의학박사 학위논문

Volume-Outcome Relationships for Endovascular Recanalization Therapy of Acute Ischemic Stroke in Korea and Identifying Volume Thresholds

국내 허혈성 뇌졸중 환자의 혈관내 재개통치료에서, 시술량-시술결과 관련성 및 최소 시술량 탐색

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by

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A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Health Policy and Management at Seoul National University College of Medicine

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Abstract

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Introduction:

Endovascular recanalization therapy (ERT) is becoming increasingly important in the management of acute ischemic stroke (AIS), but the hospital threshold volume for optimal ERT remains unknown. We investigated whether there was a correlation between hospital volume of ERT and risk-adjusted patient outcomes.

Materials and Methods:

From the National Health Insurance (NHI) claims data, we selected 11,745 AIS patients who underwent ERT from 2011 to 2015, in 111 hospitals. The outcome measures of the study were 30-day mortality, readmission rate, and symptomatic intracranial hemorrhage (ICH) rate. For each outcome measure, risk-adjusted mortality prediction models incorporating demographic variables, modified Charlson comorbidity index, and stroke severity index (SSI) were built, and validated through a comparison with two independent hospital registries. Hospitals were divided into quartiles and risk-adjusted outcomes of AIS cases were compared across the hospital quartile to confirm volume-outcome relationship (VOR) in ERT. Spline regression was performed to determine the volume threshold.

Results:

The mean AIS volume was 14.8 cases per hospital per year and the unadjusted means of outcome variables were mortality 11.6%, readmission 4.6%, and ICH rate 8.6%. The VOR was observed in the risk-adjusted 30-day mortality rate across all quartile groups, and in the ICH rate between the first and fourth quartiles (*P* value <0.05). Volume threshold was 24 cases per year, which was estimated by examining the relative effect on the adjusted odds of outcome for an increase in hospital volume by 10 cases/year for a hospital of a given size.

Discussion:

In this study, the trends of most ERT procedures performed in Korea for the past 5 years, demographic information of patients, and patient histories were obtained. Hyperlipidemia showed abnormally high, and it seems to be the matter of claims of health insurance. Comparing administrative and clinical database showed relatively good

result, but there was no comparative studies. For derivation and validation of SSI, risk-adjustment modelling methods were successful, and these methods would be helpful in the future studies. In the VOR analysis, there were many 'low-volume good-outcome' hospitals, so various dichotomous comparisons from quartile groups were made to calculate the volume thresholds. Volume threshold may be used for hospital management of ERT. However, as technology and knowledge of ERT continues to evolve, and other clinical factors critical to the ERT outcomes were not included into the category of severity correction, the above results should be used with caution.

We found an association between hospital volume and outcomes, and we identified the volume threshold in ERT. Policies to ensure the implementation of the AIS volume threshold for hospitals performing ERT is needed.

Keywords: Acute ischemic stroke, Endovascular recanalization therapy, Volume, Volume-outcome relationship, Thrombectomy, Thrombolysis

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List of Abbreviations

ERT: endovascular recanalization therapy
AIS: acute ischemic stroke
VOR: volume-outcome relationship
HIRA: the Health Insurance Review and Assessment Service in Korea
ICH: intracranial hemorrhage
NIHSS: National Institute of Health (NIH) Stroke Scale
IRB: institutional review board
ICD-10: the 10th revision of the International Statistical Classification of Diseases and Related Health Problems
DAUH: Dong-A University Hospital
PNUYH: Pusan National University Yangsan Hospital
mCCI: modified Charlson comorbidity index
O/E ratio: observed to expected ratio
SSI: stroke severity index
ICU: intensive care unit
OR: odds ratio

1. Introduction

1.1. Background

Ischemic stroke is one of the major leading cause of death and morbidity.[1] Endovascular recanalization therapy (ERT) has opened a new paradigm of treatment for acute ischemic stroke (AIS), with seven large studies[2-8], including Mister Clean[2], published in early 2015. The AHA/ASA (American Heart Association/American Stroke Association) guideline for the treatment of AIS has recently been revised two times in 2015[9] and 2018[10], with ERT becoming as important as administration of intravenous alteplase. Since the result of ERT superior to conventional medical therapy, 2 randomized controlled trials[11,12] have recently been conducted on ERT for patients with onset time > 6 hours. In these studies, appropriate selection of AIS patients whose onset time > 6 hours showed good clinical outcome when ERT was performed. With this trend, it is highly likely that the number of ERT procedures will increase in the future. Since 2015, the procedural volume of ERT is increasing in Korea.[13]

ERT of AIS has many complicated issues, such as decision making (who and when to treat or not[11,12]), technical challenge (incapability of access to the occlusive lesion[14]), choice of device (suction device versus stentriever).[8] There were many studies on the patient element. However, researches about practitioners seems to be relatively small.

The certification requirements for TSC (Thrombectomy-capable Stroke Center) in the Joint Commission have recently been proposed.[15] This certification program was developed in collaboration with the AHA/ASA, and provides procedural volume requirements of ERT for hospitals which require more than 15 ERT cases per year for each hospital. Assuming that at least 2 (or 3) neurointerventionsts (NIs) are needed in one hospital to be able to perform the ERT, 24 hours a day, 7 days a week, annual 7.5 cases (or 5 cases) per NI are minimum requirement ERT procedural volume.[16] However, to our knowledge, no studies have been conducted to suggest a scientific basis for determining this volume threshold.

In other medical fields, there are many studies demonstrating the relationship between the volumes and the outcomes of the procedures, so-called “volume-outcome relationship (VOR)”.[17-20] By using the concept of VOR, it could be possible to estimate the minimum volume of ERT for AIS.

1.2. The concept and method of volume-outcome relationship

The most basic concept of VOR is that "the result is good if there is a lot of procedures", and it is known that the complex procedure is highly relevant (Figure 1).[17]

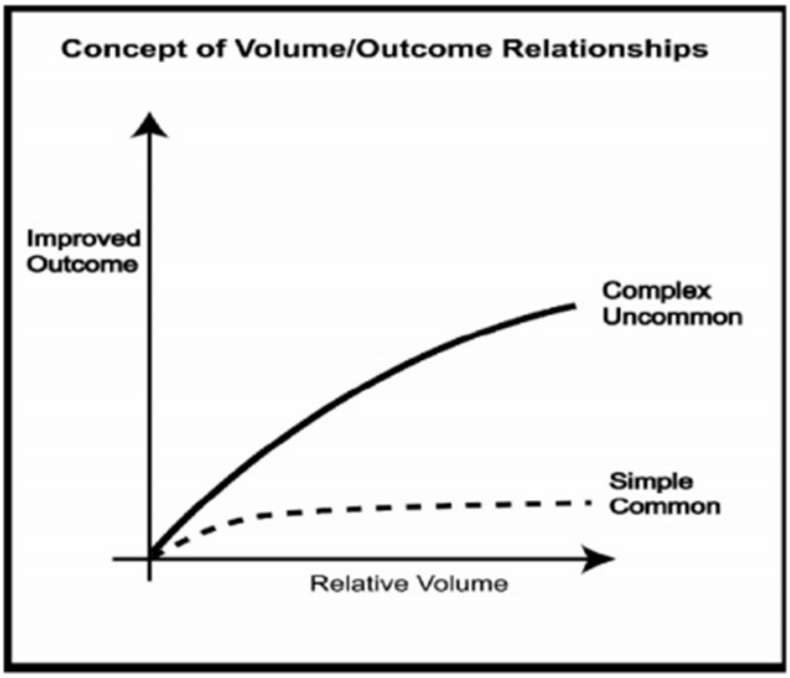

Figure 1. The basic concept of volume-outcome relationship[17]

There are 2 theories of the reason why VOR is present. One of them is the idea of “practice-makes-perfect”, and another is “selective-referral pattern.” Those 2 theories seemed to be relevant in the various studies.[20,21] At first, “practice-makes-perfect” theory was the predominant explanatory theory. After that, “selective-referral pattern” theory emerged later.

