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Association Between Hospital Volume, Process of Care, and Outcomes after Acute Ischemic Stroke: A Retrospective Observational Study

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Abstract

Objectives Uncertainty remains about hospital volume and clinical outcomes for patients with stroke. The study was aimed to assess the association between hospital volume, process of care, and outcomes after ischemic stroke.

Methods The patients with acute ischemic stroke from China National Stroke Registry II were included in this study. According to quartiles of the hospital volume, the patients were categorized into four groups. We compared the difference in the process of care across the groups. We used Cox proportional hazard models and generalized estimating equations to estimate the effect of hospital volume on 1-year mortality and poor outcome, respectively. Hazard ratios or odds ratios and corresponding 95% confidence intervals were used to qualify the association between hospital volume and outcomes with the highest quartile as reference. We also used restricted cubic splines to model the association between hospital volume and clinical outcomes.

Results A total of 16,651 ischemic strokes from 133 hospitals across China were included. The were no significant differences in process of care across the four groups. The hazard ratio of 1-year mortality was 1.39 (95%CI, 1.08-1.79) for Q1, 0.99 (95%CI, 0.77-1.27) for Q2, 1.16 (95%CI, 0.93-1.44) for Q3, compared with Q4. When adjusted for other confounders, the effect of hospital volume on mortality was not significant. However, compared with the highest quartile, the patients in the lowest quartile of hospital volume tend to be with poor outcome at 1 year (OR, 1.36; 95% CI, 1.05-1.77; P=0.0221) after adjusting for confounders. The restricted cubic spline analyses suggested a U-shaped relationship between hospital volume and poor outcome.

Conclusions We found no significant associations between hospital volume, the process of care at the hospital, and 1-year mortality in patients with ischemic stroke. However, hospital volume may be associated with poor outcome at 1 year.

Strengths and limitations of this study

The number of participants with ischemic stroke was large and 133 hospitals across China were included.

This is the first time the association between stroke volume, process of care and poor outcome was explored in China.

Some process of care, especially the process of care after discharge, cannot be obtained in this study.

The hospitals participated were volunteers and unavoidable selection bias may exist.

Introduction

Previous studies have shown that the number of patients treated in a hospital (hospital volume) may be associated with outcomes in specific surgical procedures involving aortic valve replacement, carotid endarterectomy, coronary artery bypass surgery, and cancer-related surgeries.[1-5] The volume-outcome relationship is also described in some medical conditions, including heart failure, acute myocardial infarction, pneumonia, and brain injury.[6-8] The magnitude of the association was varied significantly in studies.[9] If there were inverse relation between hospital volume and outcomes, it was of significance to make volume-based referral strategies.[10] Several studies have examined the association between hospital stroke volume and mortality for stroke patients. However, the results were controversial. Some[11, 12] found that stroke patients in high-volume hospitals had decreased case fatality, but some[13, 14] were not. What's more, most of the studies evaluated the short-term mortality, and limited data exist to characterize the associations between hospital volume and long-term mortality and poor outcome.

We hypothesize that the hospitals with higher volume may character with high quality of care, which in turn improved the prognosis of patients with stroke. In this study, we aimed to examine the association between hospital stroke volume and outcomes, including mortality and poor outcome at 1 year after stroke onset. We also examined the association between hospital stroke volume and the process of care for ischemic stroke.

Methods

Ethics approval

This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-005-01). The rewritten informed consent was obtained from the patients or their relatives.

Study Design and Setting

This retrospective analysis used data from the China National Stroke Registry II (CNSR II), which was a national multicenter hospital-based cohort study. CNSR II was launched in June 2012 in China and the primary objectives were to evaluate the delivery of stroke care and identify suboptimal performance metrics to be improved.[15] The hospitals were selected based on similar criteria in CNSR I launched in 2007, which had been published elsewhere.[16] After assessing the hospital characteristics, such as location, teaching status, number of beds, and annual stroke discharges by the steering committee, a total of 219 hospitals were included in CNSR II.[17]

Study Population

The patients were consecutively recruited from June 2012 to January 2013. The inclusion criteria were as follow (1) age 18 years or above; (2) presented within seven days of the index event of acute ischemic stroke (AIS), transient ischemic attack (TIA), intracerebral hemorrhage, or subarachnoid hemorrhage, confirmed by brain computed tomography or magnetic resonance imaging; (3) direct hospital admission from a physician’s clinic or emergency department. A total of 25,018 patients were included in CNSR Ⅱ, of them 19,604 were AIS.

Considering the representativeness of the included patients, we excluded those hospitals in which the number of patients included in the study was less than 10% of annual stroke discharges. We also excluded the patients who were lost to follow-up at 1 year. Finally, 16,651 patients with AIS from 133 hospitals were included to investigate the association between hospital volume, the process of care, and outcomes.

Data Collection

Data were collected following a standardized form by trained research coordinators. The information on demographics, health insurance, education, smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and medication history were abstracted from medical records. National Institutes of Health Stroke Scale (NIHSS) at admission and modified Rankin Scale (mRS) prior to the index event were assessed through a face-to-face interview.

Hospital stroke volume was defined as the annual number of stroke discharges. The annual stroke discharges of each hospital were obtained via the hospital survey when they applied to participate in this study. Additionally, the hospital characteristics including location, academic status, and the number of beds were obtained by the survey.

Process Measures

We selected nine guideline-recommended process measures according to the national guideline and the Get With The Guidelines-Stroke (GWTG-Stroke).[18] There were three acute phage process measures, including (1) antithrombotics within 2 days after admission, (2) deep vein thrombosis (DVT) prophylaxis, and (3) dysphagia screening. There were six process measures at discharge, including (1) antithrombotic medication, (2) antihypertensive medication for patients with hypertension, (3) hypoglycemic medication for patients with diabetes, (4) anticoagulation for atrial fibrillation, (5) lowering low-density lipoprotein cholesterol (LDL-C) medication, and (6) smoking cessation. The definitions of the process measures were shown in Supplemental Table 1. Additionally, we calculated a binary defect-free measure of care, which was defined as the patient receiving all the processes for which they were eligible.[19, 20] Process measures are applied only to eligible patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.[21]

Clinical Outcomes

According to the study protocol, all patients were followed up at 3, 6, and 12 months by telephone or face-to-face interview. Trained research coordinators collected the clinical outcomes. In this study, the primary outcomes were all-cause mortality and poor outcome at 1 year. The poor outcome was defined as mRS of 3 to 6.

Statistical Analysis

The patients were categorized into four groups according to the quartiles of hospital volume: Q1 (<264 /year), Q2 (264-370 /year), Q3 (371-508 /year), Q4 (>508 /year). Continuous variables were described as mean ± standard deviation (SD) or median and interquartile range. Categorical variables were described as proportions. The patient characteristics were compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, in order to obtain the P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for continuous variables and Cochran-Mantel-Haenszel row mean scores for categorical variables.

The generalized estimating equations with exchangeable working correlation matrix were used to evaluate the association between hospital volume, the process of care, and poor outcome adjusting for the cluster effect within the hospital. In the adjusted models, age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, and hospital characteristics (academic status and location) were included. Additionally, the composite measure of care was included in the adjusted model when estimating the association between hospital volume and outcomes. We used the Kaplan-Meier method to depict the cumulative hazards of all-cause mortality. Cox proportional hazards model was used to estimate the association between hospital volume and mortality. In order to adjust for the intra-hospital correlation, the hospitals were added as clusters in the model and the robust sandwich variance estimator was used to deal with the correlation. ORs or HRs and corresponding 95% confidence intervals (CIs) were used with the hospital volume of Q4 as reference. Additionally, we used restricted cubic splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the association between hospital volume and mortality and poor outcome. We tested for non-linearity by using the Wald statistics.

All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P values were two-tailed with a significant level of 0.05.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

A total of 16,651 patients with AIS from 133 hospitals across China were included in this study. Patients included in the study and those excluded were largely comparable (Supplemental Table 2). Table 1 described the baseline characteristics of the included hospitals and patients.

Of the 133 included hospitals, 73 (54.9%) were teaching hospitals, and the high-volume hospitals were likely to be teaching hospitals. There were 76 hospitals in the east of China, 35 in the middle of China, and 22 in the west of China. The average hospital volume was 441 per year, ranging from 136 to 1334 per year.

The mean age was 65.0±12.0 and 62.9% of the patients were males. The median NIHSS at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared with the high-volume hospitals, there were more females and the patients were older in low-volume hospitals. The patients in high-volume hospitals were more likely to be with diabetes and hyperlipidemia, but less likely to be with atrial fibrillation. The proportions of taking antiplatelet and lipid-lowing medicine were higher in high-volume hospitals than that in low-volume hospitals.

Association between Hospital Volume and Process Measures

Compared with the hospitals of Q4, the unadjusted OR of defect-free measure of care was 0.83 (95% CI, 0.54-1.27) for Q1, 0.97 (95% CI, 0.65-1.46) for Q2, and 1.00 (95% CI, 0.66-1.52) for Q3. No significant difference was found in individual process measures, except the anticoagulation for AF for Q1 (OR, 0.53; 95% CI, 0.29-0.98; P=0.044) (Supplemental Table 3).

Table 2 shows the adjusted ORs for process measures. After adjusting for the patients and hospital characteristics, the adjusted OR of defect-free measure of care was 0.71 (95% CI, 0.41-1.23) for Q1, 0.99 (95% CI, 0.60-1.64) for Q2, and 0.81 (95% CI, 0.48-1.38) for Q3. All the individual performance measures show no significant association (all P >0.05).

Association between Hospital Volume and Clinical Outcomes

There were 1397 patients who died and 3434 patients experienced the poor outcome at 1 year after stroke onset. The Kaplan-Meier plot for mortality at 1 year was shown in Figure 1. The unadjusted Cox proportional hazard models showed HR of mortality was 1.08 (95%CI, 1.08-1.79) for Q1, 0.99 (95%CI, 0.77-1.27) for Q2, and 1.16 (95%CI, 0.93-1.44) for Q3, with Q4 as reference. However, after adjusting for patient, hospital characteristics, and process of care, no significant associations were observed (HR, 1.24; 95% CI, 0.94-1.63 for Q1; HR, 0.94; 95% CI, 0.73-1.21 for Q2; HR, 1.06; 95% CI, 0.86-1.31 for Q3).

Figure 2 displayed the rates of poor outcome at 1 year by quartiles of hospital volume. Compared with Q4, the rate of poor outcome was significantly higher in Q1 hospitals, but not in Q2 and Q3 hospitals (unadjusted OR, 1.40; 95%CI, 1.16-1.70 for Q1; unadjusted OR, 0.98; 95%CI 0.80-1.20 for Q2; unadjusted OR, 1.06, 95%CI, 0.90-1.25 for Q3). When adjusted for the covariates, the rate of poor outcome was still higher in Q1 hospitals compared with Q4 hospitals (adjusted OR, 1.36; 95%CI, 1.05-1.77), but not in Q2 and Q3 (Table 3).

In Figure 3, we used restricted cubic splines to flexible model and visualize the relation of all-cause mortality and poor outcome with hospital stroke volume. The multivariable-adjusted restricted cubic splines suggested a "J-shaped" association between volume and all-cause mortality and a "U-shaped" association between volume and poor outcome. The analyses indicated a significant nonlinear association between volume and poor outcome (P for non-linear <0.001), but not all-cause mortality (P for non-linear = 0.472).

Discussion

Our analysis of a large population of 16,651 patients with ischemic stroke suggested that no significant difference in the process of care was observed for patients in lower-volume hospitals in comparison with higher-volume hospitals. There was no association between hospital volume and mortality at 1 year after stroke onset. In contrast, we found the patients in the lowest volume quartile had a significantly higher rate of poor outcome at 1 year compared with the highest quartile.

Previous studies found that high volume was associated with improved outcomes suggesting that volume may be a surrogate for quality of care. The quality of care can be assessed from outcome, process, and structure.[22] Usually, hospital volume is used as a structure metric of quality of care. However, the underlying mechanisms of interplay between structure and process are complex.[23] Two existing studies[13, 23] showed that the patients in high-volume hospitals received more process of care compared with patients in low-volume hospitals. Potential mechanisms were proposed to explain this association, including more experience ("practice makes perfect") and availability for advanced techniques and devices in high-volume hospitals.[7, 23] In contrast, we did not find the association between hospital stroke volume and process measures in the current study. This was similar to a study from GWTG-Stroke. This study from 790 US hospitals including 322,847 patients with ischemic stroke or transient ischemic attack observed no differences in performance measures between high-volume hospitals and low-volume hospitals after adjusting for patient baseline characteristics.[18] In the past years, many initiatives for improving the quality of care have been implemented to homogenize the quality of care in hospitals, such as GWTG-Stroke, Australian Stroke Clinical Registry, and CNSR,[24] which may attenuate the difference of quality of care between high-volume and low-volume hospitals.

During the past decades, a great number of studies evaluated the volume-outcome association, and many, but not all, found the reverse relationship between volume and outcome.[9] There were several studies revealed that stroke patients in high-volume hospitals may experience lower mortality than the patients in low-volume hospitals.[11, 12, 25, 26] However, we found no benefit in mortality for patients in high-volume hospitals. Several reasons may explain this discrepancy. First, most of the above-mentioned studies used in-hospital mortality or 30-day mortality as the outcome, however, 1-year mortality was used in our study. What's more, stroke severity is an important factor affecting the patient's prognosis. Whether stroke severity was adjusted may contribute to the results.[13] Lacking data on stroke severity, most of the studies used comorbidity or comorbidity index score to adjust the case-mix.[11, 12, 25, 26] In this study we used the NIHSS score at admission to adjust the stroke severity. Our finding is compatible with a Danish nationwide cohort study of 63,995 patients admitted to stroke units.[23] This study found no association between volume and 30-day mortality and 1-year mortality after adjusting for patient baseline characteristics, stroke unit, university status, and quality of care. Mortality may be insensitive to detecting underlying changes in patient prognosis.[23]

Besides mortality, we also examined the association between hospital volume and poor outcome. To our knowledge, it was the first time to evaluate the association between volume and poor outcome at 1 year in patients with acute ischemic stroke. Compared with the highest quartile of hospitals, patients in the lowest quartile of hospitals had a higher rate of poor outcome after adjusting for potential confounders. The poor outcome may be more sensitive to detect the changes in patient prognosis. The underlying mechanisms of volume on poor outcome are not known. Though there was no significant difference in the process of care during acute phage and at discharge between low- and high-volume hospitals, the differences in some other processes of care after discharge may explain this association. Patients in high-volume hospitals may receive more processes after discharge, for example, limb rehabilitation, which can improve the poor outcome. The association between volume and the poor outcome may be mediated by medical care after discharge. However, we could not identify the medical care after discharge in the current study. In the future, the association between volume, the process of care after discharge, and long-term outcomes are needed for further exploration. Though the significant association, we did not think it is reasonable to regionalize stroke care. Because the transferring may lead to a delay in admission which may offset some benefits of being admitted to large-volume hospitals.[11]

Several limitations in this study should be acknowledged. First, the hospitals that participated in the CNSR were volunteers. There may exist unavoidable selection bias. And the hospitals enrolled may not fully represent the general hospitals in China. Second, though nine processes of care were evaluated, some other processes of care, for example, endovascular therapy, and the care patients received after discharge could not be assessed. The differences in unassessed process measures may explain the association between volume and poor outcome. Third, there is a cluster effect within hospitals and physicians. Tough, we take into consideration of the cluster effect within hospitals by using the generalized estimating equations, we cannot adjust the cluster effect within physicians. Forth, because of the differences in patients, hospital characteristics, and performance of care across varied regions and countries, our results may not generalize to other countries. Further studies on volume and clinical outcome, especially the poor outcome, are needed to confirm our results.

Conclusions

Using the large national stroke registry, we found no association between hospital stroke volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile of hospitals had increased rates of poor outcome compared with the patients in the highest quartile of hospitals. Further work needs to be done to examine whether the medical care after discharge mediates the association between stroke volume and poor outcome. Better understanding the association between structure, process, and outcome can help to identify the best way to improve stroke prognosis.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation: RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG Zhou and YJ Wang take responsibility for the integrity of the work.

References

1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol*. 2017;2:732-741

2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA*. 1998;279:1278-1281

3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg*. 2016;263:664-672

4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J Public Health*. 2007;97:539-544

5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886

6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common medical conditions. *N Engl J Med*. 2010;362:1110-1118

7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume, Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661-1670

8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in patients with traumatic brain injury: A retrospective observational study using a national inpatient database in Japan. *Injury*. 2017;48:1423-1431

9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520

10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med Care*. 2010;48:149-156

11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes*. 2015;8:S141-147

12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it matter? *Neurology*. 2007;69:1142-1151

13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients: Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753

14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. *Int J Stroke*. 2015;10:73-78

15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement in Stroke Care in China. *Stroke*. 2016;47:2843-2849

16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*. 2011;6:355-361

17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients hospitalized with acute ischemic stroke in China: Findings from the China National Stroke Registry II. *Int J Stroke*. 2017;12:254-263

18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107-115

19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238

20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419

21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239

22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729

23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045

24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40

25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke fatality in Canada. *Stroke*. 2008;39:3360-3366

26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788

Table 1. Hospital and patient characteristics by quartiles of hospital volume

Characteristic	Total (n=16651)	Q1 hospitals <264/year (n=2800)	Q2 hospitals 264-370/year (n=3428)	Q3 hospitals 371-508/year (n=4188)	Q4 hospitals >508/year (n=6235)	P	P for trend
Hospital characteristics							
Number of hospitals	133	35	31	33	34		
Teaching hospital	73 (54.9%)	13 (37.1%)	16 (51.6%)	20 (60.6%)	24 (70.6%)	0.0383	0.0039
Geographic region							
East	76 (57.1%)	18 (51.4%)	23 (74.2%)	16 (48.5%)	19 (55.9%)	0.3971	<.0001
Middle	35 (26.3%)	10 (28.6%)	4 (12.9%)	12 (36.4%)	9 (26.5%)		
West	22 (16.5%)	7 (20%)	4 (12.9%)	5 (15.2%)	6 (17.6%)		
Patient characteristics							
Male	10467 (62.9%)	1749 (62.5%)	2114 (61.7%)	2589 (61.8%)	4015 (64.4%)	0.0147	0.0214
Age	65.0±12.0	65.9±12.0	65.3±12.1	65.0±12.1	64.4±11.81	<.0001	<.0001
Health insurance							

URBMI	8312 (49.9%)	1273 (45.5%)	1779 (51.9%)	1985 (47.4%)	3275 (52.5%)	<.0001	<.0001
NRCMS	6850 (41.1%)	1283 (45.8%)	1391 (40.6%)	1830 (43.7%)	2346 (37.6%)		
Commercial insurance	62 (0.4%)	3 (0.1%)	16 (0.5%)	18 (0.4%)	25 (0.4%)		
Self-payment	1427 (8.6%)	241 (8.6%)	242 (7.1%)	355 (8.5%)	589 (9.4%)		
Education							
Elementary or below	7755 (46.6%)	1541 (55.0%)	1608 (46.9%)	1842 (44.0%)	2764 (44.3%)	<.0001	<.0001
Middle school	3859 (23.2%)	547 (19.5%)	722 (21.1%)	1029 (24.6%)	1561 (25.0%)		
High School or above	5037 (30.3%)	712 (25.4%)	1098 (32.0%)	1317 (31.4%)	1910 (30.6%)		
Previous or current smoking	9315 (55.9%)	1595 (57%)	1873 (54.6%)	2478/ (59.2%)	3369 (54%)	<.0001	0.0636
Drinking	5010 (30.1%)	688 (24.6%)	1088 (31.7%)	1162 (27.7%)	2072 (33.2%)	<.0001	0.0001
Medical history							
Hypertension	10775 (64.7%)	1779 (63.5%)	2244 (65.5%)	2658 (63.5%)	4094 (65.7%)	0.0494	0.1454
Diabetes	3405 (20.4%)	524 (18.7%)	702 (20.5%)	850 (20.3%)	1329 (21.3%)	0.0437	0.0091
Hyperlipidemia	1944 (11.7%)	283 (10.1%)	558 (16.3%)	481 (11.5%)	622 (10.0%)	<.0001	0.0001
Atrial fibrillation	1139 (6.8%)	202 (7.2%)	267 (7.8%)	314 (7.5%)	356 (5.7%)	0.0001	0.0006

Stroke or TIA	5556 (33.4%)	842 (30.1%)	1231 (35.9%)	1384 (33.0%)	2099 (33.7%)	<.0001	0.0851
Medication history							
Antiplatelet	3156 (19%)	480 (17.1%)	706 (20.6%)	721 (17.2%)	1249 (20.0%)	<.0001	0.0447
Anticoagulation	168 (1.0%)	29 (1.0%)	45 (1.3%)	42 (1.0%)	52 (0.8%)	0.1647	0.1098
Antihypertension	7382 (44.3%)	1145 (40.9%)	1712 (49.9%)	1869 (44.6%)	2656 (42.6%)	<.0001	0.1288
Lipid-lowering medicine	1141 (6.9%)	153 (5.5%)	351 (10.2%)	292 (7.0%)	345 (5.5%)	<.0001	0.0008
Antidiabetics	2590 (15.6%)	387 (13.8%)	564 (16.5%)	661 (15.8%)	978 (15.7%)	0.0327	0.1504
NIHSS at admission	4(2-7)	4(2-7)	4(2-6)	4(2-8)	4(2-7)	<.0001	0.0055
Days of hospitalization	13 (9-16)	13 (9-16)	13 (10-15)	13 (9-16)	13 (10-16)	<.0001	0.0195

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

Table 2. The association between hospital volume and process measures

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Early antithrombotic	0.80 (0.29-2.18)	0.6582	1.63 (0.63-4.21)	0.3151	0.83 (0.31-2.24)	0.7091
Dysphagia screening	0.64 (0.31-1.31)	0.2208	1.46 (0.63-3.38)	0.3740	1.29 (0.52-3.21)	0.5793
DVT prophylaxis	0.79 (0.38-1.65)	0.5348	0.77 (0.39-1.52)	0.4524	0.94 (0.49-1.79)	0.8421
Antithrombotic medication	1.00 (0.49-2.04)	0.9896	1.20 (0.55-2.62)	0.6403	0.68 (0.34-1.36)	0.2782
Antihypertensive medication for hypertension	0.78 (0.55-1.12)	0.1787	0.87 (0.61-1.24)	0.4516	0.76 (0.54-1.06)	0.1056
Hypoglycemic medication for diabetes	1.03 (0.67-1.60)	0.8799	1 .00(0.65-1.53)	0.9966	0.73 (0.48-1.11)	0.1399
Anticoagulation for AF	0.67 (0.37-1.19)	0.1731	1.14 (0.69-1.86)	0.6094	0.87 (0.52-1.47)	0.6064
Lowering LDL-C medication	0.85 (0.54-1.32)	0.4602	0.87 (0.50-1.51)	0.6107	0.7 (0.42-1.16)	0.1658
Smoking cessation	0.43 (0.12-1.55)	0.1985	0.39 (0.10-1.44)	0.1567	0.54 (0.15-1.95)	0.3469
Defect-free measure of care	0.71 (0.41-1.23)	0.2212	0.99 (0.60-1.64)	0.9780	0.81 (0.48-1.38)	0.4337

DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 3. The association between hospital volume and clinical outcomes

		Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
Outcome		HR/OR (95% CI)	P	HR/OR (95% CI)	P	HR/OR (95% CI)	P
Mortality	Unadjusted	1.39 (1.08-1.79)	0.0109	0.99 (0.77-1.27)	0.9045	1.16 (0.93-1.44)	0.1810
	Adjusted	1.18 (0.88-1.58)	0.2703	0.96 (0.75-1.22)	0.7281	1.04 (0.84-1.27)	0.7479
Poor functional outcome	Unadjusted	1.40 (1.16-1.70)	0.0006	0.98 (0.80-1.20)	0.8517	1.06 (0.90-1.25)	0.5123
	Adjusted	1.36 (1.05-1.77)	0.0221	1.01 (0.76-1.34)	0.9588	0.98 (0.71-1.33)	0.8744

The adjusted covariates included age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, hospital characteristics (academic status and location), and the composite measure of care.

