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The Relationships Among Regionalization, Processes, and Outcomes for Stroke Care

A Nationwide Population-based Study

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Abstract: Regionalization for stroke care, including stroke center designation, is being implemented in the United States, Canada, or other countries. Limited information is available, however, concerning the relationships among regionalization, processes, and outcomes for stroke care.

We examined the association of regionalization with processes and outcomes, and the mediating effect of processes of care on the association between regionalization and mortality for acute stroke in Taiwan.

We analyzed all 229,568 admissions with acute ischemic stroke from January 2004 to September 2012 through Taiwan's National Health Insurance Research Database.

Regionalized care for acute stroke has been implemented since July 2009 in Taiwan.

Rates of thrombolytic therapy within 3 hours after onset of ischemic stroke, average numbers of processes of care, and 30-day mortality rates at monthly intervals for baseline (66 months) and 39 months after the implementation of regionalization.

After accounting for secular trends and other confounders, changes in rates of thrombolytic therapy (level change 0.269% per month, $P = 0.017$ and trend change 0.010% per month, $P = 0.048$), average numbers of processes of care (trend change 0.001 per month, $P = 0.030$), and 30-day mortality rates (level change −0.442% per month, $P = 0.007$ and trend change −0.021% per month, $P = 0.015$) were attributable to regionalization. The processes of care were mediators of the association between regionalization and 30-day mortality after stroke.

Regionalization for stroke care may improve timeliness and processes of stroke care, including access to timely thrombolytic therapy from emergency medical services to hospital care, which may in turn enhance stroke outcomes.

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Abbreviations: ARIMA = autoregressive integrated moving average, DVT = Deep venous thrombosis, ED = emergency department, EMS = emergency medical services, ICU = intensive care unit, IV tPA = intravenous tissue plasminogen activator, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Stroke is the second leading cause of death worldwide.[1] Stroke mortality has in the United States been endorsed as an inpatient quality indicator by the Agency for Healthcare Research and Quality because of significant variations in the mortality among hospitals.[2] Regionalization for stroke care is designed to facilitate access to optimal stroke care across an entire region and to improve processes of stroke care, which leads to improved stroke outcomes. However, as far as we know, no study has examined the relationships among regionalization for stroke care, processes of stroke care, and stroke outcomes using nationwide population-based data.

One of the strategies to improve processes and outcomes of stroke care is to regionalize stroke care to ensure that all patients with signs or symptoms of stroke are transported to the nearest stroke designated hospital (stroke center), and given the available acute therapeutic interventions (especially thrombolytic therapy within 3 hours of ischemic stroke onset).[3–6] The regionalization of acute stroke care, which is a reality in the United States, Canada, and other countries, includes emergency medical services (EMS) training, pre-hospital triage to ensure that patients are taken only to designated hospitals, and the use of evidence-based treatment protocols.[5,7] Designated hospital programs are primarily according to the Brain Attack Coalition's recommendations for establishing comprehensive or primary stroke centers, which have the necessary staffing, infrastructure, and programs to treat patients with acute stroke.[3,8] Moreover, hospitals also have an incentive to become designated hospitals in order to ensure continued access to patients.[9] Prior research verified that stroke designated hospitals were associated with lower mortality[10] or more frequent use of thrombolytic therapy.[10,11] However, no study until now has specifically examined the relationships among regionalization, processes, and outcomes for stroke care.

In Taiwan, in order to improve processes and outcomes of care for time-sensitive, emergency conditions, regionalized care for acute stroke, acute coronary syndrome, trauma, and high-risk pregnant women and newborns has been implemented since July 2009. Stroke-designated hospitals are also classified as comprehensive or primary stroke centers that meet certain standards as Brain Attack Coalition's recommendations. The

national health insurance scheme has been implemented for the entire population since March 1995. The National Health Insurance Administration (NHIA) is the sole insurer. Patients enjoy comprehensive benefits with a low coinsurance policy (10% for inpatient care with a yearly cap of about US$1700). Patients are free to go to hospitals or clinics because almost all providers have contracts with the NHIA.[6] Therefore, Taiwan's health care system provides an excellent opportunity to examine the influence of regionalization for stroke care on processes of stroke care and stroke outcomes.

The primary goal of this study was to use nationwide population-based data from Taiwan from January 2004 to September 2012 with interrupted time-series designs to examine whether the implementation of regionalization had an association with processes of care and 30-day mortality for acute stroke. Our secondary objective was to examine whether processes of stroke care explained the association between regionalization for stroke care and 30-day mortality for acute stroke.

