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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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5 **Association Between Hospital Volume, Process of Care, and Outcomes after Acute**  
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7 **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. There 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.

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4 **Conclusions** We found no significant associations between hospital volume, the process of  
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6 care at the hospital, and 1-year mortality in patients with ischemic stroke. However, hospital  
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8 volume may be associated with poor outcome at 1 year.  
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#### 11 12 13 14 **Strengths and limitations of this study**

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17 The number of participants with ischemic stroke was large and 133 hospitals across China  
18  
19 were included.  
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22 This is the first time the association between stroke volume, process of care and poor  
23  
24 outcome was explored in China.  
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27 Some process of care, especially the process of care after discharge, cannot be obtained in  
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29 this study.  
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32 The hospitals participated were volunteers and unavoidable selection bias may exist.  
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## 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.<sup>1-5</sup> The volume-outcome relationship is also described in some medical conditions, including heart failure, acute myocardial infarction, pneumonia, and brain injury.<sup>6-8</sup> The magnitude of the association was varied significantly in studies.<sup>9</sup> If there were inverse relation between hospital volume and outcomes, it was of significance to make volume-based referral strategies.<sup>10</sup> Several studies have examined the association between hospital stroke volume and mortality for stroke patients. However, the results were controversial. Some<sup>11, 12</sup> found that stroke patients in high-volume hospitals had decreased case fatality, but some<sup>13, 14</sup> 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

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4 This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-  
5  
6 005-01). The rewritten informed consent was obtained from the patients or their relatives.  
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### 10 11 **Study Design and Setting**

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14 This retrospective analysis used data from the China National Stroke Registry II (CNSR II),  
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16 which was a national multicenter hospital-based cohort study. CNSR II was launched in June  
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18 2012 in China and the primary objectives were to evaluate the delivery of stroke care and  
19  
20 identify suboptimal performance metrics to be improved.<sup>15</sup> The hospitals were selected based  
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22 on similar criteria in CNSR I launched in 2007, which had been published elsewhere.<sup>16</sup> After  
23  
24 assessing the hospital characteristics, such as location, teaching status, number of beds, and  
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26 annual stroke discharges by the steering committee, a total of 219 hospitals were included in  
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28 CNSR II.<sup>17</sup>  
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### 38 **Study Population**

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40 The patients were consecutively recruited from June 2012 to January 2013. The inclusion  
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42 criteria were as follow (1) age 18 years or above; (2) presented within seven days of the index  
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44 event of acute ischemic stroke (AIS), transient ischemic attack (TIA), intracerebral  
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46 hemorrhage, or subarachnoid hemorrhage, confirmed by brain computed tomography or  
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48 magnetic resonance imaging; (3) direct hospital admission from a physician's clinic or  
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50 emergency department. A total of 25,018 patients were included in CNSR II, of them 19,604  
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52 were AIS.  
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58 Considering the representativeness of the included patients, we excluded those hospitals in  
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4 which the number of patients included in the study was less than 10% of annual stroke  
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6 discharges. We also excluded the patients who were lost to follow-up at 1 year. Finally,  
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8 16,651 patients with AIS from 133 hospitals were included to investigate the association  
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10 between hospital volume, the process of care, and outcomes.  
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### 17 **Data Collection**

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19 Data were collected following a standardized form by trained research coordinators. The  
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21 information on demographics, health insurance, education, smoking, drinking, comorbidities  
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23 (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and  
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25 medication history were abstracted from medical records. National Institutes of Health Stroke  
26  
27 Scale (NIHSS) at admission and modified Rankin Scale (mRS) prior to the index event were  
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29 assessed through a face-to-face interview.  
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35 Hospital stroke volume was defined as the annual number of stroke discharges. The annual  
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37 stroke discharges of each hospital were obtained via the hospital survey when they applied to  
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39 participate in this study. Additionally, the hospital characteristics including location,  
40  
41 academic status, and the number of beds were obtained by the survey.  
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### 48 **Process Measures**

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50 We selected nine guideline-recommended process measures according to the national  
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52 guideline and the Get With The Guidelines-Stroke (GWTG-Stroke).<sup>18</sup> There were three acute  
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54 phage process measures, including (1) antithrombotics within 2 days after admission, (2)  
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56 deep vein thrombosis (DVT) prophylaxis, and (3) dysphagia screening. There were six  
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4 process measures at discharge, including (1) antithrombotic medication, (2) antihypertensive  
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6 medication for patients with hypertension, (3) hypoglycemic medication for patients with  
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8 diabetes, (4) anticoagulation for atrial fibrillation, (5) lowering low-density lipoprotein  
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10 cholesterol (LDL-C) medication, and (6) smoking cessation. The definitions of the process  
11  
12 measures were shown in Supplemental Table 1. Additionally, we calculated a binary defect-  
13  
14 free measure of care, which was defined as the patient receiving all the processes for which  
15  
16 they were eligible.<sup>19,20</sup> Process measures are applied only to eligible patients in the absence  
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18 of documented contraindications or any other rationale as to why therapy was not provided.<sup>21</sup>  
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### 27 **Clinical Outcomes**

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

44  
45 The patients were categorized into four groups according to the quartiles of hospital volume:  
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47 Q1 (<264 /year), Q2 (264-370 /year), Q3 (371-508 /year), Q4 (>508 /year). Continuous  
48  
49 variables were described as mean  $\pm$  standard deviation (SD) or median and interquartile  
50  
51 range. Categorical variables were described as proportions. The patient characteristics were  
52  
53 compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, in order to  
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55 obtain the P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for  
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4 continuous variables and Cochran-Mantel-Haenszel row mean scores for categorical  
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6 variables.  
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9 The generalized estimating equations with exchangeable working correlation matrix were  
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11 used to evaluate the association between hospital volume, the process of care, and poor  
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13 outcome adjusting for the cluster effect within the hospital. In the adjusted models, age, sex,  
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15 health insurance (urban resident basic medical insurance, new rural cooperative medical  
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17 scheme, commercial insurance, self-payment), education (elementary or below, middle  
18  
19 school, high school or above), previous or current smoking, drinking, comorbidities  
20  
21 (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at  
22  
23 admission, and hospital characteristics (academic status and location) were included.  
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25 Additionally, the composite measure of care was included in the adjusted model when  
26  
27 estimating the association between hospital volume and outcomes. We used the Kaplan-  
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29 Meier method to depict the cumulative hazards of all-cause mortality. Cox proportional  
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31 hazards model was used to estimate the association between hospital volume and mortality.  
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33 In order to adjust for the intra-hospital correlation, the hospitals were added as clusters in the  
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35 model and the robust sandwich variance estimator was used to deal with the correlation. ORs  
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37 or HRs and corresponding 95% confidence intervals (CIs) were used with the hospital  
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39 volume of Q4 as reference. Additionally, we used restricted cubic splines with five knots at  
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41 the 5th, 35th, 50th, and 95th centiles to model the association between hospital volume and  
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43 mortality and poor outcome. We tested for non-linearity by using the Wald statistics.  
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55 All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P  
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57 values were two-tailed with a significant level of 0.05.  
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## 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  $65.0 \pm 12.0$  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-lowering medicine were higher in high-volume hospitals than that in low-volume hospitals.

## Association between Hospital Volume and Process Measures

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4 Compared with the hospitals of Q4, the unadjusted OR of defect-free measure of care was  
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6 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-  
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8 1.52) for Q3. No significant difference was found in individual process measures, except the  
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10 anticoagulation for AF for Q1 (OR, 0.53; 95% CI, 0.29-0.98; P=0.044) (Supplemental Table  
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12 3).

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17 Table 2 shows the adjusted ORs for process measures. After adjusting for the patients and  
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19 hospital characteristics, the adjusted OR of defect-free measure of care was 0.71 (95% CI,  
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21 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  
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23 the individual performance measures show no significant association (all P >0.05).  
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### 30 **Association between Hospital Volume and Clinical Outcomes**

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32 There were 1397 patients who died and 3434 patients experienced the poor outcome at 1 year  
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34 after stroke onset. The Kaplan-Meier plot for mortality at 1 year was shown in Figure 1. The  
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36 unadjusted Cox proportional hazard models showed HR of mortality was 1.08 (95%CI, 1.08-  
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38 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  
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40 as reference. However, after adjusting for patient, hospital characteristics, and process of  
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42 care, no significant associations were observed (HR, 1.24; 95% CI, 0.94-1.63 for Q1; HR,  
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44 0.94; 95% CI, 0.73-1.21 for Q2; HR, 1.06; 95% CI, 0.86-1.31 for Q3).  
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51 Figure 2 displayed the rates of poor outcome at 1 year by quartiles of hospital volume.  
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53 Compared with Q4, the rate of poor outcome was significantly higher in Q1 hospitals, but not  
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55 in Q2 and Q3 hospitals (unadjusted OR, 1.40; 95%CI, 1.16-1.70 for Q1; unadjusted OR,  
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57 0.98; 95%CI 0.80-1.20 for Q2; unadjusted OR, 1.06, 95%CI, 0.90-1.25 for Q3). When  
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4 adjusted for the covariates, the rate of poor outcome was still higher in Q1 hospitals  
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6 compared with Q4 hospitals (adjusted OR, 1.36; 95%CI, 1.05-1.77), but not in Q2 and Q3  
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9 (Table 3).

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

## 22 23 24 25 26 27 28 **Discussion**

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31 Our analysis of a large population of 16,651 patients with ischemic stroke suggested that no  
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33 significant difference in the process of care was observed for patients in lower-volume  
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35 hospitals in comparison with higher-volume hospitals. There was no association between  
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37 hospital volume and mortality at 1 year after stroke onset. In contrast, we found the patients  
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39 in the lowest volume quartile had a significantly higher rate of poor outcome at 1 year  
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41 compared with the highest quartile.  
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48 Previous studies found that high volume was associated with improved outcomes  
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50 suggesting that volume may be a surrogate for quality of care. The quality of care can be  
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52 assessed from outcome, process, and structure.<sup>22</sup> Usually, hospital volume is used as a  
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54 structure metric of quality of care. However, the underlying mechanisms of interplay between  
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56 structure and process are complex.<sup>23</sup> Two existing studies<sup>13, 23</sup> showed that the patients in  
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4 high-volume hospitals received more process of care compared with patients in low-volume  
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6 hospitals. Potential mechanisms were proposed to explain this association, including more  
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8 experience (“practice makes perfect”) and availability for advanced techniques and devices in  
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10 high-volume hospitals.<sup>7, 23</sup> In contrast, we did not find the association between hospital stroke  
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12 volume and process measures in the current study. This was similar to a study from GWTG-  
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14 Stroke. This study from 790 US hospitals including 322,847 patients with ischemic stroke or  
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16 transient ischemic attack observed no differences in performance measures between high-  
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18 volume hospitals and low-volume hospitals after adjusting for patient baseline  
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20 characteristics.<sup>18</sup> In the past years, many initiatives for improving the quality of care have  
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22 been implemented to homogenize the quality of care in hospitals, such as GWTG-Stroke,  
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24 Australian Stroke Clinical Registry, and CNSR,<sup>24</sup> which may attenuate the difference of  
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26 quality of care between high-volume and low-volume hospitals.  
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35 During the past decades, a great number of studies evaluated the volume-outcome  
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37 association, and many, but not all, found the reverse relationship between volume and  
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39 outcome.<sup>9</sup> There were several studies revealed that stroke patients in high-volume hospitals  
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41 may experience lower mortality than the patients in low-volume hospitals.<sup>11, 12, 25, 26</sup> However,  
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43 we found no benefit in mortality for patients in high-volume hospitals. Several reasons may  
44  
45 explain this discrepancy. First, most of the above-mentioned studies used in-hospital  
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47 mortality or 30-day mortality as the outcome, however, 1-year mortality was used in our  
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49 study. What’s more, stroke severity is an important factor affecting the patient's prognosis.  
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51 Whether stroke severity was adjusted may contribute to the results.<sup>13</sup> Lacking data on stroke  
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53 severity, most of the studies used comorbidity or comorbidity index score to adjust the case-  
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4 mix.<sup>11, 12, 25, 26</sup> In this study we used the NIHSS score at admission to adjust the stroke  
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6 severity. Our finding is compatible with a Danish nationwide cohort study of 63,995 patients  
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8 admitted to stroke units.<sup>23</sup> This study found no association between volume and 30-day  
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10 mortality and 1-year mortality after adjusting for patient baseline characteristics, stroke unit,  
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12 university status, and quality of care. Mortality may be insensitive to detecting underlying  
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14 changes in patient prognosis.<sup>23</sup>  
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19 Besides mortality, we also examined the association between hospital volume and poor  
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21 outcome. To our knowledge, it was the first time to evaluate the association between volume  
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23 and poor outcome at 1 year in patients with acute ischemic stroke. Compared with the highest  
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25 quartile of hospitals, patients in the lowest quartile of hospitals had a higher rate of poor  
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27 outcome after adjusting for potential confounders. The poor outcome may be more sensitive  
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29 to detect the changes in patient prognosis. The underlying mechanisms of volume on poor  
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31 outcome are not known. Though there was no significant difference in the process of care  
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33 during acute phase and at discharge between low- and high-volume hospitals, the differences  
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35 in some other processes of care after discharge may explain this association. Patients in high-  
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37 volume hospitals may receive more processes after discharge, for example, limb  
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39 rehabilitation, which can improve the poor outcome. The association between volume and the  
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41 poor outcome may be mediated by medical care after discharge. However, we could not  
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43 identify the medical care after discharge in the current study. In the future, the association  
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45 between volume, the process of care after discharge, and long-term outcomes are needed for  
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47 further exploration. Though the significant association, we did not think it is reasonable to  
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49 regionalize stroke care. Because the transferring may lead to a delay in admission which may  
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4 offset some benefits of being admitted to large-volume hospitals.<sup>11</sup>  
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6 Several limitations in this study should be acknowledged. First, the hospitals that  
7 participated in the CNSR were volunteers. There may exist unavoidable selection bias. And  
8 the hospitals enrolled may not fully represent the general hospitals in China. Second, though  
9 nine processes of care were evaluated, some other processes of care, for example,  
10 endovascular therapy, and the care patients received after discharge could not be assessed.  
11 The differences in unassessed process measures may explain the association between volume  
12 and poor outcome. Third, there is a cluster effect within hospitals and physicians. Though, we  
13 take into consideration of the cluster effect within hospitals by using the generalized  
14 estimating equations, we cannot adjust the cluster effect within physicians. Fourth, because of  
15 the differences in patients, hospital characteristics, and performance of care across varied  
16 regions and countries, our results may not generalize to other countries. Further studies on  
17 volume and clinical outcome, especially the poor outcome, are needed to confirm our results.  
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## 41 **Conclusions**

42 Using the large national stroke registry, we found no association between hospital stroke  
43 volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile  
44 of hospitals had increased rates of poor outcome compared with the patients in the highest  
45 quartile of hospitals. Further work needs to be done to examine whether the medical care  
46 after discharge mediates the association between stroke volume and poor outcome. Better  
47 understanding the association between structure, process, and outcome can help to identify  
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### 9 **Availability of data and materials**

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11 The datasets used and analyzed during the current study are available from the corresponding  
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13 author on reasonable request.  
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35 **Disclosures:** None.  
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### 40 **Author contributions**

41  
42 Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or  
43  
44 patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation:  
45  
46 RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG  
47  
48 Zhou and YJ Wang take responsibility for the integrity of the work.  
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### 57 **References**

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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

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2  
3  
4 9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review  
5  
6 and methodologic critique of the literature. *Ann Intern Med.* 2002;137:511-520  
7  
8
- 9 10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med*  
10  
11 *Care.* 2010;48:149-156  
12  
13
- 14 11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to  
15  
16 Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes.*  
17  
18 2015;8:S141-147  
19  
20
- 21 12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it  
22  
23 matter? *Neurology.* 2007;69:1142-1151  
24  
25
- 26 13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients:  
27  
28 Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis.* 2020;29:104753  
29  
30
- 31 14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early  
32  
33 outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen  
34  
35 activator. *Int J Stroke.* 2015;10:73-78  
36  
37
- 38 15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement  
39  
40 in Stroke Care in China. *Stroke.* 2016;47:2843-2849  
41  
42
- 43 16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute  
44  
45 cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke.*  
46  
47 2011;6:355-361  
48  
49
- 50 17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients  
51  
52 hospitalized with acute ischemic stroke in China: Findings from the China National Stroke  
53  
54 Registry II. *Int J Stroke.* 2017;12:254-263  
55  
56  
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4 18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated  
5  
6 with sustained improvement in care for patients hospitalized with acute stroke or transient  
7  
8 ischemic attack. *Circulation*. 2009;119:107-115  
9  
10  
11  
12 19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke:  
13  
14 findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238  
15  
16  
17 20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and  
18  
19 Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419  
20  
21  
22 21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center  
23  
24 for Healthcare Quality Management in Neurological Diseases, China National Clinical  
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26 Research Center for Neurological Diseases, the Chinese Stroke Association, National Center  
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28 for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for  
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30 Disease Control and Prevention and Institute for Global Neuroscience and Stroke  
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32 Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239  
33  
34  
35  
36  
37 22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729  
38  
39  
40 23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved  
41  
42 quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045  
43  
44  
45 24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving  
46  
47 the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40  
48  
49  
50 25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke  
51  
52 fatality in Canada. *Stroke*. 2008;39:3360-3366  
53  
54  
55 26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality  
56  
57 and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788  
58  
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**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=2235)	P	P for trend
<b>Hospital characteristics</b>							
Number of hospitals	133	35	31	33	34		
Teaching hospital	73 (54.9%)	13 (37.1%)	16 (51.6%)	20 (60.6%)	24 (76.6%)	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 (26.0%)		
West	22 (16.5%)	7 (20%)	4 (12.9%)	5 (15.2%)	6 (17.1%)		
<b>Patient characteristics</b>							
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)	0.315	0.83 (0.31-2.24)	0.7091
Dysphagia screening	0.64 (0.31-1.31)	0.2208	1.46 (0.63-3.38)	0.374	1.29 (0.52-3.21)	0.5793
DVT prophylaxis	0.79 (0.38-1.65)	0.5348	0.77 (0.39-1.52)	0.452	0.94 (0.49-1.79)	0.8421
Antithrombotic medication	1.00 (0.49-2.04)	0.9896	1.20 (0.55-2.62)	0.640	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)	0.451	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)	0.996	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)	0.609	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)	0.610	0.7 (0.42-1.16)	0.1658
Smoking cessation	0.43 (0.12-1.55)	0.1985	0.39 (0.10-1.44)	0.156	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)	0.978	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

Outcome		Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
		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.

