Hospital Volume and Mortality in Acute Ischemic Stroke Patients: Effect of Adjustment for Stroke Severity

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Objective: Stroke severity of 1 hospital is a crucial information when assessing hospital performance. We aimed to determine the effect of stroke severity in the association between hospital patient volume and outcome after acute ischemic stroke. *Methods:* Data from National Acute Stroke Quality Assessment in 2013 and 2014 were analyzed. Hospital patient volume was defined as the annual number of acute ischemic stroke patients who admitted to each hospital. Comparisons among hospital patient volume quartiles before and after adjusting age, sex, onset to arrival and stroke severity were made to determine the associations between hospital patient volume and mortality at 30 days, 90 days and 1 year. Assessments for the nonlinear associations, with treating hospital patient volume as a continuous variable, and the associations between hospital patient volume and quality of care were also made. *Results:* A total of 14,666 acute ischemic stroke patients admitted to 202 hospitals were analyzed. In the crude analysis, patients admitted to hospitals with lower patient volume showed higher mortality with a non-linear inverse association with a cut-off value of 227 patients/year. While the associations remained significant after adjusting age, sex and onset to arrival time (P's < .05), they disappeared when stroke severity was further adjusted (P's > .05). In contrary, hospital patient volume showed a nonlinear positive association with a plateau for summary measures of quality indicators even after adjustments for covariates including stroke severity (P < .001). *Conclusions:* Our study implicates that stroke severity should be considered when assessing hospital performance regarding outcomes of acute stroke care.

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Introduction

Larger hospital patient volume generally correlates with better outcomes in various diseases or medical procedures.[1-4] Previous studies showed that outcomes, which were mortality in most studies, were better in hospitals with larger patient volume than those with smaller one, and this relationship might be attenuated above a specific threshold. A study based on the Medicare claim data between 2004 and 2006 in the US reported that admission to higher-volume hospitals was associated with lower 30-day mortality for acute myocardial infarction, heart failure, and pneumonia, and there was a volume threshold, for example, 910 patients for acute myocardial infarction, above which a higher hospital patient volume had no impact on outcomes.[1] However, another study based on the Get With The Guidelines-Heart Failure registry has reported that hospital patient volume was not associated with in-hospital and 30-day mortality but process measures in patients hospitalized with acute heart failure,[5] which implicates that hospital patient volume would be a structure metric reflecting quality of hospital care rather than an outcome determinant.

Similar results were replicated in stroke studies using large national databases.[6-8] These studies showed an inverse relationship between hospital patient volume and mortality in acute stroke population as in other diseases. However, since it has been addressed that stroke severity is the most important prognostic factor for individual stroke patients and inclusion of a stroke severity measure in risk adjustment models for comparing hospital performance on outcomes is recommended,[9,10] previous studies had their weakness of not including stroke severity in their multivariable models. Especially, previous studies showed that information on stroke severity is crucial for assessing one hospital's performance, especially when mortality is used as an indicator of outcome.[11,12] However, only 1 study from Denmark adjusted stroke severity for evaluating the effect of stroke patient volume on outcomes and reported that hospital patient volume was not associated with 30-day or 1-year mortality.[13] However, this study included patients discharged from stroke units only and its results have not been reproduced in other studies.

In this context, using data obtained from a national stroke audit in Korea, we intended to elucidate the effect of stroke severity on the associations of hospital patient volume with poststroke mortality at various time points, along with quality of stroke care.

Methods

Study Subjects

The study population was derived from the National Acute Stroke Quality Assessment (NASQA) program performed by Health Insurance Review and Assessment Service (HIRA) in South Korea.[14] The purpose of NASQA was to evaluate the quality of inpatient care in acute stroke care facilities, and it was conducted at a national level according to the National Health Insurance Act and the Medial Aid Act. Hospitals to which more than ten acute stroke patients were admitted during 3 consecutive months of an assessment period were subjected to this program. Acute stroke patients who had primary diagnostic codes for stroke (I60-I63) by *International Classification of Diseases, Tenth Revision (ICD-10)* at discharge and who were hospitalized via emergency room within 7 days of symptom onset were enrolled into this program. Since the first assessment in 2005, the assessment was repeated in 2008, 2010, 2011, 2013, 2014, and 2017. For this study, we analyzed the most recent 2-year data from the fifth and sixth assessments in 2013 and 2014 (the 2017's assessment data have not been accessible yet).