METHODS

Database

This study used the National Health Insurance Research Database (NHIRD), published by Taiwan's National Health Research Institutes. This dataset contains the detailed records of all hospital admissions and emergency/outpatient visits for each patient. The records include principal and secondary diagnosis codes, and prescription codes. Therefore, the NHIRD provides an opportunity to examine the associations among regionalization, processes, and outcomes for stroke care. This study was approved by the Institutional Review Board of the National Taiwan University Hospital.

Study Patients

All emergency hospitalizations aged 18 years or older for ischemic stroke between January 2004 and September 2012 were identified by the principal International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes 433 and 434. We excluded admissions that were transferred out to ensure accurate reporting of processes and outcomes of care.

Measures of Variables

Regionalized Care

The intervention of regionalized care was measured as whether the intervention has been implemented since July 2009. The nationwide regionalization for five time-sensitive, emergency conditions (including acute stroke) is a collaboration between the Ministry of Health and Welfare, the National Fire Agency, and the Joint Commission of Taiwan (previously the Taiwan Joint Commission of Hospital Accreditation), so the regionalization also includes pre-hospital triage and posthospital triage.[12–15] The Ministry of Health and Welfare plans, takes charge of, and evaluates the policy. The Joint Commission of Taiwan is responsible for the certification and audit of designated hospitals (comprehensive and primary stroke centers), which are assessed every 4 years for recertification. EMS personnel can preferentially transport patients with suspected stroke to the nearest designated hospitals capable of providing more treatment to patients with stroke. Some of the patients may arrive at an ED via private car, taxi, or another mode of transportation (other than an ambulance). In this case, the ED triage component is also of key importance for improving access to acute stroke care. In addition to public reporting of the list of these designated hospitals, hospitals have an incentive to become designated hospitals in order to ensure continued access to patients.[9]

Process Measures

Our process measures included the rate of receiving thrombolytic therapy and the average number of processes of care for ischemic stroke. Because the main objective of regionalization for stroke care is to increase the use of thrombolytic therapy, the rate of receiving thrombolytic therapy was measured as the number of admissions who received intravenous tissue plasminogen activator (IV tPA) within 3 hours after their symptoms started divided by the number of admissions during the study period.[10,11,16] We were able to measure the exact timing of the use of thrombolytic therapy because the NHIA only reimburses the use of IV tPA within 3 hours of ischemic stroke onset. Thrombolytic therapy for acute ischemic stroke has been reimbursed since January 2004.

The average number of processes of care was measured because of the inverse dose–response association between the number of care processes and mortality.[17] On the basis of process measures for stroke care used by the Centers for Medicare and Medicaid Services,[18] we used available process indicators in our analysis: thrombolytic therapy, antithrombotic use, statin use, and rehabilitation assessment.[6] Deep venous thrombosis (DVT) prophylaxis was not adopted because DVT is rarer in Asians.[19] Stroke education is not used because there is no individual reimbursement. Antithrombotic/statin use was defined as prescription of the medication during hospital stays and at discharge. The rehabilitation assessment was defined as use of the service during a stay in hospital. The maximum number of processes of care was therefore only 4.

Death from Any Cause at 30 Days

Our outcome measure was the 30-day mortality rate (calculated as the total number of deaths from any cause within 30 days after hospitalization divided by the number of admissions during the study period).

Covariates

The covariates included patient and hospital characteristics, cuts in reimbursement, month of admission, and time trends based on previous related studies.[10,20–26] To control for changes in trends in patient characteristics that might influence trends in processes and outcomes of care for stroke, the proportion of male patients, average age, average index of comorbid conditions, rate of surgery, and rate of using intensive care units (ICUs) were included. The Charlson–Deyo index was used to quantify the comorbidities of stroke patients. This index was the sum of weighted scores based on the presence or absence of 17 different medical conditions. Cerebrovascular disease and hemiplegia were excluded, however, because they were reflected in the condition we were evaluating.[21] The higher the scores, the greater the comorbidity burden. The use of ICU was regarded as a surrogate for severe stroke.[20,22,23,26] The hospital covariate was the proportion of admissions to high-volume hospitals because high hospital volume was associated with lower mortality.[22] For hospital volume, each admission was linked with the number of admissions admitted to that hospital in the calendar year. These ''annualized'' volumes were then divided into tertiles (low, medium, and high volumes).