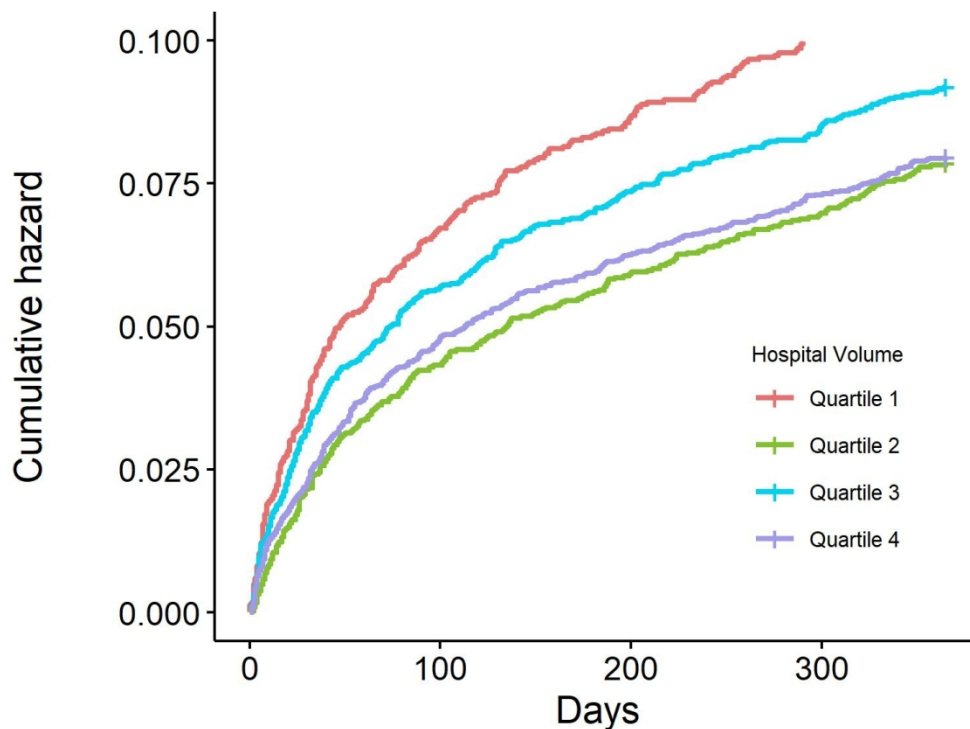
**Figure legends**

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.



Number at risk

Quartile 1	2800	2618	2568	2528
Quartile 2	3428	3283	3231	3197
Quartile 3	4188	3957	3891	3847
Quartile 4	6235	5945	5857	5796

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

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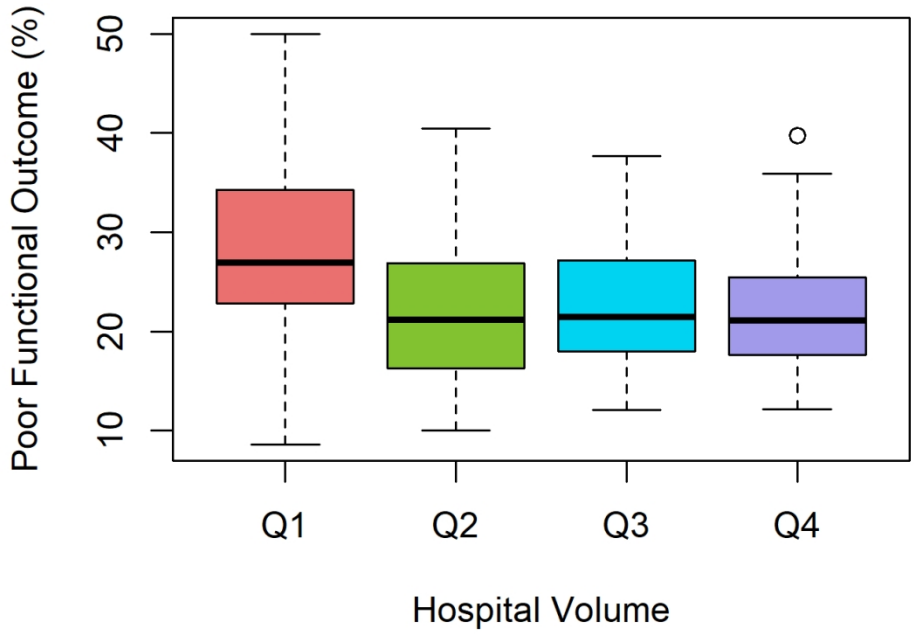


Figure 2. The rates of poor outcome at 1 year by quartiles of hospital volume  
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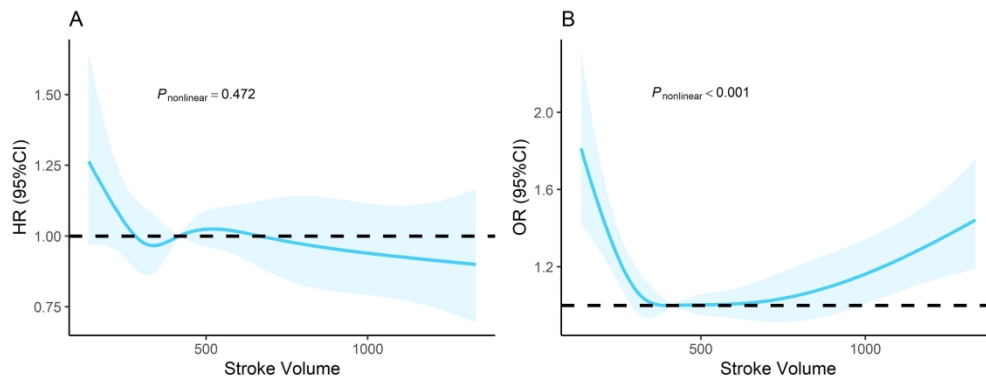


Figure 3. Association between hospital stroke volume and clinical outcomes. A, Hospital volume and all-cause mortality at 1 year. B, Hospital volume and poor outcome at 1 year. The reference point is the median value of hospital volume (416 annual stroke discharges) in all patients.

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*Supplementary Material*

For peer review only

Table 1. The definition of process measures

	<b>Definition*</b>
<b>Acute phase process measures</b>	
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
<b>Process measures at discharge</b>	
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 $\geq$ 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
<b>Patient characteristics</b>				
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
<b>Hospital characteristics</b>				
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 #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			

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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	11
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

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5 **Association Between Hospital Volume, Process of Care, and Outcomes after Acute**  
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7 **Ischemic Stroke: A Prospective Observational Study**  
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12 113  
14 2 **Runhua Zhang<sup>1-3</sup>, Gaifen Liu<sup>2-3</sup>, Yuesong Pan<sup>2-3</sup>, Maigeng Zhou<sup>1\*</sup>, Yongjun Wang<sup>2-3\*</sup>**  
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4 **1 Abstract**

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6 **2 Objectives** Uncertainty remains about hospital volume and clinical outcomes for patients  
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**3** with stroke. The study was aimed to assess the association between hospital volume, process  
**4** of care, and outcomes after ischemic stroke.

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

**14 Results** A total of 17,550 ischemic strokes from 217 hospitals across China were included.  
**15** There were no significant differences in process of care across the four groups. When adjusted  
**16** for confounders, the effect of hospital volume on mortality, recurrent stroke and combined  
**17** vascular events was not significant. However, compared with the highest quartile, the patients  
**18** in the lowest quartile of hospital volume tend to be with poor outcome at 1 year (OR, 1.29,  
**19** 95% CI, 1.01-1.64, P=0.0393). The restricted cubic spline analyses suggested a non-linear  
**20** relationship between hospital volume and 1-year combined vascular events and 3-month and  
**21** 1-year poor outcome.

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



1 care at the hospital, and recurrent stroke and mortality in patients with ischemic stroke.

2 However, hospital volume may be associated with combined vascular events and poor  
3 outcome at 1 year.

#### 4 **Strengths and limitations of this study**

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

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

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

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

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## 1 Introduction

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

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

## 21 Methods

## 1 **Ethics approval**

2 This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-  
3 005-01). The rewritten informed consent was obtained from the patients or their relatives.

## 5 **Study Design and Setting**

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

## 15 **Study Population**

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

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4 1 We excluded the patients missing information on process of care and those lost to follow-  
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6 2 up at 3 months and 1 year. Finally, 17,550 patients with AIS from 217 hospitals were  
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9 3 included to investigate the association between hospital volume, the process of care, and  
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12 4 outcomes.

## 13 14 5 15 16 17 6 **Data Collection**

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19 7 Data were collected following a standardized form by trained research coordinators. The  
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22 8 information on demographics, health insurance, education, smoking, drinking, comorbidities  
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25 9 (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and  
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28 10 medication history were abstracted from medical records. National Institutes of Health Stroke  
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31 11 Scale (NIHSS) at admission and modified Rankin Scale (mRS) prior to the index event were  
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34 12 assessed through a face-to-face interview.

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37 13 Hospital stroke volume was defined as the annual number of stroke discharges. The annual  
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40 14 stroke discharges of each hospital were obtained via the hospital survey when they applied to  
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43 15 participate in this study. Additionally, the hospital characteristics including location,  
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46 16 academic status, the presence of stroke unit and the number of beds were obtained by the  
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49 17 survey.

## 50 51 18 52 53 19 **Process Measures**

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56 20 We selected ten guideline-recommended process measures according to the national  
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59 21 guideline and the Get With The Guidelines-Stroke (GWTG-Stroke).<sup>18</sup> There were four acute  
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22 phage process measures, including (1) intravenous recombinant tissue plasminogen activator

1 (rt-PA) in patients who arrive within 2 hours after symptom onset and were treated within 3  
2 hours, (2) antithrombotics within 2 days after admission, (3) deep vein thrombosis (DVT)  
3 prophylaxis, and (4) dysphagia screening. There were six process measures at discharge,  
4 including (1) antithrombotic medication, (2) antihypertensive medication for patients with  
5 hypertension, (3) hypoglycemic medication for patients with diabetes, (4) anticoagulation for  
6 atrial fibrillation, (5) lowering low-density lipoprotein cholesterol (LDL-C) medication, and  
7 (6) smoking cessation. The definitions of the process measures were shown in Supplemental  
8 Table 1. Additionally, we calculated a binary defect-free measure of care, which was defined  
9 as the patient receiving all the processes for which they were eligible.<sup>19, 20</sup> Process measures  
10 are applied only to eligible patients in the absence of documented contraindications or any  
11 other rationale as to why therapy was not provided.<sup>21</sup>

### 13 **Clinical Outcomes**

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

### 22 **Statistical Analysis**

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4 1 The patients were categorized into four groups according to the quartiles of hospital volume:  
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6 2 Q1 (<300 /year), Q2 (300-436 /year), Q3 (437-722 /year), Q4 (>722 /year). Continuous  
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9 3 variables were described as mean  $\pm$  standard deviation (SD) or median and interquartile  
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11 4 range. Categorical variables were described as proportions. The patient characteristics were  
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14 5 compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, in order to  
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17 6 obtain the P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for  
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20 7 continuous variables and Cochran-Mantel-Haenszel row mean scores for categorical  
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22 8 variables.

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25 9 The generalized estimating equations with exchangeable working correlation matrix were  
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27 10 used to evaluate the association between hospital volume, the process of care, and outcomes  
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30 11 adjusting for the cluster effect within the hospital. In the adjusted models, age, sex, health  
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33 12 insurance (urban resident basic medical insurance, new rural cooperative medical scheme,  
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36 13 commercial insurance, self-payment), education (elementary or below, middle school, high  
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38 14 school or above), previous or current smoking, drinking, comorbidities (hypertension,  
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41 15 diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, and  
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44 16 hospital characteristics (academic status, number of beds, presence of stroke unit, and  
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47 17 location) were included. Additionally, the defect-free measure of care was included in the  
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50 18 adjusted model when estimating the association between hospital volume and outcomes. We  
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53 19 used the Kaplan-Meier method to depict the cumulative hazards of all-cause mortality and  
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56 20 recurrent stroke. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were  
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59 21 used with the hospital volume of Q4 as reference. Additionally, we used restricted cubic  
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22 splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the association

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4 1 between hospital volume and outcomes. We tested for non-linearity by using the Wald  
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6 2 statistics.

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9 3 All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P  
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11 4 values were two-tailed with a significant level of 0.05.

## 12 5 **Patient and public involvement**

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17 6 Patients and the public were not involved in the design, or conduct, or reporting, or  
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19 7 dissemination plans of our research.

## 20 8 **Results**

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27 9 A total of 17,550 patients with AIS from 217 hospitals across China were included in this  
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29 10 study. The process of patient selection is shown in Figure 1. Patients included in the current  
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31 11 study and those excluded were largely comparable (supplemental Table 2). Table 1 described  
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33 12 the baseline characteristics of the included hospitals and patients.

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37 13 Of the 217 included hospitals, 125 (57.6%) were teaching hospitals, and the high-volume  
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39 14 hospitals were likely to be teaching hospitals. There were 121 hospitals in the east of China,  
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41 15 66 in the middle of China, and 30 in the west of China. The average hospital volume was 437  
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43 16 per year, ranging from 136 to 2048 per year.

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47 17 The mean age was 65 (57-74) and 63.6% of the patients were males. The median NIHSS  
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49 18 at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared  
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51 19 with the high-volume hospitals, there were more females and the patients were older in low-  
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53 20 volume hospitals. The patients in high-volume hospitals were more likely to be with diabetes  
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55 21 and hyperlipidemia, but less likely to be with atrial fibrillation. The proportions of taking

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4 1 antiplatelet and lipid-lowering medicine were higher in high-volume hospitals than that in low-  
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6 2 volume hospitals.  
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#### 10 4 **Association between Hospital Volume and Process Measures**

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14 5 Table 2 list the rates of achievement in process measures. Compared with the hospitals of Q4,  
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17 6 the unadjusted OR of defect-free measure of care was 0.88 (95% CI, 0.62-1.25) for Q1, 1.13  
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19 7 (95% CI, 0.82-1.56) for Q2, and 1.15 (95% CI, 0.81-1.62) for Q3. No significant difference  
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22 8 was found in individual process measures, except the DVT prophylaxis for A3 (OR, 2.22;  
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24 9 95%CI, 1.26-3.91; P=0.0059), antithrombotic medication at discharge for Q2 (OR, 1.74;  
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27 10 95%CI, 1.09-2.76; P=0.0196), and Lowering LDL-C medication for Q3 (OR, 1.60; 95%CI,  
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30 11 1.10-2.33; P=0.0134) (Supplemental Table 3).

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33 12 Table 3 shows the adjusted ORs for process measures. After adjusting for the patients and  
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35 13 hospital characteristics, the adjusted OR of defect-free measure of care was 0.93 (95% CI,  
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37 14 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  
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40 15 the individual performance measures show no significant association (all P >0.05).  
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#### 44 17 **Association between Hospital Volume and 3-Month and 1-Year Outcomes**

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47 18 Of the included patients, 1322 (7.53%) died within 1 year after stroke onset. The Kaplan-  
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50 19 Meier plot for mortality within 1 year was shown in Figure 2. The 3-month and 1-year  
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53 20 mortality was different across the 4 groups (3-month mortality, 4.95% versus 3.64% versus  
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56 21 4.33% versus 3.39%, P=0.0011; 1-year mortality, 9.08% versus 7.3% versus 7.8% versus  
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59 22 6.66%, P=0.0004) (Table 4). At 3 months and 1 year, the mortality was a little higher in Q1  
60



1 hospitals (OR at 3 months, 1.54; 95% CI, 1.13-2.09; P=0.0059; OR at 1 year, 1.51; 95% CI  
2 1.19- 1.91; P=0.0008), but not Q2 or Q3 hospitals in compared with Q4 hospitals. However,  
3 the difference was not significant when adjusted for potential factors (Table 5).