Acute ischemic stroke patients were defined by primary discharge diagnostic codes of I63 (ischemic stroke). Patients who were hospitalized multiple times during the assessment periods were included for only once with the first admission and those who were referred to another hospital immediately after admission were considered to be admitted to the referred hospital. Those whose stroke severity were neither checked in the form of National Institute of Health Stroke Scale (NIHSS) nor Glasgow Coma Scale (GCS) were excluded.

This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (No. X-1704-393-906), under the Joint Project on Quality Assessment Research by the HIRA. Unique identifiers for patients and hospitals were removed according to the Act on the Protection of Personal Information Maintained by Public Institutions. The database was managed by the HIRA in a separate server, and only the preauthorized researchers were able to access to the database. The data of this study will not be publicly available since it was only available to preauthorized researchers during a limited time period in a separate server managed by HIRA according to Personal Information Protection Act of South Korea.

Variables

Hospital patient volume was defined as the annual number of acute ischemic stroke patients who were admitted to each hospital. The annual number of patients was calculated by (1) summating the number of admitted patients during both of the fifth and sixth assessments which were the last 2 available periods of the program, (2) dividing the number by the sum of assessment periods in days (182 days), and (3) finally multiplying the results by 365 days. The hospital patient volume was applied at an individual level to each patient for further analysis.

For the main analysis, stroke onset was defined as the time when a patient or a witness first noticed that he/she had symptoms probably related to ischemic stroke. Onset to arrival time was defined as a time interval between stroke onset and hospital arrival.

Information on stroke severity at the time of admission was collected in a form of either the NIHSS or the GCS score and most cases without the NIHSS had information on the GCS. In order to substitute the GCS into the NIHSS in case without the NIHSS, a logistic regression model was developed for 3-month mortality on each stroke scale with nonlinear terms and adjustments for age and sex, which denotes restricted cubit spline. From the fitted model, predicted 3-month mortality was obtained for each stroke scale. In case that the NIHSS score was missing, we substituted the corresponding NIHSS score whose predicted 3-month mortality was close to that of the patient's GCS score.

The primary outcome measures were mortality at 30 days, 90 days and 1 year after stroke onset. Death was captured through the linkage of the NASQA database with the National Vital Statistics data.

Six quality indicators, which were used as performance measures in the Get With The Guideline (GWTG)-Stroke program,[15] were selected to assess the quality of acute stroke care in this study with some modifications according to clinical practice in Korea (Table S1 in the Appendix). A summery measure for quality of stroke care in general was defined as a hospital average across all eligible patients of the percentages of the quality indicators that were successfully met for each patient.[15]

Statistical Analysis

We created a variable of hospital patient volume quartiles consisting of approximate equal numbers of hospitals. Patient age, sex, onset to arrival and stroke scales were described according to the hospital patient volume quartiles. Comparisons among the quartiles were made using one-way ANOVA, Kruskal-Wallis test, Chi-square test or Fisher's exact test if appropriate.

Associations between hospital patient volume and mortality at 30 days, 90 days and 1year were assessed using generalized estimation equation methods with consideration for a clustering effect of hospitals and then comparisons of event rates among the quartiles were made using the linear contrast test. Subsequent adjustments for 2 sets of covariates were made to explore the independent effect of hospital patient volume to mortality. The first set was age, sex and onset to arrival time and the second one was age, sex, onset to arrival time and NIHSS score.

To examine the nonlinear associations between hospital patient volume and mortality and explore the optimal cut-off value of hospital patient volume for the associations, the original hospital patient volume per year in each hospital was modeled as a continuous variable using restricted cubic spline (RCS) function with 4 knots in the logistic regression model. In case that the nonlinear effect of hospital patient volume was not significant statistically, assessment for a linear effect was made. Analyses were performed without adjustments and with adjustments for 2 sets of covariates, with and without stroke scales as above. Effect modification between specified covariates (stroke severity, number of neurologists, presence of stroke unit, intravenous thrombolysis, endovascular treatment, and geographical locations (urban versus rural)) and hospital patient volume were checked, and if there were a possible effect modification ($P_{\text{interaction}} < .1$), a subgroup analysis was also performed. A sensitivity analysis for patients who admitted within 24 hours after symptom onset was done to check the robustness of the results.