Reimbursement cuts were measured as the monetary value of each point because larger cuts (the smaller monetary value of each point) were associated with higher mortality[25] and increased use of certain processes of care with high profit margins.[26] The month of admission was regarded as 1 covariate because previous studies indicated significant seasonal variation in stroke mortality.[27–31] The linear time trend was also included to capture all omitted trending variables, such as advances in medicine and medical technology, and to separate these variables from the impact of regionalized care.

Statistical Analysis

We used an interrupted time-series analysis with a longitudinal quasi-experimental design to evaluate the relationships among regionalized care, processes of care, and 30-day mortality for acute ischemic stroke at the population level.[26,32–35] Using segmented autoregressive integrated moving average (ARIMA) models, we examined the changes in the rate of receiving thrombolysis, average number of processes of care, and 30-day mortality rate in each month. After controlling for baseline levels, trends, and other covariates, we used the models to estimate changes in the levels and trends of the values after the implementation of regionalized care. The unit of analysis was time in months. The data were aggregated across the whole country at the population level, so there were 105 monthly measures of processes of care and 30-day mortality rate.

A segmented ARIMA analysis can examine the changes in levels and trends that follow an intervention. A change in level, for example, a jump or drop in the outcome after the intervention, constitutes an abrupt intervention effect. A change in trend is defined by an increase or decrease in the slope of the segment after the intervention compared with the segment preceding the intervention. The Ljung-Box Q statistic was also used to evaluate the null hypothesis that the residuals are white noise, that is, that the model fits the data well.[36] In an adequate fit model, the null hypothesis is not rejected. Because we used aggregated time series data at population level, our analyses were not affected by clustering bias and could directly estimate overall effects on the population.[37,38] Monthly risk-adjusted mortality rates were calculated as the actual rate minus the estimated rate based on the statistical model.[39]

We also used segmented ARIMA models to test whether the mediating role of processes of care could account for the relationship between regionalized care and 30-day mortality for stroke.[40] The following criteria of the mediation effect had to be met: (1) regionalized care significantly influenced processes of care, (2) processes of care significantly affected 30-day mortality, and (3) after controlled for processes of care, a previously significant relationship between regionalized care and 30-day mortality was no longer significant. The difference between confounders and mediators is that confounders are not intermediate variables in a causal pathway. Processes of care should not be adjusted for in the analysis of the relationship between regionalized care and 30-day mortality, because controlling for processes of care would result in underestimating the relationship between regionalized care and 30-day mortality.[41,42]

All analyses were conducted using SAS software, version 9.2 and SPSS software, version 20. A 2-tailed significance level of 0.05 was used to determine statistical significance.

RESULTS

Table 1 presents the characteristics of the study population. Among 229,568 patients with acute ischemic stroke, 134,461 were admitted before the implementation of regionalized care and 95,107 after the implementation.

Figure 1 exhibits monthly trends in processes of care and risk-adjusted mortality rates for acute ischemic. Before regionalization, there was a rising trend in rate of thrombolytic therapy; after regionalization, the increasing rate became much higher. The percentage of admissions receiving thrombolytic therapy increased from 0.3% in January 2004 to 2.1% in January 2009 and then increased more rapidly to 4.6% in January 2012. The average number of processes of care showed an increasing trend before regionalization, after which the trend sped up. The average number of processes of care increased slightly from 1.61 in January 2004 to 1.74 in January 2009 and then increased rapidly to 1.90 in January 2012. After regionalization, risk-adjusted mortality rates were all below 0%, and fell gradually.

Table 2 presents the results of the segmented ARIMA analyses examining the relationship between regionalized care and processes of stroke care. ARIMA(3,0,1) models (third-order autoregressive combined with first-order moving average with no differencing) were used. Before regionalization, there was a significant month-to-month change in the nationwide rate of receiving thrombolysis (P value for baseline trend <0.001), and the increasing rate of thrombolytic therapy was 0.023% per month. Right after regionalization, the rate of receiving thrombolysis jumped abruptly by 0.269% per month ($P = 0.017$). The increasing rate of receiving thrombolysis after regionalization

TABLE 1. Basic Characteristics of Patients With Stroke Before and After Regionalization of Stroke Care

	Before Regionalization	After Regionalization	*P*
Number of patients	134,461	95,107	
Male, %	59.7	60.3	0.004
Age, mean, y	68.7	69.4	<0.001
Charlson score (mean)	0.68	0.69	0.001
Surgery, %	1.7	2.0	<0.001
ICU use, %	15.4	19.3	<0.001
High-volume hospitals (%)	38.6	38.4	0.179
Cuts in reimbursement			
Monetary value per 100 points (mean)	92.9	93.4	<0.001
Processes of care			
Thrombolytic therapy within 3 hours of stroke onset (%)	0.9	3.1	<0.001
Number of processes of care (mean)	1.7	1.9	<0.001
Patient outcomes			
30-day mortality, %	4.4	4.6	0.042

ICU = intensive care unit.