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

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

19 In Figure 3-6, we used restricted cubic splines to flexible model and visualize the relation  
20 of all-cause mortality, poor outcome, stroke recurrence, and combined vascular events with  
21 hospital stroke volume. The multivariable-adjusted restricted cubic splines suggested a “J-  
22 shaped” association between volume and all-cause mortality and poor outcome. The analyses

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4 1 indicated a significant nonlinear association between volume and poor outcome at 3 months  
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6 2 and 1 year (P for non-linear =0.0096 and <0.001, respectively), as well as combined vascular  
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9 3 events at 1 year (P for non-linear = 0.0242).  
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#### 11 4 **Discussion**

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16 5 Our analysis of a large population of 17,550 patients with ischemic stroke suggested that no  
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18 6 significant difference in the process of care was observed for patients in lower-volume  
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20 7 hospitals in comparison with higher-volume hospitals. There was no association between  
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22 8 hospital volume and mortality, stroke recurrence, and combined vascular events at 3 months  
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24 9 and 1 year. In contrast, we found the patients in the lowest volume quartile had a significantly  
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28 10 higher rate of poor outcome at 1 year compared with the highest quartile.

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32 11 Previous studies found that high volume was associated with improved outcomes  
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34 12 suggesting that volume may be a surrogate for quality of care. The quality of care can be  
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36 13 assessed from outcome, process, and structure.<sup>22</sup> Usually, hospital volume is used as a  
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38 14 structure metric of quality of care. However, the underlying mechanisms of interplay between  
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40 15 structure and process are complex.<sup>23</sup> Two existing studies<sup>13, 23</sup> showed that the patients in  
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42 16 high-volume hospitals received more process of care compared with patients in low-volume  
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44 17 hospitals. Potential mechanisms were proposed to explain this association, including more  
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46 18 experience (“practice makes perfect”) and availability for advanced techniques and devices in  
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48 19 high-volume hospitals.<sup>7, 23</sup> In contrast, we did not find the association between hospital stroke  
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50 20 volume and process measures in the current study. This was similar to a study from GWTG-  
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58 21 Stroke. This study from 790 US hospitals including 322,847 patients with ischemic stroke or  
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4 1 transient ischemic attack observed no differences in performance measures between high-  
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6 2 volume hospitals and low-volume hospitals after adjusting for patient baseline  
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9 3 characteristics.<sup>18</sup> In the past years, many initiatives for improving the quality of care have  
10  
11 4 been implemented to homogenize the quality of care in hospitals, such as GWTG-Stroke,  
12  
13  
14 5 Australian Stroke Clinical Registry, and CNSR,<sup>24</sup> which may attenuate the difference of  
15  
16  
17 6 quality of care between high-volume and low-volume hospitals.

18  
19 7 During the past decades, a great number of studies evaluated the volume-outcome  
20  
21 8 association, and many, but not all, found the reverse relationship between volume and  
22  
23  
24 9 outcome.<sup>9</sup> There were several studies revealed that stroke patients in high-volume hospitals  
25  
26  
27 10 may experience lower short-term mortality than the patients in low-volume hospitals.<sup>11, 12, 25,</sup>  
28  
29  
30 11 <sup>26</sup> However, we found no benefit in mortality for patients in high-volume hospitals. Several  
31  
32  
33 12 reasons may explain this discrepancy. First, the hospital volume was varied in these studies.  
34  
35  
36 13 What's more, stroke severity is an important factor affecting the patient's prognosis. Whether  
37  
38 14 stroke severity was adjusted may contribute to the results.<sup>13</sup> Lacking data on stroke severity,  
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40  
41 15 most of the studies used comorbidity or comorbidity index score to adjust the case-mix.<sup>11, 12,</sup>  
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43  
44 16 <sup>25, 26</sup> In this study we used the NIHSS score at admission to adjust the stroke severity. Our  
45  
46  
47 17 finding is compatible with a Danish nationwide cohort study of 63,995 patients admitted to  
48  
49  
50 18 stroke units.<sup>23</sup> This study found no association between volume and 30-day mortality and 1-  
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52  
53 19 year mortality after adjusting for patient baseline characteristics, stroke unit, university status,  
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55  
56 20 and quality of care. Mortality may be insensitive to detecting underlying changes in patient  
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58  
59 21 prognosis.<sup>23</sup>

60 22 Besides mortality, we also examined the association between hospital volume and poor

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4 1 outcome, stroke recurrence, and combined vascular events. To our knowledge, it was the first  
5  
6 2 time to evaluate the association between volume and poor outcome at 3 months and 1 year in  
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8  
9 3 patients with acute ischemic stroke. Compared with the highest quartile of hospitals, patients  
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11 4 in the lowest quartile of hospitals had a higher rate of poor outcome at 1 year after adjusting  
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14 5 for potential confounders. The poor outcome may be more sensitive to detect the changes in  
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17 6 patient prognosis. The underlying mechanisms of volume on poor outcome are not known.  
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19 7 Though there was no significant difference in the process of care during acute phase and at  
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22 8 discharge between low- and high-volume hospitals, the differences in some other processes  
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24  
25 9 of care after discharge may explain this association. Patients in high-volume hospitals may  
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28 10 receive more processes after discharge, for example, limb rehabilitation, which can improve  
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30  
31 11 the poor outcome. The association between volume and the poor outcome may be mediated  
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33  
34 12 by medical care after discharge. However, we could not identify the medical care after  
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37 13 discharge in the current study. In the future, the association between volume, the process of  
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40 14 care after discharge, and long-term outcomes are needed for further exploration. Though the  
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42  
43 15 significant association, we did not think it is reasonable to regionalize stroke care. Because  
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45  
46 16 the transferring may lead to a delay in admission which may offset some benefits of being  
47  
48  
49 17 admitted to large-volume hospitals.<sup>11</sup>

50  
51 18 Several limitations in this study should be acknowledged. First, the hospitals that  
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53  
54 19 participated in the CNSR were volunteers. There may exist unavoidable selection bias. And  
55  
56  
57 20 the hospitals enrolled may not fully represent the general hospitals in China. Second, though  
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59  
60 21 ten processes of care were evaluated, some other processes of care, for example, mechanical  
22 thrombectomy, and the care patients received after discharge could not be assessed. The

1 differences in unassessed process measures may explain the association between volume and  
2 poor outcome. Third, there is a cluster effect within hospitals and physicians. Tough, we take  
3 into consideration of the cluster effect within hospitals by using the generalized estimating  
4 equations, we cannot adjust the cluster effect within physicians. Forth, because of the  
5 differences in patients, hospital characteristics, and performance of care across varied regions  
6 and countries, our results may not generalize to other countries. Further studies on volume  
7 and clinical outcome, especially the poor outcome, are needed to confirm our results.

8

## 9 **Conclusions**

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

17

## 18 **Availability of data and materials**

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

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20 7 **Disclosures:** None.  
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#### 26 9 **Author contributions**

27 10 Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or  
28  
29 11 patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation:  
30  
31 12 RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG  
32  
33 13 Zhou and YJ Wang take responsibility for the integrity of the work.  
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#### 42 15 **References**

- 43  
44  
45 16 1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day  
46  
47 17 Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol.* 2017;2:732-  
48  
49 18 741  
50  
51  
52 19 2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in  
53  
54 20 the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA.*  
55  
56 21 1998;279:1278-1281  
57  
58  
59  
60

- 1  
2  
3  
4 1 3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After  
5  
6 2 Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg.* 2016;263:664-  
7  
8 3 672  
9  
10  
11 4 4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer  
12  
13 5 operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J*  
14  
15 6 *Public Health.* 2007;97:539-544  
16  
17  
18 7 5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality  
19  
20 8 following oesophagectomy in Japan. *Br J Surg.* 2016;103:1880-1886  
21  
22  
23 9 6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common  
24  
25 10 medical conditions. *N Engl J Med.* 2010;362:1110-1118  
26  
27  
28 11 7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume,  
29  
30 12 Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get  
31  
32 13 With The Guidelines-Heart Failure. *Circulation.* 2018;137:1661-1670  
33  
34  
35 14 8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in  
36  
37 15 patients with traumatic brain injury: A retrospective observational study using a national  
38  
39 16 inpatient database in Japan. *Injury.* 2017;48:1423-1431  
40  
41  
42 17 9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review  
43  
44 18 and methodologic critique of the literature. *Ann Intern Med.* 2002;137:511-520  
45  
46  
47 19 10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med*  
48  
49 20 *Care.* 2010;48:149-156  
50  
51  
52 21 11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to  
53  
54 22 Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes.*  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 1 2015;8:S141-147  
5  
6 2 12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it  
7  
8  
9 3  
10  
11 4 13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients:  
12  
13  
14 5  
15 Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis.* 2020;29:104753  
16  
17 6 14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early  
18  
19 7  
20 outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen  
21  
22 8  
23 activator. *Int J Stroke.* 2015;10:73-78  
24  
25 9 15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement  
26  
27 10  
28 in Stroke Care in China. *Stroke.* 2016;47:2843-2849  
29  
30 11 16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute  
31  
32 12  
33 cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke.*  
34  
35 13  
36 2011;6:355-361  
37  
38 14 17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients  
39  
40 15  
41 hospitalized with acute ischemic stroke in China: Findings from the China National Stroke  
42  
43 16  
44 Registry II. *Int J Stroke.* 2017;12:254-263  
45  
46 17 18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated  
47  
48 18  
49 with sustained improvement in care for patients hospitalized with acute stroke or transient  
50  
51 19  
52 ischemic attack. *Circulation.* 2009;119:107-115  
53  
54 20 19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke:  
55  
56 21  
57 findings from the National Get With The Guidelines-Stroke. *Stroke.* 2014;45:231-238  
58  
59 22 20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and  
60



- 1  
2  
3  
4 1 Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419  
5  
6 21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center  
7  
8 for Healthcare Quality Management in Neurological Diseases, China National Clinical  
9  
10 3 Research Center for Neurological Diseases, the Chinese Stroke Association, National Center  
11  
12 4 for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for  
13  
14 5 Disease Control and Prevention and Institute for Global Neuroscience and Stroke  
15  
16 6 Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239  
17  
18 7  
19 22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729  
20  
21 8  
22 23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved  
23  
24 9 23. quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045  
25  
26 10  
27 24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving  
28  
29 11 24. the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40  
30  
31 12  
32 25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke  
33  
34 13 25. fatality in Canada. *Stroke*. 2008;39:3360-3366  
35  
36 14  
37 26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality  
38  
39 15 26. and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788  
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41 16  
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**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
<b>Hospital characteristics</b>							
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
<b>Geographic region</b>							
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 (14.4%)		
<b>Patient characteristics</b>							

1								
2								
3	Male	11163 (63.6%)	2126 (63.1%)	3349 (62.2%)	2108 (64.2%)	3580 (64.9%)	0.0183	0.0085
4								
5	Age	65(57-74)	66(57-75)	65(57-74)	66(58-74)	64(55-73)	<.0001	<.0001
6								
7	Health insurance							
8								
9								
10	URBMI	8959 (51%)	1715 (50.9%)	2552 (47.4%)	1568 (47.8%)	3124 (56.7%)	<.0001	<.0001
11								
12	NRCMS	6932 (39.5%)	1369 (40.6%)	2440 (45.3%)	1394 (42.5%)	1729 (31.4%)		
13								
14	Commercial insurance	60 (0.3%)	8 (0.2%)	27 (0.5%)	4 (0.1%)	21 (0.4%)		
15								
16	Self-payment	1599 (9.1%)	279 (8.3%)	367 (6.8%)	315 (9.6%)	638 (11.6%)		
17								
18	Education							
19								
20								
21	Elementary or below	7934 (45.2%)	1693 (50.2%)	2430 (45.1%)	1678 (51.1%)	2133 (38.7%)	<.0001	<.0001
22								
23	Middle school	4109 (23.4%)	715 (21.2%)	1286 (23.9%)	661 (20.1%)	1447 (26.3%)		
24								
25	High School or above	5507 (31.4%)	963 (28.6%)	1670 (31%)	942 (28.7%)	1932 (35.1%)		
26								
27	Previous or current							
28								
29	smoking	7818 (44.5%)	1457 (43.2%)	2406 (44.7%)	1455 (44.3%)	2500 (45.4%)	0.2676	0.0836
30								
31	Drinking	5277 (30.1%)	872 (25.9%)	1681 (31.2%)	995 (30.3%)	1729 (31.4%)	<.0001	0.0001
32								
33	Medical history							
34								
35	Hypertension	11386 (64.9%)	2156 (64%)	3511 (65.2%)	2136 (65.1%)	3583 (65%)	0.6614	0.459
36								
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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	Q1 hospitals	Q2 hospitals	Q3 hospitals	Q4 hospitals
	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	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%)	2615/3289 (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%)	1523/2129 (71.8%)	2150/3609 (59.6%)
Antihypertensive	8867/13385 (66.2%)	1712/2611 (65.6%)	2764/4207 (65.7%)	1710/2476 (69.2%)	2681/4097 (65.4%)

1  
2  
3 medication for

4  
5 hypertension

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7 Hypoglycemic

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9 medication for diabetes

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11 Anticoagulation for AF

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13 Smoking cessation

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15 Defect-free measure of

16  
17 care

18	3662/4898 (74.8%)	685/907 (75.5%)	1114/1494 (74.6%)	721/901 (80.0%)	1142/1596 (71.6%)
19	303/1437 (21.1%)	43/278 (15.5%)	86/468 (18.4%)	87/325 (26.8%)	87/366 (23.8%)
20	6712/7819 (85.8%)	1227/1457 (84.2%)	2098/2406 (87.2%)	1213/1456 (83.3%)	2174/2500 (87.0%)
21	5816/17550 (33.1%)	992/3371 (29.4%)	1965/5386 (36.5%)	1150/3287 (35.1%)	1709/5512 (31.0%)

22  
23 N1 indicates the number of patients received the process of care, N2 indicates the number of patients eligible. rt-PA indicates recombinant tissue  
24  
25 plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.  
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**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)	0.334	0.71 (0.35, 1.48)	0.3634
Early antithrombotic	0.68 (0.20, 2.32)	0.5364	1.17 (0.30, 4.55)	0.824	1.07 (0.36, 3.18)	0.9020
Dysphagia screening	0.76 (0.33, 1.74)	0.5104	2.19 (0.86, 5.55)	0.098	0.90 (0.42, 1.92)	0.7845
DVT prophylaxis	1.02 (0.52, 2.01)	0.9504	1.09 (0.57, 2.09)	0.793	1.55 (0.84, 2.83)	0.1594
Antithrombotic medication	1.26 (0.61, 2.61)	0.5391	1.27 (0.61, 2.64)	0.527	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)	0.922	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)	0.615	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)	0.781	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)	0.584	1.05 (0.61, 1.78)	0.8681

Smoking cessation	0.56 (0.10, 2.97)	0.4939	0.67 (0.12, 3.63)	0.642	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.

For peer review only



**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

Outcome		Q1 VS Q4		Q2 VS Q4		Q3 VS Q4	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
<b>3 months</b>							
Mortality	Unadjusted	1.54 (1.13, 2.09)	0.0059	1.09 (0.85, 1.40)	0.4772	1.06 (0.89, 1.79)	0.1861
	Adjusted	1.27 (0.88, 1.83)	0.2062	0.99 (0.75, 1.30)	0.9179	1.08 (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	1.06 (0.85, 1.58)	0.3563
	Adjusted	1.16 (0.83, 1.62)	0.3798	1.11 (0.79, 1.56)	0.5474	1.01 (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	1.04 (0.83, 1.56)	0.4304
	Adjusted	1.15 (0.82, 1.61)	0.4109	1.09 (0.78, 1.53)	0.6167	1.02 (0.76, 1.52)	0.6763
<b>1 year</b>							
Mortality	Unadjusted	1.51 (1.19, 1.91)	0.0008	1.16 (0.95, 1.40)	0.1385	1.01 (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.