"Practice-makes-perfect" theory, literally, is based on the theory that if experience is high, proficiency increases and results are good. In industry field, this theory has often been used as a basis for reducing costs. However, some authors have also found that many patients go to the hospital because of the function of the referral system, which suggests that the overall outcome is improved. In this case, regardless of proficiency increase, the increase in patient volume and outcome is interpreted as an improvement of reputation. The explanation for the two theories is known to be different according to the characteristics of the disease. Subarachnoid hemorrhage is known as a representative disease that meets the "practice-makes-perfect" theory, and respiratory distress syndrome is a disease that meets the "selective-referral pattern" theory.[21]

Various studies demonstrated that whether VOR is existed or not, is dependant on disease entity, type of procedure, and type of outcome measurement. According to the Leapfrog group in 2003, the VOR of abdominal aortic aneurysm repair, coronary artery bypass graft (CABG), and carotid endarterectomy were confirmed, and based on this, "cut off values" were measured and compared with empirical values. Esophageal resection did not reveal any such VOR.[22]

Beyond various disease entities issue, there were another various VOR studies depending on what procedure, what outcome variables are used, and which database to use. So far, the number of studies on VOR in surgical diseases (such as colon cancer, ruptured intracranial aneurysm) has been high, and relatively medical diseases (such as pneumonia, heart failure) have been studied less. However, there are many confounding variables such as hospital staff specialty, quality level of intensive care unit, presence of systematic protocol of the disease management. These factors affect the interpretation of VOR in surgical diseases. In addition, there are differences in the method and interpretation of those studies by dividing the analysis unit of volume, of 'the hospital' or 'the surgeon.' If the volume of the hospital is used as the analysis unit, it is more useful for the study of medical diseases. It is expected that the volume of the surgeon as the analysis unit is more useful for analysis of the surgical disease.

In recently, some authors demonstrated that beyond the relationship between "Volume" and "Outcome", but also another factor, "Structure and Process", might be considered as the relationship analyses.[23] According to this paper, simply measuring the volume does not reflect quality, but could be a proxy value. Therefore, they suggested that, the relationship between volume and "Structure and Process" and the relationship between outcome and "Structure and Process" should be further analyzed, and the actual working mechanism will be known about the underlying VOR.

Another issue in the VOR study is "outcome variables." The easy and common variable to use is mortality. The reason why is that the data is easy to obtain, intuitive, and easy to interpret. However, it is unreasonable to make death as a major outcome in all diseases. In particular, in the case of ischemic stroke, it is very extreme to use death as an outcome, so it is suggested to consider other outcomes together.

In the VOR study, the administrative database is frequently used, and many related studies have been done.[24-26] Because administrative data is not a database for research purposes, and there are many factors that should be taken into account in its use. There is room to improve the process of modeling using a clinical database to solve the related methodological problems. Risk adjustment should be appropriate to obtain good research results and allow objective interpretation.[19,27-29]

1.3. Interpretations and cautions of volume-outcome relationship studies

Some studies showed simple trend of VOR, and concluded that 'there is a VOR or not in those specific disease.[30,31] However, other studies, by using more sophisticated methodologies, showed the result of calculating the volume threshold after VOR.[17,32]

It is expected that appropriate modelling of target disease will make more powerful VOR analysis, and measured minimum volume in this way could be used in the form of academic's guideline. By using this volume cautiously, it could be helpful for health policy makers and clinicians to maintain substantial proficiency and adequate quality in that specific disease. In the Leapfrog group, this methodology was applied to compare the empirical threshold to the scientific base threshold in those diseases.[22] If this figure is calculated, this could provide a proven scientific basis for the minimum volume proposed by the Joint Commission, which will enable the comparison.[15]

However, previous VOR studies have not been sufficiently examined as to why VOR occurs, and they aimed at finding only volume requirements. This could be used not only finding the minimum procedural volume for raising quality, such as centralizing the patient to a specific hospital in the specific area, but also finding factors that could improve and modify the process and structure of system.[23]

In cardiology, many papers on VOR have already been published.[18] There are also papers foreseeing how to use these results and anticipated side effects. For example, some authors warned that doctors may have tendency to practice a not-necessary procedure to maintain his or her proficiency. Over time, as the development of medical technology and/or patient prevalence changed, cardiology also experienced changes in the value of the volume indicated as the minimum requirement. In the United States, percutaneous coronary intervention (PCI) guidelines in 2011, showed annually 400 cases per hospital, but in 2013, there was a reduction to 200 cases. On the other hand, in 2015 the United Kingdom guideline suggested annual 400 cases per hospital.[16]

1.4. Research trends of volume-outcome relationships in endovascular recanalization therapy of acute ischemic stroke

In the neurointervention field, as endovascular procedures have evolved, there have been a number of studies showing that VOR is present. Coil embolizations in ruptured or unruptured intracranial aneurysms, carotid artery stenting, and ERT in AIS have been studied.[16] Some authors suggested that the reason for the success of the large AIS ERT study which mentioned above is that 'all of the seven studies were conducted at the high volume center.' This might correspond to indirect evidence that 'a VOR exists in ERT of AIS.'[33]

In 2013, the retrospective study about VOR of ERT in AIS was published in the United States.[34] 50 cases annually, was set as the cut off value of a high-volume center, and they studied 442 cases from 9 centers. They concluded that a high-volume center showed better results when compared to a low-volume center. However, we did not notice a scientific basis for choosing "50" as the reference value, the sample size was relatively small, and there is also a chance of selection bias in the sampled centers.

In the United States, the study about the correlation between the ERT procedure volume and the outcome in acute ischemic stroke, was presented in 2016.[35] They used nationwide inpatient sample (NIS) database for 3 years duration from 2008, 10 procedures were set as cut off value, and they divided centers into low and high-volume, and the outcomes were analyzed. Before risk adjustment, there was VOR, but after severity correction, the VOR was not present.

In Japan, another related study was conducted in 2016.[36]

Only 19 cases were analyzed at single center, and the difference of outcomes among thrombectomy devices (Merci, Penumbra, and stentriever) was the main purpose. The paper emphasized that the results were good with stentriever, even though the procedure volume was only 19 cases in about two years.

In Korea, volume trends of endovascular treatment of neuro-interventional fields were published in 2017.[13] Significantly increasing trends of neuro-interventions were apparent. However, the paper showed the volume trends only, and no outcomes were measured.

In another study, there was an example of calculating the volume requirement in the ERT in AIS based on the VOR study of aneurysm coil embolization. In this study, an annual hospital-based case of ERT of AIS was recommended because the Joint Commission enforced a volume of more than 20 cases for aneurysmal SAH at the certification level and epidemiologically 85% of all strokes were ischemic.[37]

As we have seen, none of these studies approached to calculate the minimum requirement based on scientific base, and most of them were based on expert opinion or crude outcomes without risk adjustment.

1.5. Purpose of this study

The hypotheses of this study are, “there is a difference in clinical outcome among the low-volume and the high-volume centers,” and “there is a difference in the structure and process among the low-volume and high-volume centers”, such as, whether the hospital has a stroke unit, or is a teaching hospital.

Thus, the research goal is divided into 4 parts. Firstly, to identify the entire volume of ERT procedures in Korean hospitals and the results of the procedure in the past 5 years. Secondly, to adequately implement the risk adjustment, by creating a new outcome model using clinical data. Thirdly, to investigate volume-outcome relationships among different volume hospital groups. Finally, if VOR is present, to estimate the volume threshold and identify the modifiable “structures and processes” that exist among the high and low volume hospitals.

2. Materials and Methods

2.1. Study framework

Authority to accessing “Medical Big Data” provided by the health insurance & review assessment service (HIRA) in Korea was requested and purchased. Almost all administrative data of Korean medical services are offered by HIRA. After reviewing various related studies, outcome variables were selected among various coded datasets in HIRA database.[31,38-44] Four variables – 30 day mortality, 30 day readmission, modified Rankin Score (mRS), and symptomatic intracranial hemorrhage (ICH) were selected as the final outcome variables.