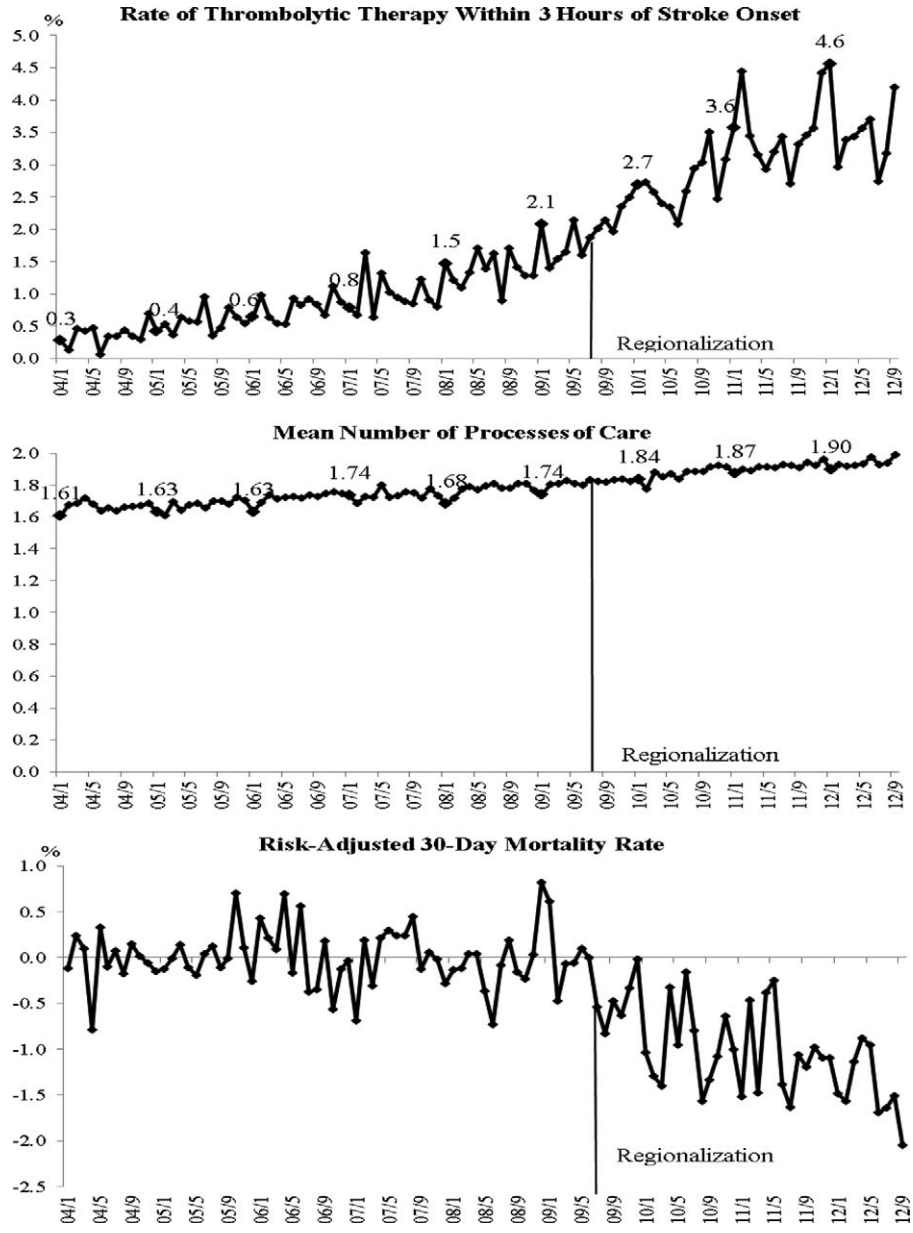

FIGURE 1. Processes and outcomes of stroke care by month.

was 0.010% per month compared with the monthly trend before regionalization ($P = 0.048$), so the increasing rate became higher (0.033% per month). The average increasing number of processes of care before regionalization was 0.002 per month ($P < 0.001$); after regionalization, the average number increased more rapidly (trend change, 0.001 per month, $P = 0.030$).