Regarding quality of stroke care, comparisons of the quality indicators and the summary measure were made according to the hospital patient volume quartiles. The association between hospital patient volume and the summary measure was assessed with similar models used for analysis of hospital patient volume and mortality. As sensitivity analysis, the robustness of the associations between hospital patient volume and mortality at each time point was examined by excluding the subjects whose NIHSS scores were missing.

All analyses were performed using SAS software ver. 9.4 (SAS institute, Cary, NC), and R software, version 3.4 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P-value lesser than .05 was considered as statistically significant.

Results

Among 20,202 acute stroke cases obtained from the fifth and sixth assessments, after excluding 87 duplicated cases and 51 cases whose stroke severity were not recorded in either NIHSS or GCS score, 14,666 acute ischemic stroke patients from 202 hospitals were analyzed (Fig S1 in the Appendix). Characteristics of hospitals and participants selected for this study were described in Table II in the online-only Data Supplement. The mean age was 70 years and 58% were men, and stroke severity in 94% of the patients was recorded in NIHSS with a median score of 3 (interquartile range (IQR), 1-7). Thirty-three percent of hospitals had a stroke unit and 91% had one or more attending neurologist. The distribution of hospital patient volume was presented in Fig S2 in the Appendix.

As dividing into equal number of hospitals, quartiles of hospital patient volume were formed in the cut-off points

Table 1. *Patient characteristics among hospital patient volume quartiles*

Variables	Hospital patient volume				
	1st quartile (≤33/year)	2nd quartile (34−81/year)	3rd quartile (82−227/year)	4th quartile (≥228/year)	*P* value*
Number of hospitals	50	51	52	49	
Number of patients	382	1197	3718	9369	
Age (mean ± SD)	73.0 ± 12.5	72.4 ± 12.0	69.9 ± 12.6	68.8 ± 12.5	<.0001
Male sex (N, %)	219 (57.3)	612 (51.1)	2166 (58.3)	5474 (58.4)	<.0001
Onset to arrival time (hr)	5 (1-24)	5 (2-20)	5 (1-22)	7 (2-26)	<.0001
Stroke scale type (N, %)					<.0001
NIHSS	274 (71.7)	974 (81.4)	3509 (94.4)	8988 (95.9)	
GCS	108 (28.3)	223 (18.6)	209 (5.6)	381 (4.1)	
Stroke scale scores (median, IQR)					
NIHSS	4 (2-9)	4 (2-9)	3 (2-7)	3 (1-7)	<.0001
GCS	14 (11-15)	15 (12-15)	15 (12-15)	15 (13-15)	.0102
NIHSS (substituted)	5 (3-11)	5 (2-10)	4 (2-8)	4 (1-7)	<.0001
NIHSS (substituted)≥10 (N, %)	110 (28.8)	300 (25.1)	773 (20.8)	1800 (19.2)	<.0001

**P* value by ANOVA, Kruskal-Wallis test or Chi-square test.

of less than or equal to 33, 34-81, 82-227, and greater than or equal to 228 patients per year. Patients treated in the lowest quartile hospitals were more likely to be older and hospitalized earlier and less likely to be men compared to those treated in the higher quartile hospitals (Table 1). The proportions of patients whose stroke severity was assessed with NIHSS increased as the hospital patient volume increased.

At each time point of 30-day, 90-day and 1 year, mortality was highest in the lowest quartile (from 8% at 30-day, to 24% at 1 year), and as the hospital patient volume increased, the crude mortality at each time point of 30-day, 90-day and 1-year decreased (P_{trend}'s < .01) (Table 2). After adjusting for age, sex and onset to arrival time, the differences among quartiles were attenuated and, after additional adjustment for NIHSS, the differences disappeared (P_{trend}'s > .05).