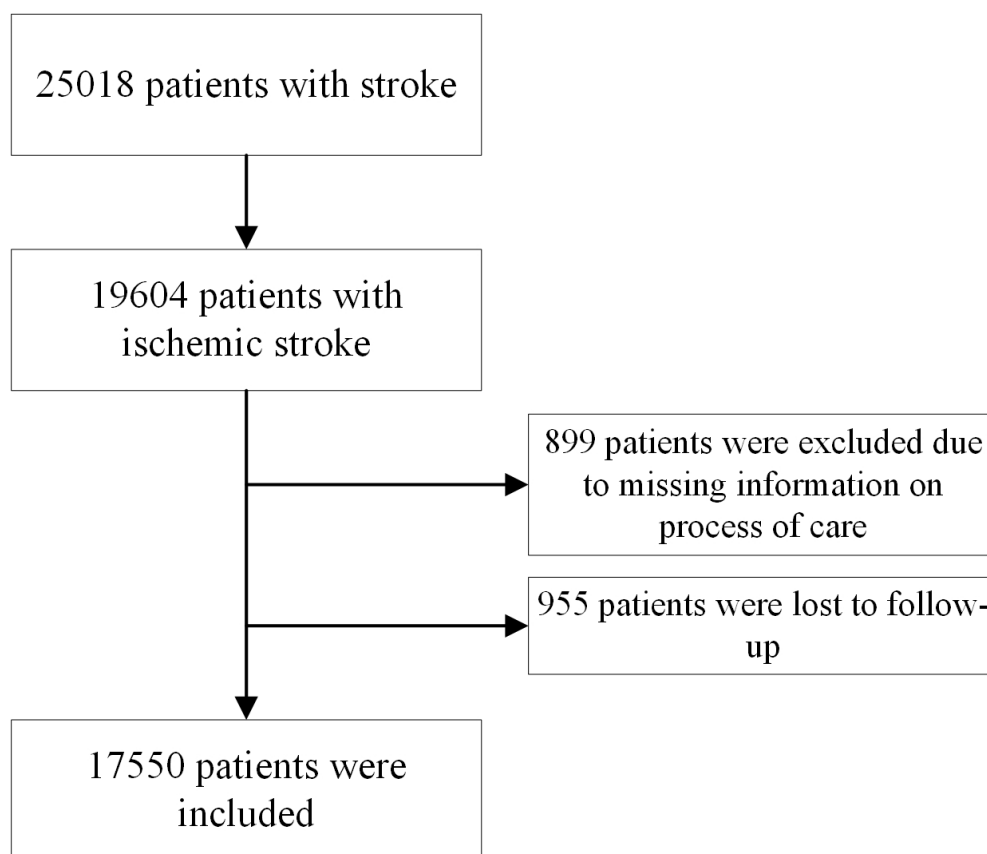


Figure 1. The flow chart for patient selection

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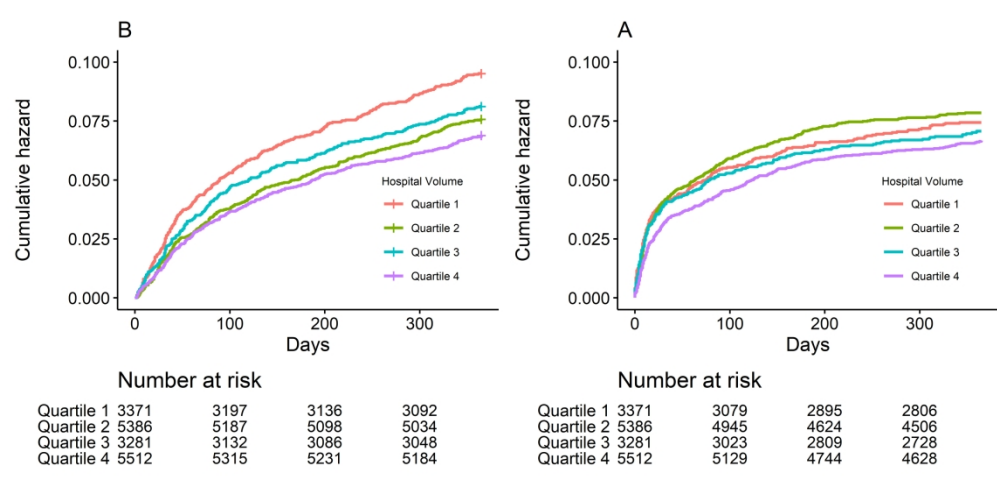


Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year  
254x118mm (300 x 300 DPI)

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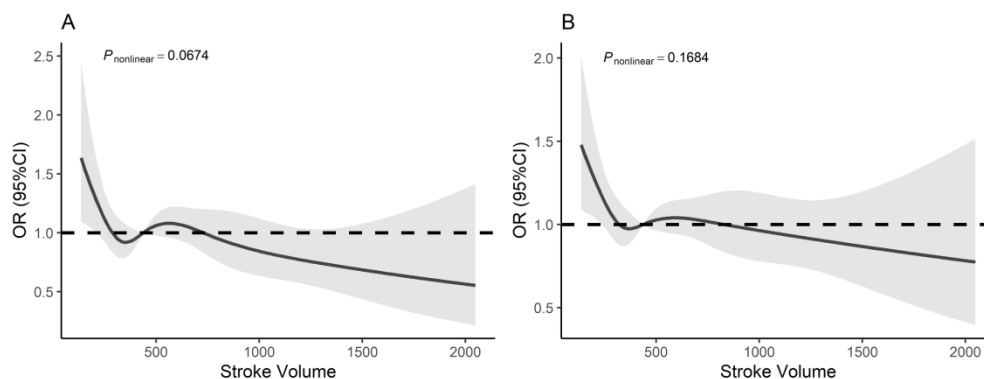


Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and all-cause mortality at 3 months. B, Hospital volume and all-cause mortality at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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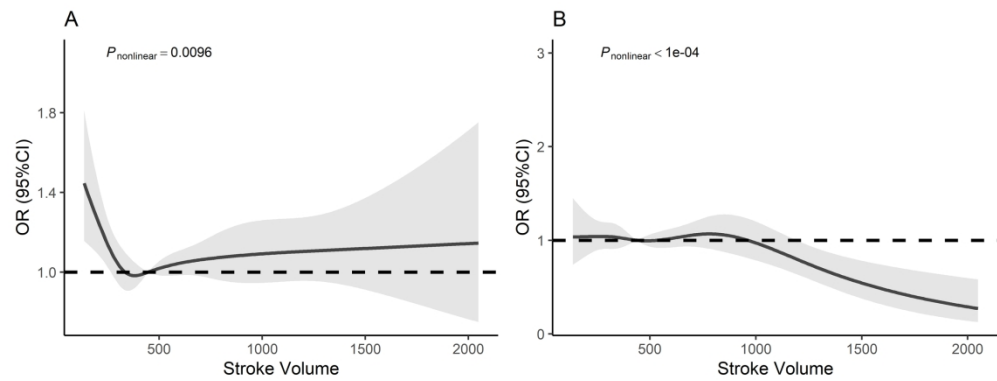


Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and poor outcome at 3 months. B, Hospital volume and poor outcome at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (300 x 300 DPI)

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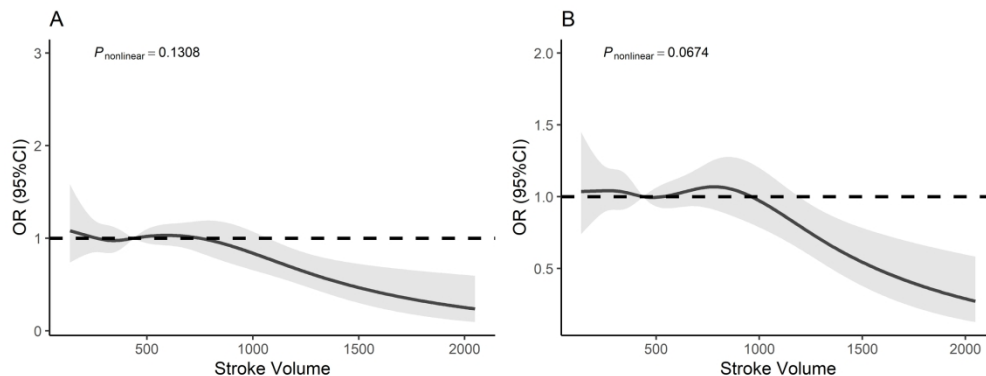


Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and recurrent stroke at 3 months. B, Hospital volume and recurrent stroke at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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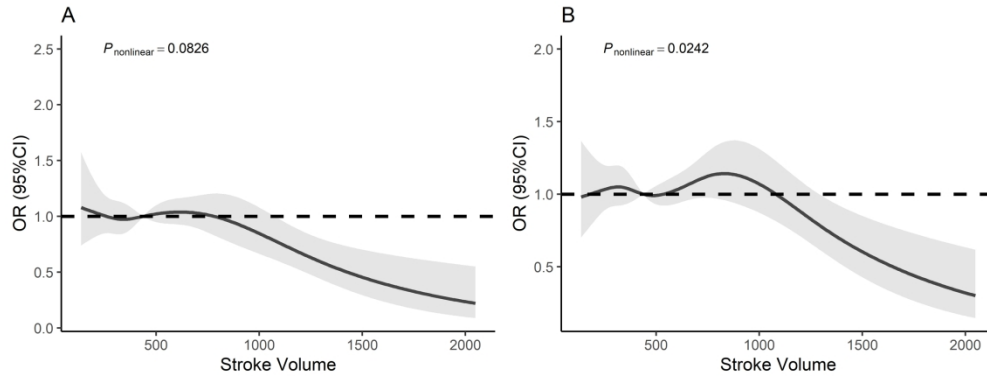


Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and combined vascular events at 3 months. B, Hospital volume and combined vascular events at 1 year. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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*Supplementary Material*

For peer review only

Table 1. The definition of process measures

	<b>Definition*</b>
<b>Acute phase process measures</b>	
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
<b>Process measures at discharge</b>	
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 $\geq$ 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
<b>Patient characteristics</b>			
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 #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			

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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	11
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-060015.R2
Article Type:	Original research
Date Submitted by the Author:	10-Apr-2022
Complete List of Authors:	Zhang, Runhua; National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention; Beijing Tiantan Hospital, Capital Medical University, Beijing, Neurology Liu, Gaifen ; Beijing Tiantan Hospital affiliated Capital Medical University, China PAN, YUESONG; Beijing Tiantan Hospital, Capital Medical University, Department of Neurology Zhou, Maigeng; Chinese Center for Disease Control and Prevention Wang, Yongjun; Capital Medical University; China National Clinical Research Center for Neurological Diseases
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Neurology
Keywords:	Stroke < NEUROLOGY, Neurology < INTERNAL MEDICINE, Adult neurology < NEUROLOGY

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14 2 **Runhua Zhang<sup>1-3</sup>, Gaifen Liu<sup>2-3</sup>, Yuesong Pan<sup>2-3</sup>, Maigeng Zhou<sup>1\*</sup>, Yongjun Wang<sup>2-3\*</sup>**  
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4 **1 Abstract**

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**3** with stroke. The study aimed to assess the association between hospital volume, processes of  
**4** care, and outcomes after ischemic stroke.

**5 Methods** The patients with acute ischemic stroke from the Second China National Stroke  
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**6** Registry were included. According to quartiles of the hospital volume, the patients were  
**7** categorized into four groups. We compared the difference in the process of care across the  
**8** groups. We used generalized estimating equations to estimate the effect of hospital volume  
**9** on mortality, poor outcome, recurrent stroke, and combined vascular events at 3 months and  
**10** 1 year. Odds ratios and corresponding 95% confidence intervals were used to qualify the  
**11** association between hospital volume and outcomes. We also used restricted cubic splines to  
**12** model the association between hospital volume and clinical outcomes.

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

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

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4 1 with ischemic stroke. However, hospital volume may be associated with poor outcome at 1  
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6 2 year.  
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#### 11 4 **Strengths and limitations of this study**

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14 5 The number of participants with ischemic stroke was large, and 217 hospitals across China  
15  
16 6 were included.

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19 7 This is the first time the association between stroke volume, processes of care, and outcomes  
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21 8 was explored in China.

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24 9 Some processes of care, especially the processes of care after discharge, cannot be obtained  
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26 10 in this study.

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29 11 The hospitals that participated were volunteers, and unavoidable selection bias may exist.

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## 1 Introduction

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

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

## 21 Methods

## 1 **Ethics approval**

2 This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-  
3 005-01). Written informed consent was obtained from the patients or their relatives.

## 5 **Study Design and Setting**

6 The Second China National Stroke Registry (CNSR II) was a national multicenter hospital-  
7 based cohort study. CNSR II was launched in June 2012 in China. The primary objectives  
8 were to evaluate the delivery of stroke care and identify suboptimal performance metrics to  
9 be improved.<sup>15</sup> The hospitals were selected based on similar criteria in CNSR I launched in  
10 2007, which had been published elsewhere.<sup>16</sup> After assessing the hospital characteristics, such  
11 as location, teaching status, number of beds, and annual stroke discharges by the steering  
12 committee, a total of 219 hospitals were included in CNSR II.<sup>17</sup>

## 14 **Study Population**

15 The patients were consecutively recruited from June 2012 to January 2013. The inclusion  
16 criteria were as follows (1) age 18 years or above; (2) presented within seven days of the  
17 index event of acute ischemic stroke (AIS), transient ischemic attack (TIA), intracerebral  
18 hemorrhage, or subarachnoid hemorrhage, confirmed by brain computed tomography or  
19 magnetic resonance imaging; (3) direct hospital admission from a physician's clinic or  
20 emergency department. A total of 25,018 patients were included in CNSR II; of them,  
21 19,604 were AIS.

22 There were 1200 (6.12%) patients lost at 3 months and 2306 (11.76%) patients lost at 1

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4 1 year. We excluded the patients who missed information on the process of care and those who  
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6 2 lost to follow-up at 3 months and 1 year. Finally, 17,550 patients and 16,482 patients with  
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9 3 AIS were available for evaluating the association between hospital volume and 3-month  
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11 4 outcomes and 1-year outcomes, respectively. A total of 17,438 patients achieved mRS at 3  
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14 5 months, and 16,462 patients achieved mRS at 1 year.  
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### 7 **Data Collection**

8 Data were collected following a standardized form by trained research coordinators. The  
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10 9 information on demographics, health insurance, education, smoking, drinking, comorbidities  
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12 10 (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and  
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14 11 medication history were abstracted from medical records. National Institutes of Health Stroke  
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16 12 Scale (NIHSS) at admission and modified Rankin Scale (mRS) prior to the index event were  
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18 13 assessed through a face-to-face interview.  
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38 14 Hospital stroke volume was defined as the annual number of stroke discharges. The annual  
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40 15 stroke discharges of each hospital were obtained via the hospital survey when they applied to  
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42 16 participate in this study. Additionally, the hospital characteristics, including location,  
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44 17 academic status, the presence of stroke unit, and the number of beds, were obtained by the  
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46 18 survey.  
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### 20 **Process Measures**

21 We selected ten guideline-recommended process measures according to the national  
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guideline and the Get With The Guidelines-Stroke (GWTG-Stroke).<sup>18</sup> There were four acute



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4 1 phage process measures, including (1) intravenous recombinant tissue plasminogen activator  
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6 2 (rt-PA) in patients who arrived within 2 hours after symptom onset and were treated within 3  
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9 3 hours, (2) antithrombotics within 2 days after admission, (3) deep vein thrombosis (DVT)  
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11 4 prophylaxis, and (4) dysphagia screening. There were six process measures at discharge,  
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14 5 including (1) antithrombotic medication, (2) antihypertensive medication for patients with  
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16 6 hypertension, (3) hypoglycemic medication for patients with diabetes, (4) anticoagulation for  
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18 7 atrial fibrillation, (5) lowering low-density lipoprotein cholesterol (LDL-C) medication, and  
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20 8 (6) smoking cessation. The definitions of the process measures are shown in Supplemental  
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24 9 Table 1. Additionally, we calculated a binary defect-free measure of care, defined as the  
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27 10 patient receiving all the processes for which they were eligible.<sup>19, 20</sup> Process measures are  
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30 11 applied only to qualified patients in the absence of documented contraindications or any other  
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33 12 rationale as to why therapy was not provided.<sup>21</sup>

### 14 **Clinical Outcomes**

15 According to the study protocol, all patients were followed up at 3, 6, and 12 months by  
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17 16 telephone or face-to-face interview. Trained research coordinators collected the clinical  
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19 17 outcomes. In this study, the outcomes included all-cause mortality, poor outcome, recurrent  
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21 18 stroke, and combined vascular events at 3 months and 1 year. The stroke recurrence was  
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23 19 defined as a new ischemic stroke or hemorrhagic stroke within 3 months or 1 year after  
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25 20 symptom onset. Composite vascular events included myocardial infarction, recurrent stroke,  
26  
27 21 and vascular death. The poor outcome was defined as mRS of 3 to 6.

## 1 **Statistical Analysis**

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

10 The generalized estimating equations with an exchangeable working correlation matrix  
11 were used to evaluate the association between hospital volume, the process of care, and  
12 outcomes adjusting for the cluster effect within the hospital. In the adjusted models, age, sex,  
13 health insurance (urban resident basic medical insurance, new rural cooperative medical  
14 scheme, commercial insurance, self-payment), education (elementary or below, middle  
15 school, high school or above), previous or current smoking, drinking, comorbidities  
16 (hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at  
17 admission, and hospital characteristics (academic status, number of beds, presence of stroke  
18 unit, and location) were included. Additionally, the defect-free measure of care was included  
19 in the adjusted model when estimating the association between hospital volume and  
20 outcomes. We used the Kaplan-Meier method to depict the cumulative hazards of all-cause  
21 mortality and recurrent stroke. Odds ratios (ORs) and corresponding 95% confidence  
22 intervals (CIs) were used with the hospital volume of Q4 as reference. Additionally, we used

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4 1 restricted cubic splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the  
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6 2 association between hospital volume and outcomes. We tested for non-linearity by using the  
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9 3 Wald statistics.