Figure legends

Figure 1. The Kaplan-Meier curve for mortality within 1 year

Figure 2. The rates of poor outcome at 1 year by quartiles of hospital volume

Figure 3. Association between hospital stroke volume and clinical outcomes. A, Hospital volume and all-cause mortality at 1 year. B, Hospital volume and poor outcome at 1 year. The reference point is the median value of hospital volume (416 annual stroke discharges) in all patients.

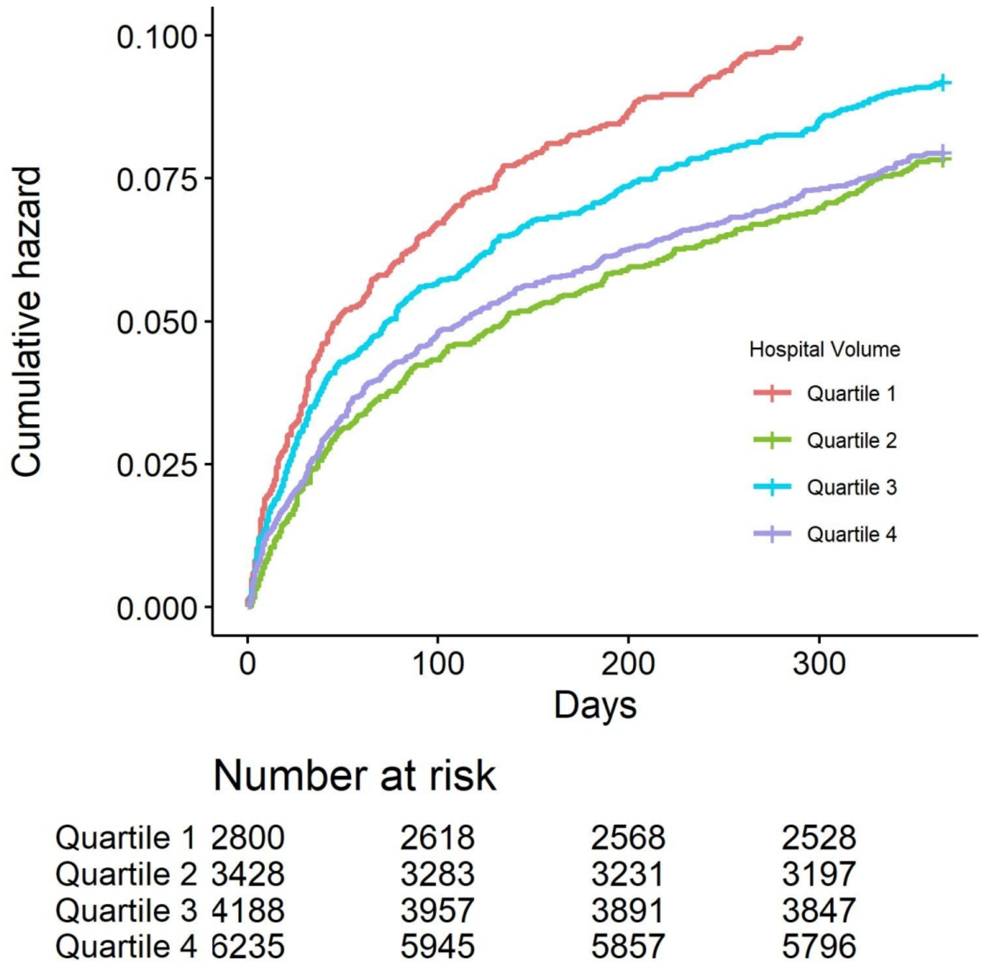

Figure 1. The Kaplan-Meier curve for mortality within 1 year

129x129mm (300 x 300 DPI)

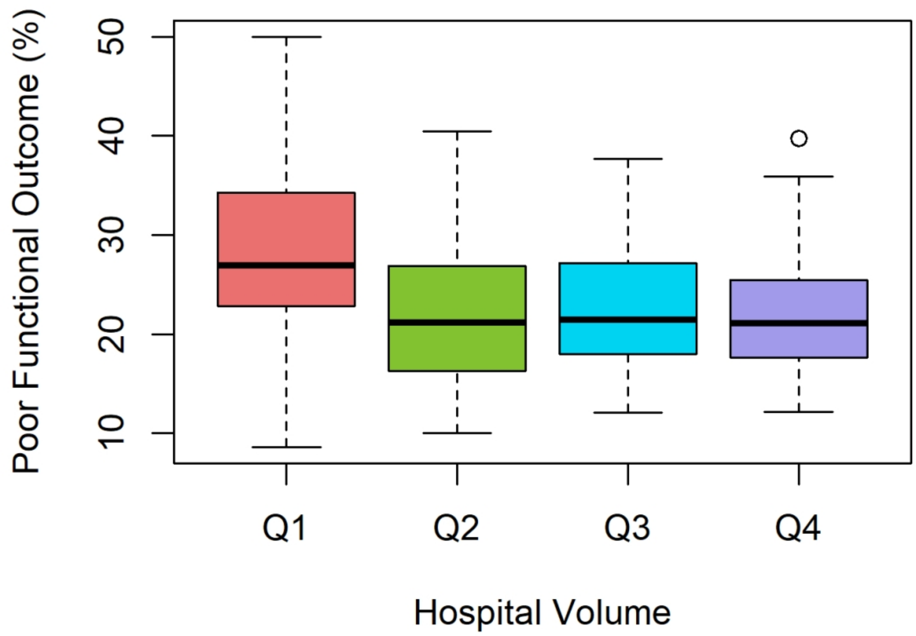

Figure 2. The rates of poor outcome at 1 year by quartiles of hospital volume

119x99mm (300 x 300 DPI)

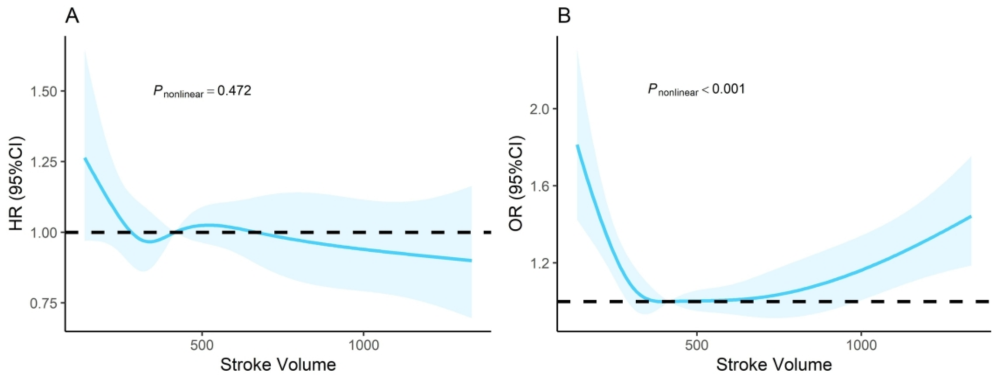

Figure 3. Association between hospital stroke volume and clinical outcomes. A, Hospital volume and all-cause mortality at 1 year. B, Hospital volume and poor outcome at 1 year. The reference point is the median value of hospital volume (416 annual stroke discharges) in all patients.

220x84mm (300 x 300 DPI)

Supplementary Material

Table 1. The definition of process measures

	Definition*
Acute phage process measures	
Early antithrombotics	Antithrombotic treatment within 2 days after admission, including antiplatelet or anticoagulant medications.
DVT prophylaxis	Patients who cannot walk received DVT prophylaxis within 2 days after admission, including pneumatic compression, heparin sodium, warfarin sodium or new oral anticoagulants.
Dysphagia screening	Dysphagia screening before oral intake
Process measures at discharge	
Antithrombotic medication	Antithrombotic medication prescribed at discharge.
Antihypertensive medication for hypertension	Antihypertensive medication prescribed at discharge for patients with hypertension.
Hypoglycemic medication for diabetes	Hypoglycemic medication prescribed at discharge for patients with diabetes.
Anticoagulation for AF	Anticoagulation medication prescribed at discharge for patients with atrial fibrillation.
Lowering LDL-C medication	Statin prescribed at discharge if LDL-C ≥100 mg/dL or patient treated with lipid-lowering agent prior to admission, or LDL-C not documented.
Smoking cessation	Smoking cessation intervention before discharge for current smokers.
Stroke education	Stroke education provided to patient and/or caregiver, including all five components: modifiable risk factors, stroke warning sign and symptoms, how to activate emergency medical services, need for follow- up and medications prescribed.

AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.
*Performance and quality measures are applied only to eligible patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.

Table 2. Baseline characteristics between included and excluded patients

Characteristic	Total （n=19604）	Included （n=16651）	Excluded (n=2953)	P
Patient characteristics				
Male	12437 (63.4%)	10467 (62.9%)	1970 (66.7%)	0.0001
Age	64.84±11.98	64.96±11.98	64.13±11.98	0.0006
Health insurance				
URBMI	10021 (51.1%)	8312 (49.9%)	1709 (57.9%)	<.0001
NRCMS	7747 (39.5%)	6850 (41.1%)	897 (30.4%)	
Commercial insurance	69 (0.4%)	62 (0.4%)	7 (0.2%)	
Self-payment	1767 (9%)	1427 (8.6%)	340 (11.5%)	
Education				
Elementary or below	8882 (45.3%)	7755 (46.6%)	1127 (38.2%)	<.0001
Middle school	4562 (23.3%)	3859 (23.2%)	703 (23.8%)	
High School or above	6160 (31.4%)	5037 (30.3%)	1123 (38.0%)	
Previous or current smoking	8672 (44.2%)	7336 (44.1%)	1336 (45.2%)	0.2322
Drinking	5859 (29.9%)	5010 (30.1%)	849 (28.8%)	0.1433
Medical history				
Hypertension	12697 (64.8%)	10775 (64.7%)	1922 (65.1%)	0.6938
Diabetes	4060 (20.7%)	3405 (20.4%)	655 (22.2%)	0.0323
Hyperlipidemia	2370 (12.1%)	1944 (11.7%)	426 (14.4%)	<.0001
Atrial fibrillation	1382 (7%)	1139 (6.8%)	243 (8.2%)	0.0066
Stroke or TIA	6640 (33.9%)	5556 (33.4%)	1084 (36.7%)	0.0004
Medication history				
Antiplatelet	3869 (19.7%)	3156 (19.0%)	713 (24.1%)	<.0001
Anticoagulation	208 (1.1%)	168 (1.0%)	40 (1.4%)	0.0912
Antihypertension	8775 (44.8%)	7382 (44.3%)	1393 (47.2%)	0.0042
Lipid-lowering medicine	1351 (6.9%)	1141 (6.9%)	210 (7.1%)	0.6086
Antidiabetics	3115 (15.9%)	2590 (15.6%)	525 (17.8%)	0.0023
NIHSS at admission	4(2-7)	4(2-7)	4(2-7)	0.0001
Days of hospitalization	13(9-16)	13(9-16)	13(9-15)	0.041
Hospital characteristics				
Number of hospitals	217	133	84	-
Teaching hospital	125 (57.6%)	73 (54.9%)	52 (61.9%)	0.3083
Geographic region				
East	121 (55.8%)	76 (57.1%)	45 (53.6%)	0.1459
Middle	66 (30.4%)	35 (26.3%)	31 (36.9%)	
West	30 (13.8%)	22 (16.5%)	8 (9.5%)	

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme.

Table 3. The association between hospital volume and performance measures from unadjusted models.

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P
Early antithrombotic	0.97 (0.36-2.61)	0.9442	1.00 (0.36-2.77)	0.9924	1.03 (0.36-2.99)	0.9529
Dysphagia screening	0.60 (0.25-1.43)	0.2480	0.93 (0.36-2.37)	0.8785	1.1 (0.43-2.83)	0.8467
DVT prophylaxis	0.90 (0.46-1.75)	0.7566	0.87 (0.43-1.76)	0.6969	1.06 (0.54-2.07)	0.8645
Antithrombotic medication	1.13 (0.59-2.18)	0.7162	1.43 (0.75-2.71)	0.2759	1.08 (0.54-2.17)	0.8194
Antihypertensive medication for hypertension	0.79 (0.55-1.14)	0.2092	0.86 (0.60-1.22)	0.3893	0.78 (0.55-1.1)	0.1547
Hypoglycemic medication for diabetes	0.94 (0.61-1.45)	0.7859	0.89 (0.58-1.37)	0.6089	0.75 (0.49-1.14)	0.1818
Anticoagulation for AF	0.53 (0.29-0.98)	0.0440	0.81 (0.48-1.37)	0.4280	0.83 (0.47-1.47)	0.522
Lowering LDL-C medication	0.97 (0.62-1.51)	0.8836	0.97 (0.61-1.55)	0.8893	0.87 (0.56-1.34)	0.522
Smoking cessation	0.95 (0.50-1.82)	0.8718	0.93 (0.48-1.78)	0.8174	0.84 (0.41-1.71)	0.6294
Defect-free measure of care	0.83 (0.54-1.27)	0.3811	0.97 (0.65-1.46)	0.9006	1.00 (0.66-1.52)	0.9838

DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association Between Hospital Volume, Process of Care, and Outcomes after Acute Ischemic Stroke: A Prospective Observational Study

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Abstract

Objectives Uncertainty remains about hospital volume and clinical outcomes for patients with stroke. The study was aimed to assess the association between hospital volume, process of care, and outcomes after ischemic stroke.

Methods The patients with acute ischemic stroke from the Second China National Stroke Registry were included in this study. According to quartiles of the hospital volume, the patients were categorized into four groups. We compared the difference in the process of care across the groups. We used generalized estimating equations to estimate the effect of hospital volume on mortality, poor outcome, recurrent stroke and combined vascular events at 3 months and 1 year. Odds ratios and corresponding 95% confidence intervals were used to qualify the association between hospital volume and outcomes with the highest quartile as reference. We also used restricted cubic splines to model the association between hospital volume and clinical outcomes.

Results A total of 17,550 ischemic strokes from 217 hospitals across China were included. The were no significant differences in process of care across the four groups. When adjusted for confounders, the effect of hospital volume on mortality, recurrent stroke and combined vascular events was not significant. However, compared with the highest quartile, the patients in the lowest quartile of hospital volume tend to be with poor outcome at 1 year (OR, 1.29, 95% CI, 1.01-1.64, P=0.0393). The restricted cubic spline analyses suggested a non-linear relationship between hospital volume and 1-year combined vascular events and 3-month and 1-year poor outcome.

Conclusions We found no significant associations between hospital volume, the process of

care at the hospital, and recurrent stroke and mortality in patients with ischemic stroke. However, hospital volume may be associated with combined vascular events and poor outcome at 1 year.

Strengths and limitations of this study

The number of participants with ischemic stroke was large and 217 hospitals across China were included.

This is the first time the association between stroke volume, process of care and poor outcome was explored in China.

Some process of care, especially the process of care after discharge, cannot be obtained in this study.

The hospitals that participated were volunteers and unavoidable selection bias may exist.

Introduction

Previous studies have shown that the number of patients treated in a hospital (hospital volume) may be associated with outcomes in specific surgical procedures involving aortic valve replacement, carotid endarterectomy, coronary artery bypass surgery, and cancer-related surgeries.[1-5] The volume-outcome relationship is also described in some medical conditions, including heart failure, acute myocardial infarction, pneumonia, and brain injury.[6-8] The magnitude of the association was varied significantly in studies.[9] If there were inverse relation between hospital volume and outcomes, it was of significance to make volume-based referral strategies.[10] Several studies have examined the association between hospital stroke volume and mortality for stroke patients. However, the results were controversial. Some[11, 12] found that stroke patients in high-volume hospitals had decreased case fatality, but some[13, 14] were not. Most of the studies evaluated the short-term mortality and the results on long-term outcomes were limited. What's more, the associations between hospital volume and recurrent stroke and poor outcome were not well characterized.

We hypothesize that the hospitals with higher volume may character with high quality of care, which in turn improved the prognosis of patients with stroke. In this study, we aimed to examine the association between hospital stroke volume and outcomes, including mortality recurrent stroke, combined vascular events, and poor outcome at 3 months and 1 year after stroke onset. We also examined the association between hospital stroke volume and the process of care for ischemic stroke.

Methods

Ethics approval

This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-005-01). The rewritten informed consent was obtained from the patients or their relatives.

Study Design and Setting

This retrospective analysis used data from the Second China National Stroke Registry (CNSR II), which was a national multicenter hospital-based cohort study. CNSR II was launched in June 2012 in China and the primary objectives were to evaluate the delivery of stroke care and identify suboptimal performance metrics to be improved.[15] The hospitals were selected based on similar criteria in CNSR I launched in 2007, which had been published elsewhere.[16] After assessing the hospital characteristics, such as location, teaching status, number of beds, and annual stroke discharges by the steering committee, a total of 219 hospitals were included in CNSR II.[17]

Study Population

The patients were consecutively recruited from June 2012 to January 2013. The inclusion criteria were as follow (1) age 18 years or above; (2) presented within seven days of the index event of acute ischemic stroke (AIS), transient ischemic attack (TIA), intracerebral hemorrhage, or subarachnoid hemorrhage, confirmed by brain computed tomography or magnetic resonance imaging; (3) direct hospital admission from a physician's clinic or emergency department. A total of 25,018 patients were included in CNSR Ⅱ, of them 19,604 were AIS.

We excluded the patients missing information on process of care and those lost to follow-up at 3 months and 1 year. Finally, 17,550 patients with AIS from 217 hospitals were included to investigate the association between hospital volume, the process of care, and outcomes.

Data Collection

Data were collected following a standardized form by trained research coordinators. The information on demographics, health insurance, education, smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and medication history were abstracted from medical records. National Institutes of Health Stroke Scale (NIHSS) at admission and modified Rankin Scale (mRS) prior to the index event were assessed through a face-to-face interview.

Hospital stroke volume was defined as the annual number of stroke discharges. The annual stroke discharges of each hospital were obtained via the hospital survey when they applied to participate in this study. Additionally, the hospital characteristics including location, academic status, the presence of stroke unit and the number of beds were obtained by the survey.

Process Measures

We selected ten guideline-recommended process measures according to the national guideline and the Get With The Guidelines-Stroke (GWTG-Stroke).[18] There were four acute phage process measures, including (1) intravenous recombinant tissue plasminogen activator (rt-PA) in patients who arrive within 2 hours after symptom onset and were treated within 3 hours, (2) antithrombotics within 2 days after admission, (3) deep vein thrombosis (DVT) prophylaxis, and (4) dysphagia screening. There were six process measures at discharge, including (1) antithrombotic medication, (2) antihypertensive medication for patients with hypertension, (3) hypoglycemic medication for patients with diabetes, (4) anticoagulation for atrial fibrillation, (5) lowering low-density lipoprotein cholesterol (LDL-C) medication, and (6) smoking cessation. The definitions of the process measures were shown in Supplemental Table 1. Additionally, we calculated a binary defect-free measure of care, which was defined as the patient receiving all the processes for which they were eligible.[19, 20] Process measures are applied only to eligible patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.[21]

Clinical Outcomes

According to the study protocol, all patients were followed up at 3, 6, and 12 months by telephone or face-to-face interview. Trained research coordinators collected the clinical outcomes. In this study, the outcomes included all-cause mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and 1 year. The stroke recurrence was defined as a new ischemic stroke or hemorrhagic stroke within 3 months or 1 year after symptom onset. Composite vascular events included myocardial infarction, recurrent stroke, and vascular death. The poor outcome was defined as mRS of 3 to 6.

Statistical Analysis

The patients were categorized into four groups according to the quartiles of hospital volume: Q1 (<300 /year), Q2 (300-436 /year), Q3 (437-722 /year), Q4 (>722 /year). Continuous variables were described as mean ± standard deviation (SD) or median and interquartile range. Categorical variables were described as proportions. The patient characteristics were compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, in order to obtain the P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for continuous variables and Cochran-Mantel-Haenszel row mean scores for categorical variables.

The generalized estimating equations with exchangeable working correlation matrix were used to evaluate the association between hospital volume, the process of care, and outcomes adjusting for the cluster effect within the hospital. In the adjusted models, age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, and hospital characteristics (academic status, number of beds, presence of stroke unit, and location) were included. Additionally, the defect-free measure of care was included in the adjusted model when estimating the association between hospital volume and outcomes. We used the Kaplan-Meier method to depict the cumulative hazards of all-cause mortality and recurrent stroke. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used with the hospital volume of Q4 as reference. Additionally, we used restricted cubic splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the association between hospital volume and outcomes. We tested for non-linearity by using the Wald statistics.