To improve the robustness of theses variables, 2 clinical databases from Dong-A University Hospital and Pusan National University Yangsan Hospital were also accessed. The reason for using 2 clinical databases was to achieve 2 objectives. First one was validating the HIRA database by comparing of administrative and 2 clinical databases.[45] Second one was, finding and validating proxy variables of clinical findings, such as NIH stroke scale (NIHSS) and modified Rankin scale (mRS), in order to make and verify risk adjustment models from administrative database. For those proxy values of NIHSS and mRS, stroke severity index and home-time were chosen.[46-51]

After developing and validating proxy variables of prediction and risk adjustment models, the models were applied to the HIRA database, and outcomes were measured. The relationship between procedural volume per hospital and outcomes were plotted and analyzed to identify volume thresholds (Figure 2.)

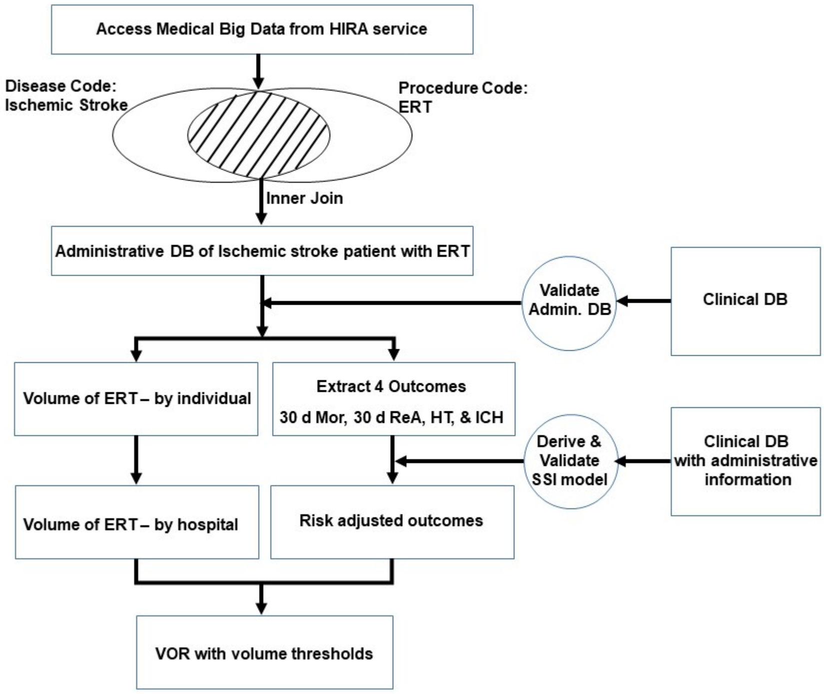

Figure 2. Study Framework

HIRA: Health insurance review and assessment service, ERT: Endovascular recanalization therapy, DB: database, Admin: administrative, 30 d Mor: 30-day mortality, 30 d ReA: 30-day readmission, HT: home-time, ICH: intracranial hemorrhage, SSI: stroke severity index, VOR: volume-outcome relationship

2.2. Establishing administrative database

Before acquisition from administrative database, HIRA service requested for the institutional review board (IRB) approval, so IRB approval from Pusan National University Yangsan Hospital was completed. After IRB approvement, various datasets were requested, those including the diagnostic code data, such as cerebral ischemic stroke, subarachnoid hemorrhage, internal carotid artery stenosis, and ruptured or unruptured intracranial aneurysm. Various procedural code dataset, for instance, mechanical and chemical thrombectomy, carotid stenting, aneurysmal coil embolization, were also requested to HIRA service. Among patients who had been diagnosed with cerebral ischemic stroke between July 2011 and June 2016, patients who underwent ERT procedures were selected. Ischemic stroke was defined by I63 code from ICD-10 code system (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems), ERT was defined by the procedure code M6631 (thrombolytic treatment – cerebral thrombus removal) or M6633 (Mechanical thrombolysis) in HIRA Code. We excluded stroke cases that occurred as an in-hospital stroke or occurred during a procedure (e.g. AIS as a complication after coil embolization of aneurysmal subarachnoid hemorrhage, Table 1). Informations about patient and hospital were accessed in a deidentified state.

Table 1. Codes of diagnosis and procedures

Fields	Descriptions	Code system / Codes
Diagnosis	Cerebral infarction	ICD-10 Code / I63
	ICH	ICD-10 Code / I61, 62
Procedure	Thrombolytic treatment, cerebral vessels	HIRA Code / M6631
	Mechanical thrombolysis	HIRA Code / M6633

ICH: intracerebral hemorrhage, ICD-10: the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, HIRA: Health insurance review and assessment service

2.3. Establishing clinical database

For the purpose of making risk-adjustment models, the data from Dong-A University Hospital (DAUH) and Pusan National University Yangsan Hospital (PNUYH) were used, which include NIHSS to verify the medical big data corresponded with the real clinical data. Same enrollment period of administrative database was chosen.

DAUH is one of a tertiary hospital in the Busan Gyeongnam area in Korea, of 940 beds, and designated as Busan-Ulsan regional cerebrovascular center. It is known to have a relatively high number of AIS patients and their severities were also high. PNUYH is also one of a tertiary hospital in the Busan Gyeongnam area in Korea, of 1,235 beds, and it has been growing rapidly. These databases were prospective, observational data set of every patients who were diagnosed ischemic stroke. Clinical part of database was composed of age, sex, admission & discharge date, initial NIHSS, whether ERT was done, and clinical outcome (dead or alive). For the same enrollment period, every administrative dataset such as procedural codes, diagnostic ICD-10 codes, and amount of medical fee were also requested.

To evaluate the accuracy of administrative database, age, sex, admission date, and discharge date were used. To derive and validate proxy value for NIHSS from the administrative database, each patients' NIHSS and suitable administrative data were used.

2.4. Comparative analysis of administrative and clinical databases

Although HIRA database was deidentified for the privacy issue, there was geographical information, city and more subsystemic scale - “gu” (corresponding to “district” in the United States). was available for the purpose of geographic information. Combining this geographical information and relative volume of ERT, produced the Dong-A University Hospital and the Pusan National University Yangsan Hospital cohorts.

2 hospitals' data from each database (administrative and clinical database) were compared to evaluate the accuracy of the HIRA database. The clinical database was defined as gold standard, and 2 by 2 contingency table was created. The numbers of true positive cases (true positive), missing cases (false negative), incorrect cases (false positive), and correctly excluded cases (true negative) were identified. The sensitivity (true positives / [false negatives + true positives]), specificity (true negatives / [false positives + true negatives]), and positive predictive value (true positives / [true positives + false positives]) were calculated. The results of that calculation were compared to other studies using administrative data.[24,45]

Patients from each database were matched using the patient’s sex, age, admission date, and discharge date. If discrepancies occurred, false negative or false positive were assigned, and true negative notation was assigned to patients who were present in the clinical database but had not undergone the ERT procedure.

2.5. Defining outcome variables

The outcome variables were 4 parameters, including 30-day mortality, 30-day readmission, home-time, and symptomatic ICH. These parameters were currently popular in other studies based on the claims data.[40]

30-day mortality was defined as 'within 30 days after initial admission and ERT procedure, every death from any cause in any hospital.' For example, if patient 'A' was admitted and ERT was performed in hospital 'B', and 15 days later he or she discharged to hospital 'C', where he/she died 7 days later, then hospital 'B' will be defined as the cause of death of patient 'A', and hospital 'C' will not be related to the result.[40]

30-day readmission was defined as 'within 30 days after initial admission and ERT procedure, readmitted to the same hospital from any cause.'

Home-time was defined by 'within 1 year after initial admission and ERT procedure, the number of days the patient was at home.' Home-time was derived and used to predict the functional status of ischemic stroke patient.[50] If home-time is bigger, than functional outcome is better.

Symptomatic ICH was defined by 'no ICH code before ERT procedure, and within 30 days after initial admission and ERT procedure, ICH occurred.' The choice to use '30 days' was influenced by the fact that 30-day mortality was used as the major outcome variable.