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11 4 All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P  
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14 5 values were two-tailed with a significant level of 0.05.

## 16 6 **Patient and public involvement**

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19 7 Patients and the public were not involved in the design, conduct, reporting, or dissemination  
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22 8 plans of our research.

## 25 9 **Results**

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29 10 A total of 17,550 patients with AIS from 217 hospitals across China were included in this  
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32 11 study. The process of patient selection is shown in Figure 1. Patients included in the current  
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35 12 study and those excluded were largely comparable (supplemental Table 2). Table 1 describes  
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37 13 the baseline characteristics of the included hospitals and patients.

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40 14 Of the 217 included hospitals, 125 (57.6%) were teaching hospitals, and the high-volume  
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42 15 hospitals were likely to be teaching hospitals. There were 121 hospitals in the east of China,  
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45 16 66 in the middle of China, and 30 in the west of China. The average hospital volume was 437  
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48 17 per year, ranging from 136 to 2048.

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50 18 The mean age was 65 (57-74), and 63.6% of the patients were males. The median NIHSS  
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53 19 at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared  
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56 20 with the high-volume hospitals, there were more females, and the patients were older in low-  
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58 21 volume hospitals. The patients in high-volume hospitals were more likely to be with diabetes  
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1 and hyperlipidemia but less likely to be with atrial fibrillation. The proportions of taking  
2 antiplatelet and lipid-lowering medicine were higher in high-volume hospitals than that in low-  
3 volume hospitals.

#### 4 **Association between Hospital Volume and Process Measures**

5 Table 2 list the rates of achievement in process measures. Compared with the hospitals of Q4,  
6 the unadjusted OR of defect-free measure of care was 0.88 (95% CI, 0.62-1.25) for Q1, 1.13  
7 (95% CI, 0.82-1.56) for Q2, and 1.15 (95% CI, 0.81-1.62) for Q3. No significant difference  
8 was found in individual process measures, except the DVT prophylaxis for A3 (OR, 2.22;  
9 95%CI, 1.26-3.91; P=0.0059), antithrombotic medication at discharge for Q2 (OR, 1.74;  
10 95%CI, 1.09-2.76; P=0.0196), and Lowering LDL-C medication for Q3 (OR, 1.60; 95%CI,  
11 1.10-2.33; P=0.0134) (Supplemental Table 3).

12 Table 3 shows the adjusted ORs for process measures. After adjusting for the patients and  
13 hospital characteristics, the adjusted OR of defect-free measure of care was 0.93 (95% CI,  
14 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  
15 the individual performance measures show no significant association (all P >0.05).

#### 16 **Association between Hospital Volume and 3-Month and 1-Year Outcomes**

17 Of the included patients, 1322 (7.53%) died within 1 year after stroke onset. The Kaplan-  
18 Meier plot for mortality within 1 year was shown in Figure 2. The 3-month and 1-year  
19 mortality was different across the 4 groups (3-month mortality, 4.95% versus 3.64% versus  
20 4.33% versus 3.39%, P=0.0011; 1-year mortality, 9.59% versus 7.69% versus 8.39% versus  
21 4.33% versus 3.39%, P=0.0011; 1-year mortality, 9.59% versus 7.69% versus 8.39% versus  
22 4.33% versus 3.39%, P=0.0011).

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

5 A total of 3683 (21.12%) patients experienced poor outcome at 3 months and 3701  
6 (22.48%) at 1 year (Table 4). Patients presenting to low-volume hospitals were more likely to  
7 have a higher rate of poor outcome at 3 months (23.41% versus 19.51% versus 21.37%  
8 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  
9 (25.69% versus 20.71% versus 21.81% versus 22.65%,  $P<0.0001$ ;  $OR_{Q1 \text{ versus } Q4}=1.29$ , 95%  
10 CI 1.08-1.54,  $P=0.0043$ ). When adjusted for potential factors, there was still a higher rate of  
11 poor outcome at 1 year among Q1 hospitals in comparison with Q4 hospitals ( $OR_{Q1 \text{ versus } Q4}$   
12 =1.29, 95% CI 1.01-1.64,  $P=0.0393$ ).

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

18 In Figures 3-6, we used restricted cubic splines to flexible model and visualize the relation  
19 of all-cause mortality, poor outcome, stroke recurrence, and combined vascular events with  
20 hospital stroke volume. The multivariable-adjusted restricted cubic splines suggested a “J-  
21 shaped” association between volume and all-cause mortality and poor outcome. The analyses  
22 indicated a significant non-linear association between volume and poor outcome at 3 months

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4 1 and 1 year (P for non-linear =0.0096 and <0.001, respectively), as well as combined vascular  
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6 2 events at 1 year (P for non-linear = 0.0242).  
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### 10 3 **Discussion**

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13 4 Our analysis of a large population of 17,550 patients with ischemic stroke suggested that no  
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15 5 significant difference in the process of care was observed for patients in lower-volume  
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17 6 hospitals compared to higher-volume hospitals. There was no association between hospital  
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19 7 volume and mortality, stroke recurrence, and combined vascular events at 3 months and 1  
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21 8 year. In contrast, we found that the patients in the lowest volume quartile had a significantly  
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23 9 higher rate of poor outcome at 1 year than the highest quartile.  
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29 10 Previous studies found that high volume was associated with improved outcomes  
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31 11 suggesting that volume may be a surrogate for quality of care. The quality of care can be  
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33 12 assessed from outcome, process, and structure.<sup>22</sup> Usually, hospital volume is used as a  
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35 13 structure metric of quality of care. However, the underlying mechanisms of interplay between  
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37 14 structure and process are complex.<sup>23</sup> Two existing studies<sup>13, 23</sup> showed that the patients in  
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39 15 high-volume hospitals received more process of care compared with patients in low-volume  
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41 16 hospitals. Potential mechanisms were proposed to explain this association, including more  
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43 17 experience (“practice makes perfect”) and the availability of advanced techniques and  
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45 18 devices in high-volume hospitals.<sup>7, 23</sup> In contrast, we did not find an association between  
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47 19 hospital stroke volume and process measures in the current study. This was similar to a study  
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49 20 from GWTG-Stroke. This study from 790 US hospitals, including 322,847 patients with  
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51 21 ischemic stroke or transient ischemic attack, observed no differences in performance  
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4 1 measures between high-volume and low-volume hospitals after adjusting for patient baseline  
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6 2 characteristics.<sup>18</sup> In the past years, many initiatives for improving the quality of care have  
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9 3 been implemented to homogenize the quality of care in hospitals, such as GWTG-Stroke,  
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11 4 Australian Stroke Clinical Registry, and CNSR,<sup>24</sup> which may attenuate the difference in  
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14 5 quality of care between high-volume and low-volume hospitals.  
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17 6 During the past decades, a significant number of studies evaluated the volume-outcome  
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19 7 association. Many, but not all, found the reverse relationship between volume and outcome.<sup>9</sup>  
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22 8 Several studies revealed that stroke patients in high-volume hospitals may experience lower  
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24 9 short-term mortality than patients in low-volume hospitals.<sup>11, 12, 25, 26</sup> However, we found no  
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27 10 benefit in mortality for patients in high-volume hospitals. Several reasons may explain this  
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30 11 discrepancy. First, the hospital volume was varied in these studies. Moreover, stroke severity  
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32 12 is an essential factor affecting the patient's prognosis. Whether stroke severity was adjusted  
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35 13 may contribute to the results.<sup>13</sup> Lacking data on stroke severity, most studies used  
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38 14 comorbidity or comorbidity index score to adjust the case mix.<sup>11, 12, 25, 26</sup> In this study we used  
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41 15 the NIHSS score at admission to adjust the stroke severity. Our finding is compatible with a  
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43 16 Danish nationwide cohort study of 63,995 patients admitted to stroke units.<sup>23</sup> This study  
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46 17 found no association between volume and 30-day mortality and 1-year mortality after  
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49 18 adjusting for patient baseline characteristics, stroke unit, university status, and quality of care.  
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51 19 Mortality may be insensitive to detecting underlying changes in patient prognosis.<sup>23</sup>  
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53 20 Besides mortality, we also examined the association between hospital volume and poor  
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56 21 outcome, stroke recurrence, and combined vascular events. To our knowledge, it was the first  
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59 22 time to evaluate the association between volume and poor outcome at 3 months and 1 year in  
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4 1 patients with acute ischemic stroke. Compared with the highest quartile of hospitals, patients  
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6 2 in the lowest quartile had a higher rate of poor outcome at 1 year after adjusting for potential  
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9 3 confounders. The poor outcome may be more sensitive to detecting the changes in patient  
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11 4 prognosis. The underlying mechanisms of volume on poor outcome are not known. Though  
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14 5 there was no significant difference in the process of care during acute phase and at discharge  
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17 6 between low- and high-volume hospitals, the differences in some other processes of care after  
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20 7 discharge may explain this association. Patients in high-volume hospitals may receive more  
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22 8 processes after discharge, such as, limb rehabilitation, which can improve the poor outcome.  
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25 9 The association between volume and the poor outcome may be mediated by medical care  
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27 10 after discharge. However, we could not identify the medical care after discharge in the  
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30 11 current study. In the future, the association between volume, the process of care after  
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32 12 discharge, and long-term outcomes are needed for further exploration. Though the significant  
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35 13 association, we did not think it is reasonable to regionalize stroke care. Because the  
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38 14 transferring may lead to a delay in admission, which may offset some benefits of being  
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41 15 admitted to large-volume hospitals.<sup>11</sup>

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43 16 Several limitations in this study should be acknowledged. First, the hospitals that  
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46 17 participated in the CNSR were volunteers. There may exist unavoidable selection bias. And  
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49 18 the hospitals enrolled may not fully represent the general hospitals in China. Second, though  
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52 19 ten processes of care were evaluated, some other processes of care, such as, mechanical  
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55 20 thrombectomy, and the care patients received after discharge could not be assessed. The  
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58 21 differences in unassessed process measures may explain the association between volume and  
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60 22 poor outcome. Third, there is a cluster effect within hospitals and physicians. Tough we take



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4 1 into consideration of the cluster effect within hospitals by using the generalized estimating  
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6 2 equations, we cannot adjust the cluster effect within physicians. Forth, because of the  
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9 3 differences in patients, hospital characteristics, and performance of care across varied regions  
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11 4 and countries, our results may not generalize to other countries. Further studies on volume  
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14 5 and clinical outcome, especially the poor outcome, are needed to confirm our results.  
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## 7 **Conclusions**

8 Using the large national stroke registry, we found no association between hospital stroke  
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10 9 volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile  
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12 10 of hospitals had increased rates of poor outcome compared with the patients in the highest  
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14 11 quartile of hospitals. Further work needs to be done to examine whether the medical care  
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16 12 after discharge mediates the association between stroke volume and poor outcome. Better  
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18 13 understanding the association between structure, processes, and outcomes can help to identify  
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20 14 the best way to improve stroke prognosis.  
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## 16 **Availability of data and materials**

17 The datasets used and analyzed during the current study are available from the corresponding  
18  
19 18 author on reasonable request.  
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9 3 Commission (D171100003017002).  
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14 5 **Disclosures:** None.  
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19 7 **Author contributions**

20  
21  
22 8 Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or  
23  
24 9 patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation:  
25  
26  
27 10 RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG  
28  
29  
30 11 Zhou and YJ Wang take responsibility for the integrity of the work.  
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36 13 **References**  
37  
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39

- 40 14 1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day  
41  
42 15 Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol.* 2017;2:732-  
43  
44 16 741  
45  
46  
47 17 2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in  
48  
49 18 the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA.*  
50  
51 19 1998;279:1278-1281  
52  
53  
54  
55 20 3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After  
56  
57 21 Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg.* 2016;263:664-  
58  
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7 2 4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer  
8  
9 3 operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J*  
10  
11 4 *Public Health*. 2007;97:539-544  
12  
13  
14 5 5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality  
15  
16 6 following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886  
17  
18  
19 7 6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common  
20  
21 8 medical conditions. *N Engl J Med*. 2010;362:1110-1118  
22  
23  
24 9 7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume,  
25  
26 10 Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get  
27  
28 11 With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661-1670  
29  
30  
31  
32 12 8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in  
33  
34 13 patients with traumatic brain injury: A retrospective observational study using a national  
35  
36 14 inpatient database in Japan. *Injury*. 2017;48:1423-1431  
37  
38  
39  
40 15 9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review  
41  
42 16 and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520  
43  
44  
45 17 10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med*  
46  
47 18 *Care*. 2010;48:149-156  
48  
49  
50 19 11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to  
51  
52 20 Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes*.  
53  
54 21 2015;8:S141-147  
55  
56  
57  
58 22 12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it  
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3  
4 1 matter? *Neurology*. 2007;69:1142-1151  
5  
6 2 13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients:  
7  
8  
9 3 Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753  
10  
11 4 14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early  
12  
13  
14 5 outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen  
15  
16  
17 6 activator. *Int J Stroke*. 2015;10:73-78  
18  
19 7 15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement  
20  
21  
22 8 in Stroke Care in China. *Stroke*. 2016;47:2843-2849  
23  
24  
25 9 16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute  
26  
27  
28 10 cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*.  
29  
30 11 2011;6:355-361  
31  
32 12 17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients  
33  
34  
35 13 hospitalized with acute ischemic stroke in China: Findings from the China National Stroke  
36  
37  
38 14 Registry II. *Int J Stroke*. 2017;12:254-263  
39  
40 15 18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated  
41  
42  
43 16 with sustained improvement in care for patients hospitalized with acute stroke or transient  
44  
45  
46 17 ischemic attack. *Circulation*. 2009;119:107-115  
47  
48 18 19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke:  
49  
50  
51 19 findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238  
52  
53 20 20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and  
54  
55  
56 21 Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419  
57  
58 22 21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center  
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4 1 for Healthcare Quality Management in Neurological Diseases, China National Clinical  
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7 2 Research Center for Neurological Diseases, the Chinese Stroke Association, National Center  
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9 3 for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for  
10  
11 4 Disease Control and Prevention and Institute for Global Neuroscience and Stroke  
12  
13  
14 5 Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239  
15  
16  
17 6 22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729  
18  
19  
20 7 23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved  
21  
22 8 quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045  
23  
24  
25 9 24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving  
26  
27 10 the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40  
28  
29  
30 11 25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke  
31  
32 12 fatality in Canada. *Stroke*. 2008;39:3360-3366  
33  
34  
35 13 26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality  
36  
37 14 and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788  
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**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
<b>Hospital characteristics</b>							
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
<b>Geographic region</b>							
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 (14.4%)		
<b>Patient characteristics</b>							

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.



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**Table 2. The rates of achievement in process measures**

Process measures	Total	Q1 hospitals	Q2 hospitals	Q3 hospitals	Q4 hospitals
	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	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%)	2839/3081 (91.9%)	4557/5090 (89.5%)
Lowering LDL-C medication	7700/11597 (66.4%)	1436/2247 (63.9%)	2591/3621 (71.6%)	1523/2129 (71.8%)	2150/3609 (59.6%)
Antihypertensive	8867/13385 (66.2%)	1712/2611 (65.6%)	2764/4207 (65.7%)	1710/2476 (69.2%)	2681/4097 (65.4%)

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3	medication for				
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7	Hypoglycemic				
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9	medication for diabetes	3662/4898 (74.8%)	685/907 (75.5%)	1114/1494 (74.6%)	721/901 (80.0%)
10					
11	Anticoagulation for AF	303/1437 (21.1%)	43/278 (15.5%)	86/468 (18.4%)	87/325 (26.8%)
12					
13	Smoking cessation	6712/7819 (85.8%)	1227/1457 (84.2%)	2098/2406 (87.2%)	1213/1456 (83.3%)
14					
15	Defect-free measure of				
16					
17	care	5816/17550 (33.1%)	992/3371 (29.4%)	1965/5386 (36.5%)	1150/3287 (35.1%)
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22 N1 indicates the number of patients who received the process of care, and N2 indicates the number of patients eligible. Rt-PA indicates recombinant  
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 25 tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.  
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**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)	0.334	0.71 (0.35, 1.48)	0.3634
Early antithrombotic	0.68 (0.20, 2.32)	0.5364	1.17 (0.30, 4.55)	0.824	1.07 (0.36, 3.18)	0.9020
Dysphagia screening	0.76 (0.33, 1.74)	0.5104	2.19 (0.86, 5.55)	0.098	0.90 (0.42, 1.92)	0.7845
DVT prophylaxis	1.02 (0.52, 2.01)	0.9504	1.09 (0.57, 2.09)	0.793	1.55 (0.84, 2.83)	0.1594
Antithrombotic medication	1.26 (0.61, 2.61)	0.5391	1.27 (0.61, 2.64)	0.527	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)	0.922	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)	0.615	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)	0.781	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)	0.584	1.05 (0.61, 1.78)	0.8681

Smoking cessation	0.56 (0.10, 2.97)	0.4939	0.67 (0.12, 3.63)	0.642	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 (5.39%)	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	1.06 (0.89, 1.79)	0.1861
	Adjusted	1.27 (0.88, 1.83)	0.2062	0.99 (0.75, 1.30)	0.9179	1.08 (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	1.06 (0.85, 1.58)	0.3563
	Adjusted	1.16 (0.83, 1.62)	0.3798	1.11 (0.79, 1.56)	0.5474	1.01 (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	1.04 (0.83, 1.56)	0.4304
	Adjusted	1.15 (0.82, 1.61)	0.4109	1.09 (0.78, 1.53)	0.6167	1.02 (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	1.03 (0.83, 1.40)	0.5552
	Adjusted	1.08 (0.81, 1.43)	0.6025	1.05 (0.80, 1.37)	0.7277	1.00 (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.