All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P values were two-tailed with a significant level of 0.05.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

A total of 17,550 patients with AIS from 217 hospitals across China were included in this study. The process of patient selection is shown in Figure 1. Patients included in the current study and those excluded were largely comparable (supplemental Table 2). Table 1 described the baseline characteristics of the included hospitals and patients.

Of the 217 included hospitals, 125 (57.6%) were teaching hospitals, and the high-volume hospitals were likely to be teaching hospitals. There were 121 hospitals in the east of China, 66 in the middle of China, and 30 in the west of China. The average hospital volume was 437 per year, ranging from 136 to 2048 per year.

The mean age was 65 (57-74) and 63.6% of the patients were males. The median NIHSS at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared with the high-volume hospitals, there were more females and the patients were older in low-volume hospitals. The patients in high-volume hospitals were more likely to be with diabetes and hyperlipidemia, but less likely to be with atrial fibrillation. The proportions of taking antiplatelet and lipid-lowing medicine were higher in high-volume hospitals than that in low-volume hospitals.

Association between Hospital Volume and Process Measures

Table 2 list the rates of achievement in process measures. Compared with the hospitals of Q4, the unadjusted OR of defect-free measure of care was 0.88 (95% CI, 0.62-1.25) for Q1, 1.13 (95% CI, 0.82-1.56) for Q2, and 1.15 (95% CI, 0.81-1.62) for Q3. No significant difference was found in individual process measures, except the DVT prophylaxis for A3 (OR, 2.22; 95%CI, 1.26-3.91; P=0.0059), antithrombotic medication at discharge for Q2 (OR, 1.74; 95%CI, 1.09-2.76; P=0.0196), and Lowering LDL-C medication for Q3 (OR, 1.60; 95%CI, 1.10-2.33; P=0.0134) (Supplemental Table 3).

Table 3 shows the adjusted ORs for process measures. After adjusting for the patients and hospital characteristics, the adjusted OR of defect-free measure of care was 0.93 (95% CI, 0.61-1.42) for Q1, 1.25 (95% CI, 0.85-1.85) for Q2, and 1.11 (95% CI, 0.76-1.63) for Q3. All the individual performance measures show no significant association (all P >0.05).

Association between Hospital Volume and 3-Month and 1-Year Outcomes

Of the included patients, 1322 (7.53%) died within 1 year after stroke onset. The Kaplan-Meier plot for mortality within 1 year was shown in Figure 2. The 3-month and 1-year mortality was different across the 4 groups (3-month mortality, 4.95% versus 3.64% versus 4.33% versus 3.39%, P=0.0011; 1-year mortality, 9.08% versus 7.3% versus 7.8% versus 6.66%, P=0.0004) (Table 4). At 3 months and 1 year, the mortality was a little higher in Q1 hospitals (OR at 3 months, 1.54; 95% CI, 1.13-2.09; P=0.0059; OR at 1 year, 1.51; 95% CI 1.19- 1.91; P=0.0008), but not Q2 or Q3 hospitals in compared with Q4 hospitals. However, the difference was not significant when adjusted for potential factors (Table 5).

There were 112 and 1088 patients who failed to achieve the mRS evaluation at 3 months and 1 year, respectively. A total of 3683 (21.12%) patients experienced poor outcome at 3 months and 3701 (22.48%) at 1 year (Table 4). Patients presenting to low-volume hospitals were more likely to have a higher rate of poor outcome at 3 months (23.41% versus 19.51% versus 21.37% versus 21.15%, P=0.0003; $OR_{Q1\ versus\ Q4}$,1.22; 95% CI, 1.01-1.47, P=0.0377) and 1 year (25.69% versus 20.71% versus 21.81% versus 22.65%, P<0.0001; $OR_{Q1\ versus\ Q4}$,1.29; 95% CI, 1.08-1.54, P=0.0043). When adjusted for potential factors, there was still a higher rate of poor outcome at 1 year among Q1 hospitals in comparison with Q4 hospitals ($OR_{Q1\ versus\ Q4}$, 1.29; 95% CI, 1.01-1.64; P=0.0393).

There were 1199 (6.83%) patients with recurrent stroke within 1 year. The Kaplan-Meier plot for recurrent stroke within 1 year was shown in Figure 3. The rate of recurrence was similar across the 4 groups (7.00% versus 7.41% versus 6.64% versus 6.28%, P=0.1214) (Table 4). No significant association was found between hospital volume and stroke recurrence at 3 months and 1 year. Similar results were observed for combined vascular events (Table 5).

In Figure 3-6, we used restricted cubic splines to flexible model and visualize the relation of all-cause mortality, poor outcome, stroke recurrence, and combined vascular events with hospital stroke volume. The multivariable-adjusted restricted cubic splines suggested a "J-shaped" association between volume and all-cause mortality and poor outcome. The analyses indicated a significant nonlinear association between volume and poor outcome at 3 months and 1 year (P for non-linear =0.0096 and <0.001, respectively), as well as combined vascular events at 1 year (P for non-linear = 0.0242).

Discussion

Our analysis of a large population of 17,550 patients with ischemic stroke suggested that no significant difference in the process of care was observed for patients in lower-volume hospitals in comparison with higher-volume hospitals. There was no association between hospital volume and mortality, stroke recurrence, and combined vascular events at 3 months and 1 year. In contrast, we found the patients in the lowest volume quartile had a significantly higher rate of poor outcome at 1 year compared with the highest quartile.

Previous studies found that high volume was associated with improved outcomes suggesting that volume may be a surrogate for quality of care. The quality of care can be assessed from outcome, process, and structure.[22] Usually, hospital volume is used as a structure metric of quality of care. However, the underlying mechanisms of interplay between structure and process are complex.[23] Two existing studies[13, 23] showed that the patients in high-volume hospitals received more process of care compared with patients in low-volume hospitals. Potential mechanisms were proposed to explain this association, including more experience ("practice makes perfect") and availability for advanced techniques and devices in high-volume hospitals.[7, 23] In contrast, we did not find the association between hospital stroke volume and process measures in the current study. This was similar to a study from GWTG-Stroke. This study from 790 US hospitals including 322,847 patients with ischemic stroke or transient ischemic attack observed no differences in performance measures between high-volume hospitals and low-volume hospitals after adjusting for patient baseline characteristics.[18] In the past years, many initiatives for improving the quality of care have been implemented to homogenize the quality of care in hospitals, such as GWTG-Stroke, Australian Stroke Clinical Registry, and CNSR,[24] which may attenuate the difference of quality of care between high-volume and low-volume hospitals.

During the past decades, a great number of studies evaluated the volume-outcome association, and many, but not all, found the reverse relationship between volume and outcome.[9] There were several studies revealed that stroke patients in high-volume hospitals may experience lower short-term mortality than the patients in low-volume hospitals.[11, 12, 25, 26] However, we found no benefit in mortality for patients in high-volume hospitals. Several reasons may explain this discrepancy. First, the hospital volume was varied in these studies. What’s more, stroke severity is an important factor affecting the patient's prognosis. Whether stroke severity was adjusted may contribute to the results.[13] Lacking data on stroke severity, most of the studies used comorbidity or comorbidity index score to adjust the case-mix.[11, 12, 25, 26] In this study we used the NIHSS score at admission to adjust the stroke severity. Our finding is compatible with a Danish nationwide cohort study of 63,995 patients admitted to stroke units.[23] This study found no association between volume and 30-day mortality and 1-year mortality after adjusting for patient baseline characteristics, stroke unit, university status, and quality of care. Mortality may be insensitive to detecting underlying changes in patient prognosis.[23]

Besides mortality, we also examined the association between hospital volume and poor outcome, stroke recurrence, and combined vascular events. To our knowledge, it was the first time to evaluate the association between volume and poor outcome at 3 months and 1 year in patients with acute ischemic stroke. Compared with the highest quartile of hospitals, patients in the lowest quartile of hospitals had a higher rate of poor outcome at 1 year after adjusting for potential confounders. The poor outcome may be more sensitive to detect the changes in patient prognosis. The underlying mechanisms of volume on poor outcome are not known. Though there was no significant difference in the process of care during acute phage and at discharge between low- and high-volume hospitals, the differences in some other processes of care after discharge may explain this association. Patients in high-volume hospitals may receive more processes after discharge, for example, limb rehabilitation, which can improve the poor outcome. The association between volume and the poor outcome may be mediated by medical care after discharge. However, we could not identify the medical care after discharge in the current study. In the future, the association between volume, the process of care after discharge, and long-term outcomes are needed for further exploration. Though the significant association, we did not think it is reasonable to regionalize stroke care. Because the transferring may lead to a delay in admission which may offset some benefits of being admitted to large-volume hospitals.[11]

Several limitations in this study should be acknowledged. First, the hospitals that participated in the CNSR were volunteers. There may exist unavoidable selection bias. And the hospitals enrolled may not fully represent the general hospitals in China. Second, though ten processes of care were evaluated, some other processes of care, for example, mechanical thrombectomy, and the care patients received after discharge could not be assessed. The differences in unassessed process measures may explain the association between volume and poor outcome. Third, there is a cluster effect within hospitals and physicians. Tough, we take into consideration of the cluster effect within hospitals by using the generalized estimating equations, we cannot adjust the cluster effect within physicians. Forth, because of the differences in patients, hospital characteristics, and performance of care across varied regions and countries, our results may not generalize to other countries. Further studies on volume and clinical outcome, especially the poor outcome, are needed to confirm our results.

Conclusions

Using the large national stroke registry, we found no association between hospital stroke volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile of hospitals had increased rates of poor outcome compared with the patients in the highest quartile of hospitals. Further work needs to be done to examine whether the medical care after discharge mediates the association between stroke volume and poor outcome. Better understanding the association between structure, process, and outcome can help to identify the best way to improve stroke prognosis.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation: RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG Zhou and YJ Wang take responsibility for the integrity of the work.

References

1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol*. 2017;2:732-741

2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA*. 1998;279:1278-1281

3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg*. 2016;263:664-672

4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J Public Health*. 2007;97:539-544

5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886

6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common medical conditions. *N Engl J Med*. 2010;362:1110-1118

7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume, Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661-1670

8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in patients with traumatic brain injury: A retrospective observational study using a national inpatient database in Japan. *Injury*. 2017;48:1423-1431

9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520

10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med Care*. 2010;48:149-156

11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes*.

2015;8:S141-147

12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it matter? *Neurology*. 2007;69:1142-1151

13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients: Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753

14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. *Int J Stroke*. 2015;10:73-78

15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement in Stroke Care in China. *Stroke*. 2016;47:2843-2849

16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*. 2011;6:355-361

17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients hospitalized with acute ischemic stroke in China: Findings from the China National Stroke Registry II. *Int J Stroke*. 2017;12:254-263

18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107-115

19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238

20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and

Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419

21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239

22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729

23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045

24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40

25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke fatality in Canada. *Stroke*. 2008;39:3360-3366

26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788

Table 1. Hospital and patient characteristics by quartiles of hospital volume

Characteristic	Total （n=17550）	Q1 hospitals <300/year （n=3371）	Q2 hospitals 300-436/year (n=5386)	Q3 hospitals 437-722/year (n=3281)	Q4 hospitals >722/year (n=5512)	P	P for trend
Hospital characteristics							
Number of hospitals	217	53	56	53	55		
Teaching hospital	125 (57.6%)	23 (43.4%)	23 (41.1%)	37 (69.8%)	42 (76.4%)	<.0001	<.0001
Stroke unit	121 (55.8%)	24 (45.3%)	24 (42.9%)	35 (66%)	38 (69.1%)	0.0062	0.0017
Beds	1000(600-1650)	600(500-800)	780(515-1000)	1300(1000-2000)	1500(1200-2200)	<.0001	<.0001
Geographic region							
East	121 (55.8%)	29 (54.7%)	35 (62.5%)	28 (52.8%)	29 (52.7%)	0.6967	<.0001
Middle	66 (30.4%)	15 (28.3%)	13 (23.2%)	20 (37.7%)	18 (32.7%)		
West	30 (13.8%)	9 (17%)	8 (14.3%)	5 (9.4%)	8 (14.5%)		
Patient characteristics							

Male	11163 (63.6%)	2126 (63.1%)	3349 (62.2%)	2108 (64.2%)	3580 (64.9%)	0.0183	0.0085
Age	65(57-74)	66(57-75)	65(57-74)	66(58-74)	64(55-73)	<.0001	<.0001
Health insurance							
URBMI	8959 (51%)	1715 (50.9%)	2552 (47.4%)	1568 (47.8%)	3124 (56.7%)	<.0001	<.0001
NRCMS	6932 (39.5%)	1369 (40.6%)	2440 (45.3%)	1394 (42.5%)	1729 (31.4%)		
Commercial insurance	60 (0.3%)	8 (0.2%)	27 (0.5%)	4 (0.1%)	21 (0.4%)		
Self-payment	1599 (9.1%)	279 (8.3%)	367 (6.8%)	315 (9.6%)	638 (11.6%)		
Education							
Elementary or below	7934 (45.2%)	1693 (50.2%)	2430 (45.1%)	1678 (51.1%)	2133 (38.7%)	<.0001	<.0001
Middle school	4109 (23.4%)	715 (21.2%)	1286 (23.9%)	661 (20.1%)	1447 (26.3%)		
High School or above	5507 (31.4%)	963 (28.6%)	1670 (31%)	942 (28.7%)	1932 (35.1%)		
Previous or current smoking	7818 (44.5%)	1457 (43.2%)	2406 (44.7%)	1455 (44.3%)	2500 (45.4%)	0.2676	0.0836
Drinking	5277 (30.1%)	872 (25.9%)	1681 (31.2%)	995 (30.3%)	1729 (31.4%)	<.0001	0.0001
Medical history							
Hypertension	11386 (64.9%)	2156 (64%)	3511 (65.2%)	2136 (65.1%)	3583 (65%)	0.6614	0.459

Diabetes	3630 (20.7%)	658 (19.5%)	1097 (20.4%)	673 (20.5%)	1202 (21.8%)	0.0599	0.0086
Hyperlipidemia	2128 (12.1%)	372 (11%)	808 (15%)	384 (11.7%)	564 (10.2%)	<.0001	0.0001
Atrial fibrillation	1185 (6.8%)	212 (6.3%)	402 (7.5%)	280 (8.5%)	291 (5.3%)	0.0001	0.0174
Stroke or TIA	5918 (33.7%)	1084 (32.2%)	1886 (35%)	1113 (33.9%)	1835 (33.3%)	0.0411	0.8641
Medication history							
Antiplatelet	3444 (19.6%)	599 (17.8%)	1008 (18.7%)	712 (21.7%)	1125 (20.4%)	<.0001	0.0002
Anticoagulation	178 (1%)	33 (1%)	69 (1.3%)	35 (1.1%)	41 (0.7%)	0.0467	0.0696
Antihypertension	7868 (44.8%)	1454 (43.1%)	2592 (48.1%)	1401 (42.7%)	2421 (43.9%)	<.0001	0.1248
Lipid-lowering medicine	1207 (6.9%)	195 (5.8%)	487 (9%)	241 (7.3%)	284 (5.2%)	<.0001	0.0002
Antidiabetics	2782 (15.9%)	500 (14.8%)	875 (16.2%)	509 (15.5%)	898 (16.3%)	0.2276	0.1842
NIHSS at admission	4(2-7)	4(2-7)	4(2-6)	4(2-8)	4(2-7)	<.0001	<.0001
Days of hospitalization	13 (9-16)	13 (10-16)	13 (9-15)	13 (9-16)	13 (10-16)	<.0001	0.0211

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

Table 2. The rates of achievement in process measures

Process measures	Total N1/N2 (achievement rate, %)	Q1 hospitals N1/N2 (achievement rate, %)	Q2 hospitals N1/N2 (achievement rate, %)	Q3 hospitals N1/N2 (achievement rate, %)	Q4 hospitals N1/N2 (achievement rate, %)
rt-PA in 2h	217/1303 (16.7%)	36/250 (14.4%)	75/497 (15.1%)	25/200 (12.5%)	81/356 (22.8%)
Early antithrombotic	14555/17243 (84.4%)	2802/3303 (84.8%)	4508/5307 (84.9%)	2903/3199 (90.7%)	4342/5434 (79.9%)
Dysphagia screening	14876/17550 (84.8%)	2630/3371 (78.0%)	4860/5386 (90.2%)	2615/3281 (79.7%)	4771/5512 (86.6%)
DVT prophylaxis	3367/5079 (66.3%)	630/944 (66.7%)	1006/1481 (67.9%)	689/914 (75.4%)	1042/1740 (59.9%)
Antithrombotic medication	14722/16002 (92%)	2845/3058 (93.0%)	4481/4765 (94.0%)	2839/3089 (91.9%)	4557/5090 (89.5%)
Lowering LDL-C medication	7700/11597 (66.4%)	1436/2247 (63.9%)	2591/3621 (71.6%)	1523/2120 (71.8%)	2150/3609 (59.6%)
Antihypertensive	8867/13385 (66.2%)	1712/2611 (65.6%)	2764/4207 (65.7%)	1710/2470 (69.2%)	2681/4097 (65.4%)

medication for hypertension					
Hypoglycemic medication for diabetes	3662/4898 (74.8%)	685/907 (75.5%)	1114/1494 (74.6%)	721/901 (80.0%)	1142/1596 (71.6%)
Anticoagulation for AF	303/1437 (21.1%)	43/278 (15.5%)	86/468 (18.4%)	87/325 (26.8%)	87/366 (23.8%)
Smoking cessation	6712/7819 (85.8%)	1227/1457 (84.2%)	2098/2406 (87.2%)	1213/1456 (83.3%)	2174/2500 (87.0%)
Defect-free measure of care	5816/17550 (33.1%)	992/3371 (29.4%)	1965/5386 (36.5%)	1150/3281 (35.1%)	1709/5512 (31.0%)

N1 indicates the number of patients received the process of care, N2 indicates the number of patients eligible; rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 3. The association between hospital volume and process measures

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
rt-PA	1.54 (0.61, 3.89)	0.3614	1.46 (0.68, 3.14)	0.3343	0.71 (0.35, 1.48)	0.3634
Early antithrombotic	0.68 (0.20, 2.32)	0.5364	1.17 (0.30, 4.55)	0.8245	1.07 (0.36, 3.18)	0.9020
Dysphagia screening	0.76 (0.33, 1.74)	0.5104	2.19 (0.86, 5.55)	0.0987	0.90 (0.42, 1.92)	0.7845
DVT prophylaxis	1.02 (0.52, 2.01)	0.9504	1.09 (0.57, 2.09)	0.7936	1.55 (0.84, 2.83)	0.1594
Antithrombotic medication	1.26 (0.61, 2.61)	0.5391	1.27 (0.61, 2.64)	0.5277	1.16 (0.63, 2.15)	0.6375
Lowering LDL-C medication	0.92 (0.57, 1.50)	0.7460	1.03 (0.62, 1.70)	0.9224	1.20 (0.78, 1.84)	0.4134
Antihypertensive medication for hypertension	0.99 (0.71, 1.38)	0.9395	0.92 (0.67, 1.27)	0.6152	1.11 (0.81, 1.53)	0.5041
Hypoglycemic medication for diabetes	1.02 (0.67, 1.55)	0.9210	1.06 (0.69, 1.65)	0.7818	0.97 (0.65, 1.46)	0.8888
Anticoagulation for AF	0.63 (0.34, 1.16)	0.1365	0.87 (0.53, 1.44)	0.5848	1.05 (0.61, 1.78)	0.8681

Smoking cessation	0.56 (0.10, 2.97)	0.4939	0.67 (0.12, 3.63)	0.6421	2.08 (0.25, 17.2)	0.4961
Defect-free measure of care	0.93 (0.61, 1.42)	0.7412	1.25 (0.85, 1.85)	0.2634	1.11 (0.76, 1.63)	0.5853

rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 4. The rates of clinical outcomes according to quartiles of hospital volume

Outcome		Q1	Q2	Q3	Q4	P
3 months	Mortality, No. (%)	167 (5.0%)	196 (3.6%)	142 (4.3%)	187 (3.4%)	0.0011
	*Poor outcome, No. (%)	783 (23.4%)	1042 (19.5%)	698 (21.4%)	1160 (21.1%)	0.0003
	Stroke recurrence, No. (%)	178 (5.3%)	297 (5.5%)	166 (5.1%)	238 (4.3%)	0.0298
	Combined vascular events, No. (%)	183 (5.4%)	303 (5.6%)	168 (5.1%)	247 (4.5%)	0.0440
1 year	Mortality, No. (%)	306 (9.1%)	393 (7.3%)	256 (7.8%)	367 (6.7%)	0.0004
	#Poor outcome, No. (%)	817 (25.7%)	1058 (20.7%)	665 (21.8%)	1161 (22.7%)	<.0001
	Stroke recurrence, No. (%)	236 (7.0%)	399 (7.4%)	218 (6.6%)	346 (6.3%)	0.1214
	Combined vascular events, No. (%)	244 (7.2%)	418 (7.8%)	225 (6.9%)	389 (7.1%)	0.3724

* A total of 17,438 patients achieved modified Rankin Scale at 3 months. # A total of 16,462 patients achieved modified Rankin Scale at 1 year.