RCS curves describing the associations between hospital patient volume and mortality at each time point and treating hospital patient volume per year as a continuous variable without adjustment shows a decreasing trend of mortality with increase of hospital patient volume followed by a plateau above a certain cut-off point (Fig 1). The nonlinear term of hospital patient volume was statistically significant for mortality at 30 days, 90 days and 1 year, respectively (P's < .001), with the cut-off value for the starting point of the plateau at 227 patients/year defined by the knot formed in the RCS curves. When adjusted for age, sex and onset to arrival time, the RCS curves seemed to be more flattened. The nonlinear terms

Table 2. *Mortality at 30 days, 90 days and 1-year according to hospital patient volume quartiles*

	Hospital patient volume				*P* value for trend (P_{trend})‡
	1st quartile (≤33/year)	2nd quartile (34-81/year)	3rd quartile (82-227/year)	4th quartile (≥228/year)	
Crude Mortality (%)					
30-day	8.4	7.4	5.8	4.6	.0077
90-day	14.8	11.1	8.6	7.2	.0004
1-year	24.2	20.2	15.9	13.2	<.0001
Adjusted mortality 1 (%)*					
30-day	5.0	4.4	3.9	3.3	.054
90-day	9.4	7.0	6.1	5.5	.0049
1-year	14.8	12.4	10.8	9.3	.0013
Adjusted mortality 2 (%)†					
30-day	2.3	1.9	2.2	2.2	.90
90-day	5.4	3.7	3.9	4.0	.23
1-year	10.5	8.7	8.6	8.1	.12

Logistic regression with generalized estimating equation model was used in all models to account for the hospital clustering effect.
*Adjusted for age, sex, onset to arrival time.
†Adjusted for age, sex, onset to arrival time and NIHSS.
‡P-value by linear contrast test.