Table 3 presents the results of the segmented ARIMA analyses examining the relationship between regionalized care and 30-day mortality, and the mediating effect of processes of care in the relationship between regionalized care and 30-day mortality. Before regionalization, there was no significant month-to-month change in the nationwide 30-day mortality rate for stroke. After regionalization, the mortality rate dropped abruptly by 0.442% per month ($P = 0.007$) and showed a decreasing trend at a rate of 0.021% per month ($P = 0.015$), which equated to a total reduction of 828 deaths during the 39 months. In other words, the implementation of regionalization was associated with saved 828 lives (16% of potential deaths). According to mediational analysis, the number of processes of care was a mediator between regionalized care and the trend in 30-day mortality.

DISCUSSION AND CONCLUSION

Our study used nationwide longitudinal population-based data and quasi-experimental study designs to evaluate the relationship of regionalization to processes and outcomes for stroke care, and the mediating role of processes of care in the

TABLE 2. Segmented Autoregressive Integrated Moving Average Analysis of Processes of Stroke Care*

	Rate of Thrombolytic Therapy Within 3 hours of Stroke Onset (%)†			Mean Number of Processes of Care‡		
	β	SE	*P*	β	SE	*P*
Baseline trend	0.023	0.003	<0.001	0.002	0.000	<0.001
Level change after regionalization	0.269	0.110	0.017	0.008	0.011	0.464
Trend change after regionalization	0.010	0.005	0.048	0.001	0.001	0.030
Percentage of male patients, %	0.042	0.030	0.169	0.002	0.002	0.292
Mean patient age	0.053	0.143	0.714	0.003	0.009	0.744
Mean Charlson score	−0.863	1.352	0.525	0.254	0.097	0.011
Surgery use rate, %	0.040	0.100	0.687	0.002	0.007	0.751
ICU use rate, %	0.125	0.038	0.002	0.005	0.003	0.090
Percentage of admission to high-volume hospitals, %	−0.005	0.016	0.772	0.003	0.001	0.036
Mean monetary value per 100 points	−0.064	0.024	0.008	−0.001	0.002	0.676
January	0.265	0.152	0.084	−0.044	0.011	<0.001
February	0.084	0.174	0.629	−0.029	0.011	0.008
March	0.118	0.181	0.516	0.012	0.010	0.257
April	0.090	0.201	0.655	−0.001	0.013	0.961
May	0.181	0.203	0.374	0.006	0.013	0.657
June	0.096	0.209	0.646	−0.004	0.013	0.758
July	0.021	0.212	0.923	−0.003	0.013	0.806
August	−0.112	0.220	0.612	0.002	0.013	0.853
September	0.157	0.217	0.473	0.005	0.012	0.682
October	0.109	0.200	0.589	0.002	0.012	0.887
November	−0.096	0.168	0.572	0.013	0.012	0.315
AR1	1.043	0.168	<0.001	0.070	0.657	0.916
AR2	−0.298	0.171	0.085	0.083	0.135	0.541
AR3	−0.016	0.133	0.904	0.166	0.129	0.203
MA1	0.997	1.152	0.389	0.185	0.662	0.780
Intercept	−1.330	10.106	0.896	1.073	0.655	0.105

AR = autoregressive, ICU = intensive care unit, MA = moving average.

*All the models passed the Ljung–Box Q test.

†Outcome is monthly rate of thrombolytic therapy within 3 hours of stroke onset, measured in percentage. Thus, the unit of the coefficient is percent. For example, a unit increase in the percentage of ICU use is associated with a 0.125% increase in monthly rate of thrombolytic therapy within 3 hours of stroke onset.

‡Outcome is monthly mean number of processes of care. For example, a unit increase in the mean Charlson score is associated with a 0.254 increase in monthly mean number of processes of care.

relationship between regionalization and stroke outcomes. A simple before-and-after analysis would have produced spurious effects of regionalization due to the lack of control for secular trends and other covariates. The study, using a time-series analysis, showed that the implementation of regionalized care had an effect on processes of care and 30-day mortality, and processes of care could account for the relationship between regionalized care and 30-day mortality for acute stroke care.