Table 5. The association between hospital volume and clinical outcomes

		Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
Outcome		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
3 months							
Mortality	Unadjusted	1.54 (1.13, 2.09)	0.0059	1.09 (0.85, 1.40)	0.4772	1.26 (0.89, 1.79)	0.1861
	Adjusted	1.27 (0.88, 1.83)	0.2062	0.99 (0.75, 1.30)	0.9179	1.18 (0.82, 1.68)	0.3708
Poor outcome	Unadjusted	1.22 (1.01, 1.47)	0.0377	0.95 (0.81, 1.11)	0.5341	1.06 (0.89, 1.26)	0.4937
	Adjusted	1.17 (0.91, 1.52)	0.2269	0.95 (0.74, 1.22)	0.6891	0.96 (0.75, 1.22)	0.7185
Recurrent stroke	Unadjusted	1.27 (0.92, 1.75)	0.1403	1.21 (0.91, 1.61)	0.1992	1.16 (0.85, 1.58)	0.3563
	Adjusted	1.16 (0.83, 1.62)	0.3798	1.11 (0.79, 1.56)	0.5474	1.11 (0.78, 1.56)	0.5620
Combined vascular events	Unadjusted	1.27 (0.92, 1.76)	0.1391	1.19 (0.89, 1.60)	0.2437	1.14 (0.83, 1.56)	0.4304
	Adjusted	1.15 (0.82, 1.61)	0.4109	1.09 (0.78, 1.53)	0.6167	1.08 (0.76, 1.52)	0.6763
1 year							
Mortality	Unadjusted	1.51 (1.19, 1.91)	0.0008	1.16 (0.95, 1.40)	0.1385	1.21 (0.97, 1.52)	0.0975
	Adjusted	1.16 (0.90, 1.49)	0.2437	0.99 (0.80, 1.24)	0.9563	1.05 (0.82, 1.34)	0.697

Poor outcome	Unadjusted	1.29 (1.08, 1.54)	0.0043	0.94 (0.81, 1.09)	0.4317	1.00 (0.86, 1.17)	0.9917
	Adjusted	1.29 (1.01, 1.64)	0.0393	0.98 (0.78, 1.24)	0.8758	0.85 (0.68, 1.06)	0.1566
Recurrent stroke	Unadjusted	1.21 (0.92, 1.59)	0.1725	1.17 (0.92, 1.49)	0.1966	1.08 (0.83, 1.40)	0.5634
	Adjusted	1.08 (0.82, 1.43)	0.5860	1.03 (0.79, 1.35)	0.8204	1.01 (0.77, 1.32)	0.9501
Combined vascular events	Unadjusted	1.11 (0.85, 1.46)	0.4440	1.09 (0.86, 1.39)	0.4706	1.00 (0.77, 1.29)	0.9771
	Adjusted	0.98 (0.75, 1.28)	0.8825	0.95 (0.74, 1.22)	0.6942	0.92 (0.71, 1.19)	0.5159

The adjusted covariates included age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, hospital characteristics (academic status, beds, stroke unit and location), and the composite measure of care.

Figure legends

Figure 1. The flow chart for patient selection

Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and all-cause mortality at 3 months. B, Hospital volume and all-cause mortality at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and poor outcome at 3 months. B, Hospital volume and poor outcome at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and recurrent stroke at 3 months. B, Hospital volume and recurrent stroke at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and combined vascular events at 3 months. B, Hospital volume and combined vascular events at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

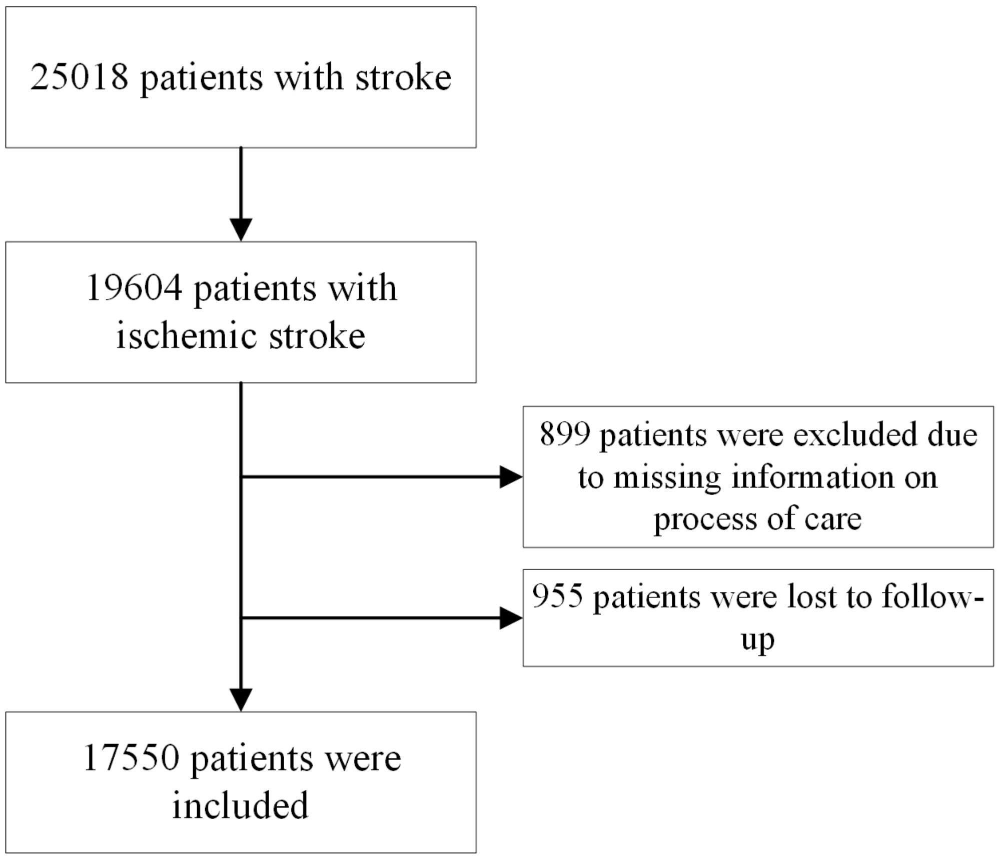

Figure 1. The flow chart for patient selection

106x90mm (300 x 300 DPI)

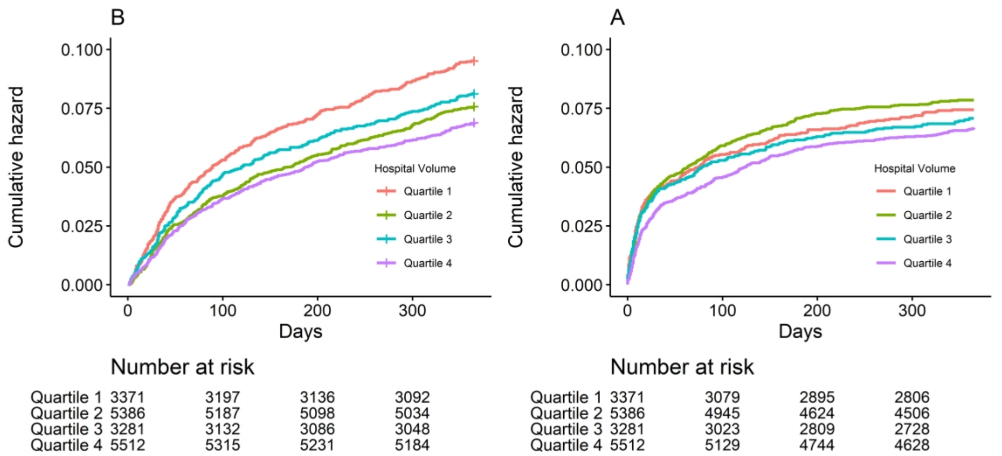

Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

254x118mm (300 x 300 DPI)

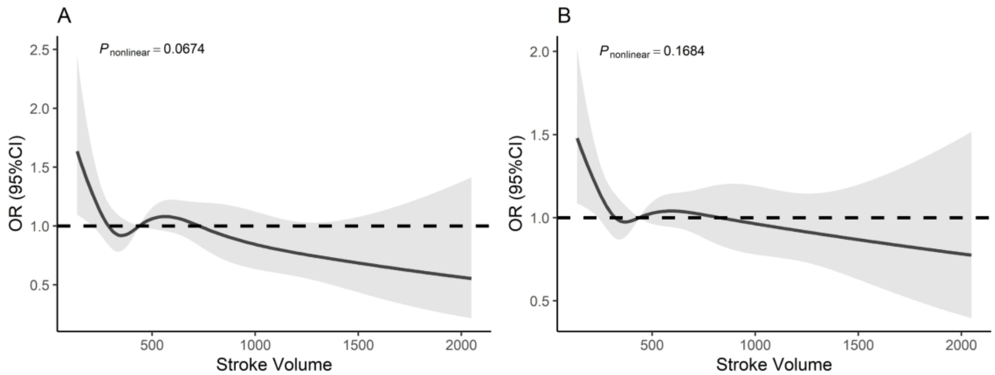

Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and all-cause mortality at 3 months. B, Hospital volume and all-cause mortality at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (300 x 300 DPI)

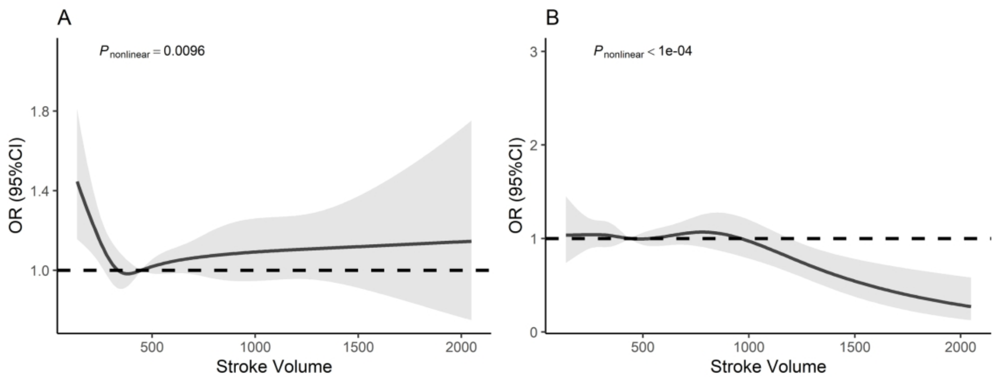

Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and poor outcome at 3 months. B, Hospital volume and poor outcome at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (300 x 300 DPI)

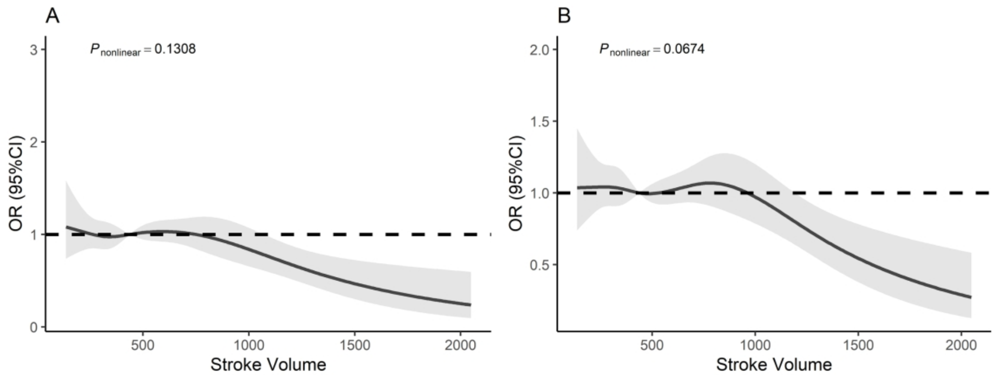

Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and recurrent stroke at 3 months. B, Hospital volume and recurrent stroke at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (300 x 300 DPI)

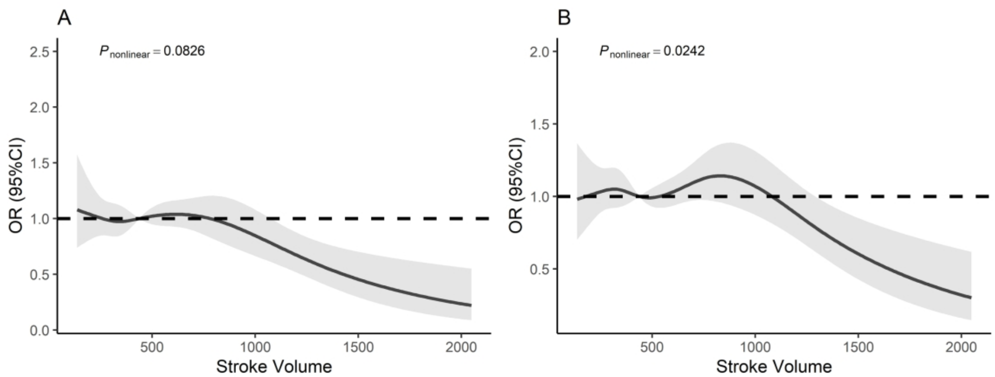

Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and combined vascular events at 3 months. B, Hospital volume and combined vascular events at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (300 x 300 DPI)

Supplementary Material

Table 1. The definition of process measures

	Definition*
Acute phage process measures	
rt-PA	intravenous tissue-type plasminogen activator (tPA) in patients who arrive within 2 hours after symptom onset and treated within 3 hours.
Early antithrombotics	Antithrombotic treatment within 2 days after admission, including antiplatelet or anticoagulant medications.
DVT prophylaxis	Patients who cannot walk received DVT prophylaxis within 2 days after admission, including pneumatic compression, heparin sodium, warfarin sodium or new oral anticoagulants.
Dysphagia screening	Dysphagia screening before oral intake
Process measures at discharge	
Antithrombotic medication	Antithrombotic medication prescribed at discharge.
Antihypertensive medication for hypertension	Antihypertensive medication prescribed at discharge for patients with hypertension.
Hypoglycemic medication for diabetes	Hypoglycemic medication prescribed at discharge for patients with diabetes.
Anticoagulation for AF	Anticoagulation medication prescribed at discharge for patients with atrial fibrillation.
Lowering LDL-C medication	Statin prescribed at discharge if LDL-C ≥100 mg/dL or patient treated with lipid-lowering agent prior to admission, or LDL-C not documented.
Smoking cessation	Smoking cessation intervention before discharge for current smokers.
Stroke education	Stroke education provided to patient and/or caregiver, including all five components: modifiable risk factors, stroke warning sign and symptoms, how to activate emergency medical services, need for follow-up and medications prescribed.

rt-PA indicates recombinant tissue plasminogen activator; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

*Performance and quality measures are applied only to eligible patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.

Table 2. Baseline characteristics between included and excluded patients

Characteristic	Included （n=17550）	Excluded (n=2054)	P
Patient characteristics			
Male	11163 (63.6%)	1274 (62.0%)	0.1591
Age	65(57-74)	65(57-75)	0.1122
Health insurance			
URBMI	8959 (51.0%)	1062 (51.7%)	0.4888
NRCMS	6932 (39.5%)	815 (39.7%)	
Commercial insurance	60 (0.3%)	9 (0.4%)	
Self-payment	1599 (9.1%)	168 (8.2%)	
Education			
Elementary or below	7934 (45.2%)	948 (46.2%)	0.3827
Middle school	4109 (23.4%)	453 (22.1%)	
High School or above	5507 (31.4%)	653 (31.8%)	
Previous or current smoking	7818 (44.5%)	854 (41.6%)	0.0104
Drinking	5277 (30.1%)	582 (28.3%)	0.1044
Medical history			
Hypertension	11386 (64.9%)	1311 (63.8%)	0.3455
Diabetes	3630 (20.7%)	430 (20.9%)	0.7905
Hyperlipidemia	2128 (12.1%)	242 (11.8%)	0.6514
Atrial fibrillation	1185 (6.8%)	197 (9.6%)	<0.0001
Stroke or TIA	5918 (33.7%)	722 (35.2%)	0.1951
Medication history			
Antiplatelet	3444 (19.6%)	425 (20.7%)	0.2501
Anticoagulation	178 (1.0%)	30 (1.5%)	0.0618
Antihypertension	7868 (44.8%)	907 (44.2%)	0.5610
Lipid-lowering medicine	1207 (6.9%)	144 (7.0%)	0.8216
Antidiabetics	2782 (15.9%)	333 (16.2%)	0.6725
NIHSS at admission	4(2-7)	4(1-8)	0.6146
Days of hospitalization	13(9-16)	13(9-15)	0.3805

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme.

Table 3. The association between hospital volume and performance measures from unadjusted models.

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P
rt-PA	0.64 (0.31, 1.34)	0.2386	0.72 (0.35, 1.49)	0.3811	0.62 (0.28, 1.37)	0.2389
Early antithrombotic	0.86 (0.39, 1.90)	0.7114	1.10 (0.49, 2.47)	0.8241	1.02 (0.44, 2.36)	0.9626
Dysphagia screening	0.78 (0.38, 1.60)	0.5015	2.03 (0.93, 4.42)	0.0754	1.08 (0.53, 2.18)	0.8327
DVT prophylaxis	1.31 (0.76, 2.28)	0.3329	1.37 (0.80, 2.36)	0.2501	2.22 (1.26, 3.91)	0.0059
Antithrombotic medication	1.43 (0.93, 2.20)	0.1077	1.74 (1.09, 2.76)	0.0196	1.40 (0.71, 2.75)	0.3307
Lowering LDL-C medication	1.12 (0.76, 1.66)	0.5726	1.35 (0.94, 1.94)	0.101	1.60 (1.10, 2.33)	0.0134
Antihypertensive medication for hypertension	0.91 (0.66, 1.25)	0.5588	0.84 (0.62, 1.14)	0.2679	1.08 (0.79, 1.49)	0.6339
Hypoglycemic medication for diabetes	0.98 (0.67, 1.45)	0.931	1.00 (0.68, 1.46)	0.9978	1.06 (0.72, 1.58)	0.757
Anticoagulation for AF	0.58 (0.34, 1.01)	0.0528	0.77 (0.48, 1.24)	0.2842	1.24 (0.73, 2.09)	0.4229
Smoking cessation	0.72 (0.44, 1.18)	0.1959	0.83 (0.50, 1.37)	0.4646	0.81 (0.43, 1.53)	0.5187
Defect-free measure of care	0.88 (0.62, 1.25)	0.4634	1.13 (0.82, 1.56)	0.4496	1.15 (0.81, 1.62)	0.4347

rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association Between Hospital Volume, Processes of Care, and Outcomes after Acute Ischemic Stroke: A Prospective Observational Study

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Abstract

Objectives Uncertainty remains about hospital volume and clinical outcomes for patients with stroke. The study aimed to assess the association between hospital volume, processes of care, and outcomes after ischemic stroke.

Methods The patients with acute ischemic stroke from the Second China National Stroke Registry were included. According to quartiles of the hospital volume, the patients were categorized into four groups. We compared the difference in the process of care across the groups. We used generalized estimating equations to estimate the effect of hospital volume on mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and 1 year. Odds ratios and corresponding 95% confidence intervals were used to qualify the association between hospital volume and outcomes. We also used restricted cubic splines to model the association between hospital volume and clinical outcomes.

Results A total of 17,550 ischemic strokes from 217 hospitals across China were included. There were no significant differences in the process of care across the four groups. When adjusted for confounders, the effect of hospital volume on mortality, recurrent stroke, and combined vascular events was not significant. However, compared with the highest quartile, the patients in the lowest quartile of hospital volume tend to be with poor outcome at 1 year (OR=1.29, 95% CI 1.01-1.64, P=0.0393). The restricted cubic spline analyses suggested a non-linear relationship between hospital volume and 1-year combined vascular events and poor outcome at 3 months and one year.

Conclusions We found no significant associations between hospital volume, processes of care at the hospital, and mortality, recurrent stroke, and combined vascular events in patients

with ischemic stroke. However, hospital volume may be associated with poor outcome at 1 year.

Strengths and limitations of this study

The number of participants with ischemic stroke was large, and 217 hospitals across China were included.

This is the first time the association between stroke volume, processes of care, and outcomes was explored in China.

Some processes of care, especially the processes of care after discharge, cannot be obtained in this study.

The hospitals that participated were volunteers, and unavoidable selection bias may exist.

Introduction

Previous studies have shown that the number of patients treated in a hospital (hospital volume) may be associated with outcomes in specific surgical procedures involving aortic valve replacement, carotid endarterectomy, coronary artery bypass surgery, and cancer-related surgeries.[1-5] The volume-outcome relationship is also described in some medical conditions, including heart failure, acute myocardial infarction, pneumonia, and brain injury.[6-8] The magnitude of the association was varied significantly in studies.[9] If there were inverse relation between hospital volume and outcomes, it was of significance to make volume-based referral strategies.[10] Several studies have examined the association between hospital stroke volume and mortality for stroke patients. However, the results were controversial. Some[11, 12] found that stroke patients in high-volume hospitals had decreased case fatality, but some[13, 14] were not. Most of the studies evaluated the short-term mortality, and the results on long-term outcomes were limited. What's more, the associations between hospital volume and recurrent stroke and poor outcome were not well characterized.

We hypothesize that the hospitals with higher volume may character by a high quality of care, which in turn improves the prognosis of patients with stroke. This study aimed to examine the association between hospital stroke volume and outcomes, including mortality, recurrent stroke, combined vascular events, and poor outcome at 3 months and 1 year after stroke onset. We also examined the association between hospital stroke volume and the process of care for ischemic stroke.

Methods

Ethics approval

This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-005-01). Written informed consent was obtained from the patients or their relatives.

Study Design and Setting

The Second China National Stroke Registry (CNSR II) was a national multicenter hospital-based cohort study. CNSR II was launched in June 2012 in China. The primary objectives were to evaluate the delivery of stroke care and identify suboptimal performance metrics to be improved.[15] The hospitals were selected based on similar criteria in CNSR I launched in 2007, which had been published elsewhere.[16] After assessing the hospital characteristics, such as location, teaching status, number of beds, and annual stroke discharges by the steering committee, a total of 219 hospitals were included in CNSR II.[17]

Study Population

The patients were consecutively recruited from June 2012 to January 2013. The inclusion criteria were as follows (1) age 18 years or above; (2) presented within seven days of the index event of acute ischemic stroke (AIS), transient ischemic attack (TIA), intracerebral hemorrhage, or subarachnoid hemorrhage, confirmed by brain computed tomography or magnetic resonance imaging; (3) direct hospital admission from a physician's clinic or emergency department. A total of 25,018 patients were included in CNSR Ⅱ; of them, 19,604 were AIS.

There were 1200 (6.12%) patients lost at 3 months and 2306 (11.76%) patients lost at 1 year. We excluded the patients who missed information on the process of care and those who lost to follow-up at 3 months and 1 year. Finally, 17,550 patients and 16,482 patients with AIS were available for evaluating the association between hospital volume and 3-month outcomes and 1-year outcomes, respectively. A total of 17,438 patients achieved mRS at 3 months, and 16,462 patients achieved mRS at 1 year.

Data Collection

Data were collected following a standardized form by trained research coordinators. The information on demographics, health insurance, education, smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and medication history were abstracted from medical records. National Institutes of Health Stroke Scale (NIHSS) at admission and modified Rankin Scale (mRS) prior to the index event were assessed through a face-to-face interview.

Hospital stroke volume was defined as the annual number of stroke discharges. The annual stroke discharges of each hospital were obtained via the hospital survey when they applied to participate in this study. Additionally, the hospital characteristics, including location, academic status, the presence of stroke unit, and the number of beds, were obtained by the survey.