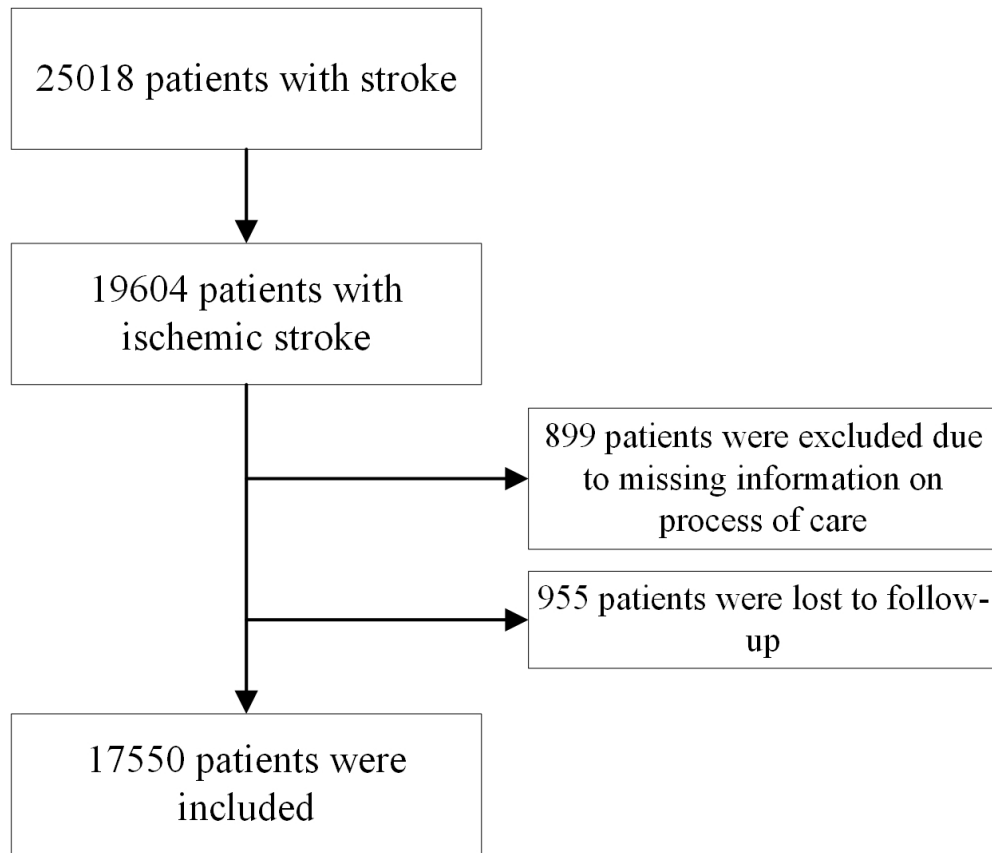


Figure 1. The flow chart for patient selection

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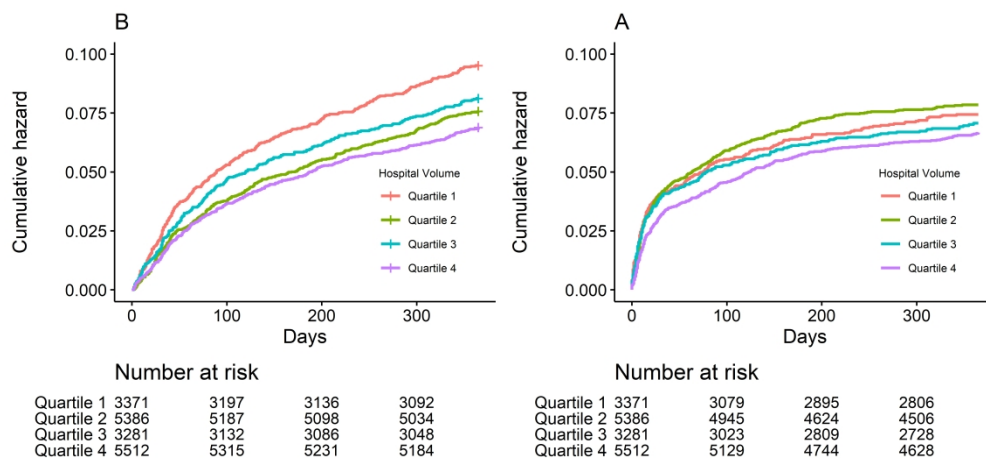


Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

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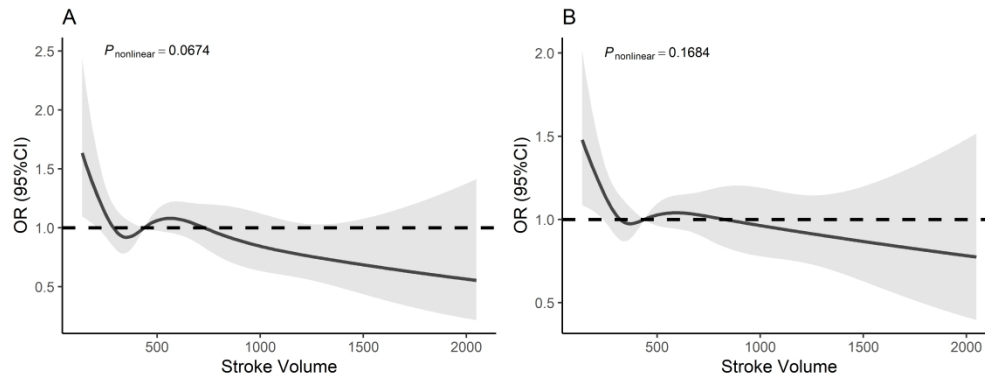


Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and 3-month all-cause mortality. B, Hospital volume and 1-year all-cause mortality. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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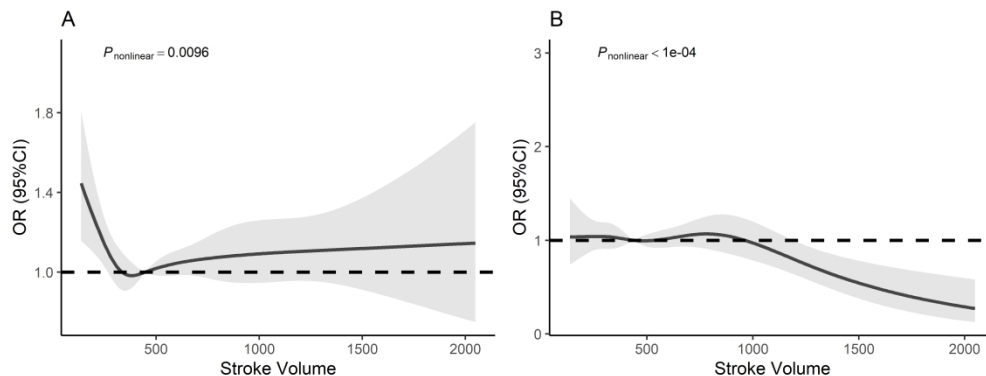


Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and 3-month poor outcome. B, Hospital volume and 1-year poor outcome. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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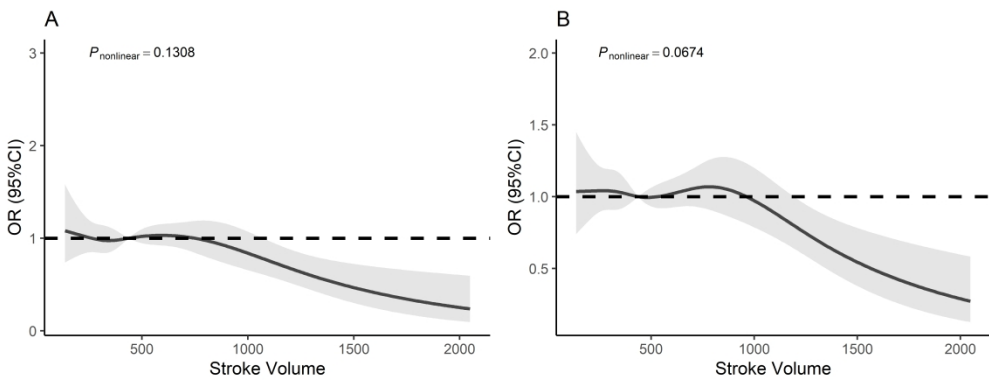


Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and 3-month recurrent stroke. B, Hospital volume and 1-year recurrent stroke. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

220x84mm (600 x 600 DPI)

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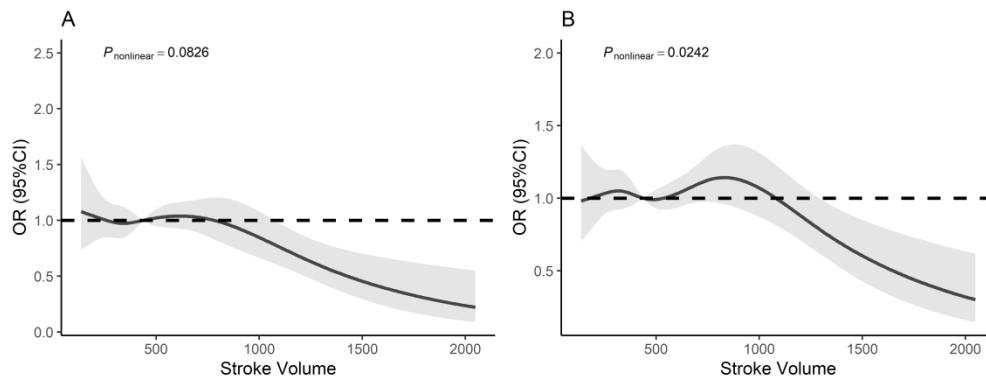


Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and 3-month combined vascular events. B, Hospital volume and 1-year combined vascular events. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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*Supplementary Material*

For peer review only



Table 1. The definition of process measures

	<b>Definition*</b>
<b>Acute phase process measures</b>	
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
<b>Process measures at discharge</b>	
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 $\geq$ 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
<b>Patient characteristics</b>			
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 #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			

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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	11
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

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<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Neurology
Keywords:	Stroke < NEUROLOGY, Neurology < INTERNAL MEDICINE, Adult neurology < NEUROLOGY

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7 **Ischemic Stroke: A Prospective Observational Study**  
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14 2 **Runhua Zhang<sup>1-3</sup>, Gaifen Liu<sup>2-3</sup>, Yuesong Pan<sup>2-3</sup>, Maigeng Zhou<sup>1\*</sup>, Yongjun Wang<sup>2-3\*</sup>**  
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4 **1 Abstract**

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6 **2 Objectives** There is uncertainty with respect to the hospital volume and clinical outcomes for  
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**3** patients with stroke. This study aimed to assess the association between hospital volume,  
**4** processes of care, and outcomes after ischemic stroke.

**5 Design** A multicenter prospective cohort study.

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

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

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

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

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4 1 **Conclusions** We found no significant associations between hospital volume, processes of  
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6 2 care at the hospital, and mortality, recurrent stroke, and combined vascular events in patients  
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8 3 with ischemic stroke. However, hospital volume may be associated with poor outcome at 1  
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10 4 year.  
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### 17 6 **Strengths and limitations of this study**

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19 7 The sample size was large, involving 217 institutions across the country.

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21 8 To the best of our knowledge, this is the first study investigating the relationship between  
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23 9 stroke volume in a hospital, process of care, and outcomes in China.  
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27 10 The study has some limitations. Some processes of care, especially post-discharge, could not  
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29 11 be obtained in this study.

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31 12 The participating hospitals were volunteers, and unavoidable selection bias could not be  
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## 1 Introduction

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1 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.<sup>1-5</sup> The volume-outcome relationship was also described in some medical conditions, including heart failure, acute myocardial infarction, pneumonia, and brain injury.<sup>6-8</sup> The magnitude of the association varied significantly in a previous study.<sup>9</sup> Studies reporting an inverse relationship lacked significance to make volume-based referral recommendations.<sup>10</sup> 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,<sup>11, 12</sup> but some had not.<sup>13, 14</sup> 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.

15 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.

## 21 Methods

## 1 **Ethics approval**

2 This study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. ky2012-  
3 005-01). Written informed consent was obtained from the patients or their relatives.

## 5 **Study design and setting**

6 The Second China National Stroke Registry (CNSR II) was a national multicenter hospital-  
7 based cohort study. CNSR II was launched in June 2012 in China. The primary objectives  
8 were to evaluate the delivery of stroke care and identify suboptimal performance metrics to  
9 be improved.<sup>15</sup> The hospitals were selected based on similar criteria in CNSR I launched in  
10 2007, which had been published elsewhere.<sup>16</sup> After assessing the hospital characteristics, such  
11 as location, teaching status, number of beds, and annual stroke discharges by the steering  
12 committee, a total of 219 hospitals were included in CNSR II.<sup>17</sup>

## 14 **Study population**

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

22 There were 1,200 (6.12%) patients lost at 3 months and 2,306 (11.76%) patients lost at 1

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4 1 year. We excluded the patients who missed information on the process of care and those who  
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6 2 were lost to follow-up at 3 months and 1 year. Finally, 17,550 patients and 16,482 patients  
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9 3 with AIS were eligible for evaluating the association between hospital volume and 3-month  
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11 4 outcomes and 1-year outcomes, respectively. A total of 17,438 patients achieved a modified  
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14 5 Rankin Scale (mRS) at 3 months, and 16,462 patients achieved mRS at 1 year.  
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### 7 **Data collection**

8 Data were collected following a standardized form by trained research coordinators. Data on  
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10 9 demographics, health insurance, education, smoking, drinking, comorbidities (hypertension,  
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12 10 diabetes, hyperlipidemia, atrial fibrillation, history of stroke or TIA), and medication history  
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14 11 were extracted from medical records. National Institutes of Health Stroke Scale (NIHSS) at  
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16 12 admission and mRS prior to the index event were assessed through a face-to-face interview.  
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35 13 Hospital stroke volume was defined as the annual number of stroke discharges. The annual  
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37 14 stroke discharges of each hospital were obtained via the hospital survey when they applied to  
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39 15 participate in this study. Additionally, hospital characteristics, such as location, academic  
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41 16 status, the presence of stroke unit, and the number of beds, were obtained in the survey.  
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### 18 **Process measures**

19 We selected ten recommended process measures from the national guidelines and the Get  
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21 20 With The Guidelines-Stroke (GWTG-Stroke).<sup>18</sup> Process measures are shown in Supplemental  
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21 Table 1. There were four acute phase process measures, namely (1) intravenous recombinant  
22 tissue plasminogen activator (rt-PA) in patients who arrived within 2 hours after symptom

1 onset and were treated within 3 hours, (2) antithrombotics within 2 days after admission, (3)  
2 deep vein thrombosis (DVT) prophylaxis, and (4) dysphagia screening. There were six  
3 process measures at discharge: (1) antithrombotic medication; (2) antihypertensive  
4 medication for patients with hypertension; (3) hypoglycemic medication for patients with  
5 diabetes; (4) anticoagulation for atrial fibrillation; (5) lowering low-density lipoprotein  
6 cholesterol (LDL-C) medication; and (6) smoking cessation. Additionally, we calculated a  
7 binary defect-free measure of care, defined as the patient receiving all the processes for  
8 which they were eligible.<sup>19, 20</sup> Process measures were applied only to qualified patients in the  
9 absence of documented contraindications or any other rationale as to why therapy was not  
10 provided.<sup>21</sup>

## 12 **Clinical outcomes**

13 All patients were followed up at 3, 6, and 12 months by telephone or face-to-face interview.  
14 Trained research coordinators collected the clinical outcomes. In this study, the outcomes  
15 included all-cause mortality, poor outcome, recurrent stroke, and combined vascular events at  
16 3 months and 1 year. Each case fatality was identified from the attended hospital where the  
17 patient was treated or by a death certificate from the local citizen registry. Stroke recurrence  
18 was defined as a new ischemic stroke or hemorrhagic stroke within 3 months or 1 year after  
19 symptom onset. Composite vascular events included myocardial infarction, recurrent stroke,  
20 and vascular death. The poor outcome was defined as mRS of 3 to 6.