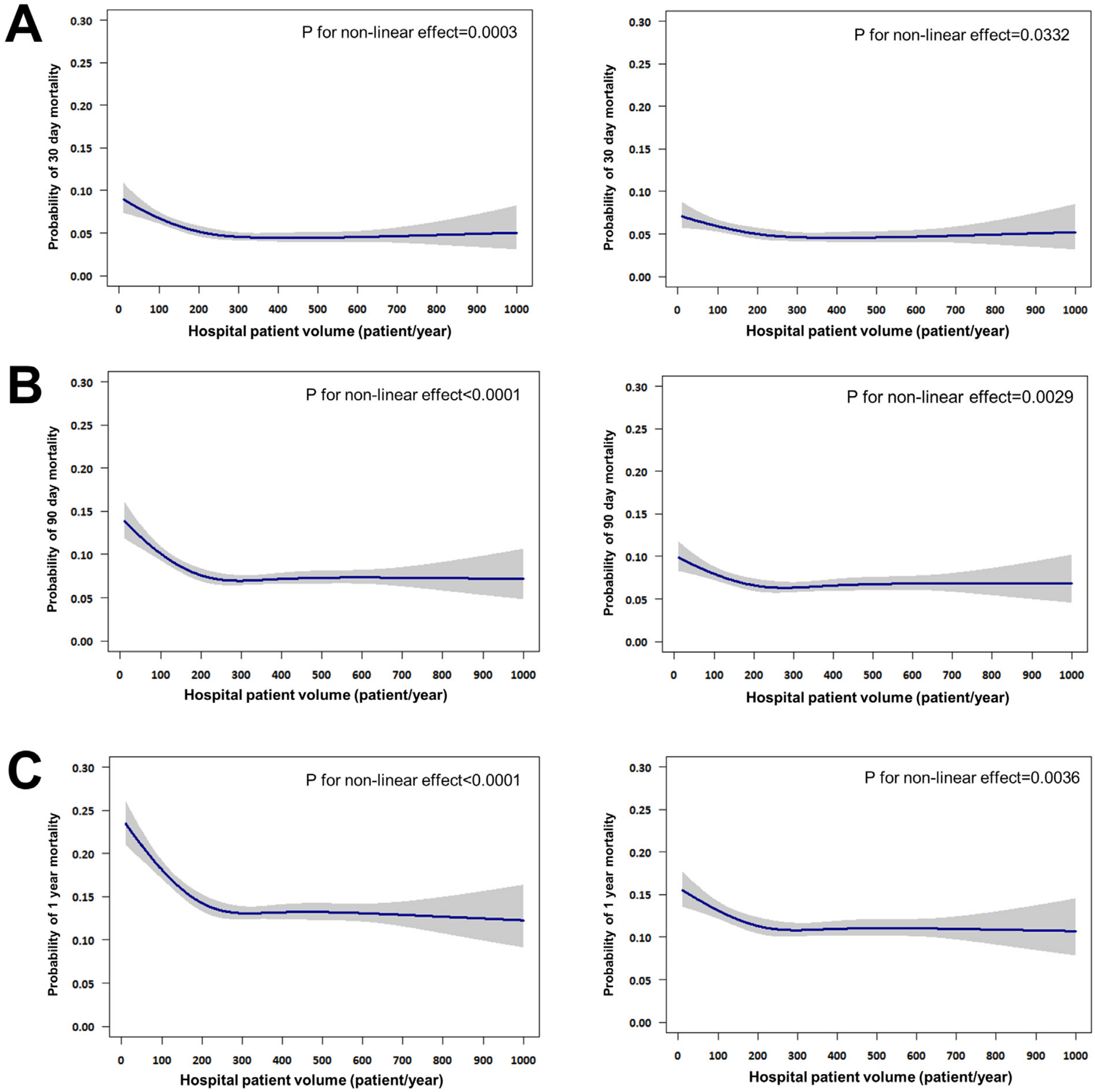

Figure 1. *Association between hospital patient volume and mortality at (A) 30-days, (B) 90-days, and (C) 1-year time points, before and after adjusting age, sex and onset to arrival time.*

of hospital patient volume were still statistically significant for mortality at 30 days ($P = .03$), 90 days ($P = .003$) and 1 year ($P = .004$), with the identical cut-off value of 227 patients per year. After additionally adjusted for NIHSS, the statistical significance for the nonlinear term of hospital patient volume disappeared (P's $\geq .05$) (Fig 2).

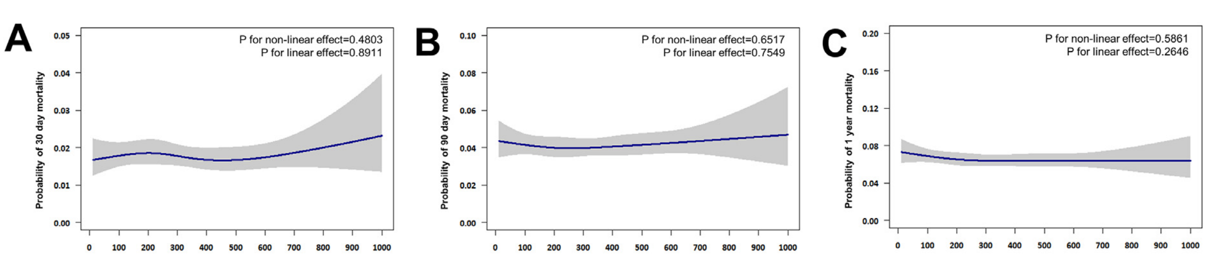

Figure 2. *Association between hospital patient volume and mortality at (A) 30-days, (B) 90-days, and (C) 1-year time points after adjusting age, sex, onset to arrival time and stroke severity.*

Table 3. *Quality of care indicators according to hospital patient volume*

Quality of care indicators	Hospital patient volume				
	1st quartile (≤33/year)	2nd quartile (34-81/year)	3rd quartile (82-227/year)	4th quartile (≥228/year)	P value*
Acute management					
IV tPA within adequate time window	23 (79.3)	94 (86.2)	341 (97.7)	760 (98.4)	<.0001
Early antithrombotics	359 (99.7)	1152 (99.9)	3608 (100.0)	9031 (100.0)	.0769
Discharge management					
Antithrombotics at discharge	310 (86.1)	1021 (88.6)	3308 (91.7)	8546 (94.6)	<.0001
Anticoagulation for AF or flutter	33 (82.5)	95 (92.2)	467 (99.8)	1356 (99.9)	<.0001
Education for smoking cessation	64 (90.1)	299 (98.7)	1059 (100.0)	2478 (100.0)	<.0001
Lipid lowering agent at discharge	242 (63.4)	704 (58.8)	2674 (71.9)	7415 (79.1)	<.0001
Summary measure of quality of care (per hospital)†	81.6 ± 12.5	82.2 ± 10.1	88.4 ± 7.8	91.3 ± 5.5	<.0001

**P*-value by ANOVA, Chi-square test or Fisher's exact test.
†Hospital average across all eligible patients of the percentages of the quality indicators that were successfully met for each patient.