Process Measures

We selected ten guideline-recommended process measures according to the national guideline and the Get With The Guidelines-Stroke (GWTG-Stroke).[18] There were four acute phage process measures, including (1) intravenous recombinant tissue plasminogen activator (rt-PA) in patients who arrived within 2 hours after symptom onset and were treated within 3 hours, (2) antithrombotics within 2 days after admission, (3) deep vein thrombosis (DVT) prophylaxis, and (4) dysphagia screening. There were six process measures at discharge, including (1) antithrombotic medication, (2) antihypertensive medication for patients with hypertension, (3) hypoglycemic medication for patients with diabetes, (4) anticoagulation for atrial fibrillation, (5) lowering low-density lipoprotein cholesterol (LDL-C) medication, and (6) smoking cessation. The definitions of the process measures are shown in Supplemental Table 1. Additionally, we calculated a binary defect-free measure of care, defined as the patient receiving all the processes for which they were eligible.[19, 20] Process measures are applied only to qualified patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.[21]

Clinical Outcomes

According to the study protocol, all patients were followed up at 3, 6, and 12 months by telephone or face-to-face interview. Trained research coordinators collected the clinical outcomes. In this study, the outcomes included all-cause mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and 1 year. The stroke recurrence was defined as a new ischemic stroke or hemorrhagic stroke within 3 months or 1 year after symptom onset. Composite vascular events included myocardial infarction, recurrent stroke, and vascular death. The poor outcome was defined as mRS of 3 to 6.

Statistical Analysis

The patients were categorized into four groups according to the quartiles of hospital volume: Q1 (<300 /year), Q2 (300-436 /year), Q3 (437-722 /year), Q4 (>722 /year). Continuous variables were described as mean ± standard deviation (SD) or median and interquartile range. Categorical variables were described as proportions. The patient characteristics were compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, in order to obtain the P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for continuous variables and Cochran-Mantel-Haenszel row mean scores for categorical variables.

The generalized estimating equations with an exchangeable working correlation matrix were used to evaluate the association between hospital volume, the process of care, and outcomes adjusting for the cluster effect within the hospital. In the adjusted models, age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, and hospital characteristics (academic status, number of beds, presence of stroke unit, and location) were included. Additionally, the defect-free measure of care was included in the adjusted model when estimating the association between hospital volume and outcomes. We used the Kaplan-Meier method to depict the cumulative hazards of all-cause mortality and recurrent stroke. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used with the hospital volume of Q4 as reference. Additionally, we used restricted cubic splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the association between hospital volume and outcomes. We tested for non-linearity by using the Wald statistics.

All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P values were two-tailed with a significant level of 0.05.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

A total of 17,550 patients with AIS from 217 hospitals across China were included in this study. The process of patient selection is shown in Figure 1. Patients included in the current study and those excluded were largely comparable (supplemental Table 2). Table 1 describes the baseline characteristics of the included hospitals and patients.

Of the 217 included hospitals, 125 (57.6%) were teaching hospitals, and the high-volume hospitals were likely to be teaching hospitals. There were 121 hospitals in the east of China, 66 in the middle of China, and 30 in the west of China. The average hospital volume was 437 per year, ranging from 136 to 2048.

The mean age was 65 (57-74), and 63.6% of the patients were males. The median NIHSS at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared with the high-volume hospitals, there were more females, and the patients were older in low-volume hospitals. The patients in high-volume hospitals were more likely to be with diabetes and hyperlipidemia but less likely to be with atrial fibrillation. The proportions of taking antiplatelet and lipid-lowing medicine were higher in high-volume hospitals than that in low-volume hospitals.

Association between Hospital Volume and Process Measures

Table 2 list the rates of achievement in process measures. Compared with the hospitals of Q4, the unadjusted OR of defect-free measure of care was 0.88 (95% CI, 0.62-1.25) for Q1, 1.13 (95% CI, 0.82-1.56) for Q2, and 1.15 (95% CI, 0.81-1.62) for Q3. No significant difference was found in individual process measures, except the DVT prophylaxis for A3 (OR, 2.22; 95%CI, 1.26-3.91; P=0.0059), antithrombotic medication at discharge for Q2 (OR, 1.74; 95%CI, 1.09-2.76; P=0.0196), and Lowering LDL-C medication for Q3 (OR, 1.60; 95%CI, 1.10-2.33; P=0.0134) (Supplemental Table 3).

Table 3 shows the adjusted ORs for process measures. After adjusting for the patients and hospital characteristics, the adjusted OR of defect-free measure of care was 0.93 (95% CI, 0.61-1.42) for Q1, 1.25 (95% CI, 0.85-1.85) for Q2, and 1.11 (95% CI, 0.76-1.63) for Q3. All the individual performance measures show no significant association (all P >0.05).

Association between Hospital Volume and 3-Month and 1-Year Outcomes

Of the included patients, 1322 (7.53%) died within 1 year after stroke onset. The Kaplan-Meier plot for mortality within 1 year was shown in Figure 2. The 3-month and 1-year mortality was different across the 4 groups (3-month mortality, 4.95% versus 3.64% versus 4.33% versus 3.39%, P=0.0011; 1-year mortality, 9.59% versus 7.69% versus 8.39% versus

7.16%, P=0.0006) (Table 4). At 3 months and 1 year, the mortality was a little higher in Q1 hospitals (OR at 3 months=1.54, 95% CI 1.13-2.09, P=0.0059; OR at 1 year=1.48, 95% CI 1.17- 1.88; P=0.0013), but not Q2 or Q3 hospitals in compared with Q4 hospitals. However, the difference was not significant when adjusted for potential factors (Table 5).

A total of 3683 (21.12%) patients experienced poor outcome at 3 months and 3701 (22.48%) at 1 year (Table 4). Patients presenting to low-volume hospitals were more likely to have a higher rate of poor outcome at 3 months (23.41% versus 19.51% versus 21.37% versus 21.15%, P=0.0003; $OR_{Q1\ versus\ Q4}$=1.22, 95% CI 1.01-1.47, P=0.0377) and 1 year (25.69% versus 20.71% versus 21.81% versus 22.65%, P<0.0001; $OR_{Q1\ versus\ Q4}$=1.29, 95% CI 1.08-1.54, P=0.0043). When adjusted for potential factors, there was still a higher rate of poor outcome at 1 year among Q1 hospitals in comparison with Q4 hospitals ($OR_{Q1\ versus\ Q4}$ =1.29, 95% CI 1.01-1.64, P=0.0393).

There were 1199 (6.83%) patients with recurrent stroke within 1 year. The Kaplan-Meier plot for recurrent stroke within 1 year is shown in Figure 3. The recurrence rate was similar across the four groups (7.15% versus 7.59% versus 6.85% versus 6.38%, P=0.1121) (Table 4). No significant association was found between hospital volume and stroke recurrence at 3 months and 1 year. Similar results were observed for combined vascular events (Table 5).

In Figures 3-6, we used restricted cubic splines to flexible model and visualize the relation of all-cause mortality, poor outcome, stroke recurrence, and combined vascular events with hospital stroke volume. The multivariable-adjusted restricted cubic splines suggested a "J-shaped" association between volume and all-cause mortality and poor outcome. The analyses indicated a significant non-linear association between volume and poor outcome at 3 months and 1 year (P for non-linear =0.0096 and <0.001, respectively), as well as combined vascular events at 1 year (P for non-linear = 0.0242).

Discussion

Our analysis of a large population of 17,550 patients with ischemic stroke suggested that no significant difference in the process of care was observed for patients in lower-volume hospitals compared to higher-volume hospitals. There was no association between hospital volume and mortality, stroke recurrence, and combined vascular events at 3 months and 1 year. In contrast, we found that the patients in the lowest volume quartile had a significantly higher rate of poor outcome at 1 year than the highest quartile.

Previous studies found that high volume was associated with improved outcomes suggesting that volume may be a surrogate for quality of care. The quality of care can be assessed from outcome, process, and structure.[22] Usually, hospital volume is used as a structure metric of quality of care. However, the underlying mechanisms of interplay between structure and process are complex.[23] Two existing studies[13, 23] showed that the patients in high-volume hospitals received more process of care compared with patients in low-volume hospitals. Potential mechanisms were proposed to explain this association, including more experience ("practice makes perfect") and the availability of advanced techniques and devices in high-volume hospitals.[7, 23] In contrast, we did not find an association between hospital stroke volume and process measures in the current study. This was similar to a study from GWTG-Stroke. This study from 790 US hospitals, including 322,847 patients with ischemic stroke or transient ischemic attack, observed no differences in performance measures between high-volume and low-volume hospitals after adjusting for patient baseline characteristics.[18] In the past years, many initiatives for improving the quality of care have been implemented to homogenize the quality of care in hospitals, such as GWTG-Stroke, Australian Stroke Clinical Registry, and CNSR,[24] which may attenuate the difference in quality of care between high-volume and low-volume hospitals.

During the past decades, a significant number of studies evaluated the volume-outcome association. Many, but not all, found the reverse relationship between volume and outcome.[9] Several studies revealed that stroke patients in high-volume hospitals may experience lower short-term mortality than patients in low-volume hospitals.[11, 12, 25, 26] However, we found no benefit in mortality for patients in high-volume hospitals. Several reasons may explain this discrepancy. First, the hospital volume was varied in these studies. Moreover, stroke severity is an essential factor affecting the patient's prognosis. Whether stroke severity was adjusted may contribute to the results.[13] Lacking data on stroke severity, most studies used comorbidity or comorbidity index score to adjust the case mix.[11, 12, 25, 26] In this study we used the NIHSS score at admission to adjust the stroke severity. Our finding is compatible with a Danish nationwide cohort study of 63,995 patients admitted to stroke units.[23] This study found no association between volume and 30-day mortality and 1-year mortality after adjusting for patient baseline characteristics, stroke unit, university status, and quality of care. Mortality may be insensitive to detecting underlying changes in patient prognosis.[23]

Besides mortality, we also examined the association between hospital volume and poor outcome, stroke recurrence, and combined vascular events. To our knowledge, it was the first time to evaluate the association between volume and poor outcome at 3 months and 1 year in patients with acute ischemic stroke. Compared with the highest quartile of hospitals, patients in the lowest quartile had a higher rate of poor outcome at 1 year after adjusting for potential confounders. The poor outcome may be more sensitive to detecting the changes in patient prognosis. The underlying mechanisms of volume on poor outcome are not known. Though there was no significant difference in the process of care during acute phage and at discharge between low- and high-volume hospitals, the differences in some other processes of care after discharge may explain this association. Patients in high-volume hospitals may receive more processes after discharge, such as, limb rehabilitation, which can improve the poor outcome. The association between volume and the poor outcome may be mediated by medical care after discharge. However, we could not identify the medical care after discharge in the current study. In the future, the association between volume, the process of care after discharge, and long-term outcomes are needed for further exploration. Though the significant association, we did not think it is reasonable to regionalize stroke care. Because the transferring may lead to a delay in admission, which may offset some benefits of being admitted to large-volume hospitals.[11]

Several limitations in this study should be acknowledged. First, the hospitals that participated in the CNSR were volunteers. There may exist unavoidable selection bias. And the hospitals enrolled may not fully represent the general hospitals in China. Second, though ten processes of care were evaluated, some other processes of care, such as, mechanical thrombectomy, and the care patients received after discharge could not be assessed. The differences in unassessed process measures may explain the association between volume and poor outcome. Third, there is a cluster effect within hospitals and physicians. Tough we take into consideration of the cluster effect within hospitals by using the generalized estimating equations, we cannot adjust the cluster effect within physicians. Forth, because of the differences in patients, hospital characteristics, and performance of care across varied regions and countries, our results may not generalize to other countries. Further studies on volume and clinical outcome, especially the poor outcome, are needed to confirm our results.

Conclusions

Using the large national stroke registry, we found no association between hospital stroke volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile of hospitals had increased rates of poor outcome compared with the patients in the highest quartile of hospitals. Further work needs to be done to examine whether the medical care after discharge mediates the association between stroke volume and poor outcome. Better understanding the association between structure, processes, and outcomes can help to identify the best way to improve stroke prognosis.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation: RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG Zhou and YJ Wang take responsibility for the integrity of the work.

References

1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol*. 2017;2:732-741

2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA*. 1998;279:1278-1281

3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg*. 2016;263:664-

672

4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J Public Health*. 2007;97:539-544

5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886

6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common medical conditions. *N Engl J Med*. 2010;362:1110-1118

7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume, Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661-1670

8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in patients with traumatic brain injury: A retrospective observational study using a national inpatient database in Japan. *Injury*. 2017;48:1423-1431

9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520

10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med Care*. 2010;48:149-156

11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes*. 2015;8:S141-147

12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it

matter? *Neurology*. 2007;69:1142-1151

13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients: Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753

14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. *Int J Stroke*. 2015;10:73-78

15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement in Stroke Care in China. *Stroke*. 2016;47:2843-2849

16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*. 2011;6:355-361

17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients hospitalized with acute ischemic stroke in China: Findings from the China National Stroke Registry II. *Int J Stroke*. 2017;12:254-263

18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107-115

19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238

20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419

21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center

for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239

22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729

23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045

24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40

25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke fatality in Canada. *Stroke*. 2008;39:3360-3366

26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788

Table 1. Hospital and patient characteristics by quartiles of hospital volume

Characteristic	Total (n=17550)	Q1 hospitals <300/year (n=3371)	Q2 hospitals 300-436/year (n=5386)	Q3 hospitals 437-722/year (n=3281)	Q4 hospitals >722/year (n=5512)	P	P for trend
Hospital characteristics							
Number of hospitals	217	53	56	53	55		
Teaching hospital	125 (57.6%)	23 (43.4%)	23 (41.1%)	37 (69.8%)	42 (76.4%)	<.0001	<.0001
Stroke unit	121 (55.8%)	24 (45.3%)	24 (42.9%)	35 (66%)	38 (69.1%)	0.0062	0.0017
Beds	1000 (600-1650)	600 (500-800)	780 (515-1000)	1300 (1000-2000)	1500 (1200-2200)	<.0001	<.0001
Geographic region							
East	121 (55.8%)	29 (54.7%)	35 (62.5%)	28 (52.8%)	29 (52.7%)	0.6967	<.0001
Middle	66 (30.4%)	15 (28.3%)	13 (23.2%)	20 (37.7%)	18 (32.7%)		
West	30 (13.8%)	9 (17%)	8 (14.3%)	5 (9.4%)	8 (14.5%)		
Patient characteristics							

Male	11163 (63.6%)	2126 (63.1%)	3349 (62.2%)	2108 (64.2%)	3580 (64.9%)	0.0183	0.0085
Age	65(57-74)	66(57-75)	65(57-74)	66(58-74)	64(55-73)	<.0001	<.0001
Health insurance							
URBMI	8959 (51%)	1715 (50.9%)	2552 (47.4%)	1568 (47.8%)	3124 (56.7%)	<.0001	<.0001
NRCMS	6932 (39.5%)	1369 (40.6%)	2440 (45.3%)	1394 (42.5%)	1729 (31.4%)		
Commercial insurance	60 (0.3%)	8 (0.2%)	27 (0.5%)	4 (0.1%)	21 (0.4%)		
Self-payment	1599 (9.1%)	279 (8.3%)	367 (6.8%)	315 (9.6%)	638 (11.6%)		
Education							
Elementary or below	7934 (45.2%)	1693 (50.2%)	2430 (45.1%)	1678 (51.1%)	2133 (38.7%)	<.0001	<.0001
Middle school	4109 (23.4%)	715 (21.2%)	1286 (23.9%)	661 (20.1%)	1447 (26.3%)		
High School or above	5507 (31.4%)	963 (28.6%)	1670 (31%)	942 (28.7%)	1932 (35.1%)		
Previous or current smoking	7818 (44.5%)	1457 (43.2%)	2406 (44.7%)	1455 (44.3%)	2500 (45.4%)	0.2676	0.0836
Drinking	5277 (30.1%)	872 (25.9%)	1681 (31.2%)	995 (30.3%)	1729 (31.4%)	<.0001	0.0001
Medical history							
Hypertension	11386 (64.9%)	2156 (64%)	3511 (65.2%)	2136 (65.1%)	3583 (65%)	0.6614	0.459

Diabetes	3630 (20.7%)	658 (19.5%)	1097 (20.4%)	673 (20.5%)	1202 (21.8%)	0.0599	0.0086
Hyperlipidemia	2128 (12.1%)	372 (11%)	808 (15%)	384 (11.7%)	564 (10.2%)	<.0001	0.0001
Atrial fibrillation	1185 (6.8%)	212 (6.3%)	402 (7.5%)	280 (8.5%)	291 (5.3%)	0.0001	0.0174
Stroke or TIA	5918 (33.7%)	1084 (32.2%)	1886 (35%)	1113 (33.9%)	1835 (33.3%)	0.0411	0.8641
Medication history							
Antiplatelet	3444 (19.6%)	599 (17.8%)	1008 (18.7%)	712 (21.7%)	1125 (20.4%)	<.0001	0.0002
Anticoagulation	178 (1%)	33 (1%)	69 (1.3%)	35 (1.1%)	41 (0.7%)	0.0467	0.0696
Antihypertension	7868 (44.8%)	1454 (43.1%)	2592 (48.1%)	1401 (42.7%)	2421 (43.9%)	<.0001	0.1248
Lipid-lowering medicine	1207 (6.9%)	195 (5.8%)	487 (9%)	241 (7.3%)	284 (5.2%)	<.0001	0.0002
Antidiabetics	2782 (15.9%)	500 (14.8%)	875 (16.2%)	509 (15.5%)	898 (16.3%)	0.2276	0.1842
NIHSS at admission	4(2-7)	4(2-7)	4(2-6)	4(2-8)	4(2-7)	<.0001	<.0001
Days of hospitalization	13 (9-16)	13 (10-16)	13 (9-15)	13 (9-16)	13 (10-16)	<.0001	0.0211

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

Table 2. The rates of achievement in process measures

Process measures	Total N1/N2 (achievement rate, %)	Q1 hospitals N1/N2 (achievement rate, %)	Q2 hospitals N1/N2 (achievement rate, %)	Q3 hospitals N1/N2 (achievement rate, %)	Q4 hospitals N1/N2 (achievement rate, %)
Rt-PA	217/1303 (16.7%)	36/250 (14.4%)	75/497 (15.1%)	25/200 (12.5%)	81/356 (22.8%)
Early antithrombotic	14555/17243 (84.4%)	2802/3303 (84.8%)	4508/5307 (84.9%)	2903/3199 (90.7%)	4342/5434 (79.9%)
Dysphagia screening	14876/17550 (84.8%)	2630/3371 (78.0%)	4860/5386 (90.2%)	2615/3281 (79.7%)	4771/5512 (86.6%)
DVT prophylaxis	3367/5079 (66.3%)	630/944 (66.7%)	1006/1481 (67.9%)	689/914 (75.4%)	1042/1740 (59.9%)
Antithrombotic medication	14722/16002 (92%)	2845/3058 (93.0%)	4481/4765 (94.0%)	2839/3089 (91.9%)	4557/5090 (89.5%)
Lowering LDL-C medication	7700/11597 (66.4%)	1436/2247 (63.9%)	2591/3621 (71.6%)	1523/2120 (71.8%)	2150/3609 (59.6%)
Antihypertensive	8867/13385 (66.2%)	1712/2611 (65.6%)	2764/4207 (65.7%)	1710/2470 (69.2%)	2681/4097 (65.4%)

medication for hypertension					
Hypoglycemic medication for diabetes	3662/4898 (74.8%)	685/907 (75.5%)	1114/1494 (74.6%)	721/901 (80.0%)	1142/1596 (71.6%)
Anticoagulation for AF	303/1437 (21.1%)	43/278 (15.5%)	86/468 (18.4%)	87/325 (26.8%)	87/366 (23.8%)
Smoking cessation	6712/7819 (85.8%)	1227/1457 (84.2%)	2098/2406 (87.2%)	1213/1456 (83.3%)	2174/2500 (87.0%)
Defect-free measure of care	5816/17550 (33.1%)	992/3371 (29.4%)	1965/5386 (36.5%)	1150/3281 (35.1%)	1709/5512 (31.0%)

N1 indicates the number of patients who received the process of care, and N2 indicates the number of patients eligible. Rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 3. The association between hospital volume and process measures

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Rt-PA	1.54 (0.61, 3.89)	0.3614	1.46 (0.68, 3.14)	0.3343	0.71 (0.35, 1.48)	0.3634
Early antithrombotic	0.68 (0.20, 2.32)	0.5364	1.17 (0.30, 4.55)	0.8245	1.07 (0.36, 3.18)	0.9020
Dysphagia screening	0.76 (0.33, 1.74)	0.5104	2.19 (0.86, 5.55)	0.0987	0.90 (0.42, 1.92)	0.7845
DVT prophylaxis	1.02 (0.52, 2.01)	0.9504	1.09 (0.57, 2.09)	0.7936	1.55 (0.84, 2.83)	0.1594
Antithrombotic medication	1.26 (0.61, 2.61)	0.5391	1.27 (0.61, 2.64)	0.5277	1.16 (0.63, 2.15)	0.6375
Lowering LDL-C medication	0.92 (0.57, 1.50)	0.7460	1.03 (0.62, 1.70)	0.9224	1.20 (0.78, 1.84)	0.4134
Antihypertensive medication for hypertension	0.99 (0.71, 1.38)	0.9395	0.92 (0.67, 1.27)	0.6152	1.11 (0.81, 1.53)	0.5041
Hypoglycemic medication for diabetes	1.02 (0.67, 1.55)	0.9210	1.06 (0.69, 1.65)	0.7818	0.97 (0.65, 1.46)	0.8888
Anticoagulation for AF	0.63 (0.34, 1.16)	0.1365	0.87 (0.53, 1.44)	0.5848	1.05 (0.61, 1.78)	0.8681

Smoking cessation	0.56 (0.10, 2.97)	0.4939	0.67 (0.12, 3.63)	0.6421	2.08 (0.25, 17.2)	0.4961
Defect-free measure of care	0.93 (0.61, 1.42)	0.7412	1.25 (0.85, 1.85)	0.2634	1.11 (0.76, 1.63)	0.5853

Rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 4. The rates of clinical outcomes according to quartiles of hospital volume

Outcome		Q1	Q2	Q3	Q4	P
Three months	Mortality, No. (%)	167 (4.95%)	196 (3.64%)	142 (4.33%)	187 (3.39%)	0.0011
	*Poor outcome, No. (%)	783 (23.41%)	1042 (19.51%)	698 (21.37%)	1160 (21.15%)	0.0003
	Stroke recurrence, No. (%)	178 (5.28%)	297 (5.51%)	166 (5.06%)	238 (4.32%)	0.0298
	Combined vascular events, No. (%)	183 (5.43%)	303 (5.63%)	168 (5.12%)	247 (4.48%)	0.0440
One year	Mortality, No. (%)	306 (9.59%)	393 (7.69%)	256 (8.39%)	367 (7.16%)	0.0006
	#Poor outcome, No. (%)	817 (25.69%)	1058 (20.71%)	665 (21.81%)	1161 (22.65%)	<.0001
	Stroke recurrence, No. (%)	228(7.15%)	388 (7.59%)	209 (6.85%)	327 (6.38%)	0.1121
	Combined vascular events, No. (%)	236 (7.40%)	406 (7.94%)	216 (7.08%)	368 (7.18%)	0.3986

* A total of 17,438 patients achieved modified Rankin Scale at 3 months. # A total of 16,462 patients achieved modified Rankin Scale at 1 year.