## 22 **Statistical analysis**

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4 1 The patients were categorized into four groups based on quartiles of hospital volume: Q1  
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6 2 (<300 /year), Q2 (300-436 /year), Q3 (437-722 /year), and Q4 (>722 /year). Continuous  
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9 3 variables were described as mean  $\pm$  standard deviation or median and interquartile range.  
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11 4 Categorical variables were described as proportions. The patient characteristics were  
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14 5 compared using ANOVA, Kruskal-Wallis test, or chi-square test. Additionally, to obtain the  
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17 6 P for trend, we used Cochran-Mantel-Haenszel non-zero correlation tests for continuous  
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19  
20 7 variables and Cochran-Mantel-Haenszel row mean scores for categorical variables.

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22 8 Generalized estimating equations with an exchangeable working correlation matrix were  
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24  
25 9 used to evaluate the association between hospital volume, the process of care, and outcomes  
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27  
28 10 adjusting for the cluster effect within the hospital. In the adjusted models, age, sex, health  
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31 11 insurance (urban resident basic medical insurance, new rural cooperative medical scheme,  
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34 12 commercial insurance, self-payment), education (elementary or below, middle school, high  
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37 13 school or above), previous or current smoking, drinking, comorbidities (hypertension,  
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40 14 diabetes, hyperlipidemia, atrial fibrillation, history of stroke), NIHSS at admission, and  
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43 15 hospital characteristics (academic status, number of beds, presence of stroke unit, and  
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45  
46 16 location) were included. Additionally, the defect-free measure of care was included in the  
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48  
49 17 adjusted model when estimating the association between hospital volume and outcomes. We  
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51  
52 18 used the Kaplan-Meier method to depict the cumulative hazards of all-cause mortality and  
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55 19 recurrent stroke. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were  
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57  
58 20 used with the hospital volume of Q4 as reference. Additionally, we used restricted cubic  
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61 21 splines with five knots at the 5th, 35th, 50th, and 95th centiles to model the association  
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64 22 between hospital volume and outcomes. We tested for non-linearity by using the Wald

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4 1 statistics.

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6 2 All analyses were performed by SAS version 9.4 (SAS Institute) and R version 3.5.1. All P  
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8  
9 3 values were two-tailed with a significant level of 0.05.

#### 10 4 **Patient and public involvement**

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12  
13  
14 5 Patients and the public were not involved in the design, conduct, reporting, or dissemination  
15  
16  
17 6 plans of our research.

#### 18 19 20 7 **Results**

21  
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24 8 A total of 17,550 patients with AIS from 217 hospitals across China were included in this  
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26  
27 9 study. The process of patient selection is shown in Figure 1. Patients included in the current  
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29  
30 10 study and those excluded were largely comparable (supplemental Table 2). Table 1 describes  
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32 11 the baseline characteristics of the included hospitals and patients.

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34 12 Of the 217 hospitals, 125 (57.6%) were teaching hospitals. The high-volume hospitals  
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36  
37 13 were likely to be teaching hospitals. Overall, 121 hospitals (55.8%) had certified stroke units.  
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40 14 There were 121 hospitals in the east of China, 66 around the middle, and 30 in the west. The  
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43 15 average hospital volume was 437 per year, ranging from 136 to 2048.

44  
45 16 The mean age was 65 (57-74), and 63.6% of the patients were males. The median NIHSS  
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48 17 at admission was 4 (2-7) and the median days of hospitalization were 13 (9-16). Compared  
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51 18 with the high-volume hospitals, there were more females, and the patients were older in low-  
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53  
54 19 volume hospitals. The patients in high-volume hospitals were more likely to have diabetes  
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56  
57 20 and hyperlipidemia but less likely to have atrial fibrillation. The proportions of patients  
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60 21 taking antiplatelet and lipid lowering agents were higher in high-volume hospitals than that in



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4 1 low-volume hospitals.  
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### 9 3 **Association between Hospital Volume and Process Measures**

10 4 Table 2 lists the rates of achievement in process measures. Compared with the hospitals of  
11  
12 5 Q4, the unadjusted OR of defect-free measure of care was 0.88 (95% CI, 0.62-1.25) for Q1,  
13  
14 6 1.13 (95% CI, 0.82-1.56) for Q2, and 1.15 (95% CI, 0.81-1.62) for Q3. No significant  
15  
16 7 difference was found in individual process measures, except the DVT prophylaxis for A3  
17  
18 8 (OR, 2.22; 95%CI, 1.26-3.91; P = 0.0059), antithrombotic medication at discharge for Q2  
19  
20 9 (OR, 1.74; 95%CI, 1.09-2.76; P = 0.0196), and LDL-C-lowering medication for Q3 (OR,  
21  
22 10 1.60; 95%CI, 1.10-2.33; P = 0.0134) (Supplemental Table 3).  
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30 11 Table 3 shows the adjusted ORs for process measures. After adjusting for the patients and  
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32 12 hospital characteristics, the adjusted OR of defect-free measure of care was 0.93 (95% CI,  
33  
34 13 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  
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36 14 the individual performance measures show no significant association (all P >0.05).  
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### 43 16 **Association between Hospital Volume and 3-Month and 1-Year Outcomes**

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45 17 Of the included patients, 1,322 (7.53%) died within 1 year after stroke onset. The Kaplan-  
46  
47 18 Meier plot for mortality within 1 year is shown in Figure 2. The 3-month and 1-year mortality  
48  
49 19 was different across the 4 groups (3-month mortality, 4.95% versus 3.64% versus 4.33%  
50  
51 20 versus 3.39%, P = 0.0011; 1-year mortality, 9.59% versus 7.69% versus 8.39% versus 7.16%,  
52  
53 21 P = 0.0006) (Table 4). At 3 months and 1 year, the mortality was slightly higher in Q1  
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56  
57 22 hospitals (OR at 3 months=1.54, 95% CI 1.13-2.09, P = 0.0059; OR at 1 year = 1.48, 95% CI  
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1 1.17- 1.88;  $P = 0.0013$ ), but not Q2 or Q3 hospitals in compared with Q4 hospitals. However,  
2 the difference was not significant when adjusted for potential factors (Table 5).

3 A total of 3,683 (21.12%) patients experienced poor outcome at 3 months and 3701  
4 (22.48%) at 1 year (Table 4). Patients treated in low-volume hospitals were more likely to  
5 have a higher rate of poor outcome at 3 months (23.41% versus 19.51% versus 21.37%  
6 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  
7 (25.69% versus 20.71% versus 21.81% versus 22.65%,  $P < 0.0001$ ;  $OR_{Q1 \text{ versus } Q4} = 1.29$ , 95%  
8 CI 1.08-1.54,  $P = 0.0043$ ). When adjusted for potential factors, Q1 hospitals still had a higher  
9 rate of poor outcome at 1 year compared with Q4 hospitals ( $OR_{Q1 \text{ versus } Q4} = 1.29$ , 95% CI  
10 1.01-1.64,  $P = 0.0393$ ).

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

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

## 1 Discussion

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

8 Previous studies found that high volume was associated with improved outcomes  
9 suggesting that volume is a surrogate for quality of care. The quality of care can be assessed  
10 from outcome, process, and structure.<sup>22</sup> Usually, hospital volume is used as a structure metric  
11 of quality of care. However, the underlying mechanisms of interplay between structure and  
12 process are complex.<sup>23</sup> Two existing studies showed that the patients in high-volume  
13 hospitals received more process of care than patients in low-volume hospitals.<sup>13, 23</sup> Potential  
14 mechanisms were proposed to explain this association, including substantial experience  
15 (“practice makes perfect”) and the availability of advanced techniques and devices in high-  
16 volume hospitals.<sup>7, 23</sup> In contrast, we did not find an association between hospital stroke  
17 volume and process measures in the current study. This was similar to a study from GWTG-  
18 Stroke, wherein 790 US hospitals (322,847 patients with ischemic stroke or TIA) were  
19 assessed and no differences in performance measures were observed between high-volume  
20 and low-volume hospitals after adjusting for patient baseline characteristics.<sup>18</sup> Previously,  
21 many initiatives for improving the quality of care have been implemented to standardize the

1 quality of care in hospitals, such as GWTG-Stroke, Australian Stroke Clinical Registry, and  
2 CNSR,<sup>24</sup> which may minimize the variability in the quality of care between high-volume and  
3 low-volume hospitals.

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

18 Besides mortality, we also examined the association between hospital volume and poor  
19 outcome, stroke recurrence, and combined vascular events. To our knowledge, this is the first  
20 time the association between volume and poor outcome at 3 months and 1 year in patients  
21 with AIS was evaluated in a study. Compared with the highest quartile of hospitals, patients  
22 in the lowest quartile had a higher rate of poor outcome at 1 year after adjusting for potential

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4 1 confounders. The poor outcome may be more sensitive in detecting changes in patient  
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6 2 prognosis. The underlying mechanisms of the association between volume and poor outcome  
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8  
9 3 are not known. Though there was no significant difference in the process of care during the  
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11 4 acute phase and at discharge between low- and high-volume hospitals, the differences in  
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14 5 some other processes of care after discharge may explain this association. Patients in high-  
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16 6 volume hospitals may undergo more processes after discharge, such as limb rehabilitation,  
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19 7 which can improve poor outcome. The association between volume and poor outcome may  
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22 8 be mediated by medical care after discharge. However, data on post-discharge management  
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25 9 were not routinely documented; hence, data could not be extracted from all patients and  
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28 10 analyzed. In the future, the association between volume, the process of care after discharge,  
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31 11 and long-term outcomes are needed for further exploration. Despite the significant  
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34 12 association, we did not think it was reasonable to regionalize stroke care because patient  
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37 13 transfers may lead to a delay in admission, offsetting some benefits of being admitted to  
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40 14 large-volume hospitals.<sup>11</sup>

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43 15 Several limitations in this study should be acknowledged. First, the hospitals that  
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46 16 participated in the CNSR were volunteers; therefore, selection bias cannot be completely  
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49 17 eliminated. The sampled hospitals enrolled may not be representative of the general hospitals  
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52 18 in China. Second, although ten processes of care were evaluated, other processes of care such  
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55 19 as mechanical thrombectomy and the care patients received after discharge could not be  
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58 20 assessed. The differences in unassessed process measures may explain the association  
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61 21 between volume and poor outcome. Third, there is a cluster effect within hospitals and  
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64 22 physicians. Although we considered the cluster effect within hospitals by using the

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4 1 generalized estimating equations, we could not adjust the cluster effect within physicians.  
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6 2 Moreover, due to variability among patients, hospital characteristics, and performance of care  
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9 3 across varied regions and countries, our results may not be applicable to other countries.  
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11 4 Finally, the mortality rate in our study was lower than the studies from other countries.  
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14 5 Several reasons could explain this. First, most of the included patients were minor strokes  
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16 6 (NIHSS $\leq$ 4). Second, although we used the central death registry to obtain the vital status of  
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19 7 those patients lost to follow up, we failed to obtain the vital status of all patients. This may  
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22 8 lead to bias. Further studies on volume and clinical outcome, especially the poor outcome, are  
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25 9 needed to confirm our results.  
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## 32 **Conclusions**

33  
34 12 Using the large national stroke registry, we found no association between hospital stroke  
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37 13 volume, the process of care, and 1-year mortality. However, the patients in the lowest quartile  
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40 14 of hospitals had increased rates of poor outcome compared with the patients in the highest  
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43 15 quartile of hospitals. Further studies need to be conducted to examine whether the medical  
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46 16 care after discharge mediates the association between stroke volume and poor outcome.  
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49 17 Better understanding of the association between structure, processes, and outcomes can help  
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51  
52 18 identify the best way to improve stroke prognosis.  
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## 55 **Availability of data and materials**

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58 21 The datasets used and analyzed during the current study are available from the corresponding  
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4 1 author on reasonable request.  
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### 30 11 **Author contributions**

31  
32 12 Conception and design: RH Zhang, MG Zhou, YJ Wang; Provision of study materials or  
33  
34 13 patients: YJ Wang; Collection and assembly of data: YJ Wang; Data analysis and interpretation:  
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36 14 RH Zhang, GF Liu, YS Pan; Manuscript preparation, editing, and review: All authors. MG  
37  
38 15 Zhou and YJ Wang take responsibility for the integrity of the work.  
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### 46 17 **References**

- 47  
48  
49  
50 18 1. Khera S, Kolte D, Gupta T, et al. Association Between Hospital Volume and 30-Day  
51  
52 19 Readmissions Following Transcatheter Aortic Valve Replacement. *JAMA Cardiol.* 2017;2:732-  
53  
54 20 741  
55  
56  
57 21 2. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in  
58  
59  
60

- 1  
2  
3  
4 1 the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA*.  
5  
6 2 1998;279:1278-1281  
7  
8  
9 3 3. Hata T, Motoi F, Ishida M, et al. Effect of Hospital Volume on Surgical Outcomes After  
10  
11 4 Pancreaticoduodenectomy: A Systematic Review and Meta-analysis. *Ann Surg*. 2016;263:664-  
12  
13 5 672  
14  
15  
16 6 4. Gilligan MA, Neuner J, Zhang X, et al. Relationship between number of breast cancer  
17  
18 7 operations performed and 5-year survival after treatment for early-stage breast cancer. *Am J*  
19  
20 8 *Public Health*. 2007;97:539-544  
21  
22  
23 9 5. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality  
24  
25 10 following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886  
26  
27  
28 11 6. Ross JS, Normand SL, Wang Y, et al. Hospital volume and 30-day mortality for three common  
29  
30 12 medical conditions. *N Engl J Med*. 2010;362:1110-1118  
31  
32  
33 13 7. Kumbhani DJ, Fonarow GC, Heidenreich PA, et al. Association Between Hospital Volume,  
34  
35 14 Processes of Care, and Outcomes in Patients Admitted With Heart Failure: Insights From Get  
36  
37 15 With The Guidelines-Heart Failure. *Circulation*. 2018;137:1661-1670  
38  
39  
40 16 8. Wada T, Yasunaga H, Doi K, et al. Relationship between hospital volume and outcomes in  
41  
42 17 patients with traumatic brain injury: A retrospective observational study using a national  
43  
44 18 inpatient database in Japan. *Injury*. 2017;48:1423-1431  
45  
46  
47 19 9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review  
48  
49 20 and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520  
50  
51  
52 21 10. Ogbu UC, Slobbe LC, Arah OA, et al. Hospital stroke volume and case-fatality revisited. *Med*  
53  
54 22 *Care*. 2010;48:149-156  
55  
56  
57  
58  
59  
60



- 1  
2  
3  
4 1 11. Hall RE, Fang J, Hodwitz K, et al. Does the Volume of Ischemic Stroke Admissions Relate to  
5  
6 2 Clinical Outcomes in the Ontario Stroke System? *Circ Cardiovasc Qual Outcomes*.  
7  
8  
9 3 2015;8:S141-147  
10  
11 4 12. Saposnik G, Baibergenova A, O'Donnell M, et al. Hospital volume and stroke outcome: does it  
12  
13  
14 5 matter? *Neurology*. 2007;69:1142-1151  
15  
16  
17 6 13. Lee KJ, Kim JY, Kang J, et al. Hospital Volume and Mortality in Acute Ischemic Stroke Patients:  
18  
19 7 Effect of Adjustment for Stroke Severity. *J Stroke Cerebrovasc Dis*. 2020;29:104753  
20  
21  
22 8 14. Wada T, Yasunaga H, Inokuchi R, et al. Relationship between hospital volume and early  
23  
24 9 outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen  
25  
26  
27 10 activator. *Int J Stroke*. 2015;10:73-78  
28  
29  
30 11 15. Li Z, Wang C, Zhao X, et al. Substantial Progress Yet Significant Opportunity for Improvement  
31  
32 12 in Stroke Care in China. *Stroke*. 2016;47:2843-2849  
33  
34  
35 13 16. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute  
36  
37 14 cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*.  
38  
39 15 2011;6:355-361  
40  
41  
42  
43 16 17. Bettger JP, Li Z, Xian Y, et al. Assessment and provision of rehabilitation among patients  
44  
45 17 hospitalized with acute ischemic stroke in China: Findings from the China National Stroke  
46  
47  
48 18 Registry II. *Int J Stroke*. 2017;12:254-263  
49  
50  
51 19 18. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated  
52  
53 20 with sustained improvement in care for patients hospitalized with acute stroke or transient  
54  
55  
56 21 ischemic attack. *Circulation*. 2009;119:107-115  
57  
58  
59 22 19. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke:  
60