2.6. Risk adjustment parameters

Literature suggests that the use of claims data requires a "risk adjustment method".[40] Based on this, the outcome variables were adjusted by using the multivariate analysis method which controls for the parameters delineated below.

For individual parameters, sex and age for basic demographic information were included. Risk factors for ischemic stroke, parameters in modified Charlson Comorbidity Index (mCCI), and the stroke severity index (SSI), published in Taiwan and used as a proxy of NIHSS, were included in the model (Table 2).[28,46]

For hospital parameters, 4 factors were considered; whether the hospital was teaching hospital, its geographical location – whether it was situated in a metropolitan city, whether the hospital had a stroke unit, and if the hospital was a public or private entity. Each hospital's information on the administrative database was de-identified, and HIRA service did not provide this information. Thus, identification of the hospitals was done by combining the location information and the relative volume of ERT. Except for the geographical location, the other 3 hospital parameters were searched and acquired from official Korean Hospital Association website[52], Korean Stroke Association website, and each hospital's website.

Table 2. Parameters for risk adjustment - individual and hospital level

Fields	Name (ICD-10 Codes)
Demographics	Age, Sex
Risk factor and modified Charlon comorbidity index items	AMI or CHD or CAD (I21, I22, I23, I34, I35) Congestive heart failure (I50) Peripheral vascular disease (I73) Dementia (F00, F01, F02, F03) Chronic obstructive pulmonary disease (J40, J41, J42, J43, J44) Connective tissue disease (L94) Peptic Ulcer (K25, K26, K27) Mild Liver disease (K73, K74) Diabetes mellitus (E10, E11, E12, E13, E14) Diabetes with end organ disease (E13, E14) Renal disease (N17, N18, N19) Nonmetastatic solid tumor (C41, C46, C47, D00, D01, D02, D04, D05, D06, D07, D09) Leukemia (C91, C92, C93, C94, C95) Lymphoma and multiple myeloma (C81, C82, C83, c84, C85, C86, C90) Metastatic tumor (C77, C78, C79) AIDS (B20, B21, B22, B23, B34, R75)

(continued)

Fields	Name (ICD-10 Codes)
Risk factor and modified Charlon comorbidity index items	Prior Stroke (I63) Transient ischemic attack (G45) Hypertension (I10, I11, I12, I13, I15) Atrial fibrillation (I48) other cardiac disease - DCMP, valvular heart disease, PFO (I42.0, Io5, Q21.10) Extracranial arterial stenosis (I65) Intracranial arterial stenosis (I66) Dyslipidemia (E78)
Severity for ischemic stroke	Stroke severity index (no Codes, modelled from other items)
Hospital level items	Teaching hospital or not Geographical location - whether in metropolitan city or not Stroke unit or not Public or private

AIDS: acquired immune deficiency syndrome, AMI: acute myocardial infarction, CHD: Coronary heart disease, CAD: Coronary arterial disease, ICD-10: the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, PFO: patent foramen ovale, DCMP: dilated cardiomyopathy

2.7. Using proxy values – stroke severity index and home-time

NIH stroke scale (NIHSS) is a measure of the severity of the stroke. Many studies have established the advantages of this measure; values are easy to check, and correlate with clinical outcome fairly.[40] However, it is impossible to obtain all the patient values directly unless the hospital's medical records can be accessed. To overcome this, we searched for possible proxies of NIHSS, and stroke severity index (SSI) was selected.

The medical insurance system in Taiwan is similar to that of Korea's, they both utilize fee-for-service, compulsory insurance system, and covers almost everyone in the nation.[53] Hence, we used the same methodology of the Taiwan study in this study.[46] It is known that SSI could be used as the proxy value of NIHSS, as they both carry the same weight.[47-49]

Seven parameters (airway suctioning, bacterial sensitivity test, general ward stay, intensive care unit (ICU) stay, nasogastric tube, osmotherapy, urinary catheterization) were also selected from the results of the Taiwan study. We agree with methodology of selecting these seven parameters. However, validating the methodology of the Korean cohort was beyond the purpose of this study. We thought that the coefficient values of each 7 parameters could be customized to Korean HIRA database, and multiple linear regression from the clinical database performed (Table 3).

For derivation and validation of SSI, the selection of the 7 parameters in Taiwanese study was predicated on the high frequency of each procedure in the relatively large number of patients, the possibility of under-reporting was low. However, the coefficient result of

‘ICU stay’ was different from Taiwanese study, this may be attributed to differences between the Korean and Taiwanese healthcare system. In the HIRA code, patients coded 'AJxxx' cannot be distinguished from admittance to the stroke unit or 'admittance to ICU.' If stroke unit entry is correctly coded, it is likely that most stroke patients go to the stroke unit because it is recommended in the guidelines, and is not correlated with NIHSS and SSI. However, if it is coded as 'admittance to ICU' due to increased severity, it may be related to the real ICU proposed in the Taiwanese study.

Home-time, defined as 'time spent alive and out of a hospital, inpatient rehabilitation, or skilled nursing facilities' was used as the proxy for functional status of ischemic stroke.[50] This is simple and intuitive method.

Table 3. 7 parameters of stroke severity index and its explanation

Descriptions	Explanation	Code system / Codes
Airway suctioning	suctioning of patient's airway in case of altered mental state / or undergoing anesthesia when patient had ERT procedure	HIRA Code / M0135, M0137
Bacterial sensitivity test	Almost every patients who have shot intravenous antibiotics, they had this test	HIRA Code / B40xx, B413xx, B414x
General ward stay	relatively mild stroke patients who admitted from emergency department usually go to general ward first	HIRA Code / ABxx
ICU stay	severe stroke patients who admitted from emergency department almost always go to ICU first	HIRA Code / AJxxx
Nasogastric tube	severe stroke patients can not eat orally by themselves, and this tube is usually inserted	HIRA Code / Q2621, Q2622
Osmotherapy	For severe stroke patient whose brain tissue damaged massively, usually osmotherapy prescribed to prevent brain herniation	Main Component Code / 14800xBIJ, 148010BIJ, 148011BIJ
Urinary catheterization	severe stroke patient can not walk by themselves and usually they void by urinary catheterization	HIRA Code / M0060

ERT: endovascular recanalization therapy, HIRA: Health insurance review and assessment service, ICU: intensive care unit, "x" means various numbers, from 1 to 9

2.8. Derivation and validation of stroke severity index model

Based on NIHSS data from the Dong-A University Hospital and the data requested by the HIRA, multiple regression analysis was done to obtain regression equations for seven parameters, and a multiple correlation coefficient of 0.7 was considered relatively high (Table 4).

The model was validated using the Pusan National University Yangsan Hospital cohort, and Pearson correlation coefficient was 0.6824. The regression coefficient values of the final regression equation were observed similar to those in the Taiwan paper. However, 'ICU stay' showed no significant statistical power (Table 5).

Table 4. Regression statistics of stroke severity index model

Multiple Regression Correlation Coefficient	0.70
R Square	0.49
Adjusted R Square	0.49
Standard Error	4.52
Observations	3,13

Table 5. Multiple linear regression model for the stroke severity index

Feature	**Coefficient**	***P-value***
Airway suctioning	3.7345	< 0.001
Bacterial sensitivity test	1.1990	< 0.001
General ward stay	-2.9088	< 0.001
ICU stay	-0.1125	0.51
Nasogastric intubation	3.4404	< 0.001
Osmotherapy	1.8908	< 0.001
Urinary catheterization	2.7366	< 0.001
Constant	5.8726	< 0.001

ICU: intensive care unit

2.9. Creating risk-adjusted models and identifying volume thresholds

How to make risk adjusted models were as follows. First, the crude results for each of the 4 outcomes were obtained on an individual basis. Second, each risk adjustment model was created and applied to individual parameters. Third, following the same method, the individual's expected outcome variable (for instance, risk-adjusted 30-day mortality chance, risk-adjusted 30-day readmission chance) could be calculated. Fourth, outcome values were summed on a hospital basis. Finally, these summation values of hospital-level outcomes were divided by the hospital volumes.

