JCS at admission, proportions of severe disabilities/death were larger during off hours/nighttime than during working hours among IS and ICH patients with a JCS of 0. Proportions of primary outcome were larger during working hours than off hours/nighttime among

**Table 5.** Patient Demographic and Clinical Characteristics by Admission Time for Each Stroke Subtype

Stroke Subtype	IS (n=20 758)					SAH (n=3899)					ICH (n=11 111)				
	W	O	P Value*	N	P Value*	W	O	P Value*	N	P Value*	W	O	P Value*	N	P Value*
Number, %	9275 (44.7)	9630 (46.4)		1853 (8.9)		1407 (36.1)	1886 (48.4)		606 (15.5)		4436 (39.9)	5434 (48.9)		1241 (11.2)	
Male, %	56.7	55.2	0.047	60.7	<0.001	33.6	31.9	0.289	34.5	0.705	57.3	55.8	0.134	44.7	0.208
Age mean (SD)	74.2 (12.4)	74.5 (12.5)	0.046	71.4 (13.0)	<0.001	64.0 (14.6)	64.6 (14.7)	0.219	61.2 (15.3)	<0.001	71.3 (13.7)	69.6 (13.6)	<0.001	67.2 (14.3)	<0.001
Comorbidity, %															
Hypertension	68.5	68.6	0.930	67.6	0.411	88.2	86.2	0.085	84.2	0.013	83.5	89.6	<0.001	90.1	<0.001
Diabetes mellitus	28.0	26.1	0.003	26.2	0.111	24.1	23.3	0.610	21.5	0.198	18.9	19.8	0.215	22.6	0.004
Hyperlipidemia	35.9	32.3	<0.001	32.0	0.002	28.8	29.6	0.594	28.7	0.974	16.3	15.1	0.107	15.9	0.734
Smoking history (n=30 179) (%)	30.9	28.8	0.002	33.1	0.092	28.7	27.7	0.550	28.9	0.943	28.5	27.7	0.388	29.6	0.492
JCS, %															
0	47.3	42.1	<0.001	42.2	<0.001	24.5	17.9	<0.001	16.5	<0.001	24.1	19.2	<0.001	16.0	<0.001
1-digit code	38.2	40.2		38.5		24.5	22.9		23.4		40.6	38.2		32.1	
2-digit code	9.6	11.5		11.7		17.8	18.0		18.2		16.4	18.9		20.4	
3-digit code	4.8	6.3		7.7		33.3	41.3		41.9		19.0	23.8		31.5	
Ambulance admission (%)	46.9	62.8	<0.001	77.1	<0.001	72.2	80.9	<0.001	86.6	<0.001	63.9	78.7	<0.001	85.4	<0.001

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; JCS, Japan Coma Scale; SAH, subarachnoid hemorrhage.  
\*Off-hour (O) and Nighttime (N) were separately compared with Working-hour (W).

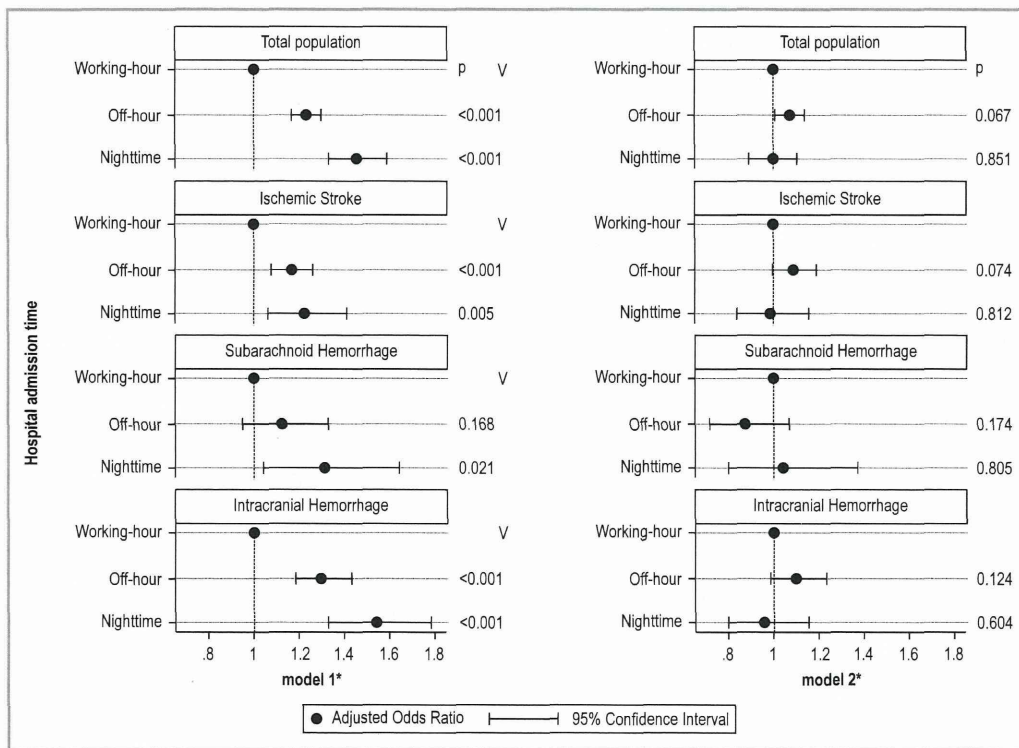
**Table 6.** Crude Primary Outcome Comparisons Between Each Admission Time by Stroke Subtype