Most of the quality indicators seemed to be better in the highest quartile hospitals with the average summary measure of 91% (Table 3). *IV tPA within adequate time window* was much lower in the lowest quartile hospitals (79%) compared to the highest quartile hospitals (98%). Also, other quality indicators which were *antithrombotics at discharge* (86% in the lowest quartile versus 94% in the highest quartile), *anticoagulation for atrial fibrillation or flutter* (83% in the lowest quartile versus 99% in the highest quartile), *education for smoking cessation* (90% in the lowest quartile versus 100% in the highest quartile) and *lipid lowering drug at discharge* (63% in the lowest quartile versus 79% in the highest quartile) showed marked differences according to hospital patient volume quartiles. Analysis of the association between hospital patient volume and the summary measure of quality of care showed an increasing trend among quartiles even after the adjustments for age, sex, onset to arrival time and NIHSS, and using hospital patient volume per year as continuous variable and applying RCS curves to models also revealed a nonlinear association ($P < 0.001$) with a cutoff value of 309 patients per year (Fig S3 and Table S3 in the Appendix).

An effect modification ($P_{interaction}<.05$) was found for stroke severity (30-day mortality), number of neurologists (30-day, 90-day and 1-year mortality), and geographical area (30-day and 90-day mortality) in the association between hospital patient volume and mortality. However, the subgroup analysis of each variable showed a statistically significant nonlinear association only in the urban areas ($P = .03$) for hospital patient volume and 90-day mortality (Fig S4 to S8 in the Appendix).

Sensitivity analysis confining the analysis to the patients whose stroke severity was checked in the form of NIHSS showed the same results that the non-linear association between hospital patient volume and mortality at each time point with a certain cut-off value disappeared after adjustment for NIHSS and the differences in mortality among hospital patient volume quartiles were markedly attenuated (Fig S9 to S11 in the Appendix). Also, sensitivity analysis for the patients who admitted within 24 hours after symptom onset showed a similar result, supporting the robustness of our results (Table S4 and Fig S12 in the Appendix).

Discussion

The results of crude analysis regarding the association between hospital patient volume and mortality in our study were similar to those of previous studies;[7,13] decreasing mortality with increasing hospital patient volume with a certain ceiling, 227 ischemic stroke patients per year in our study. However, after adjusting for stroke severity, the associations between hospital patient volume and mortality disappeared regardless of mortality time points. In contrast, the effect of hospital patient volume on quality of stroke care remained significant even after adjustment for stroke severity.

Inverse correlations between hospital patient volume and mortality in acute ischemic stroke were previously reported in large population-based studies. One study which analyzed 26,676 Canadian stroke patients from a national database showed lower mortality at discharge and 7-day time point in higher patient volume hospitals.[6] Another study which included more than 70,000 patients from 162 Canadian hospitals showed a ceiling point at 165 or 100 ischemic stroke patients per year for 30-day mortality by 2 different analytical methods.[7] These studies had an important implication for stroke care with the message that more experiences and better process in patient care might improve patient outcome.

But these previous studies did not consider stroke severity in the analysis. The importance of stroke severity in comparing hospital performance should not be ignored. A recent study showed that adjusting NIHSS scores substantially changed the performance ranking among hospitals and noted that stroke severity should be considered in the model for evaluating 30-day mortality as an indicator for hospital performance.[11] NIHSS score is a strong determinant of outcome in stroke and should be considered in outcome assessment.[16,17] In this aspect, we have confirmed that stroke severity is an important confounder which can affect the results of a study seriously and should be considered when analyzing the effect of hospital patient volume on stroke outcomes. Also, our study has an own strength with assessing the effect of hospital patient volume on outcomes at various time points from short-term (30-days) to long-term (1-year) perspectives. Mortality at 30-day time point is the widely used indicator for hospital performance.[1,11] Otherwise, the outcomes at 3-month time point is the classically used outcomes in clinical trials for acute stroke treatment.[18,19] Also, mortality at 1-year shows high correlation with functional outcome at 3-month, thus could be a surrogate of 3-month functional outcome.[20]