- 1  
2  
3  
4 1 findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231-238  
5  
6 20. Man S, Cox M, Patel P, et al. Differences in Acute Ischemic Stroke Quality of Care and  
7  
8  
9 3 Outcomes by Primary Stroke Center Certification Organization. *Stroke*. 2017;48:412-419  
10  
11  
12 4 21. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center  
13  
14 5 for Healthcare Quality Management in Neurological Diseases, China National Clinical  
15  
16 6 Research Center for Neurological Diseases, the Chinese Stroke Association, National Center  
17  
18 7 for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for  
19  
20 8 Disease Control and Prevention and Institute for Global Neuroscience and Stroke  
21  
22 9 Collaborations. *Stroke Vasc Neurol*. 2020;5:211-239  
23  
24  
25  
26  
27 10 22. Donabedian A. Evaluating the quality of medical care. . *Milbank Q*. 2005;83:691-729  
28  
29  
30 11 23. Svendsen ML, Ehlers LH, Ingeman A, et al. Higher stroke unit volume associated with improved  
31  
32 12 quality of early stroke care and reduced length of stay. *Stroke*. 2012;43:3041-3045  
33  
34  
35 13 24. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving  
36  
37 14 the quality of hospital care: A systematic review. *Int J Stroke*. 2016;11:28-40  
38  
39  
40 15 25. Saposnik G, Jeerakathil T, Selchen D, et al. Socioeconomic status, hospital volume, and stroke  
41  
42 16 fatality in Canada. *Stroke*. 2008;39:3360-3366  
43  
44  
45 17 26. Tsugawa Y, Kumamaru H, Yasunaga H, et al. The association of hospital volume with mortality  
46  
47 18 and costs of care for stroke in Japan. *Med Care*. 2013;51:782-788  
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**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
<b>Hospital characteristics</b>							
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 (14.6%)		
<b>Patient characteristics</b>							

1								
2								
3	Male	11163 (63.6%)	2126 (63.1%)	3349 (62.2%)	2108 (64.2%)	3580 (64.9%)	0.0183	0.0085
4								
5	Age	65(57-74)	66(57-75)	65(57-74)	66(58-74)	64(55-73)	<.0001	<.0001
6								
7	Health insurance							
8								
9								
10	URBMI	8959 (51%)	1715 (50.9%)	2552 (47.4%)	1568 (47.8%)	3124 (56.7%)	<.0001	<.0001
11								
12	NRCMS	6932 (39.5%)	1369 (40.6%)	2440 (45.3%)	1394 (42.5%)	1729 (31.4%)		
13								
14	Commercial insurance	60 (0.3%)	8 (0.2%)	27 (0.5%)	4 (0.1%)	21 (0.4%)		
15								
16	Self-payment	1599 (9.1%)	279 (8.3%)	367 (6.8%)	315 (9.6%)	638 (11.6%)		
17								
18	Education							
19								
20								
21	Elementary or below	7934 (45.2%)	1693 (50.2%)	2430 (45.1%)	1678 (51.1%)	2133 (38.7%)	<.0001	<.0001
22								
23	Middle school	4109 (23.4%)	715 (21.2%)	1286 (23.9%)	661 (20.1%)	1447 (26.3%)		
24								
25	High School or above	5507 (31.4%)	963 (28.6%)	1670 (31%)	942 (28.7%)	1932 (35.1%)		
26								
27	Previous or current							
28								
29	smoking	7818 (44.5%)	1457 (43.2%)	2406 (44.7%)	1455 (44.3%)	2500 (45.4%)	0.2676	0.0836
30								
31	Drinking	5277 (30.1%)	872 (25.9%)	1681 (31.2%)	995 (30.3%)	1729 (31.4%)	<.0001	0.0001
32								
33	Medical history							
34								
35	Hypertension	11386 (64.9%)	2156 (64%)	3511 (65.2%)	2136 (65.1%)	3583 (65%)	0.6614	0.459
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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 (0.8%)	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.

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**Table 2. The rates of achievement in process measures**

Process measures	Total	Q1 hospitals	Q2 hospitals	Q3 hospitals	Q4 hospitals
	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	N1/N2 (achievement rate, %)	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%)	2839/3081 (91.9%)	4557/5090 (89.5%)
Lowering LDL-C medication	7700/11597 (66.4%)	1436/2247 (63.9%)	2591/3621 (71.6%)	1523/2129 (71.8%)	2150/3609 (59.6%)
Antihypertensive	8867/13385 (66.2%)	1712/2611 (65.6%)	2764/4207 (65.7%)	1710/2476 (69.2%)	2681/4097 (65.4%)

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3	medication for					
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5	hypertension					
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7	Hypoglycemic					
8						
9	medication for diabetes	3662/4898 (74.8%)	685/907 (75.5%)	1114/1494 (74.6%)	721/901 (80.0%)	1142/1596 (71.6%)
10						
11	Anticoagulation for AF	303/1437 (21.1%)	43/278 (15.5%)	86/468 (18.4%)	87/325 (26.8%)	87/366 (23.8%)
12						
13	Smoking cessation	6712/7819 (85.8%)	1227/1457 (84.2%)	2098/2406 (87.2%)	1213/1456 (83.3%)	2174/2500 (87.0%)
14						
15	Defect-free measure of					
16						
17	care	5816/17550 (33.1%)	992/3371 (29.4%)	1965/5386 (36.5%)	1150/3287 (35.1%)	1709/5512 (31.0%)
18						
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21						

22 N1 indicates the number of patients who received the process of care, and N2 indicates the number of patients eligible. Rt-PA indicates recombinant  
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 25 tissue plasminogen activator; DVT, deep vein thrombosis; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol.  
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**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)	0.334	0.71 (0.35, 1.48)	0.3634
Early antithrombotic	0.68 (0.20, 2.32)	0.5364	1.17 (0.30, 4.55)	0.824	1.07 (0.36, 3.18)	0.9020
Dysphagia screening	0.76 (0.33, 1.74)	0.5104	2.19 (0.86, 5.55)	0.098	0.90 (0.42, 1.92)	0.7845
DVT prophylaxis	1.02 (0.52, 2.01)	0.9504	1.09 (0.57, 2.09)	0.793	1.55 (0.84, 2.83)	0.1594
Antithrombotic medication	1.26 (0.61, 2.61)	0.5391	1.27 (0.61, 2.64)	0.527	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)	0.922	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)	0.615	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)	0.781	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)	0.584	1.05 (0.61, 1.78)	0.8681

Smoking cessation	0.56 (0.10, 2.97)	0.4939	0.67 (0.12, 3.63)	0.642	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 (5.39%)	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	1.06 (0.89, 1.79)	0.1861
	Adjusted	1.27 (0.88, 1.83)	0.2062	0.99 (0.75, 1.30)	0.9179	1.08 (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	1.06 (0.85, 1.58)	0.3563
	Adjusted	1.16 (0.83, 1.62)	0.3798	1.11 (0.79, 1.56)	0.5474	1.01 (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	1.04 (0.83, 1.56)	0.4304
	Adjusted	1.15 (0.82, 1.61)	0.4109	1.09 (0.78, 1.53)	0.6167	1.02 (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	1.09 (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	1.03 (0.83, 1.40)	0.5552
	Adjusted	1.08 (0.81, 1.43)	0.6025	1.05 (0.80, 1.37)	0.7277	1.00 (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.

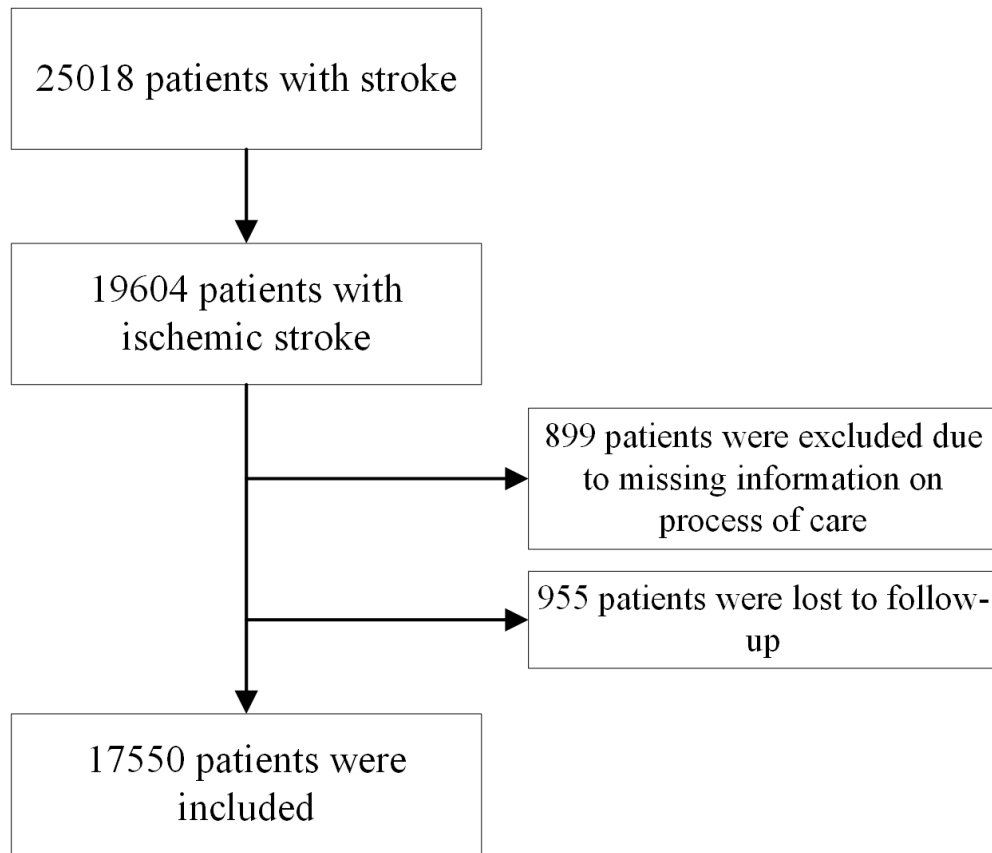


Figure 1. The flow chart for patient selection

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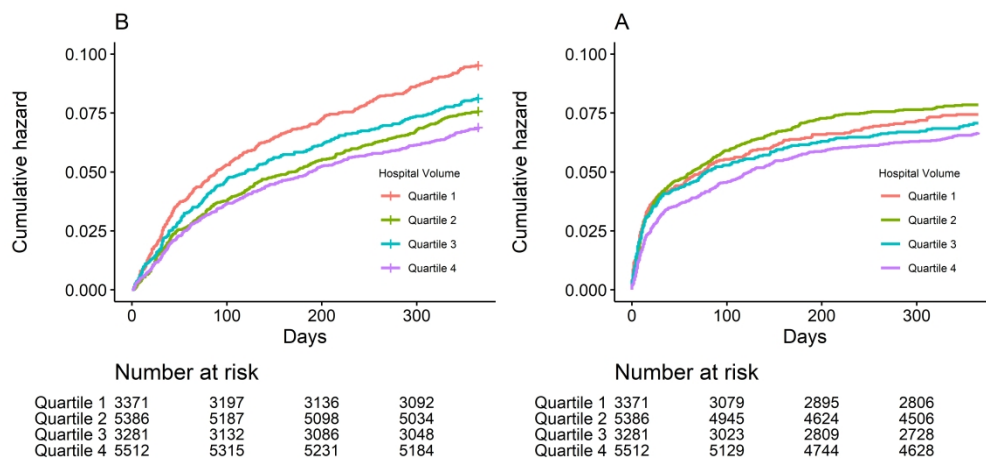


Figure 2. The Kaplan-Meier curve for mortality (A) and recurrent stroke (B) within 1 year

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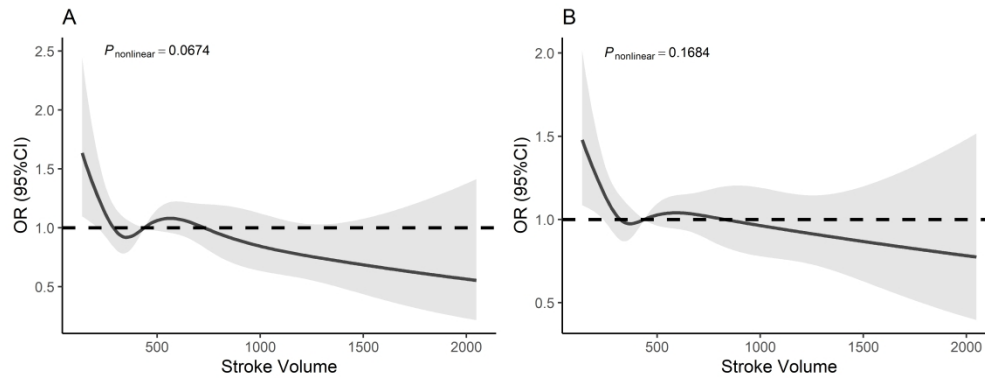


Figure 3. Association between hospital stroke volume and all-cause mortality. A, Hospital volume and 3-month all-cause mortality. B, Hospital volume and 1-year all-cause mortality. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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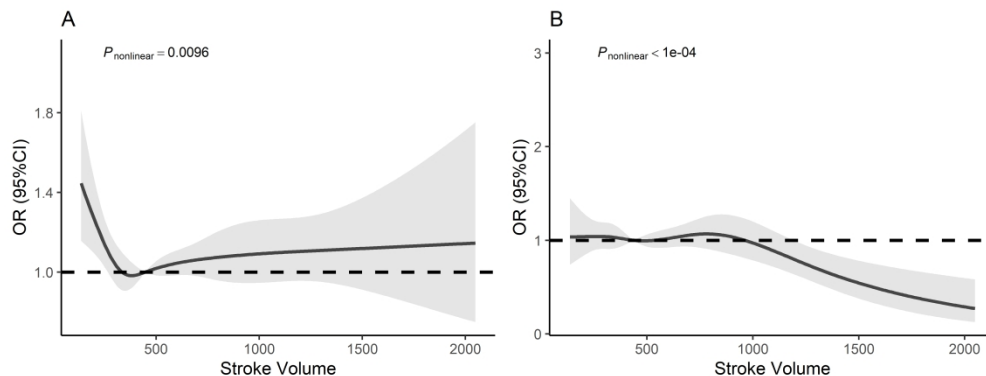


Figure 4. Association between hospital stroke volume and poor outcome. A, Hospital volume and 3-month poor outcome. B, Hospital volume and 1-year poor outcome. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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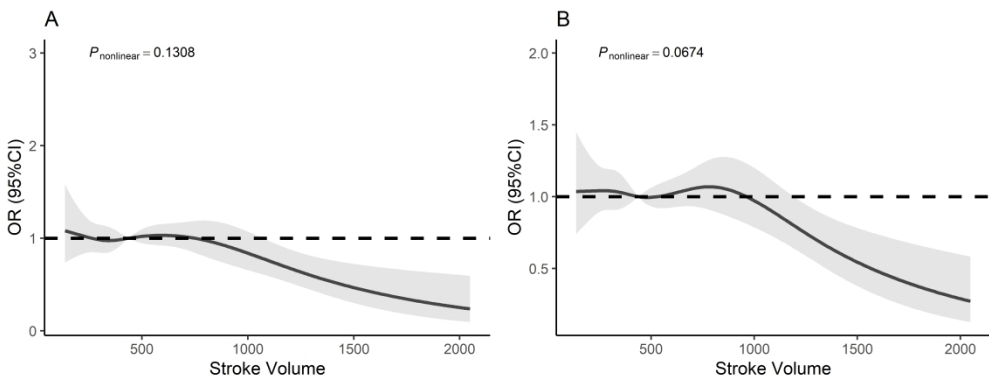


Figure 5. Association between hospital stroke volume and recurrent stroke. A, Hospital volume and 3-month recurrent stroke. B, Hospital volume and 1-year recurrent stroke. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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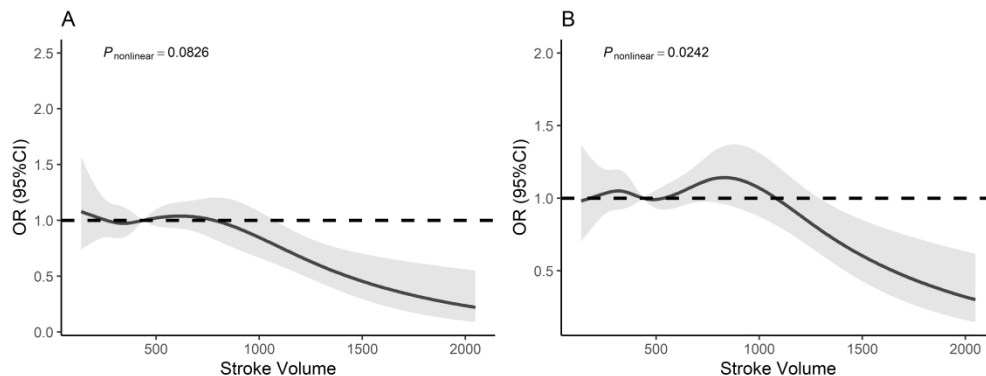


Figure 6. Association between hospital stroke volume and combined vascular events. A, Hospital volume and 3-month combined vascular events. B, Hospital volume and 1-year combined vascular events. The reference point is the median value of hospital volume (476 annual stroke discharges) in all patients.

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*Supplementary Material*

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Table 1. The definition of process measures

	<b>Definition*</b>
<b>Acute phase process measures</b>	
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
<b>Process measures at discharge</b>	
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 $\geq$ 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
<b>Patient characteristics</b>			
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 #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			

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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	11
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).