Stroke Subtype	Admission Time	N	Severe Disability/Death at Discharge, n (%)	Crude OR (95% CI)	P Value
Total population	Working-hour	15 084	3434 (22.8)	—	
	Off-hour	16 908	4597 (27.2)	1.24 (1.18 to 1.31)	<0.001
	Nighttime	3693	1042 (28.2)	1.30 (1.19 to 1.41)	<0.001
IS	Working-hour	9275	1659 (17.9)	—	—
	Off-hour	9630	2039 (21.2)	1.21 (1.13 to 1.31)	<0.001
	Nighttime	1853	355 (19.2)	1.06 (0.93 to 1.21)	0.361
SAH	Working-hour	1407	499 (35.5)	—	—
	Off-hour	1886	733 (38.9)	1.14 (0.99 to 1.32)	0.077
	Nighttime	606	240 (39.6)	1.18 (0.97 to 1.44)	0.105
ICH	Working-hour	4436	1293 (29.2)	—	—
	Off-hour	5434	1842 (33.9)	1.24 (1.13 to 1.35)	<0.001
	Nighttime	1241	449 (36.2)	1.38 (1.20 to 1.58)	<0.001

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

IS and ICH patients who had a 3-digit JCS score (Table 8). Table 9 shows the results of subgroup analysis adjusted for age, sex, comorbidities, and number of hospital beds. Effects of nighttime admission were significantly higher (adjusted OR, 1.59; 95% CI, 1.11 to 2.29; IS and adjusted OR, 2.87; 95% CI, 1.66 to 4.98; for ICH) in patients with a JCS score of 0 and

significantly lower (adjusted OR, 0.50; 95% CI, 0.31 to 0.81; for IS and adjusted OR, 0.67; 95% CI, 0.49 to 0.90; for ICH) in patients with a 3-digit JCS score. Furthermore, no sex-based differences were present in these trends. Results obtained with age as a continuous variable were comparable with those obtained when it was treated as a categorical variable.



**Figure 3.** Effects of admission time on primary outcomes (modified Rankin Scale [mRS]=5 to 6) among acute stroke patients with 2 different models. \*Model 1 adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and number of beds. Model 2 further adjusted for Japan Coma Scale.

**Table 7.** Effects of Consciousness Level at Admission on Primary Outcomes (mRS=5 to 6) Among Acute Stroke Patients Determined Using Model 2

Admission Time	Japan Coma Scale	Total Population			IS			SAH			ICH		
		Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value		
Off-hour	0	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	1 digit	3.53 (3.18 to 3.90)	<0.001	4.08 (3.60 to 4.62)	<0.001	1.72 (1.22 to 2.44)	0.002	1.72 (1.22 to 2.44)	0.002	2.87 (2.32 to 3.56)	<0.001	2.87 (2.32 to 3.56)	<0.001
	2 digit	12.31 (11.00 to 13.78)	<0.001	16.70 (14.41 to 19.35)	<0.001	2.68 (1.88 to 3.81)	<0.001	2.68 (1.88 to 3.81)	<0.001	10.33 (8.25 to 12.92)	<0.001	10.33 (8.25 to 12.92)	<0.001
	3 digit	72.27 (64.01 to 81.59)	<0.001	45.98 (38.17 to 55.39)	<0.001	24.79 (17.93 to 34.28)	<0.001	24.79 (17.93 to 34.28)	<0.001	90.05 (71.19 to 113.91)	<0.001	90.05 (71.19 to 113.91)	<0.001
Nighttime	0	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	1 digit	3.10 (2.72 to 3.53)	<0.001	3.66 (3.10 to 4.31)	<0.001	1.73 (1.13 to 2.64)	0.011	1.73 (1.13 to 2.64)	0.011	2.28 (1.75 to 2.97)	<0.001	2.28 (1.75 to 2.97)	<0.001
	2 digit	10.89 (9.42 to 12.58)	<0.001	15.89 (13.08 to 19.31)	<0.001	2.96 (1.90 to 4.59)	<0.001	2.96 (1.90 to 4.59)	<0.001	7.79 (5.91 to 10.26)	<0.001	7.79 (5.91 to 10.26)	<0.001
	3 digit	69.17 (59.18 to 80.85)	<0.001	51.80 (40.27 to 66.64)	<0.001	24.79 (16.49 to 37.28)	<0.001	24.79 (16.49 to 37.28)	<0.001	68.28 (51.33 to 90.82)	<0.001	68.28 (51.33 to 90.82)	<0.001