In order to solve the problem of multicollinearity and to analyze multi-level risk adjustment accurately, individual and hospital level parameters were divided and univariate analyses were performed for each of them. The parameters which showed statistically significant correlation in this state were selected, and all the selected parameters were included as parameters for the multivariate analysis. SAS GLIMMIX protocol (SAS Institute Inc.) was used for the analysis, and modeling was performed using the stepwise method.

Using the ratio between the crude hospital level outcome and the expected hospital level outcome, the observed to expected ratio (O/E ratio) was calculated and multiplied by the all average outcome rate. This result was defined as the final risk-adjusted outcome value of each hospital.

There were many methods of risk-adjustments, and O/E ratio was chosen. Predicted to expected ratio (P/E ratio) was also used in other studies. However, P/E ratio is excluded because the assumption of this method is that “there is no volume outcome relationship."[19] The O/E ratio is the ratio between the actual and expected results. If the ratio is 1, the two results are the same. If the ratio is more than or less than 1, the outcome of the hospital is bad or good.

Determination of the relationship between the outcomes of the risk-adjusted model and the hospital volumes were performed in various ways. The relationship of crude hospital outcome values and the volumes were analyzed. Attempts were made to divide the volume into various forms such as dichotomous, trichotomous, quartiles, and quintiles. Finally, in order to calculate the volume threshold, we sorted all the hospital's 5-year volumes, divided into 4 groups, and measured the relationships between volume and outcomes. Before sorting hospitals by their volume, a substantial proportion of hospitals (51 hospitals) were excluded for two reasons, the first reason being no record of cases in 2015, and second was the total number of cases were less than 20 for 5 years.

Volume and outcome relationships existed, so the volume thresholds for that outcome was estimated. The volume threshold was calculated by examining the relative effect on the adjusted outcome odds, for increasing hospital volume of 10 patients for a given-size hospital, and varying the given-size hospital from an annual volume from boundary value between quartile groups, increments of 1 case per year. 10 cases were simply selected as standardized increment. The threshold was set to the point at which the odds for outcome approaches 1 as the total volume falls.

This method was originally came from the study of Ross et al[32], and slightly modified. In the study of Ross et. al., the odds-of-death interval was monitored for acute myocardial infarction, heart failure, and pneumonia. The hospital procedure volume was increased by 100 cases per year from the reference volume to a threshold value that minimized the decrease in odds of death. Total patient numbers were 734,972 (acute myocardial infarction), 1,324,287 (heart failure), and 1,418,252 (pneumonia). The odd change was continuously sampled when the volume increases, from the reference volume 100 case per year. The authors named this method bootstrapping procedure.[32]

Finally, in order to evaluate modifiable structures and processes, a stratified analysis was performed according to two hospital characteristics that were hypothesized to be strongly associated with outcome variable in ERT of AIS: teaching status and stroke unit.

2.10. Statistical analyses

All analyses were conducted with the SAS Enterprise Guide statistical software package, version 7.13 (SAS Institute Inc.), and Microsoft Excel 2013 (Microsoft Inc.). Various statistical methods were used, including Pearson's Chi-square test and t-Test – for comparison of administrative and clinical database, multiple linear regression analysis – for SSI model, simple and multiple logistic regression analyses – for selecting appropriate parameters of risk adjustment modeling and final risk adjustment modelling and odds ratio by quartile in volume-outcome relationship, *C*-statistics – for validation of risk adjustment model, Pearson & Spearman correlation analysis – for VOR distribution, and restricted cubic spline regression – for threshold volume estimation.

3. Results

3.1. Baseline characteristics of administrative database

Baseline characteristics are shown in Table 6. Of the 111 hospitals included in the analysis, the ERT volumes corresponding to half of all patients were performed in 21 hospitals. 51 hospitals (31.4 percent) were excluded due to very low volume.

Excluding small number hospitals (previous described), VOR analyses were conducted on the total case number of the remaining 111 hospitals, which is 11,745 (97.7% compared to 12,013 cases). The basis for dividing the sample into four groups is to have roughly the same number of patients in each group. About 2,900 cases from the most voluminous hospitals were defined as the first quartile (more than 61 cases per year), and the second (31-60 cases per year), the third (19-30 cases per year), and the fourth qurtile (less than 18 cases per year) respectively.

Overall, the incidence of atrial fibrillation was as high as 61.62%. Diabetes was also quite high at 67.95%. Many hyperlipidemia patients seemed to be the matter of prescription of statin. Age and the proportion of comorbidities tends to be higher in the first quartile group than in the other groups.

The mCCI was newly calculated by applying the method of the study[28] as it is, and the distribution of the value resulting from the calculation was also similar to the known result (Figure 3).

Table 6. Baseline characteristics of administrative database, according to medical condition and hospital volume quartile group (n=12,013)

Variable	**All patients**	**1Q group**	**2Q group**	**3Q group**	**4Q group**
No. of hospitals (included in analysis)*	162 (111)	7	14	25	116 (65)
No. of patients (included in analysis)*	12,013 (11,777)	2,970	2,942	2,927	3,175 (2,938)
Age - median (IQR)	71 (61-78)	72 (64-78)	71 (61-77)	70 (60-77)	70 (60-77)
Male Sex - no.(%)	6735 (56.06)	1607 (54.10)	1635 (55.57)	1684 (57.53)	1675 (57.01)
Stroke Severity Index					
Median (IQR)	10.33 (6.89-13.95)	10.22 (6.41 – 13.95)	10.33 (7.59 – 13.95)	10.48 (7.48 – 13.95)	12.11 (8.6 – 15.01)
Range	2.86 - 18.74				
Prior Stroke – no.(%)	5478 (46.51)	1450 (48.82)	1318 (44.79)	1284 (43.86)	1426 (48.53)
HTN – no.(%)	3692 (31.34)	983 (33.09)	875 (29.74)	840 (28.69)	994 (33.83)
AF – no.(%)					
(pre-diagnosed)	2441 (20.72)	669 (22.52)	553 (18.79)	579 (19.78)	640 (21.78)
(after 90 days)	7258 (61.62)	1885 (63.46)	1745 (59.31)	1755 (59.95)	1873 (63.75)
DM – no.(%)	8003 (67.95)	2146 (72.25)	1761 (59.85)	2024 (69.14)	2072 (70.52)
Charlson comorbidity index – median (IQR)	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-3)
Hyperlipidemia – no.(%)	9281 (78.80)	2553 (85.95)	2253 (76.58)	2128 (72.70)	2347 (79.88)
ICAS – no.(%)	1707 (14.49)	527 (17.74)	391 (13.29)	393 (13.42)	396 (13.47)
TIA – no.(%)	221 (1.87)	64 (2.15)	49 (1.66)	53 (1.81)	55 (1.87)
MI – no.(%)	6035 (51.24)	1510 (50.84)	1410 (47.92)	1396 (47.69)	1719 (58.50)

* substantial proportion of hospitals were excluded in volume-outcome relationship analsys due to very low volume (no cases in 2015 or less than 20 cases per 5 years)

Q: quartile, IQR: interquartile range, TIA: transient ischemic attack, HTN: hypertension, AF: atrial fibrillation, MI: myocardial infarction, CHF: congestive heart failure, ECAS: extracranial artery stenosis, ICAS: intracranial artery stenosis, vasc.: vascular, DM: diabetes mellitus, CCI: Charlson comorbidity index