Table 5. The association between hospital volume and clinical outcomes

Outcome		Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Three months							
Mortality	Unadjusted	1.54 (1.13, 2.09)	0.0059	1.09 (0.85, 1.40)	0.4772	1.26 (0.89, 1.79)	0.1861
	Adjusted	1.27 (0.88, 1.83)	0.2062	0.99 (0.75, 1.30)	0.9179	1.18 (0.82, 1.68)	0.3708
Poor outcome	Unadjusted	1.22 (1.01, 1.47)	0.0377	0.95 (0.81, 1.11)	0.5341	1.06 (0.89, 1.26)	0.4937
	Adjusted	1.17 (0.91, 1.52)	0.2269	0.95 (0.74, 1.22)	0.6891	0.96 (0.75, 1.22)	0.7185
Recurrent stroke	Unadjusted	1.27 (0.92, 1.75)	0.1403	1.21 (0.91, 1.61)	0.1992	1.16 (0.85, 1.58)	0.3563
	Adjusted	1.16 (0.83, 1.62)	0.3798	1.11 (0.79, 1.56)	0.5474	1.11 (0.78, 1.56)	0.5620
Combined vascular events	Unadjusted	1.27 (0.92, 1.76)	0.1391	1.19 (0.89, 1.60)	0.2437	1.14 (0.83, 1.56)	0.4304
	Adjusted	1.15 (0.82, 1.61)	0.4109	1.09 (0.78, 1.53)	0.6167	1.08 (0.76, 1.52)	0.6763
One year							
Mortality	Unadjusted	1.48 (1.17, 1.88)	0.0013	1.13 (0.93, 1.38)	0.2097	1.22 (0.96, 1.54)	0.0996
	Adjusted	1.15 (0.89, 1.47)	0.2829	0.98 (0.79, 1.22)	0.8663	1.05 (0.82, 1.35)	0.6743

Poor outcome	Unadjusted	1.29 (1.08, 1.54)	0.0043	0.94 (0.81, 1.09)	0.4317	1.00 (0.86, 1.17)	0.9917
	Adjusted	1.29 (1.01, 1.64)	0.0393	0.98 (0.78, 1.24)	0.8758	0.85 (0.68, 1.06)	0.1566
Recurrent stroke	Unadjusted	1.20 (0.91, 1.59)	0.1939	1.18 (0.93, 1.49)	0.1853	1.08 (0.83, 1.40)	0.5552
	Adjusted	1.08 (0.81, 1.43)	0.6025	1.05 (0.80, 1.37)	0.7277	1.01 (0.77, 1.32)	0.9491
Combined vascular events	Unadjusted	1.11 (0.84, 1.45)	0.4583	1.10 (0.87, 1.39)	0.4307	1.00 (0.77, 1.30)	0.9906
	Adjusted	0.97 (0.75, 1.27)	0.8487	0.96 (0.75, 1.24)	0.7727	0.92 (0.71, 1.19)	0.5181

The adjusted covariates included age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, hospital characteristics (academic status, beds, stroke unit, and location), and the composite measure of care.

Figure legends

Figure 1. The flow chart for patient selection

Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and 3-month all-cause mortality. B, Hospital volume and 1-year all-cause mortality. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and 3-month poor outcome. B, Hospital volume and 1-year poor outcome. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and 3-month recurrent stroke. B, Hospital volume and 1-year recurrent stroke. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and 3-month combined vascular events. B, Hospital volume and 1-year combined vascular events. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

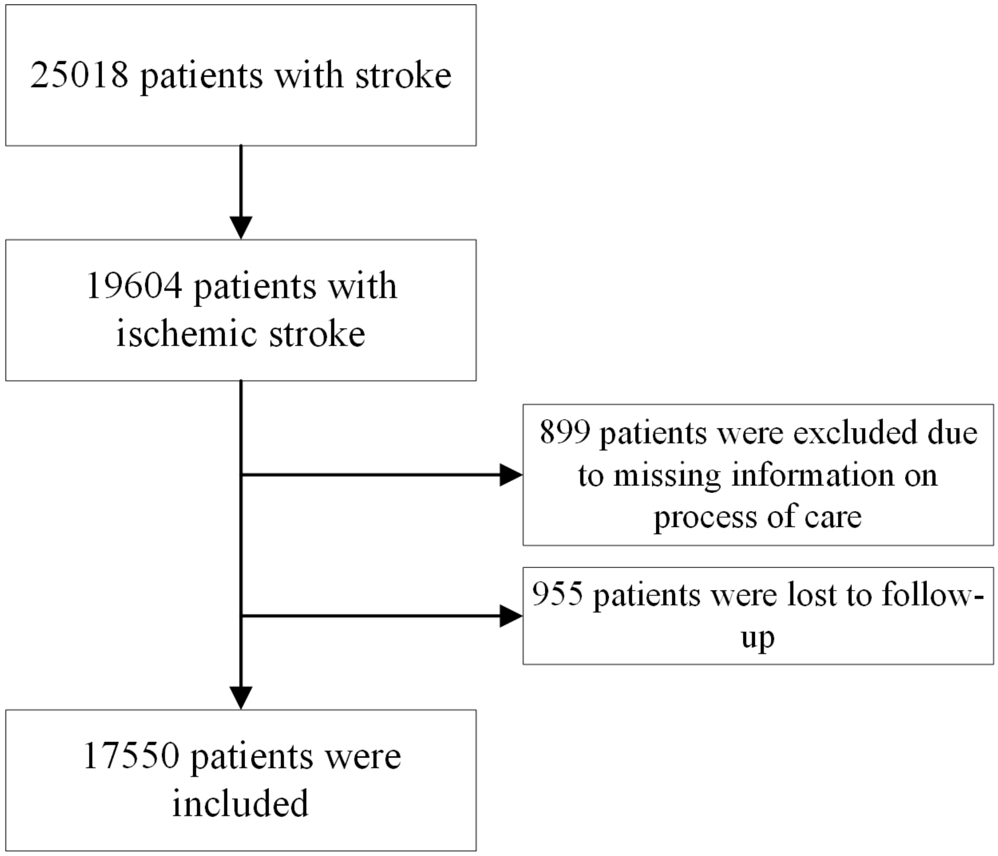

Figure 1. The flow chart for patient selection

106x90mm (300 x 300 DPI)

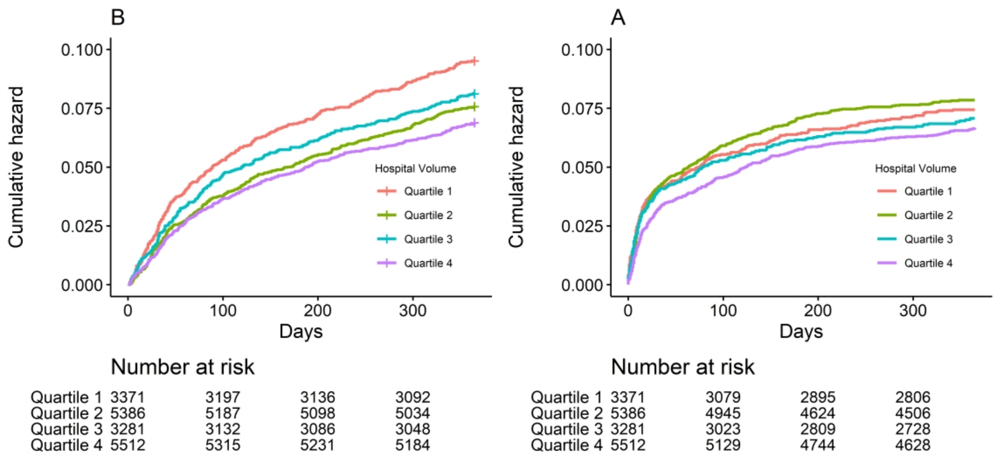

Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

254x118mm (600 x 600 DPI)

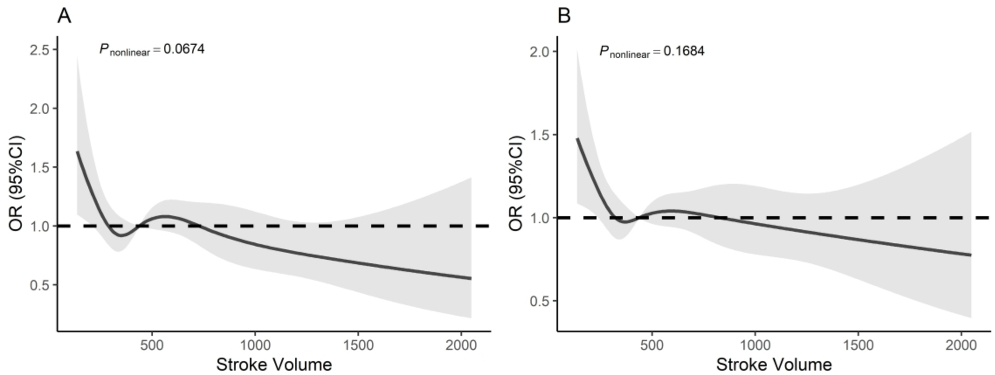

Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and 3-month all-cause mortality. B, Hospital volume and 1-year all-cause mortality. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

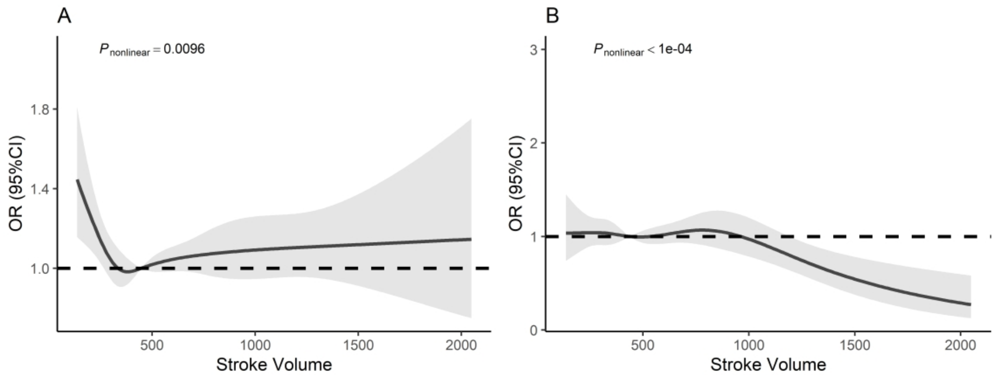

Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and 3-month poor outcome. B, Hospital volume and 1-year poor outcome. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

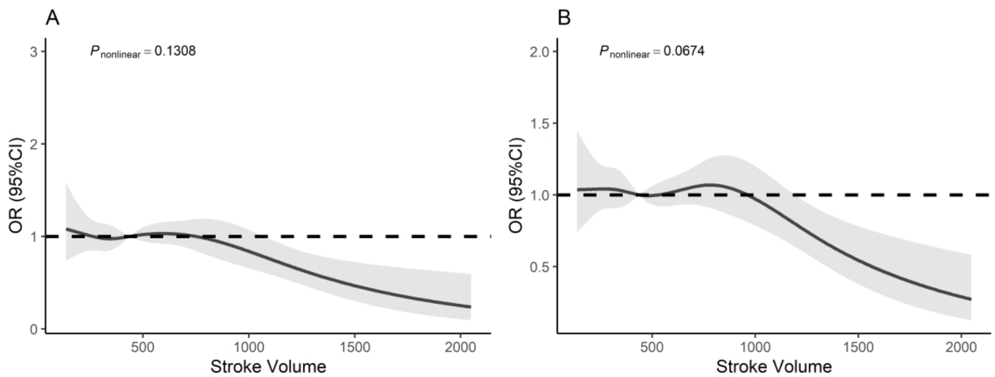

Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and 3-month recurrent stroke. B, Hospital volume and 1-year recurrent stroke. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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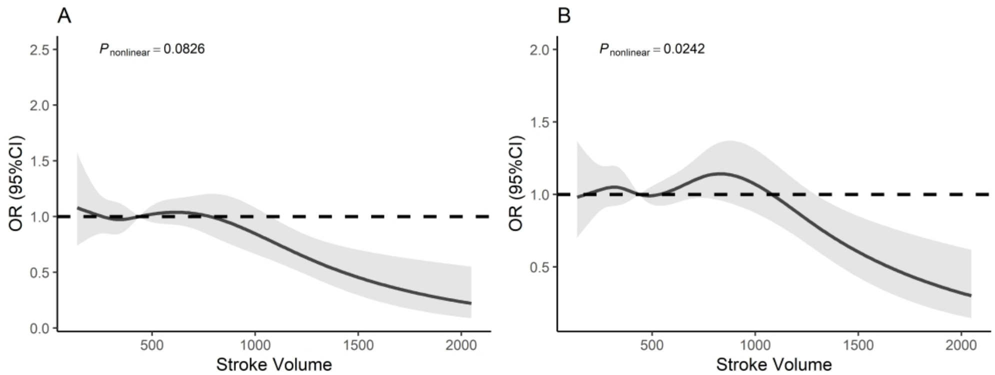

Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and 3-month combined vascular events. B, Hospital volume and 1-year combined vascular events. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

Supplementary Material

Table 1. The definition of process measures

	Definition*
Acute phage process measures	
rt-PA	intravenous tissue-type plasminogen activator (tPA) in patients who arrive within 2 hours after symptom onset and treated within 3 hours.
Early antithrombotics	Antithrombotic treatment within 2 days after admission, including antiplatelet or anticoagulant medications.
DVT prophylaxis	Patients who cannot walk received DVT prophylaxis within 2 days after admission, including pneumatic compression, heparin sodium, warfarin sodium or new oral anticoagulants.
Dysphagia screening	Dysphagia screening before oral intake
Process measures at discharge	
Antithrombotic medication	Antithrombotic medication prescribed at discharge.
Antihypertensive medication for hypertension	Antihypertensive medication prescribed at discharge for patients with hypertension.
Hypoglycemic medication for diabetes	Hypoglycemic medication prescribed at discharge for patients with diabetes.
Anticoagulation for AF	Anticoagulation medication prescribed at discharge for patients with atrial fibrillation.
Lowering LDL-C medication	Statin prescribed at discharge if LDL-C ≥100 mg/dL or patient treated with lipid-lowering agent prior to admission, or LDL-C not documented.
Smoking cessation	Smoking cessation intervention before discharge for current smokers.
Stroke education	Stroke education provided to patient and/or caregiver, including all five components: modifiable risk factors, stroke warning sign and symptoms, how to activate emergency medical services, need for follow-up and medications prescribed.

rt-PA indicates recombinant tissue plasminogen activator; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

*Performance and quality measures are applied only to eligible patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.

Table 2. Baseline characteristics between included and excluded patients

Characteristic	Included (n=17550)	Excluded (n=2054)	P
Patient characteristics			
Male	11163 (63.6%)	1274 (62.0%)	0.1591
Age	65(57-74)	65(57-75)	0.1122
Health insurance			
URBMI	8959 (51.0%)	1062 (51.7%)	0.4888
NRCMS	6932 (39.5%)	815 (39.7%)	
Commercial insurance	60 (0.3%)	9 (0.4%)	
Self-payment	1599 (9.1%)	168 (8.2%)	
Education			
Elementary or below	7934 (45.2%)	948 (46.2%)	0.3827
Middle school	4109 (23.4%)	453 (22.1%)	
High School or above	5507 (31.4%)	653 (31.8%)	
Previous or current smoking	7818 (44.5%)	854 (41.6%)	0.0104
Drinking	5277 (30.1%)	582 (28.3%)	0.1044
Medical history			
Hypertension	11386 (64.9%)	1311 (63.8%)	0.3455
Diabetes	3630 (20.7%)	430 (20.9%)	0.7905
Hyperlipidemia	2128 (12.1%)	242 (11.8%)	0.6514
Atrial fibrillation	1185 (6.8%)	197 (9.6%)	<0.0001
Stroke or TIA	5918 (33.7%)	722 (35.2%)	0.1951
Medication history			
Antiplatelet	3444 (19.6%)	425 (20.7%)	0.2501
Anticoagulation	178 (1.0%)	30 (1.5%)	0.0618
Antihypertension	7868 (44.8%)	907 (44.2%)	0.5610
Lipid-lowering medicine	1207 (6.9%)	144 (7.0%)	0.8216
Antidiabetics	2782 (15.9%)	333 (16.2%)	0.6725
NIHSS at admission	4(2-7)	4(1-8)	0.6146
Days of hospitalization	13(9-16)	13(9-15)	0.3805

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme.

Table 3. The association between hospital volume and performance measures from unadjusted models.

Performance measures	Q1 VS Q4 Unadjusted OR (95% CI)	Q1 VS Q4 P	Q2 VS Q4 Unadjusted OR (95% CI)	Q2 VS Q4 P	Q3 VS Q4 Unadjusted OR (95% CI)	Q3 VS Q4 P
rt-PA	0.64 (0.31, 1.34)	0.2386	0.72 (0.35, 1.49)	0.3811	0.62 (0.28, 1.37)	0.2389
Early antithrombotic	0.86 (0.39, 1.90)	0.7114	1.10 (0.49, 2.47)	0.8241	1.02 (0.44, 2.36)	0.9626
Dysphagia screening	0.78 (0.38, 1.60)	0.5015	2.03 (0.93, 4.42)	0.0754	1.08 (0.53, 2.18)	0.8327
DVT prophylaxis	1.31 (0.76, 2.28)	0.3329	1.37 (0.80, 2.36)	0.2501	2.22 (1.26, 3.91)	0.0059
Antithrombotic medication	1.43 (0.93, 2.20)	0.1077	1.74 (1.09, 2.76)	0.0196	1.40 (0.71, 2.75)	0.3307
Lowering LDL-C medication	1.12 (0.76, 1.66)	0.5726	1.35 (0.94, 1.94)	0.101	1.60 (1.10, 2.33)	0.0134
Antihypertensive medication for hypertension	0.91 (0.66, 1.25)	0.5588	0.84 (0.62, 1.14)	0.2679	1.08 (0.79, 1.49)	0.6339
Hypoglycemic medication for diabetes	0.98 (0.67, 1.45)	0.931	1.00 (0.68, 1.46)	0.9978	1.06 (0.72, 1.58)	0.757
Anticoagulation for AF	0.58 (0.34, 1.01)	0.0528	0.77 (0.48, 1.24)	0.2842	1.24 (0.73, 2.09)	0.4229
Smoking cessation	0.72 (0.44, 1.18)	0.1959	0.83 (0.50, 1.37)	0.4646	0.81 (0.43, 1.53)	0.5187
Defect-free measure of care	0.88 (0.62, 1.25)	0.4634	1.13 (0.82, 1.56)	0.4496	1.15 (0.81, 1.62)	0.4347

rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between Hospital Volume, Processes of Care, and Outcomes after Acute Ischemic Stroke: A Prospective Observational Study

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Abstract

Objectives There is uncertainty with respect to the hospital volume and clinical outcomes for patients with stroke. This study aimed to assess the association between hospital volume, processes of care, and outcomes after ischemic stroke.

Design A multicenter prospective cohort study.

Setting Two hundred and seventeen secondary or tertiary public hospitals from China.

Participants A total of 17,550 patients within seven days of acute ischemic stroke were included.

Main outcome measures The outcomes included all-cause mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and 1 year. The patients were divided into four groups based on quartiles of the hospital volume. We compared the difference in the process of care across the groups and estimated the effects of hospital volume on mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and 1 year. Restricted cubic splines were used to illustrate the association between hospital volume and clinical outcomes.

Results There were no significant differences in the process of care across the four groups. When adjusted for confounders, the effect of hospital volume on mortality, recurrent stroke, and combined vascular events was not significant. However, compared with the highest quartile, the patients in the lowest quartile of hospital volume tend to have poor outcome at 1 year (OR = 1.29, 95% CI 1.01-1.64, P = 0.0393). The restricted cubic spline analyses suggested a non-linear relationship between hospital volume and 1-year combined vascular events and poor outcome at 3 months and one year.

Conclusions We found no significant associations between hospital volume, processes of care at the hospital, and mortality, recurrent stroke, and combined vascular events in patients with ischemic stroke. However, hospital volume may be associated with poor outcome at 1 year.

Strengths and limitations of this study

The sample size was large, involving 217 institutions across the country.

To the best of our knowledge, this is the first study investigating the relationship between stroke volume in a hospital, process of care, and outcomes in China.

The study has some limitations. Some processes of care, especially post-discharge, could not be obtained in this study.

The participating hospitals were volunteers, and unavoidable selection bias could not be eliminated.

Introduction

Previous studies have shown that the number of patients treated in a hospital (hospital volume) may be associated with surgical outcomes in aortic valve replacement, carotid endarterectomy, coronary artery bypass surgery, and cancer-related surgeries.[1-5] The volume-outcome relationship was also described in some medical conditions, including heart failure, acute myocardial infarction, pneumonia, and brain injury.[6-8] The magnitude of the association varied significantly in a previous study.[9] Studies reporting an inverse relationship lacked significance to make volume-based referral recommendations.[10] Several studies have examined the association between hospital stroke volume and mortality for stroke patients. However, the results were controversial. Some found that stroke patients in high-volume hospitals had decreased case fatality,[11, 12] but some had not.[13, 14] Most of the studies evaluated the short-term mortality; studies investigating long-term outcomes were limited. Furthermore, the associations between hospital volume and recurrent stroke and poor outcome were not well characterized.