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage.

Two sensitivity analyses that used different outcomes showed almost the same trend observed in the original analysis, except for ICH patients in sensitivity analysis 2 (Figure 4). Here, the effect of admission time was observed in ICH patients even when adjusted for consciousness level at admission (adjusted OR, 1.17; 95% CI 1.06 to 1.30;  $P=0.003$  for off-hour compared to working-hour). Additional sensitivity analyses performed using mRS at admission as a confounder instead of JCS revealed a trend similar to that observed in the original analysis (Figure 5). Here, the effects of admission time were no longer significant even when stratified to each stroke subtype.

### Discussion

Using nationwide population data on acute stroke patients, we found that outcome varied with admission time. Patients admitted outside of regular working hours were about 1.2 times more likely to have a poor outcome than those admitted during working hours. The effect of admission time remained significant for almost all stroke subtypes without adjusting for consciousness level at admission, which is similar to what has been reported previously. However, once we adjusted for consciousness level, the effects of admission time were dramatically attenuated; comatose patients were approximately 70 times more likely to suffer severe disabilities or death than lucid patients. Therefore, the different outcomes observed depending upon admission times were because of differences in stroke severity.

This study has several strengths. First, we included a large number of subjects from hospitals certified for training by the Japan Neurosurgical Society, the Societas Neurologica Japonica, and/or the Japan Stroke Society. Therefore, our results accurately reflect current practice in acute stroke care and are not influenced by changes in therapeutic strategy. The second strength is that we highlighted risks associated with nighttime admission. During the nighttime shift, hospital functions are reduced, and we observed a higher percentage of poorer outcomes for nighttime admitted patients. This finding is in accordance with a Dutch study that did not adjust for case severity, but did describe risk among IS patients admitted during the night.<sup>27</sup> Third, we adjusted for case severity at admission by using consciousness level. Case severity is a major confounding factor because it is one of the most important prognosis factors and is related to healthcare-seeking behaviors in stroke patients.<sup>10–13</sup> However, only 5 previous studies adjusted for case severity and they reported inconsistent results.<sup>14–18</sup> Among these, the Canadian study was the only one including a large number of subjects and reported a positive relationship between weekend hospital admission and stroke mortality among 20 000 acute stroke

**Table 8.** Crude Primary Outcome Comparisons Between Each Admission Time by Stroke Subtype and Japan Coma Scale

Japan Coma Scale	Admission Time	Total Population		IS		SAH		ICH	
		Admission (n)	Severe Disability/Death at Discharge, n (%)	Admission (n)	Severe Disability/Death at Discharge, n (%)	Admission (n)	Severe Disability/Death at Discharge, n (%)	Admission (n)	Severe Disability/Death at Discharge, n (%)
0	Working-hours	5793	286 (4.9)	4388	193 (4.4)	345	37 (10.7)	1069	56 (5.2)
	Off-hour	5420	293 (5.4)	4051	203 (5.0)	337	29 (8.6)	1042	62 (6.0)
	Nighttime	1079	78 (7.2)	781	46 (5.9)	100	8 (8.0)	199	25 (12.6)
1-digit	Working-hours	5679	991 (17.5)	3546	664 (18.7)	344	57 (16.6)	1799	276 (15.3)
	Off-hour	6354	1243 (19.6)	3869	831 (21.5)	431	65 (15.1)	2075	355 (17.1)
	Nighttime	1250	202 (16.2)	713	120 (16.8)	142	25 (17.6)	398	57 (14.3)
2-digit	Working-hours	1867	774 (41.5)	894	451 (50.5)	250	55 (22.0)	727	271 (37.3)
	Off-hour	2469	1034 (41.9)	1108	576 (52.0)	340	74 (21.8)	1026	387 (37.7)
	Nighttime	579	195 (33.7)	217	94 (43.3)	110	29 (26.4)	253	73 (28.9)
3-digit	Working-hours	1745	1383 (79.3)	447	351 (78.5)	468	350 (74.8)	841	690 (82.1)
	Off-hour	2665	2027 (76.1)	602	429 (71.3)	778	565 (72.6)	1291	1038 (80.4)
	Nighttime	785	567 (72.2)	142	95 (66.9)	254	178 (70.1)	391	294 (75.2)