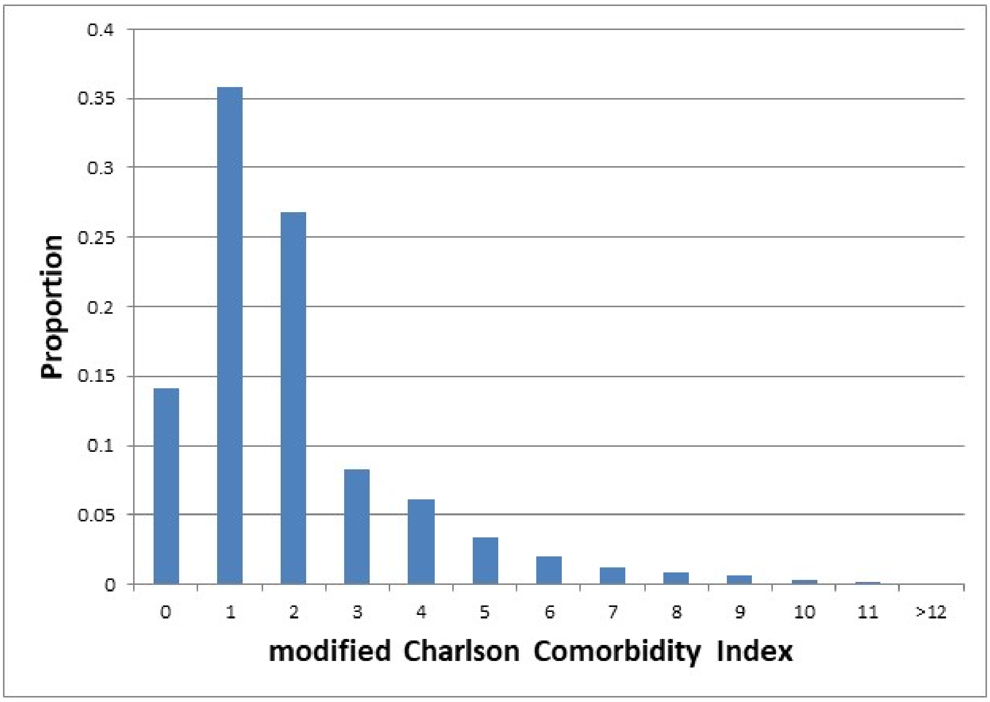

Figure 3. Distribution of modified Charlson comorbidity index scores in the administrative database (n=12,013)

3.2. Comparative analysis of administrative and clinical databases

General characteristics of the 2 hospitals are shown in Table 7. Patients' age were slightly older in PNUYH group (67.2 vs 70.0, *P* <0.01). The distribution of NIHSS was similar. However, there was a difference in length of stay (LOS) between DAUH (7 days) and PNUYH (9 days) (*P* value <0.01), which seems to be difference between private hospital and public hospital. Age, NIHSS, LOS were tested by t-test and sex by Chi square test.

Table 7. Characteristics of the patients in clinical databases (n=4,932)

Characteristic	DAUH N = 3,176	PNUYH N = 1,756	*P*-value
Age, mean (SD)	67.2 (12.6)	70.0 (12.9)	$P < 0.001$
Female, n (%)	1,243 (39.7)	713 (40.5)	$P = 0.55$
NIHSS, median (IQR)	4 (1-10)	4 (1-9)	$P = 0.18$
LOS, median (IQR)	7 (4-11)	9 (6-14)	$P < 0.001$

DAUH: Dong-A University Hospital, PNUYH: Pusan National University Yangsan Hospital, SD: standard deviation, NIHSS: NIH stroke scale, IQR: interqurtile range, LOS: length of stay

Among the 4,932 cases enrolled, the true positive (TP) cases that received ERT were total 223 (108 in DAUH + 115 in PNUYH) cases, true negative (TN) cases who did not receive ERT were confirmed are 4,609 cases (1,589 + 3,020), and the remaining false positive (FP) and false negative (FN) cases are 55 (10 in DAUH + 45 in PNUYH) and 45 (3 in DAUH + 42 in PNUYH). Table 8 shows the sensitivity, specificity, and positive predictive value.

To evaluate the discrepancies, in-depth analyses were done for the 115 true positives and 42 false negatives of PNUYH cases (Table 9). False positive cases were unable to be analyzed because de-identification of HIRA database. In yearly analysis, false negative cases showed relatively high proportion in 2013. In 42 false negatives of PNUYH cohort, 1 case did not admitted from emergency department, and 13 cases concomitantly deployed the stentriever in the intracranial arterial stenosis cases. The latter 13 cases were coded not as ERT procedure but as intracranial stent deployment.

Table 8. Comparison of the clinical and administrative databases (n=4,932)

	DAUH	PNUYH	Overall
Sensitivity (%)	97.2	73.2	83.2
Specificity (%)	98.5	99.3	98.8
Positive predictive value (%)	70.5	92	80.2

DAUH: Dong-A University Hospital, PNUYH: Pusan National University Yangsan Hospital

Table 9. Analysis by year, sensitivities of comparison – clinical and administrative databases of Pusan National University Yangsan Hospital (n=1,756)

	Sensitivity (TP / TP + FN)
2015 (2015.01.~ 2016.06.)	83.3 % (45/54)
2014 (2014.01.~ 2014.12.)	73 % (22/30)
2013 (2013.01.~ 2013.12.)	5.5 % (1/18)
2012 (2012.01.~ 2012.12.)	77.7 % (14/18)
2011 (2011.07.~ 2011.12.)	67 % (33/49)

TP: true positive, FN: false negative

3.3. Hospital volumes analyses

Table 10 summarizes the results of hospital volume in 2015 (from July 2015 to June 2016) and annual volume trends for the top 20 hospitals, sorted by the volume rank. Overall, the number of ERT cases has been on the rise, but it has declined slightly between 2012 and 2013. For 5 years, 12,013 procedures were done, and there were some patients (0.009 %) who undergone twice (111 people) or thrice (2 people). Most of them showed a time gap of six months or one year.

There were 162 hospitals in total, of 21 hospitals did not perform the ERT procedure in 2015 perhaps due to closure or owner transference of hospitals. The mean volume was 14.8 cases per year (74.1 cases per 5 years), and 59 hospitals (38 %) were higher than the mean volume.

Table 10. The results of hospital endovascular recanalization therapy volume in 2015 and annual volume trends for the top 20 hospitals, sorted by the volume rank (n=12,013)

Ranking in 2015	2011	2012	2013	2014	2015	Total	Cumulative Ranking
1	50	69	75	86	135	415	5
2	96	88	96	101	121	502	2
3	67	112	102	96	118	495	3
4	29	30	78	66	99	302	7
5	70	110	85	144	95	504	1
6	83	102	78	84	86	433	4
7	43	25	3	44	69	184	16
8	55	38	20	77	63	253	11
9	54	75	64	68	58	319	6
10	37	60	61	72	57	287	8
11	49	47	52	49	57	254	10
12	40	46	36	72	55	249	12
13	52	38	43	41	53	227	13
14	29	34	11	46	53	173	18
15	28	30	7	35	50	150	23
16	18	19	11	33	49	130	27
17	42	61	56	50	48	257	9
18	8	39	35	57	48	187	15
19	37	16	1	27	48	129	28
20	22	44	33	62	45	206	14
Total (every hospital)	1,932	2,117	1,951	2,769	3,244	12,013	

3.4. Outcome variables analyses

Overall 30-day mortality rate of all Korean hospital in ERT of AIS was 11.6%, and 30-day readmission rate was 4.6%. Overall Home-time was 195.9 days, and overall symptomatic ICH rate was 8.6%.