We hypothesize that the hospitals with higher volume may be characterized by a high quality of care, which in turn improves the prognosis of patients with stroke. This study aimed to examine the association between hospital stroke volume and outcomes, including mortality, recurrent stroke, combined vascular events, and poor outcome at 3 months and 1 year after stroke onset. We also examined the association between hospital stroke volume and the process of care for ischemic stroke.

Methods

Ethics approval

This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-005-01). Written informed consent was obtained from the patients or their relatives.

Study design and setting

The Second China National Stroke Registry (CNSR II) was a national multicenter hospital-based cohort study. CNSR II was launched in June 2012 in China. The primary objectives were to evaluate the delivery of stroke care and identify suboptimal performance metrics to be improved.[15] The hospitals were selected based on similar criteria in CNSR I launched in 2007, which had been published elsewhere.[16] After assessing the hospital characteristics, such as location, teaching status, number of beds, and annual stroke discharges by the steering committee, a total of 219 hospitals were included in CNSR II.[17]

Study population

Consecutive patients were recruited from June 2012 to January 2013. The inclusion criteria were as follows: (1) age 18 years or above; (2) presentation within seven days of onset of index acute ischemic stroke (AIS), transient ischemic attack (TIA), intracerebral hemorrhage, or subarachnoid hemorrhage, which were confirmed by brain computed tomography or magnetic resonance imaging; and (3) direct hospital admission from a physician's clinic or emergency department. A total of 25,018 patients (19,604 [78%] with AIS) were included in CNSR Ⅱ.

There were 1,200 (6.12%) patients lost at 3 months and 2,306 (11.76%) patients lost at 1 year. We excluded the patients who missed information on the process of care and those who were lost to follow-up at 3 months and 1 year. Finally, 17,550 patients and 16,482 patients with AIS were eligible for evaluating the association between hospital volume and 3-month outcomes and 1-year outcomes, respectively. A total of 17,438 patients achieved a modified Rankin Scale (mRS) at 3 months, and 16,462 patients achieved mRS at 1 year.

Data collection

Data were collected following a standardized form by trained research coordinators.Data on demographics, health insurance, education, smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and medication history were extracted from medical records. National Institutes of Health Stroke Scale (NIHSS) at admission and mRS prior to the index event were assessed through a face-to-face interview.

Hospital stroke volume was defined as the annual number of stroke discharges. The annual stroke discharges of each hospital were obtained via the hospital survey when they applied to participate in this study. Additionally, hospital characteristics, such as location, academic status, the presence of stroke unit, and the number of beds, were obtained in the survey.

Process measures

We selected ten recommended process measures form the national guidelines and the Get With The Guidelines-Stroke (GWTG-Stroke).[18] Process measures are shown in Supplemental Table 1. There were four acute phase process measures, namely (1) intravenous recombinant tissue plasminogen activator (rt-PA) in patients who arrived within 2 hours after symptom onset and were treated within 3 hours, (2) antithrombotics within 2 days after admission, (3) deep vein thrombosis (DVT) prophylaxis, and (4) dysphagia screening. There were six process measures at discharge: (1) antithrombotic medication; (2) antihypertensive medication for patients with hypertension; (3) hypoglycemic medication for patients with diabetes; (4) anticoagulation for atrial fibrillation; (5) lowering low-density lipoprotein cholesterol (LDL-C) medication; and (6) smoking cessation. Additionally, we calculated a binary defect-free measure of care, defined as the patient receiving all the processes for which they were eligible.[19, 20] Process measures were applied only to qualified patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.[21]

Clinical outcomes

All patients were followed up at 3, 6, and 12 months by telephone or face-to-face interview. Trained research coordinators collected the clinical outcomes. In this study, the outcomes included all-cause mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and 1 year. Each case fatality was identified from the attended hospital where the patient was treated or by a death certificate from the local citizen registry. Stroke recurrence was defined as a new ischemic stroke or hemorrhagic stroke within 3 months or 1 year after symptom onset. Composite vascular events included myocardial infarction, recurrent stroke, and vascular death. The poor outcome was defined as mRS of 3 to 6.

Statistical analysis

The patients were categorized into four groups based on quartiles of hospital volume: Q1 (<300 /year), Q2 (300-436 /year), Q3 (437-722 /year), and Q4 (>722 /year). Continuous variables were described as mean ± standard deviation or median and interquartile range. Categorical variables were described as proportions. The patient characteristics were compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, to obtain the P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for continuous variables and Cochran-Mantel-Haenszel row mean scores for categorical variables.

Generalized estimating equations with an exchangeable working correlation matrix were used to evaluate the association between hospital volume, the process of care, and outcomes adjusting for the cluster effect within the hospital. In the adjusted models, age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, and hospital characteristics (academic status, number of beds, presence of stroke unit, and location) were included. Additionally, the defect-free measure of care was included in the adjusted model when estimating the association between hospital volume and outcomes. We used the Kaplan-Meier method to depict the cumulative hazards of all-cause mortality and recurrent stroke. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used with the hospital volume of Q4 as reference. Additionally, we used restricted cubic splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the association between hospital volume and outcomes. We tested for non-linearity by using the Wald statistics.

All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P values were two-tailed with a significant level of 0.05.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

A total of 17,550 patients with AIS from 217 hospitals across China were included in this study. The process of patient selection is shown in Figure 1. Patients included in the current study and those excluded were largely comparable (supplemental Table 2). Table 1 describes the baseline characteristics of the included hospitals and patients.

Of the 217 hospitals, 125 (57.6%) were teaching hospitals. The high-volume hospitals were likely to be teaching hospitals. Overall, 121 hospitals (55.8%) had certified stroke units. There were 121 hospitals in the east of China, 66 around the middle, and 30 in the west. The average hospital volume was 437 per year, ranging from 136 to 2048.

The mean age was 65 (57-74), and 63.6% of the patients were males. The median NIHSS at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared with the high-volume hospitals, there were more females, and the patients were older in low-volume hospitals. The patients in high-volume hospitals were more likely to have diabetes and hyperlipidemia but less likely to have atrial fibrillation. The proportions of patients taking antiplatelet and lipid lowing agents were higher in high-volume hospitals than that in low-volume hospitals.

Association between Hospital Volume and Process Measures

Table 2 lists the rates of achievement in process measures. Compared with the hospitals of Q4, the unadjusted OR of defect-free measure of care was 0.88 (95% CI, 0.62-1.25) for Q1, 1.13 (95% CI, 0.82-1.56) for Q2, and 1.15 (95% CI, 0.81-1.62) for Q3. No significant difference was found in individual process measures, except the DVT prophylaxis for A3 (OR, 2.22; 95%CI, 1.26-3.91; P = 0.0059), antithrombotic medication at discharge for Q2 (OR, 1.74; 95%CI, 1.09-2.76; P = 0.0196), and LDL-C-lowering medication for Q3 (OR, 1.60; 95%CI, 1.10-2.33; P = 0.0134) (Supplemental Table 3).

Table 3 shows the adjusted ORs for process measures. After adjusting for the patients and hospital characteristics, the adjusted OR of defect-free measure of care was 0.93 (95% CI, 0.61-1.42) for Q1, 1.25 (95% CI, 0.85-1.85) for Q2, and 1.11 (95% CI, 0.76-1.63) for Q3. All the individual performance measures show no significant association (all P >0.05).

Association between Hospital Volume and 3-Month and 1-Year Outcomes

Of the included patients, 1,322 (7.53%) died within 1 year after stroke onset. The Kaplan-Meier plot for mortality within 1 year is shown in Figure 2. The 3-month and 1-year mortality was different across the 4 groups (3-month mortality, 4.95% versus 3.64% versus 4.33% versus 3.39%, P = 0.0011; 1-year mortality, 9.59% versus 7.69% versus 8.39% versus 7.16%, P = 0.0006) (Table 4). At 3 months and 1 year, the mortality was slightly higher in Q1 hospitals (OR at 3 months=1.54, 95% CI 1.13-2.09, P = 0.0059; OR at 1 year = 1.48, 95% CI

1.17- 1.88; P = 0.0013), but not Q2 or Q3 hospitals in compared with Q4 hospitals. However, the difference was not significant when adjusted for potential factors (Table 5).

A total of 3,683 (21.12%) patients experienced poor outcome at 3 months and 3701 (22.48%) at 1 year (Table 4). Patients treated in low-volume hospitals were more likely to have a higher rate of poor outcome at 3 months (23.41% versus 19.51% versus 21.37% versus 21.15%, P = 0.0003; $OR_{Q1 \text{ versus } Q4}$ = 1.22, 95% CI 1.01-1.47, P = 0.0377) and 1 year (25.69% versus 20.71% versus 21.81% versus 22.65%, P<0.0001; $OR_{Q1 \text{ versus } Q4}$ = 1.29, 95% CI 1.08-1.54, P = 0.0043). When adjusted for potential factors, Q1 hospitals still had a higher rate of poor outcome at 1 year compared with Q4 hospitals ($OR_{Q1 \text{ versus } Q4}$ = 1.29, 95% CI 1.01-1.64, P = 0.0393).

There were 1,199 (6.83%) patients with recurrent stroke within 1 year. The Kaplan-Meier plot for recurrent stroke within 1 year is shown in Figure 3. The recurrence rate was similar across the four groups (7.15% versus 7.59% versus 6.85% versus 6.38%, P = 0.1121) (Table 4). No significant association was found between hospital volume and stroke recurrence at 3 months and 1 year. Similar results were observed for combined vascular events (Table 5).

In Figures 3-6, we used restricted cubic splines to illustrate the relationship of all-cause mortality, poor outcome, stroke recurrence, and combined vascular events with hospital stroke volume. The multivariable-adjusted restricted cubic splines showed a “J-shaped” association between volume and all-cause mortality and poor outcome, indicating a significant non-linear association between volume and poor outcome at 3 months and 1 year (P for non-linear = 0.0096 and <0.001, respectively), as well as combined vascular events at 1 year (P for non-linear = 0.0242).

Discussion

Our analysis of a large population of 17,550 patients with ischemic stroke suggested that no significant difference in the process of care was observed for patients in lower-volume hospitals compared to that for patients in higher-volume hospitals. There was no association between hospital volume and mortality, stroke recurrence, and combined vascular events at 3 months and 1 year. In contrast, we found that the patients in the lowest volume quartile had a significantly higher rate of poor outcome at 1 year than the patients in the highest quartile.

Previous studies found that high volume was associated with improved outcomes suggesting that volume is a surrogate for quality of care. The quality of care can be assessed from outcome, process, and structure.[22] Usually, hospital volume is used as a structure metric of quality of care. However, the underlying mechanisms of interplay between structure and process are complex.[23] Two existing studies showed that the patients in high-volume hospitals received more process of care than patients in low-volume hospitals.[13, 23] Potential mechanisms were proposed to explain this association, including substantial experience ("practice makes perfect") and the availability of advanced techniques and devices in high-volume hospitals.[7, 23] In contrast, we did not find an association between hospital stroke volume and process measures in the current study. This was similar to a study from GWTG-Stroke, wherein 790 US hospitals (322,847 patients with ischemic stroke or TIA) were assessed and no differences in performance measures were observed between high-volume and low-volume hospitals after adjusting for patient baseline characteristics.[18] Previously, many initiatives for improving the quality of care have been implemented to standardize the quality of care in hospitals, such as GWTG-Stroke, Australian Stroke Clinical Registry, and CNSR,[24] which may minimize the variability in the quality of care between high-volume and low-volume hospitals.

During the past decades, a significant number of studies evaluated the volume-outcome association. Many, but not all, found a reverse relationship between volume and outcome.[9] Several studies revealed that stroke patients in high-volume hospitals may experience lower short-term mortality than patients in low-volume hospitals.[11, 12, 25, 26] However, we found no improvement in the mortality rate for patients in high-volume hospitals. Several reasons may explain this discrepancy. First, the hospital volume varied in these studies. Moreover, stroke severity, adjusted or not, remained an essential factor affecting prognosis.[13] Most studies to date lack data on stroke severity, and use comorbidity or comorbidity index score to adjust the case mix.[11, 12, 25, 26] Herein, we used the NIHSS score at admission to adjust the stroke severity. Our findings are compatible with a Danish nationwide cohort study of 63,995 patients admitted to stroke units.[23] This study found no association between volume and 30-day mortality and 1-year mortality rates after adjusting for patient baseline characteristics, stroke unit, university status, and quality of care. Mortality may be insensitive to detecting nuances in patient prognosis.[23]

Besides mortality, we also examined the association between hospital volume and poor outcome, stroke recurrence, and combined vascular events. To our knowledge, this is the first time the association between volume and poor outcome at 3 months and 1 year in patients with AIS was evaluated in a study. Compared with the highest quartile of hospitals, patients in the lowest quartile had a higher rate of poor outcome at 1 year after adjusting for potential confounders. The poor outcome may be more sensitive in detecting changes in patient prognosis. The underlying mechanisms of the association between volume and poor outcome are not known. Though there was no significant difference in the process of care during the acute phase and at discharge between low- and high-volume hospitals, the differences in some other processes of care after discharge may explain this association. Patients in high-volume hospitals may undergo more processes after discharge, such as limb rehabilitation, which can improve poor outcome. The association between volume and poor outcome may be mediated by medical care after discharge. However, data on post-discharge management were not routinely documented; hence, data could not be extracted from all patients and analyzed. In the future, the association between volume, the process of care after discharge, and long-term outcomes are needed for further exploration. Despite the significant association, we did not think it was reasonable to regionalize stroke care because patient transfers may lead to a delay in admission, offsetting some benefits of being admitted to large-volume hospitals.[11]

Several limitations in this study should be acknowledged. First, the hospitals that participated in the CNSR were volunteers; therefore, selection bias cannot be completely eliminated. The sampled hospitals enrolled may not be representative of the general hospitals in China. Second, although ten processes of care were evaluated, other processes of care such as mechanical thrombectomy and the care patients received after discharge could not be assessed. The differences in unassessed process measures may explain the association between volume and poor outcome. Third, there is a cluster effect within hospitals and physicians. Although we considered the cluster effect within hospitals by using the generalized estimating equations, we could not adjust the cluster effect within physicians. Moreover, due to variability among patients, hospital characteristics, and performance of care across varied regions and countries, our results may not be applicable to other countries. Finally, the mortality rate in our study was lower than the studies from other countries. Several reasons could explain this. First, most of the included patients were minor strokes (NIHSS≤4). Second, although we used the central death registry to obtain the vital status of those patients lost to follow up, we failed to obtain the vital status of all patients. This may lead to bias. Further studies on volume and clinical outcome, especially the poor outcome, are needed to confirm our results.

Conclusions

Using the large national stroke registry, we found no association between hospital stroke volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile of hospitals had increased rates of poor outcome compared with the patients in the highest quartile of hospitals. Further studies need to be conducted to examine whether the medical care after discharge mediates the association between stroke volume and poor outcome. Better understanding of the association between structure, processes, and outcomes can help identify the best way to improve stroke prognosis.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation: RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG Zhou and YJ Wang take responsibility for the integrity of the work.

References

1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol*. 2017;2:732-741

2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in

the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA*. 1998;279:1278-1281

3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg*. 2016;263:664-672

4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J Public Health*. 2007;97:539-544

5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886

6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common medical conditions. *N Engl J Med*. 2010;362:1110-1118

7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume, Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661-1670

8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in patients with traumatic brain injury: A retrospective observational study using a national inpatient database in Japan. *Injury*. 2017;48:1423-1431

9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520

10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med Care*. 2010;48:149-156

11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes*. 2015;8:S141-147

12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it matter? *Neurology*. 2007;69:1142-1151

13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients: Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753

14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. *Int J Stroke*. 2015;10:73-78

15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement in Stroke Care in China. *Stroke*. 2016;47:2843-2849

16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*. 2011;6:355-361

17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients hospitalized with acute ischemic stroke in China: Findings from the China National Stroke Registry II. *Int J Stroke*. 2017;12:254-263

18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107-115

19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke:

findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238

20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419

21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239

22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729

23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045

24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40

25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke fatality in Canada. *Stroke*. 2008;39:3360-3366

26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788

Table 1. Hospital and patient characteristics by quartiles of hospital volume

Characteristic	Total (n=17550)	Q1 hospitals <300/year (n=3371)	Q2 hospitals 300-436/year (n=5386)	Q3 hospitals 437-722/year (n=3281)	Q4 hospitals >722/year (n=5512)	P	P for trend
Hospital characteristics							
Number of hospitals	217	53	56	53	55		
Teaching hospital	125 (57.6%)	23 (43.4%)	23 (41.1%)	37 (69.8%)	42 (76.4%)	<.0001	<.0001
Stroke unit	121 (55.8%)	24 (45.3%)	24 (42.9%)	35 (66%)	38 (69.1%)	0.0062	0.0017
Beds	1000 (600-1650)	600 (500-800)	780 (515-1000)	1300 (1000-2000)	1500 (1200-2200)	<.0001	<.0001
Geographic region							
East	121 (55.8%)	29 (54.7%)	35 (62.5%)	28 (52.8%)	29 (52.7%)	0.6967	<.0001
Middle	66 (30.4%)	15 (28.3%)	13 (23.2%)	20 (37.7%)	18 (32.7%)		
West	30 (13.8%)	9 (17%)	8 (14.3%)	5 (9.4%)	8 (14.5%)		
Patient characteristics							

Male	11163 (63.6%)	2126 (63.1%)	3349 (62.2%)	2108 (64.2%)	3580 (64.9%)	0.0183	0.0085
Age	65(57-74)	66(57-75)	65(57-74)	66(58-74)	64(55-73)	<.0001	<.0001
Health insurance							
URBMI	8959 (51%)	1715 (50.9%)	2552 (47.4%)	1568 (47.8%)	3124 (56.7%)	<.0001	<.0001
NRCMS	6932 (39.5%)	1369 (40.6%)	2440 (45.3%)	1394 (42.5%)	1729 (31.4%)		
Commercial insurance	60 (0.3%)	8 (0.2%)	27 (0.5%)	4 (0.1%)	21 (0.4%)		
Self-payment	1599 (9.1%)	279 (8.3%)	367 (6.8%)	315 (9.6%)	638 (11.6%)		
Education							
Elementary or below	7934 (45.2%)	1693 (50.2%)	2430 (45.1%)	1678 (51.1%)	2133 (38.7%)	<.0001	<.0001
Middle school	4109 (23.4%)	715 (21.2%)	1286 (23.9%)	661 (20.1%)	1447 (26.3%)		
High School or above	5507 (31.4%)	963 (28.6%)	1670 (31%)	942 (28.7%)	1932 (35.1%)		
Previous or current smoking	7818 (44.5%)	1457 (43.2%)	2406 (44.7%)	1455 (44.3%)	2500 (45.4%)	0.2676	0.0836
Drinking	5277 (30.1%)	872 (25.9%)	1681 (31.2%)	995 (30.3%)	1729 (31.4%)	<.0001	0.0001
Medical history							
Hypertension	11386 (64.9%)	2156 (64%)	3511 (65.2%)	2136 (65.1%)	3583 (65%)	0.6614	0.459

Diabetes	3630 (20.7%)	658 (19.5%)	1097 (20.4%)	673 (20.5%)	1202 (21.8%)	0.0599	0.0086
Hyperlipidemia	2128 (12.1%)	372 (11%)	808 (15%)	384 (11.7%)	564 (10.2%)	<.0001	0.0001
Atrial fibrillation	1185 (6.8%)	212 (6.3%)	402 (7.5%)	280 (8.5%)	291 (5.3%)	0.0001	0.0174
Stroke or TIA	5918 (33.7%)	1084 (32.2%)	1886 (35%)	1113 (33.9%)	1835 (33.3%)	0.0411	0.8641
Medication history							
Antiplatelet	3444 (19.6%)	599 (17.8%)	1008 (18.7%)	712 (21.7%)	1125 (20.4%)	<.0001	0.0002
Anticoagulation	178 (1%)	33 (1%)	69 (1.3%)	35 (1.1%)	41 (0.7%)	0.0467	0.0696
Antihypertension	7868 (44.8%)	1454 (43.1%)	2592 (48.1%)	1401 (42.7%)	2421 (43.9%)	<.0001	0.1248
Lipid-lowering medicine	1207 (6.9%)	195 (5.8%)	487 (9%)	241 (7.3%)	284 (5.2%)	<.0001	0.0002
Antidiabetics	2782 (15.9%)	500 (14.8%)	875 (16.2%)	509 (15.5%)	898 (16.3%)	0.2276	0.1842
NIHSS at admission	4(2-7)	4(2-7)	4(2-6)	4(2-8)	4(2-7)	<.0001	<.0001
Days of hospitalization	13 (9-16)	13 (10-16)	13 (9-15)	13 (9-16)	13 (10-16)	<.0001	0.0211

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

Table 2. The rates of achievement in process measures

Process measures	Total N1/N2 (achievement rate, %)	Q1 hospitals N1/N2 (achievement rate, %)	Q2 hospitals N1/N2 (achievement rate, %)	Q3 hospitals N1/N2 (achievement rate, %)	Q4 hospitals N1/N2 (achievement rate, %)
Rt-PA	217/1303 (16.7%)	36/250 (14.4%)	75/497 (15.1%)	25/200 (12.5%)	81/356 (22.8%)
Early antithrombotic	14555/17243 (84.4%)	2802/3303 (84.8%)	4508/5307 (84.9%)	2903/3199 (90.7%)	4342/5434 (79.9%)
Dysphagia screening	14876/17550 (84.8%)	2630/3371 (78.0%)	4860/5386 (90.2%)	2615/3281 (79.7%)	4771/5512 (86.6%)
DVT prophylaxis	3367/5079 (66.3%)	630/944 (66.7%)	1006/1481 (67.9%)	689/914 (75.4%)	1042/1740 (59.9%)
Antithrombotic medication	14722/16002 (92%)	2845/3058 (93.0%)	4481/4765 (94.0%)	2839/3089 (91.9%)	4557/5090 (89.5%)
Lowering LDL-C medication	7700/11597 (66.4%)	1436/2247 (63.9%)	2591/3621 (71.6%)	1523/2120 (71.8%)	2150/3609 (59.6%)
Antihypertensive	8867/13385 (66.2%)	1712/2611 (65.6%)	2764/4207 (65.7%)	1710/2470 (69.2%)	2681/4097 (65.4%)

medication for hypertension					
Hypoglycemic medication for diabetes	3662/4898 (74.8%)	685/907 (75.5%)	1114/1494 (74.6%)	721/901 (80.0%)	1142/1596 (71.6%)
Anticoagulation for AF	303/1437 (21.1%)	43/278 (15.5%)	86/468 (18.4%)	87/325 (26.8%)	87/366 (23.8%)
Smoking cessation	6712/7819 (85.8%)	1227/1457 (84.2%)	2098/2406 (87.2%)	1213/1456 (83.3%)	2174/2500 (87.0%)
Defect-free measure of care	5816/17550 (33.1%)	992/3371 (29.4%)	1965/5386 (36.5%)	1150/3281 (35.1%)	1709/5512 (31.0%)