The findings of the increased level of and the increasing trend in the rate of thrombolytic therapy, and the increasing trend in the number of processes of care after regionalization are similar to the findings of Rost et al[4] and Kapral et al.[7] One possible reason for the increase in thrombolysis is that regionalization for stroke care is implemented for treating patients with acute ischemic stroke to rapidly identify and treat them with thrombolytic therapy. The regionalization includes EMS training, pre-hospital triage, post-hospital triage, and the use of evidence-based treatment protocols to transport the patients to designated hospitals capable of performing thrombolysis within 3 hours after stroke onset. Moreover, certification, audit, and recertification of designated hospitals (comprehensive and primary stroke centers) include assessment of processes of care, especially the use of thrombolytic therapy. Therefore, it is possible that the implementation of regionalized care can improve the use of timely thrombolytic therapy and other processes of care. However, there is still room to improve the rate of thrombolytic therapy. The time from symptom onset to arrival at an ED is the greatest source of delay and a frequent cause of ineligibility for acute reperfusion therapies, which also occurs in the United States.[43,44] More specifically, a lack of patient and public awareness of stroke signs and symptoms is the main cause for delayed patient presentation to an ED. Therefore, to reduce the time delay and increase the number or percentage of patients who may be eligible for acute therapies, Taiwan Ministry of Health and Welfare also starts to improve public education about stroke symptoms and the need for rapid care.

The findings of the decreased level of and the decreasing trend in the 30-day mortality rate after regionalization are consistent with the finding of Kapral et al.[7] Further, we found

TABLE 3. Segmented Autoregressive Integrated Moving Average Analysis of 30-day Mortality[*,†]

	Model 1			Model 2[‡]		
	β	SE	*P*	β	SE	*P*
Baseline trend	0.003	0.004	0.500	0.012	0.006	0.049
Level change after regionalization	−0.442	0.159	0.007	−0.400	0.163	0.016
Trend change after regionalization	−0.021	0.008	0.015	−0.016	0.009	0.077
Mean number of processes of care	—	—	—	−4.059	1.787	0.026
Percentage of male patients, %	−0.011	0.033	0.734	−0.004	0.033	0.901
Mean patient age	−0.143	0.163	0.381	−0.140	0.156	0.371
Mean Charlson score	0.238	1.649	0.886	1.786	1.770	0.316
Surgery use rate, %	0.159	0.114	0.166	0.165	0.110	0.138
ICU use rate, %	0.272	0.048	<0.001	0.287	0.045	<0.001
Percentage of admission to high-volume hospitals, %	−0.048	0.020	0.016	−0.037	0.020	0.074
Mean monetary value per 100 points	−0.137	0.034	<0.001	−0.145	0.035	<0.001
January	0.676	0.200	0.001	0.499	0.208	0.019
February	0.420	0.228	0.070	0.300	0.226	0.187
March	0.249	0.193	0.201	0.296	0.187	0.118
April	0.236	0.224	0.295	0.222	0.221	0.317
May	−0.237	0.232	0.311	−0.222	0.227	0.331
June	−0.353	0.240	0.144	−0.381	0.232	0.104
July	−0.325	0.238	0.176	−0.348	0.232	0.138
August	−0.730	0.233	0.002	−0.724	0.229	0.002
September	−0.422	0.227	0.067	−0.410	0.219	0.065
October	−−0.331	0.255	0.199	−0.332	0.246	0.182
November	−0.541	0.215	0.014	−0.494	0.209	0.020
AR1	−0.512	0.784	0.516	−0.498	0.557	0.374
AR2	−0.342	0.126	0.008	−0.307	0.127	0.018
AR3	−0.089	0.330	0.789	−0.047	0.249	0.852
MA1	−0.548	0.771	0.480	−0.570	0.541	0.296
Intercept	24.937	11.426	0.032	29.936	11.123	0.009

AR = autoregressive, ICU = intensive care unit, MA = moving average.

[*]All the models passed the Ljung–Box Q test.

[†]Outcome is monthly rate of 30-day mortality, measured in percentage. Thus, the unit of the coefficient is percent. For example, a unit increase in the percentage of ICU use is associated with a 0.272% increase in monthly rate of 30-day mortality.

[‡]In Model 2, the mean number of processes of care was added as a mediator.

that processes of care could explain the relationship between regionalization and 30-day mortality. One possible explanation is that regionalization for stroke care makes stroke patients receive more timely and effective care, which could lead to lower mortality. Moreover, because of designated hospital certification and preferential EMS routing of suspected patients with stroke to designated hospitals, EMS routing policies might provide an incentive for designated hospital certification to continue access to patients.[9] To pass certification, audit, and recertification of designated hospitals, designated hospitals would continue to enhance processes of care, which could in turn improve outcomes.