There has been a question raised from the previous studies why small hospital patient volume seemed to be associated with poorer outcome in ischemic stroke. While the previous explanation focused on more experience in medical practice and better process of care in hospitals with large patient volume, [6] another explanation could be the difference in patient characteristics between hospitals with small and large hospital patient volume. As shown in Table 1 and Fig S3 in the Appendix, those patients who are old and have severe stroke seem to admit to hospitals with lower patient volume, thus have higher mortality. Similar patterns have been reported in the prior studies.[6,7,13]

The difference in quality of stroke care according to hospital patient volume was clearly demonstrated in our study. Figure 3 shows that quality of stroke care was better in those admitted in higher hospital patient volume regardless of age, sex, onset to arrival time or stroke severity and hospital patient volume had an association with quality of care. This is similar to a study from Denmark which used a large nationwide database.[13] This study, which included more than 60,000 patients from 61 stroke units, reported that length of hospital stay was shorter and processes of early stroke care were better in stroke units with higher patient volume.

As processes of stroke care are shown to be better in higher patient volume hospitals even after adjustment for stroke severity, another question arises whether mortality is an appropriate tool to evaluate hospital performance regarding acute stroke care. While there had been continuous attempts to use mortality as an outcome indicator for hospital performance in acute stroke care,[21-23] there was a concern that using 30 day mortality as an outcome