N1 indicates the number of patients who received the process of care, and N2 indicates the number of patients eligible. Rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 3. The association between hospital volume and process measures

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Rt-PA	1.54 (0.61, 3.89)	0.3614	1.46 (0.68, 3.14)	0.3343	0.71 (0.35, 1.48)	0.3634
Early antithrombotic	0.68 (0.20, 2.32)	0.5364	1.17 (0.30, 4.55)	0.8245	1.07 (0.36, 3.18)	0.9020
Dysphagia screening	0.76 (0.33, 1.74)	0.5104	2.19 (0.86, 5.55)	0.0987	0.90 (0.42, 1.92)	0.7845
DVT prophylaxis	1.02 (0.52, 2.01)	0.9504	1.09 (0.57, 2.09)	0.7936	1.55 (0.84, 2.83)	0.1594
Antithrombotic medication	1.26 (0.61, 2.61)	0.5391	1.27 (0.61, 2.64)	0.5277	1.16 (0.63, 2.15)	0.6375
Lowering LDL-C medication	0.92 (0.57, 1.50)	0.7460	1.03 (0.62, 1.70)	0.9224	1.20 (0.78, 1.84)	0.4134
Antihypertensive medication for hypertension	0.99 (0.71, 1.38)	0.9395	0.92 (0.67, 1.27)	0.6152	1.11 (0.81, 1.53)	0.5041
Hypoglycemic medication for diabetes	1.02 (0.67, 1.55)	0.9210	1.06 (0.69, 1.65)	0.7818	0.97 (0.65, 1.46)	0.8888
Anticoagulation for AF	0.63 (0.34, 1.16)	0.1365	0.87 (0.53, 1.44)	0.5848	1.05 (0.61, 1.78)	0.8681

Smoking cessation	0.56 (0.10, 2.97)	0.4939	0.67 (0.12, 3.63)	0.6421	2.08 (0.25, 17.2)	0.4961
Defect-free measure of care	0.93 (0.61, 1.42)	0.7412	1.25 (0.85, 1.85)	0.2634	1.11 (0.76, 1.63)	0.5853

Rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

Table 4. The rates of clinical outcomes according to quartiles of hospital volume

Outcome		Q1	Q2	Q3	Q4	P
Three months	Mortality, No. (%)	167 (4.95%)	196 (3.64%)	142 (4.33%)	187 (3.39%)	0.0011
	*Poor outcome, No. (%)	783 (23.41%)	1042 (19.51%)	698 (21.37%)	1160 (21.15%)	0.0003
	Stroke recurrence, No. (%)	178 (5.28%)	297 (5.51%)	166 (5.06%)	238 (4.32%)	0.0298
	Combined vascular events, No. (%)	183 (5.43%)	303 (5.63%)	168 (5.12%)	247 (4.48%)	0.0440
One year	Mortality, No. (%)	306 (9.59%)	393 (7.69%)	256 (8.39%)	367 (7.16%)	0.0006
	#Poor outcome, No. (%)	817 (25.69%)	1058 (20.71%)	665 (21.81%)	1161 (22.65%)	<.0001
	Stroke recurrence, No. (%)	228(7.15%)	388 (7.59%)	209 (6.85%)	327 (6.38%)	0.1121
	Combined vascular events, No. (%)	236 (7.40%)	406 (7.94%)	216 (7.08%)	368 (7.18%)	0.3986

* A total of 17,438 patients achieved modified Rankin Scale at 3 months. # A total of 16,462 patients achieved modified Rankin Scale at 1 year.

Table 5. The association between hospital volume and clinical outcomes

		Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
Outcome		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Three months							
Mortality	Unadjusted	1.54 (1.13, 2.09)	0.0059	1.09 (0.85, 1.40)	0.4772	1.26 (0.89, 1.79)	0.1861
	Adjusted	1.27 (0.88, 1.83)	0.2062	0.99 (0.75, 1.30)	0.9179	1.18 (0.82, 1.68)	0.3708
Poor outcome	Unadjusted	1.22 (1.01, 1.47)	0.0377	0.95 (0.81, 1.11)	0.5341	1.06 (0.89, 1.26)	0.4937
	Adjusted	1.17 (0.91, 1.52)	0.2269	0.95 (0.74, 1.22)	0.6891	0.96 (0.75, 1.22)	0.7185
Recurrent stroke	Unadjusted	1.27 (0.92, 1.75)	0.1403	1.21 (0.91, 1.61)	0.1992	1.16 (0.85, 1.58)	0.3563
	Adjusted	1.16 (0.83, 1.62)	0.3798	1.11 (0.79, 1.56)	0.5474	1.11 (0.78, 1.56)	0.5620
Combined vascular events	Unadjusted	1.27 (0.92, 1.76)	0.1391	1.19 (0.89, 1.60)	0.2437	1.14 (0.83, 1.56)	0.4304
	Adjusted	1.15 (0.82, 1.61)	0.4109	1.09 (0.78, 1.53)	0.6167	1.08 (0.76, 1.52)	0.6763
One year							
Mortality	Unadjusted	1.48 (1.17, 1.88)	0.0013	1.13 (0.93, 1.38)	0.2097	1.22 (0.96, 1.54)	0.0996
	Adjusted	1.15 (0.89, 1.47)	0.2829	0.98 (0.79, 1.22)	0.8663	1.05 (0.82, 1.35)	0.6743

Poor outcome	Unadjusted	1.29 (1.08, 1.54)	0.0043	0.94 (0.81, 1.09)	0.4317	1.00 (0.86, 1.17)	0.9917
	Adjusted	1.29 (1.01, 1.64)	0.0393	0.98 (0.78, 1.24)	0.8758	0.85 (0.68, 1.06)	0.1566
Recurrent stroke	Unadjusted	1.20 (0.91, 1.59)	0.1939	1.18 (0.93, 1.49)	0.1853	1.08 (0.83, 1.40)	0.5552
	Adjusted	1.08 (0.81, 1.43)	0.6025	1.05 (0.80, 1.37)	0.7277	1.01 (0.77, 1.32)	0.9491
Combined vascular events	Unadjusted	1.11 (0.84, 1.45)	0.4583	1.10 (0.87, 1.39)	0.4307	1.00 (0.77, 1.30)	0.9906
	Adjusted	0.97 (0.75, 1.27)	0.8487	0.96 (0.75, 1.24)	0.7727	0.92 (0.71, 1.19)	0.5181

The adjusted covariates included age, sex, health insurance (urban resident basic medical insurance, new rural cooperative medical scheme, commercial insurance, self-payment), education (elementary or below, middle school, high school or above), previous or current smoking, drinking, comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, hospital characteristics (academic status, beds, stroke unit, and location), and the composite measure of care.

Figure legends

Figure 1. The flow chart for patient selection

Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and 3-month all-cause mortality. B, Hospital volume and 1-year all-cause mortality. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and 3-month poor outcome. B, Hospital volume and 1-year poor outcome. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and 3-month recurrent stroke. B, Hospital volume and 1-year recurrent stroke. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and 3-month combined vascular events. B, Hospital volume and 1-year combined vascular events. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

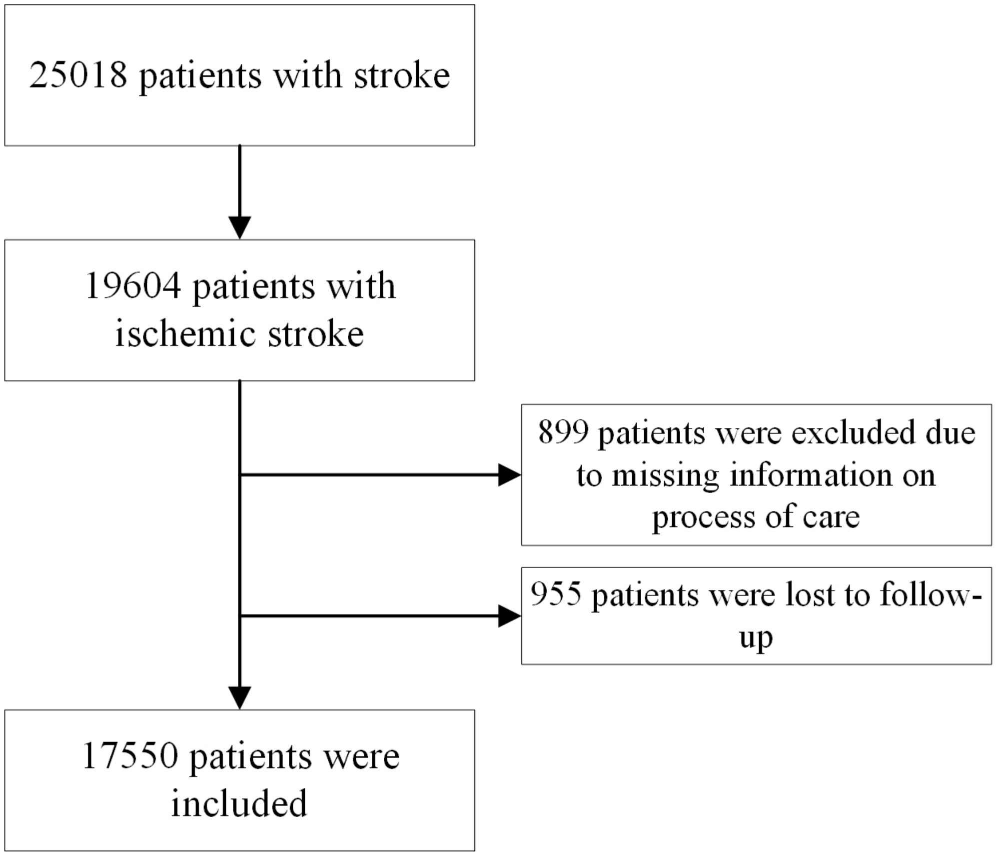

Figure 1. The flow chart for patient selection

106x90mm (300 x 300 DPI)

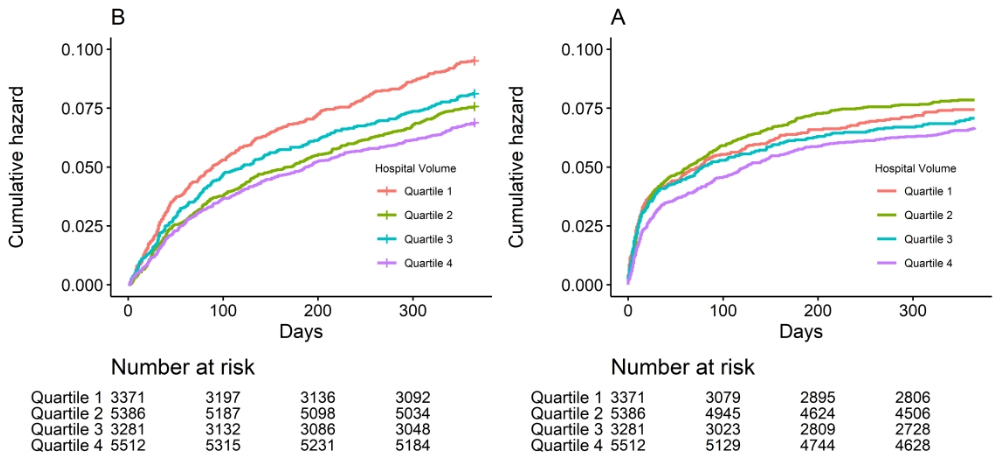

Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

254x118mm (600 x 600 DPI)

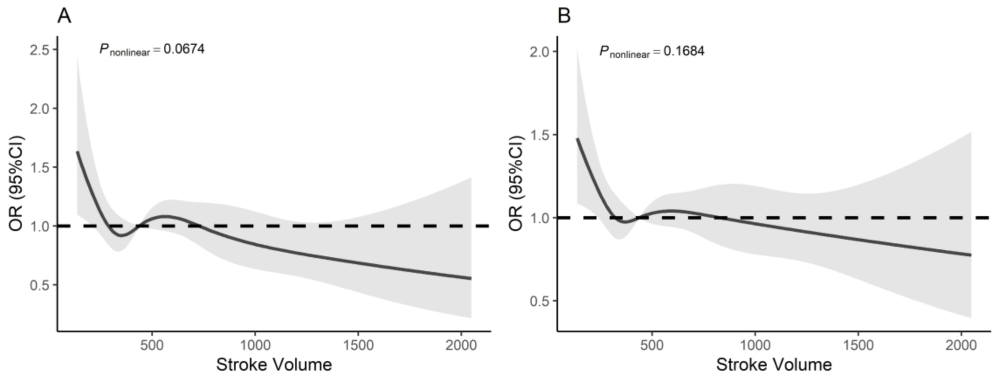

Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and 3-month all-cause mortality. B, Hospital volume and 1-year all-cause mortality. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

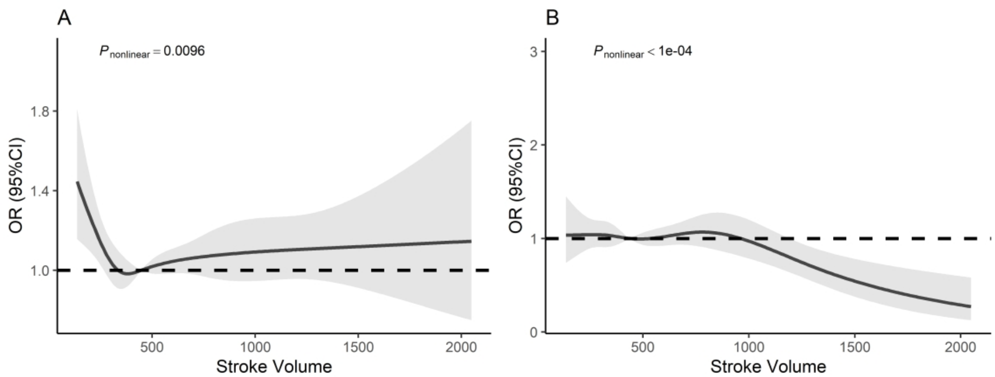

Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and 3-month poor outcome. B, Hospital volume and 1-year poor outcome. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

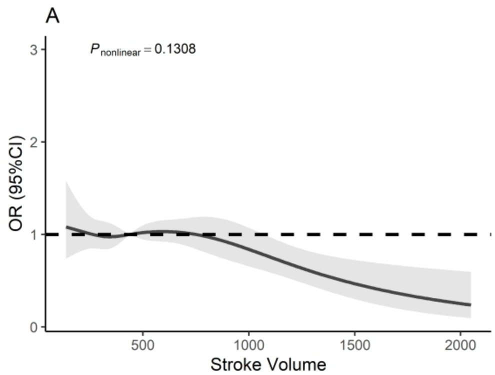

Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and 3-month recurrent stroke. B, Hospital volume and 1-year recurrent stroke. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

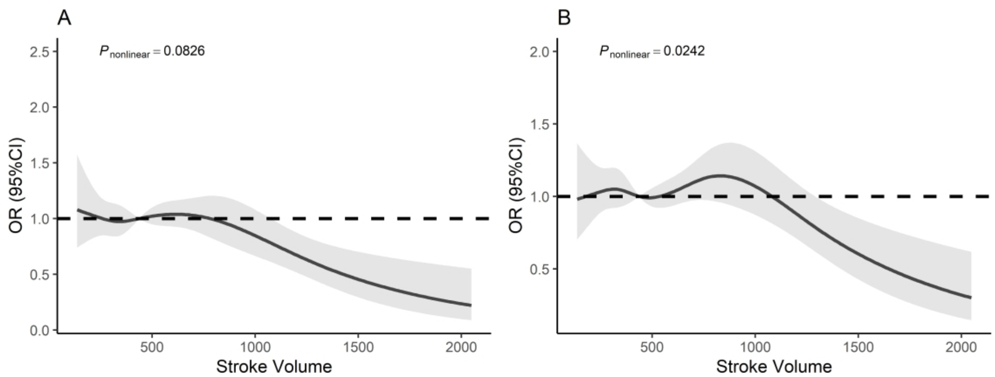

Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and 3-month combined vascular events. B, Hospital volume and 1-year combined vascular events. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

Supplementary Material

Table 1. The definition of process measures

	Definition*
Acute phage process measures	
rt-PA	intravenous tissue-type plasminogen activator (tPA) in patients who arrive within 2 hours after symptom onset and treated within 3 hours.
Early antithrombotics	Antithrombotic treatment within 2 days after admission, including antiplatelet or anticoagulant medications.
DVT prophylaxis	Patients who cannot walk received DVT prophylaxis within 2 days after admission, including pneumatic compression, heparin sodium, warfarin sodium or new oral anticoagulants.
Dysphagia screening	Dysphagia screening before oral intake
Process measures at discharge	
Antithrombotic medication	Antithrombotic medication prescribed at discharge.
Antihypertensive medication for hypertension	Antihypertensive medication prescribed at discharge for patients with hypertension.
Hypoglycemic medication for diabetes	Hypoglycemic medication prescribed at discharge for patients with diabetes.
Anticoagulation for AF	Anticoagulation medication prescribed at discharge for patients with atrial fibrillation.
Lowering LDL-C medication	Statin prescribed at discharge if LDL-C ≥100 mg/dL or patient treated with lipid-lowering agent prior to admission, or LDL-C not documented.
Smoking cessation	Smoking cessation intervention before discharge for current smokers.
Stroke education	Stroke education provided to patient and/or caregiver, including all five components: modifiable risk factors, stroke warning sign and symptoms, how to activate emergency medical services, need for follow-up and medications prescribed.

rt-PA indicates recombinant tissue plasminogen activator; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

*Performance and quality measures are applied only to eligible patients in the absence of documented contraindications or any other rationale as to why therapy was not provided.

Table 2. Baseline characteristics between included and excluded patients

Characteristic	Included (n=17550)	Excluded (n=2054)	P
Patient characteristics			
Male	11163 (63.6%)	1274 (62.0%)	0.1591
Age	65(57-74)	65(57-75)	0.1122
Health insurance			
URBMI	8959 (51.0%)	1062 (51.7%)	0.4888
NRCMS	6932 (39.5%)	815 (39.7%)	
Commercial insurance	60 (0.3%)	9 (0.4%)	
Self-payment	1599 (9.1%)	168 (8.2%)	
Education			
Elementary or below	7934 (45.2%)	948 (46.2%)	0.3827
Middle school	4109 (23.4%)	453 (22.1%)	
High School or above	5507 (31.4%)	653 (31.8%)	
Previous or current smoking	7818 (44.5%)	854 (41.6%)	0.0104
Drinking	5277 (30.1%)	582 (28.3%)	0.1044
Medical history			
Hypertension	11386 (64.9%)	1311 (63.8%)	0.3455
Diabetes	3630 (20.7%)	430 (20.9%)	0.7905
Hyperlipidemia	2128 (12.1%)	242 (11.8%)	0.6514
Atrial fibrillation	1185 (6.8%)	197 (9.6%)	<0.0001
Stroke or TIA	5918 (33.7%)	722 (35.2%)	0.1951
Medication history			
Antiplatelet	3444 (19.6%)	425 (20.7%)	0.2501
Anticoagulation	178 (1.0%)	30 (1.5%)	0.0618
Antihypertension	7868 (44.8%)	907 (44.2%)	0.5610
Lipid-lowering medicine	1207 (6.9%)	144 (7.0%)	0.8216
Antidiabetics	2782 (15.9%)	333 (16.2%)	0.6725
NIHSS at admission	4(2-7)	4(1-8)	0.6146
Days of hospitalization	13(9-16)	13(9-15)	0.3805

URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical scheme.

Table 3. The association between hospital volume and performance measures from unadjusted models.

Performance measures	Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P	Unadjusted OR (95% CI)	P
rt-PA	0.64 (0.31, 1.34)	0.2386	0.72 (0.35, 1.49)	0.3811	0.62 (0.28, 1.37)	0.2389
Early antithrombotic	0.86 (0.39, 1.90)	0.7114	1.10 (0.49, 2.47)	0.8241	1.02 (0.44, 2.36)	0.9626
Dysphagia screening	0.78 (0.38, 1.60)	0.5015	2.03 (0.93, 4.42)	0.0754	1.08 (0.53, 2.18)	0.8327
DVT prophylaxis	1.31 (0.76, 2.28)	0.3329	1.37 (0.80, 2.36)	0.2501	2.22 (1.26, 3.91)	0.0059
Antithrombotic medication	1.43 (0.93, 2.20)	0.1077	1.74 (1.09, 2.76)	0.0196	1.40 (0.71, 2.75)	0.3307
Lowering LDL-C medication	1.12 (0.76, 1.66)	0.5726	1.35 (0.94, 1.94)	0.101	1.60 (1.10, 2.33)	0.0134
Antihypertensive medication for hypertension	0.91 (0.66, 1.25)	0.5588	0.84 (0.62, 1.14)	0.2679	1.08 (0.79, 1.49)	0.6339
Hypoglycemic medication for diabetes	0.98 (0.67, 1.45)	0.931	1.00 (0.68, 1.46)	0.9978	1.06 (0.72, 1.58)	0.757
Anticoagulation for AF	0.58 (0.34, 1.01)	0.0528	0.77 (0.48, 1.24)	0.2842	1.24 (0.73, 2.09)	0.4229
Smoking cessation	0.72 (0.44, 1.18)	0.1959	0.83 (0.50, 1.37)	0.4646	0.81 (0.43, 1.53)	0.5187
Defect-free measure of care	0.88 (0.62, 1.25)	0.4634	1.13 (0.82, 1.56)	0.4496	1.15 (0.81, 1.62)	0.4347

rt-PA indicates recombinant tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.