Some limitations of our study merit emphasis. First, in common with previous stroke studies using administrative databases,[10,20–26] we were unable to adjust for stroke severity because this variable was not captured in administrative data sources. Nevertheless, we adjusted for key prognostic variables, including patient sex, age, comorbid conditions, surgical operation, and ICU use, which are also important for the adjustment of stroke complexity.[10,20–26] The use of ICU is regarded as a proxy for severe stroke.[20,22,23,26] Second, we lacked data on the exact timing of use of processes of care except for thrombolytic therapy, such as antithrombotic use within 2 days of arriving at the hospital,[18] so we could not assess the mediating effects of these process measures on the association between regionalization and outcomes. Third, no information on arrival by EMS was available in the NHIRD, so we could not assess whether the mechanism underlying the relationship between regionalization and reduced mortality was through an increase in the use of EMS.

Our national population-based study showed the overall effect of regionalization on processes and outcomes for stroke care, and the mediating role of processes of care in the relationship between regionalization and stroke outcomes. Our findings may provide support for the ongoing development and implementation of regionalization for stroke care, including a stroke center designation program. Regionalization may be a feasible and effective strategy for timely and critical stroke care and better care outcomes.

REFERENCES

1. World Health Organization. The Top 10 Causes of Death. 2012. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed July 6, 2014.