Many patients showed home-time value 'zero (n=3,222, 26.8 %)', so home-time was excluded from the volume outcome relationships analysis. The reason for this will be explained in the discussion, but it seems to be a characteristic of Korean hospital culture which has a high rate of reference to sanatorium or nursing hospitals, 'Yoyang byeongwon' in Korean. The distribution of home-time was distinct from that of normal Gaussian distribution (Figure 4), and it was very different from those in the reference paper.[50,51]

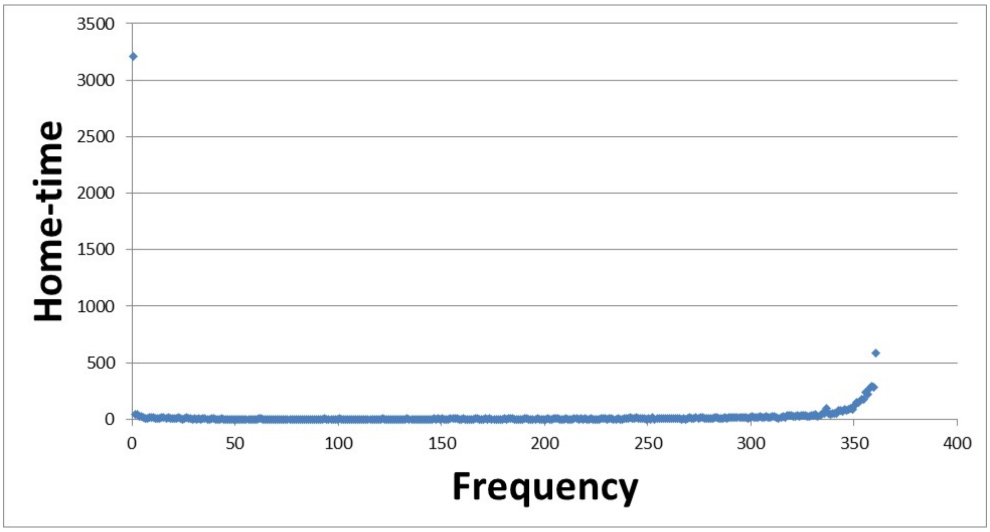

Figure 4. Distribution of home-time in the administrative database (n = 12,013)

3.5. Derivation and validation of risk-adjusted outcome models

The expected mortality rate, readmission rate, and ICH rate for each hospital were calculated by applying the multi-level logistic linear regression method. The *C*-statistics for each equation was also calculated. To solve the multicollinearity problem, other variables included in the SSI were excluded from the univariate analysis, and the statistical model was applied. In the case of mortality, the variables applied to the model were age, SSI, mCCI, sex, hypertension, and atrial fibrillation (Figure 5). No significant value was found in univariate analysis of hospital level values, including all four of these items, and no items was included in the final model. The *C*-statistics value of final model was 0.8146, which is higher than the initial target value of 0.8 (Figure 6).

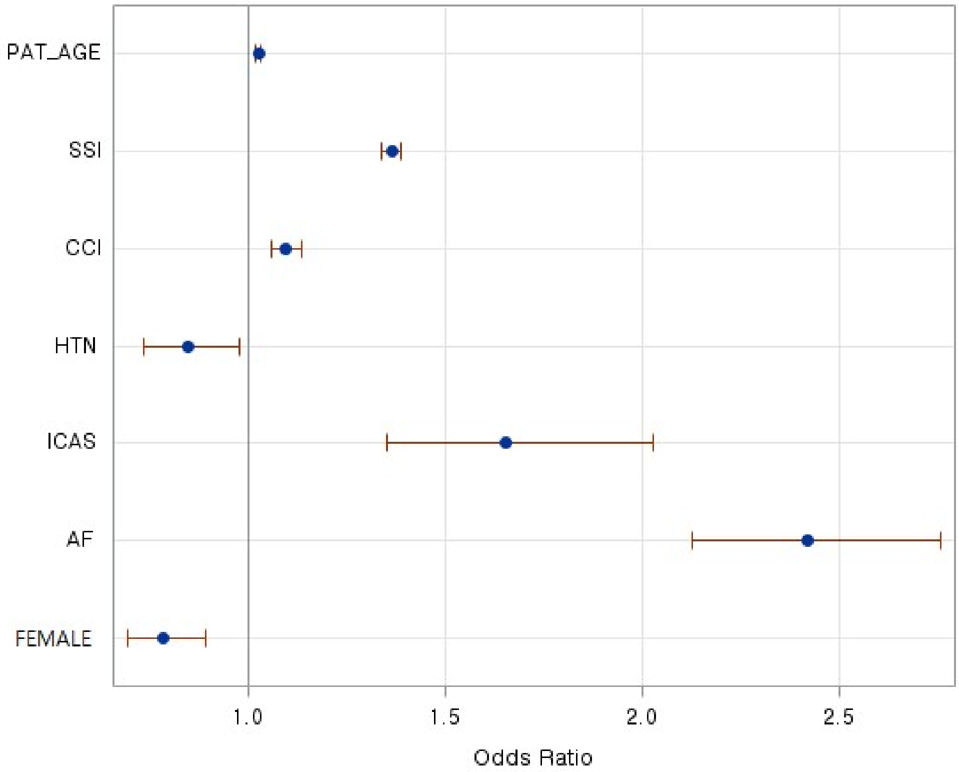

Figure 5. Selected risk adjustment items of 30-day mortality models with each odds ratios and 95% confidence intervals

PAT_AGE: patient age, SSI: stroke severity index, CCI: modified Charlson comorbidity index, HTN: hypertension, ICAS: intracranial arterial stenosis, AF: atrial fibrillation

Table 11. Analysis of maximum likelihood estimates of 30-day mortality rate model

Parameter	Estimate	Standard Error	Wald Chi-Square	*P* value
Intercept	-7.9634	0.2618	925.3185	<.0001
Age	0.0251	0.00291	73.9655	<.0001
SSI	0.3098	0.00979	100.485	<.0001
mCCI	0.0915	0.0174	27.7276	<.0001
HTN	-0.0821	0.0363	5.1294	0.0235
ICAS	0.2519	0.0515	23.948	<.0001
Af	0.4419	0.0332	177.2542	<.0001
Female	-0.1204	0.0321	14.0781	0.0002

SSI: Stroke severity index, mCCI: modified Charlson comorbidity index, HTN: hypertension, ICAS: intracranial arterial stenosis, Af: atrial fibrillation

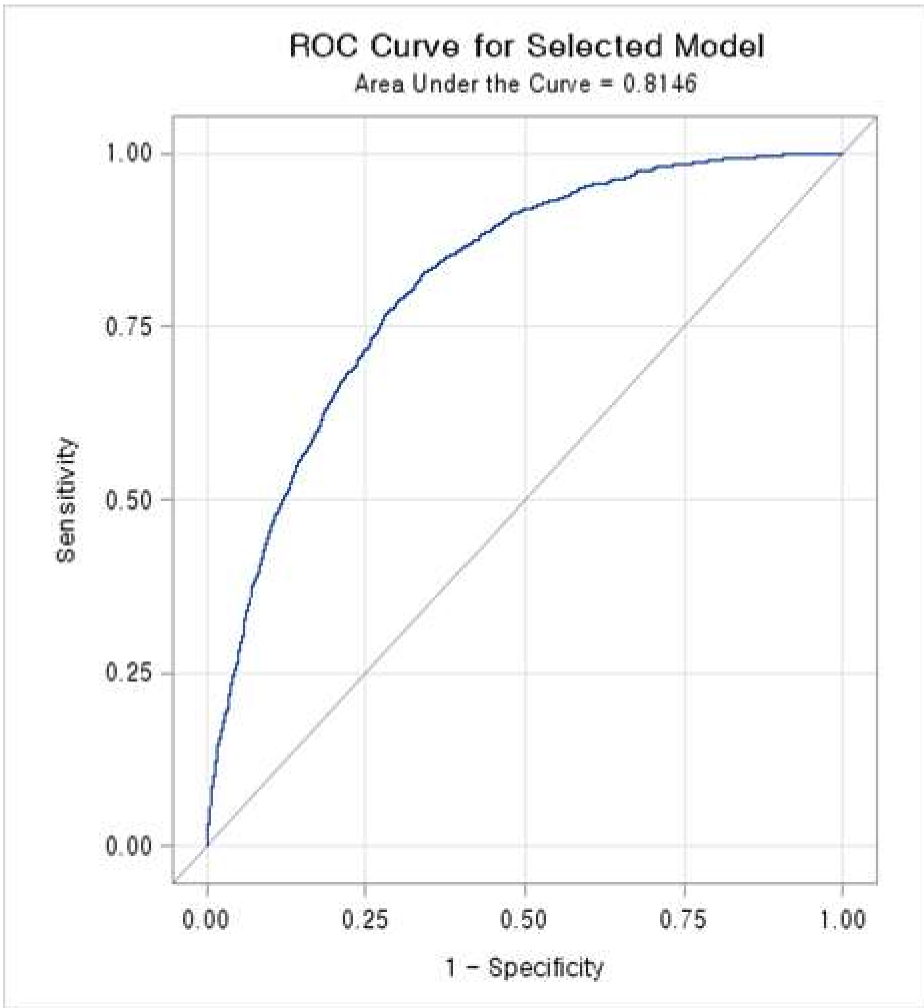

Figure 6. Receiver operating characteristic (ROC) curve for 30-day mortality rate model

In a similar way, the same modeling was done for the readmission rate, and included variables were SSI, mCCI, age, transient ischemic attack, prior stroke, and female sex (Figure 7). There were no hospital level items included neither, and *C*-statistic was 0.6052, which was relatively low (Figure 8).