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

**Table 9.** Effects of Admission Time on Primary Outcomes (mRS=5 to 6) Among Acute Stroke Patients by Japan Coma Scale

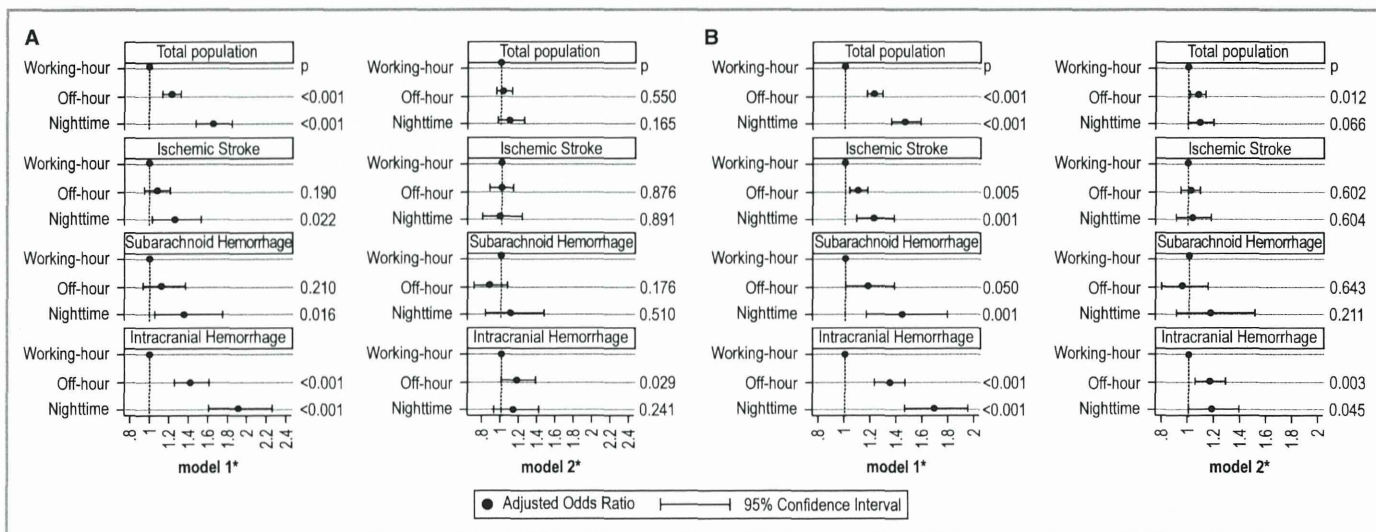
Japan Coma Scale	Admission Time	Total Population		IS		SAH		ICH	
		Adjusted OR <sup>†</sup> (95% CI)	P Value*	Adjusted OR <sup>†</sup> (95% CI)	P Value*	Adjusted OR <sup>†</sup> (95% CI)	P Value*	Adjusted OR <sup>†</sup> (95% CI)	P Value*
0	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	1.45 (1.33 to 1.58)	<0.001	1.07 (0.87 to 1.33)	0.515	0.87 (0.48 to 1.56)	0.633	1.29 (0.86 to 1.93)	0.220
	Nighttime	1.45 (1.33 to 1.58)	<0.001	1.59 (1.11 to 2.29)	0.011	0.83 (0.34 to 1.99)	0.672	2.87 (1.66 to 4.98)	<0.001
1-digit	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	1.20 (1.09 to 1.33)	<0.001	1.20 (1.07 to 1.36)	0.003	1.00 (0.64 to 1.55)	0.998	1.21 (1.00 to 1.45)	0.044
	Nighttime	1.06 (0.89 to 1.26)	0.536	0.98 (0.78 to 1.23)	0.856	1.28 (0.71 to 2.31)	0.416	1.01 (0.73 to 1.41)	0.941
2-digit	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	1.08 (0.94 to 1.24)	0.295	1.03 (0.85 to 1.25)	0.770	0.93 (0.60 to 1.44)	0.751	1.18 (0.93 to 1.48)	0.170
	Nighttime	0.91 (0.73 to 1.14)	0.406	0.89 (0.63 to 1.25)	0.498	1.56 (0.84 to 2.88)	0.160	0.81 (0.57 to 1.16)	0.250
3-digit	Working-hours	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
	Off-hour	0.81 (0.69 to 0.95)	0.008	0.65 (0.48 to 0.88)	0.006	0.81 (0.60 to 1.10)	0.169	0.89 (0.70 to 1.13)	0.325
	Nighttime	0.70 (0.57 to 0.86)	0.001	0.50 (0.31 to 0.81)	0.005	0.77 (0.51 to 1.15)	0.196	0.67 (0.49 to 0.90)	0.009