2. Agency for Healthcare Research and Quality. Inpatient Quality Indicators: Technical Specifications. 2015. Available at: http://www.qualityindicators.ahrq.gov/Modules/IQI_TechSpec.aspx. Accessed March 31, 2015.
3. Schwamm LH, Pancioli A, Acker JE, et al. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the development of stroke systems. *Circulation.* 2005;111:1078–1091.
4. Rost NS, Smith EE, Pervez MA, et al. Predictors of increased intravenous tissue plasminogen activator use among hospitals participating in the Massachusetts Primary Stroke Service Program. *Circ Cardiovasc Qual Outcomes.* 2012;5:314–320.
5. Higashida R, Alberts MJ, Alexander DN, et al. Interactions within stroke systems of care: a policy statement from the American Heart Association/American Stroke Association. *Stroke.* 2013;44:2961–2984.
6. Tung YC, Jeng JS, Chang GM, et al. Processes and outcomes of ischemic stroke care: the influence of hospital level of care. *Int J Qual Health Care.* 2015;27:260–266.
7. Kapral MK, Fang J, Silver FL, et al. Effect of a provincial system of stroke care delivery on stroke care and outcomes. *CMAJ.* 2013;185:E483–E491.
8. Alberts MJ, Latchaw RE, Selman WR, et al. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke.* 2005;36:1597–1616.
9. Schuberg S, Song S, Saver JL, et al. Impact of emergency medical services stroke routing protocols on Primary Stroke Center certification in California. *Stroke.* 2013;44:3584–3586.
10. Xian Y, Holloway RG, Chan PS, et al. Association between stroke center hospitalization for acute ischemic stroke and mortality. *JAMA.* 2011;305:373–380.
11. Gropen TI, Gagliano PJ, Blake CA, et al. Quality improvement in acute stroke: the New York State Stroke Center Designation Project. *Neurology.* 2006;67:88–93.
12. Ministry of Health and Welfare. Regionalization for Stroke Care. 2015. Available at: http://www.mohw.gov.tw/cht/DOMA/DM1_P.aspx?f_list_no=608&fod_list_no=772&doc_no=51568. Accessed January 6, 2016.
13. Ministry of Health and Welfare. Emergency Medical Services. 2014. Available at: http://www.mohw.gov.tw/cht/DOMA/DM1.aspx?f_list_no=608&fod_list_no=774. Accessed January 6, 2016.
14. National Fire Agency. Emergency Medical Services. 2014. Available at: http://www.nfa.gov.tw/main/Content.aspx?ID=2&MenuID=665. Accessed January 6, 2016.
15. Joint Commission of Taiwan. Designated Hospital Certification. 2015. Available at: http://www.tjcha.org.tw/FrontStage/page.aspx?ID=FF2E2252-F2AA-4573-9D7A-A00152BA9A63. Accessed January 6, 2016.
16. Ministry of Health and Welfare. Criteria of Designated Hospitals. 2015. Available at: http://www.mohw.gov.tw/cht/DOMA/DM1.aspx?f_list_no=608&fod_list_no=3785. Accessed January 6, 2016.
17. Ingeman A, Pedersen L, Hundborg HH, et al. Quality of care and mortality among patients with stroke: a nationwide follow-up study. *Med Care.* 2008;46:63–69.
18. Centers for Medicare & Medicaid Services. Hospital Compare: Timely and Effective Care. 2014. Available at: http://www.medicare.gov/hospitalcompare/about/timely-effective-care.html. Accessed July 22, 2014.
19. Tan SS, Venketasubramanian N, Ong PL, et al. Early deep vein thrombosis: incidence in Asian stroke patients. *Ann Acad Med Singapore.* 2007;36:815–820.
20. Rundek T, Nielsen K, Phillips S, et al. Health care resource use after acute stroke in the Glycine Antagonist in Neuroprotection (GAIN) Americas trial. *Stroke.* 2004;35:1368–1374.
21. Goldstein LB, Samsa GP, Matchar DB, et al. Charlson index comorbidity adjustment for ischemic stroke outcome studies. *Stroke.* 2004;35:1941–1945.
22. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it matter? *Neurology.* 2007;69:1142–1151.
23. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke fatality in Canada. *Stroke.* 2008;39:3360–3366.
24. Tung YC, Chang GM, Chen YH. Associations of physician volume and weekend admissions with ischemic stroke outcome in Taiwan: a nationwide population-based study. *Med Care.* 2009;47:1018–1025.
25. Tung YC, Chang GM. The effect of cuts in reimbursement on stroke outcome: a nationwide population-based study during the period 1998 to 2007. *Stroke.* 2010;41:504–509.
26. Tung YC, Chang GM, Cheng SH. Long-term effect of fee-for-service-based reimbursement cuts on processes and outcomes of care for stroke: interrupted time-series study from Taiwan. *Circ Cardiovasc Qual Outcomes.* 2015;8:30–37.
27. Lanska DJ, Hoffmann RG. Seasonal variation in stroke mortality rates. *Neurology.* 1999;52:984–990.
28. Sheth T, Nair C, Muller J, et al. Increased winter mortality from acute myocardial infarction and stroke: the effect of age. *J Am Coll Cardiol.* 1999;33:1916–1919.
29. Nakaji S, Parodi S, Fontana V, et al. Seasonal changes in mortality rates from main causes of death in Japan (1970–1999). *Eur J Epidemiol.* 2004;19:905–913.
30. Myint PK, Vowler SL, Woodhouse PR, et al. Winter excess in hospital admissions, in-patient mortality and length of acute hospital stay in stroke: a hospital database study over six seasonal years in Norfolk, UK. *Neuroepidemiology.* 2007;28:79–85.
31. Wang Y, Levi CR, Attia JR, et al. Seasonal variation in stroke in the Hunter Region, Australia: a 5-year hospital-based study, 1995–2000. *Stroke.* 2003;34:1144–1150.
32. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther.* 2002;27:299–309.
33. Ramsay CR, Matowe L, Grilli R, et al. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. *Int J Technol Assess Health Care.* 2003;19:613–623.
34. Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis.* 2007;45:901–907.
35. Serumaga B, Ross-Degnan D, Avery AJ, et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. *BMJ.* 2011;342:d108.
36. Ljung GM, Box GEP. On a measure of lack of fit in time series models. *Biometrika.* 1978;65:297–303.
37. Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-experimental Designs for Generalized Causal Inference. Boston, MA: Houghton Mifflin; 2002.
38. Kerr WC, Karriker-Jaffe K, Subbaraman M, et al. Per capita alcohol consumption and ischemic heart disease mortality in a panel of US states from 1950 to 2002. *Addiction.* 2011;106:313–322.
39. Shumway RH, Stoffer DS. Time Series Analysis and Its Applications. New York, NY: Springer; 2011.
40. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986;51:1173–1182.

41. Sterne J, Kirkwood BR. Essential Medical Statistics. Hoboken, NJ: Wiley-Blackwell; 2010.
42. Reid CE, Snowden JM, Kontgis C, et al. The role of ambient ozone in epidemiologic studies of heat-related mortality. *Environ Health Perspect.* 2012;120:1627–1630.
43. Morris DL, Rosamond W, Madden K, et al. Prehospital and emergency department delays after acute stroke: the Genentech Stroke Presentation Survey. *Stroke.* 2000;31:2585–2590.
44. Centers for Disease Control, Prevention. Prehospital and hospital delays after stroke onset—United States, 2005–2006. *MMWR Morb Mortal Wkly Rep.* 2007;56:474–478.