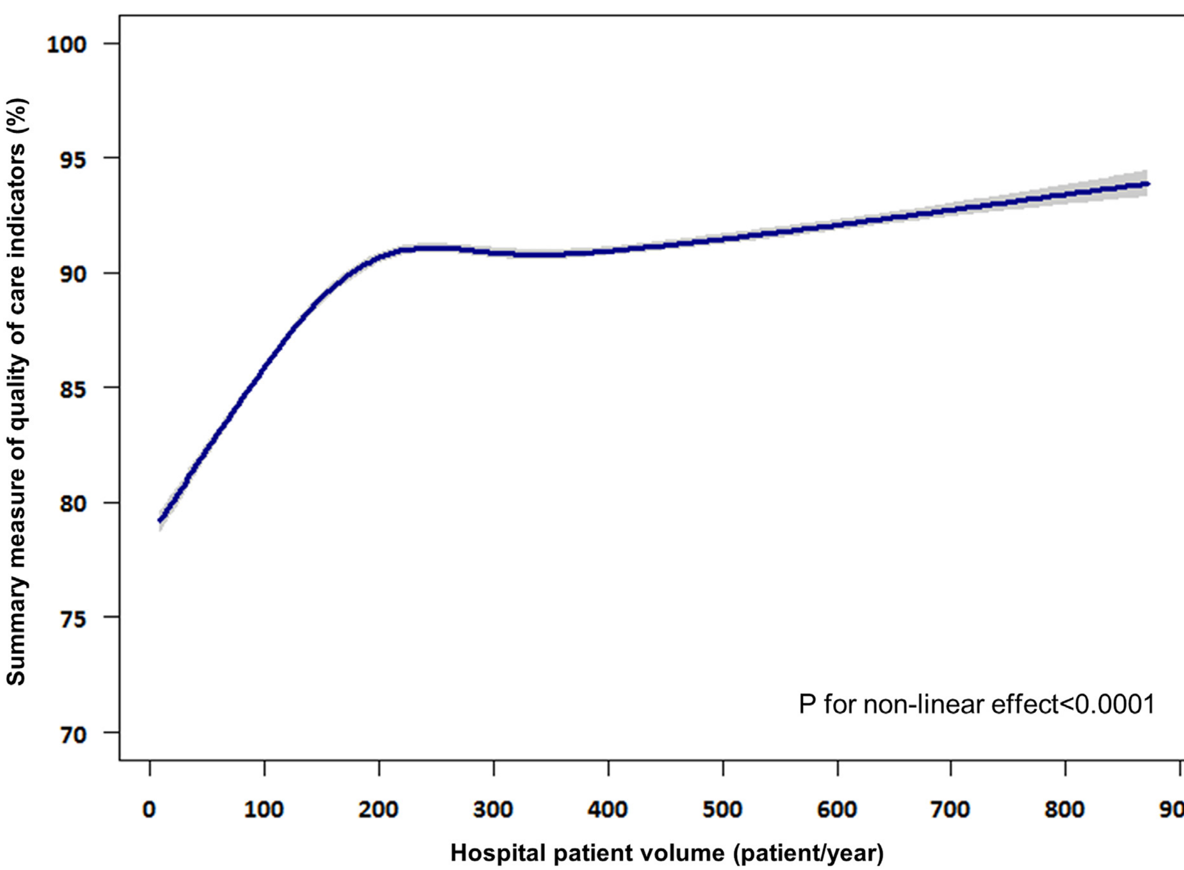

Figure 3. *Association between hospital patient volume and summary measure of quality of care indicators after adjusting age, sex, onset to arrival time and stroke severity.*

measure may mischaracterize hospital performance as those hospitals where more severe stroke patients admit would be disadvantaged.[9,10] Our results showed that even mortality at longer time points up to 1 year might not be a proper outcome measure for quality of stroke care. As recent clinical trials for the acute stroke patients adopt functional outcome rather mortality as a primary efficacy outcome,[18,19] other outcome measures such as a modified Rankin's scale could be an alternative choice and measuring them in regular terms during routine practice or in programs for assessing quality of stroke care should be considered for evaluating hospital performance.

There were possible effect modifications in the association between hospital patient volume and mortality for stroke severity, hyperacute treatments, number of neurologists, and geographical areas which suggest the association might differ in certain subgroup of patients (Fig S4 to S8 in the Appendix). For example, it could be suggested from the subgroup analysis results that hospital patient volume might be negatively correlated with mortality in patients with severe stroke, those underwent endovascular treatment, or those who live in urban areas. Further studies are needed to answer this question, under specific research hypotheses with larger sample size.

Limitations of our study should be noted. First, we transformed GCS scores into NIHSS scores and used them in analysis in patients whose NIHSS was missing. As the proportion of those patients whose NIHSS was transformed from GCS seemed to differ according to hospital patient volume, we conducted the sensitivity analysis by excluding those patients from analysis and the results did not change grossly (Fig S9 to S11 in Appendix). Second, as hospitals with very small patient volume (3 or less patients per month) were not included in the NASQA program, there was a chance for potential sampling bias. In year 2014, there were 43 tertiary hospitals and 283 general hospitals in Korea,[24] thus our study population might not fully represent stroke care hospitals in Korea. Third, as the NASQA program was conducted only for 3 months in each assessment and the HIRA gave participating hospitals a financial incentive since 2011, the assessment itself could have influenced the practice during the assessment periods in various ways. Forth, the measurement of stroke severity was not validated within or between hospitals. Fifth, the annual hospital patient volume was estimated just by extending the number of patients during the program period (6 months) to 1 year, and the actual annual number of patients could be somewhat different.

Conclusion

Unlike most of the previous studies, hospital patient volume lost its association with mortality at 30 days, 90 days and 1 year after adjusting stroke severity while the associations with quality of stroke care remained. These results implicate stroke severity should be adjusted in evaluating hospital performance regarding stroke outcomes and mortality might not be an appropriate measure for this purpose.

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Author Contributions

Keon-Joo Lee: drafting the manuscript, study concept and design, analysis and interpretation of data; Jun Yup Kim: acquisition of data; Jihoon Kang: interpretation of data; Beom Joon Kim: interpretation of data; Seong-Eun Kim: acquisition of data; Hyunji Oh: acquisition of data; Hong-Kyun Park: interpretation of data, study concept and design; Yong-Jin Cho: interpretation of data; Jong-Moo Park: interpretation of data; Kwang-Yeol Park: interpretation of data; Kyung Bok Lee: interpretation of data; Soo Joo Lee: interpretation of data; Tai Hwan Park: interpretation of data; Ji Sung Lee: analysis and interpretation of data; Juneyoung Lee: interpretation of data; Ki Hwa Yang: acquisition of data; Ah Rum Choi: acquisition of data; Mi Yeon Kang: acquisition of data; Gustavo Saposnik: interpretation of data, critical revision of manuscript for intellectual content; Hee-Joon Bae: study supervision, study concept and design, critical revision of manuscript for intellectual content, interpretation of data.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.104753.

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