ICH indicates intracerebral hemorrhage; IS, ischemic stroke; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage.

\*Off-hour and nighttime were compared with working-hours.

†Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and hospital volume.

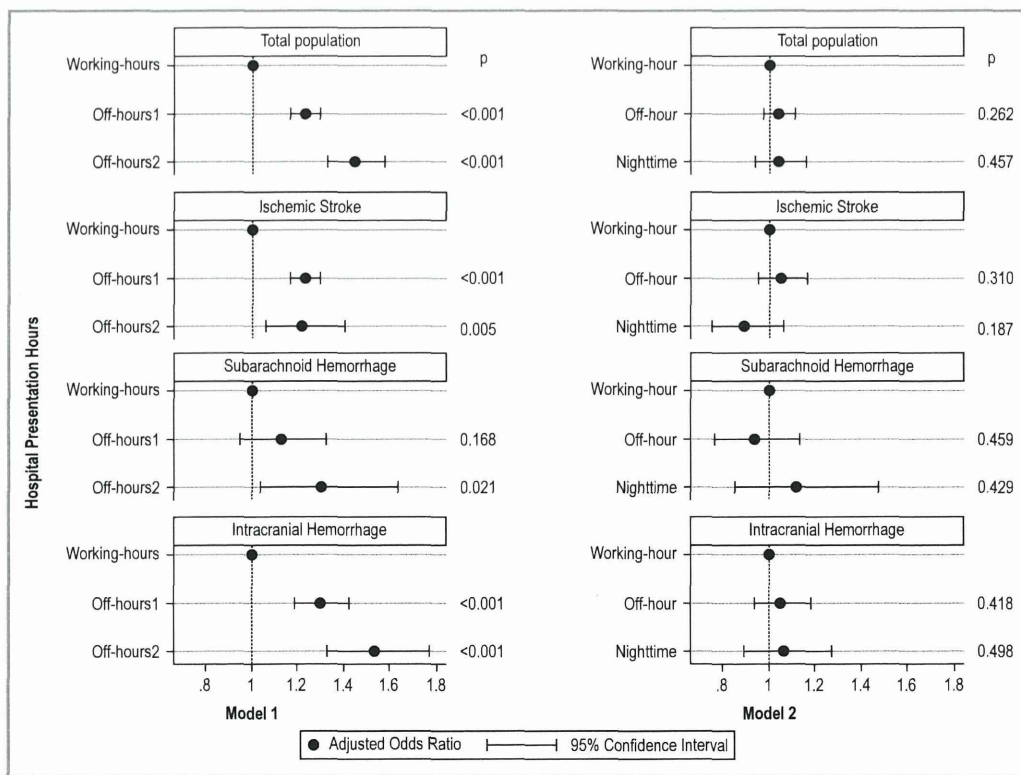




**Figure 4.** Sensitivity analyses for effects of admission time on modified Rankin Scale (mRS)=6 (A) and mRS=4 to 6 (B) among acute stroke patients with 2 different models. \*Model 1 adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and number of beds. Model 2 further adjusted for Japan Coma Scale.

or TIA patients at 11 hospitals.<sup>14</sup> The major differences of this study and the Canadian study are the number of participating hospitals and the definition of stroke subtypes. The Canadian study did not perform subtype-specific analyses, whereas we

evaluated both total population and stroke subtype outcomes. Therapeutic strategies and responses vary with stroke subtypes. Therefore, we considered that stratified analysis by subtype was more appropriate.



**Figure 5.** Sensitivity analysis for effects of admission time on primary outcomes (modified Rankin Scale [mRS]=5 to 6) among acute stroke patients with 2 different models using mRS at admission as a confounder instead of JCS. \*Model 1 adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, and hospital volume. Model 2 further adjusted for modified Rankin Scale at admission instead of Japan Coma Scale.

The reason why admission outside of working hours is related to case severity remains unknown. A circadian rhythm of stroke has been reported in large studies and may partially explain this phenomenon. Stroke is more frequent in the morning and evening,<sup>28–31</sup> and a surge in blood pressure and altered heart rate may be responsible for diurnal variation in stroke incidence.<sup>32,33</sup> However, the exact effect of circadian rhythm on stroke severity is unclear. Other factors such as limited access, minor symptoms, and age are known to be reasons that patients delay coming to the hospital.<sup>10–12</sup> Larger percentages of patients are admitted at off hours because baseline consciousness levels decrease during nighttime. Delayed perception of stroke symptoms or postponement of hospital consultation until regular working hours by patients with minor symptoms might have caused the perceived diurnal variation in stroke admission, though we could not confirm this from our data. Interestingly, in the subgroup analysis by baseline consciousness level, effects of admission time were reversed to a favorable outcome, as baseline consciousness levels got poorer in IS and ICH patients. These results may be inconsistent with the true values as a result of over stratification. Compared with patients with good consciousness level, patients with poor consciousness level could have been transferred to skilled hospitals by emergency medical services personnel and this may have led to this reverse effect of admission time, although we could not verify whether selective transfers existed in our dataset. Thus, health service managers must ensure that adequate stroke care is provided during off hours to promptly identify and treat severe stroke cases. Moreover, it is important to increase awareness among the general population about the appropriate facilities at Japanese hospitals for receiving stroke treatment in the acute phase.

In the sensitivity analyses, ICH patients admitted outside of working hours did not show robust results, but the effects of admission outside of working hours remained significant even when adjusted for baseline consciousness level among ICH patients. This is an important point because the numbers of hemorrhagic patients who are admitted outside of working hours are increasing. Although we could not measure any metrics of acute stroke care, our results suggest that the quality of acute stroke care provided by hospitals in Japan for hemorrhagic patients during the day are inconsistent. The results of a study published by the Get With The Guidelines-Stroke Program may support these findings; appropriate care and prevention were less frequently provided for ICH and SAH patients than for IS patients.<sup>34</sup> Systematic care processes for ICH and SAH may be poor during off-hours because of impaired healthcare systems, such as differential response times by night-shift workers and the presence of less skilled neurosurgeons, general physicians, residents, and paramedics.

We could not detect outcome differences for SAH patients probably because of the poor clinical prognosis associated with this stroke subtype. However, further studies that measure acute stroke care quality, such as prompt examination or available procedures during working hours and off hours, are necessary to verify this hypothesis.

This study has some limitations. Because the Japanese DPC/PDPS data were used, JCS scores were used to adjust for severity instead of the National Institute of Health Stroke Scale (NIHSS) or GCS.<sup>25,26</sup> However, our findings did not change even when data were adjusted by mRS at admission. Second, we used information on the occurrence of additional billings from the DPC/PDPS data to classify admission time; therefore, some data on the occurrence of additional billings were missing. We excluded subjects with missing values from analysis, and this may have biased our results. However, we believe that this exclusion does not alter our findings because severities of consciousness levels at admission and outcomes at discharge were not significantly different between subjects who were excluded and those who were included. Third, as for the classification of hospital admission time, we could not split the times in a more detailed manner because of data restriction, ie, daytime admissions during weekends and on national holidays were considered to be off-hour admissions. However, if patients admitted during this time exhibited less severe stroke symptoms or if hospitals during this time indeed provided better stroke care than at other off-hour times among off-hour, it could underestimate the effects of differences in severity on relationships between admission time and outcome at discharge. Fourth, although we collected nationwide data, we may have underestimated the relationship between admission time and outcomes because participating hospitals were certified training hospitals, which are considered to offer similar qualities of care. If hospitals that provide fewer resources and less professional stroke care were included in the analysis, stronger relationships may have been identified. Furthermore, we could not follow-up on post-discharge outcomes and we were unable to include multiple metrics representing acute stroke care quality, such as promptness or execution of specific procedures and protocols. Most studies have dealt with the inequality of care between working hours and off hours, such as reduced availability of highly skilled personnel and less access to urgent procedures, as the main reason for outcome disparity.<sup>2,3</sup> Further studies that focus on acute stroke care metrics are needed to better identify variability in care quality between admission times.

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