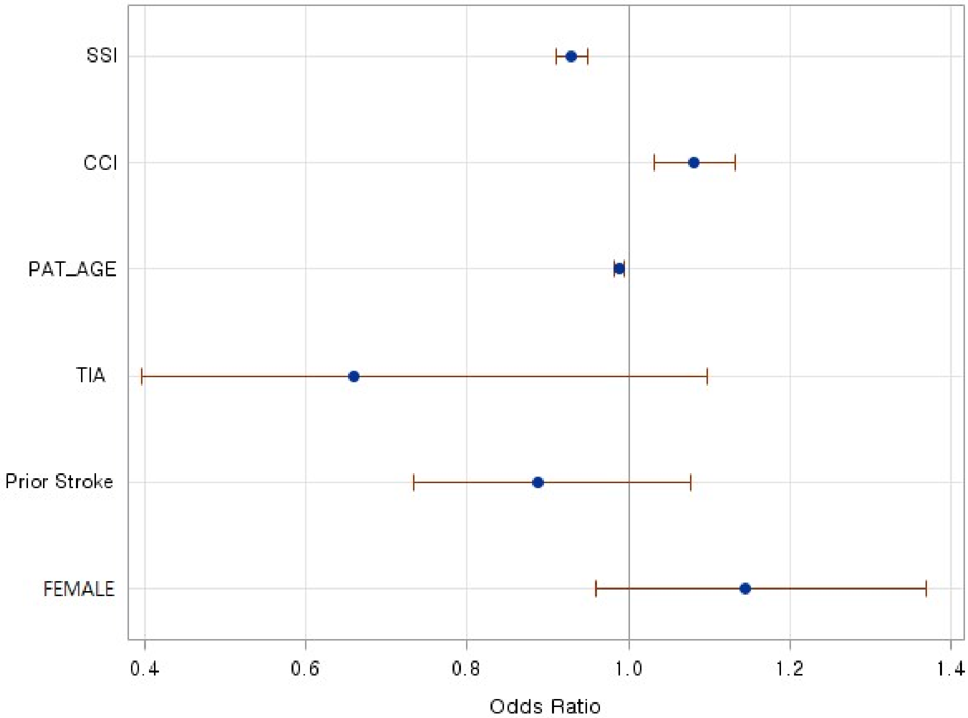

Figure 7. Selected risk adjustment items of 30-day readmission models with each odds ratios and 95% confidence intervals
SSI: stroke severity index, CCI: modified Charlson comorbidity index, PAT_AGE: patient age, TIA: transient ischemic attack

Table 12. Analysis of maximum likelihood estimates of 30-day readmission rate model

Parameter	Estimate	Standard Error	Wald Chi-Square	P value
Intercept	-1.4261	0.2841	25.1971	<.0001
SSI	-0.0737	0.0109	45.3129	<.0001
mCCI	0.0783	0.0236	10.9832	0.0009
Age	-0.0119	0.00352	11.4347	0.0007
TIA	-0.2086	0.1302	2.5657	0.1092
Prior Stroke	-0.0595	0.049	1.4694	0.2254
Female	0.0681	0.0455	2.2389	0.1346

SSI: Stroke severity index, mCCI: modified Charlson comorbidity index, TIA: transient ischemic attack

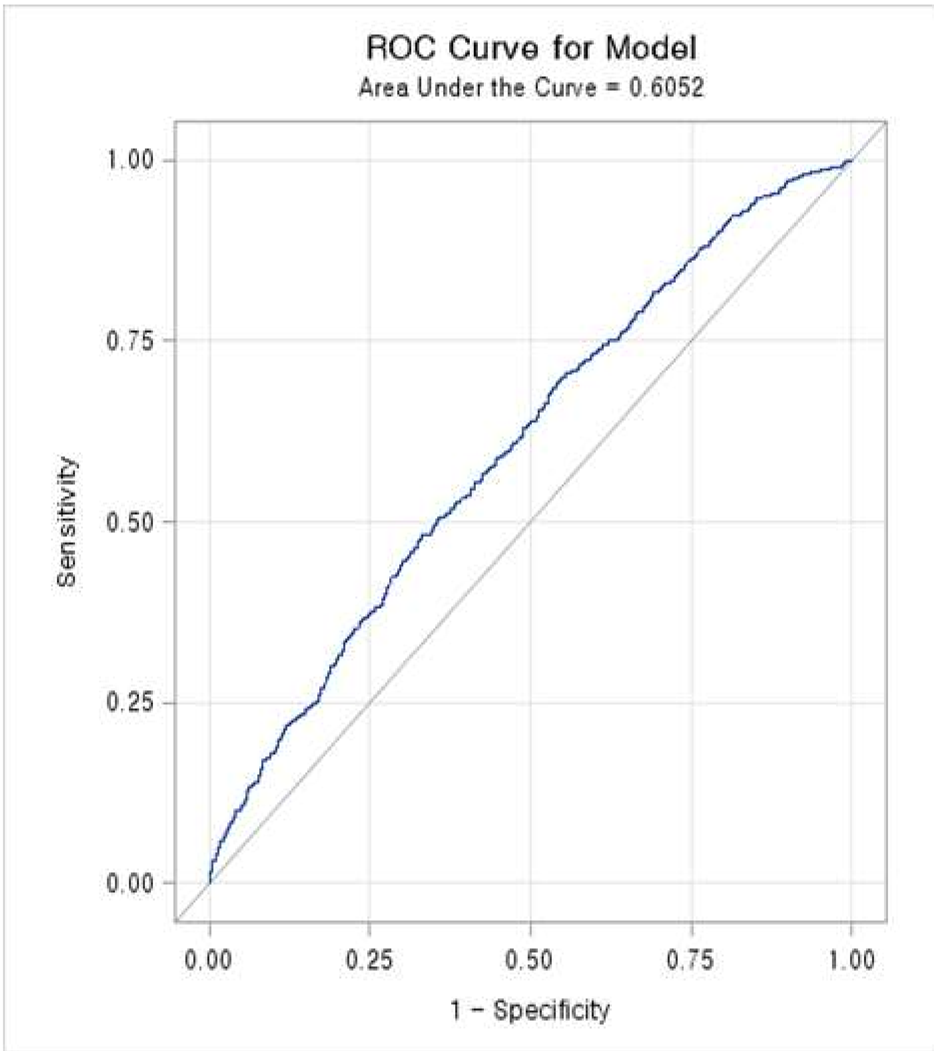

Figure 8. Receiver operating characteristic (ROC) curve for 30-day readmission rate model

For ICH rate, individual-level variables were chosen such as age, SSI, intracranial arterial stenosis, myocardial infarction, hypertension, and transient ischemic attack (Figure 9). ‘Resident training’ was included at hospital level. The final model *C*-statistical value was 0.6841 (Figure 10).

After that, the expected outcome value for each individual was calculated by applying it to the regression equation. After that, those values at hospital level were created, and then all the values in each group were combined. Finally, the O/E ratio was made by calculating the ratio between the combined value and the actual outcome in the hospital.[19]

The final risk adjusted outcome was defined as the overall rate of the O/E ratio multiplied by each crude outcome rate (mortality rate, re-admission rate, ICH rate, etc.).

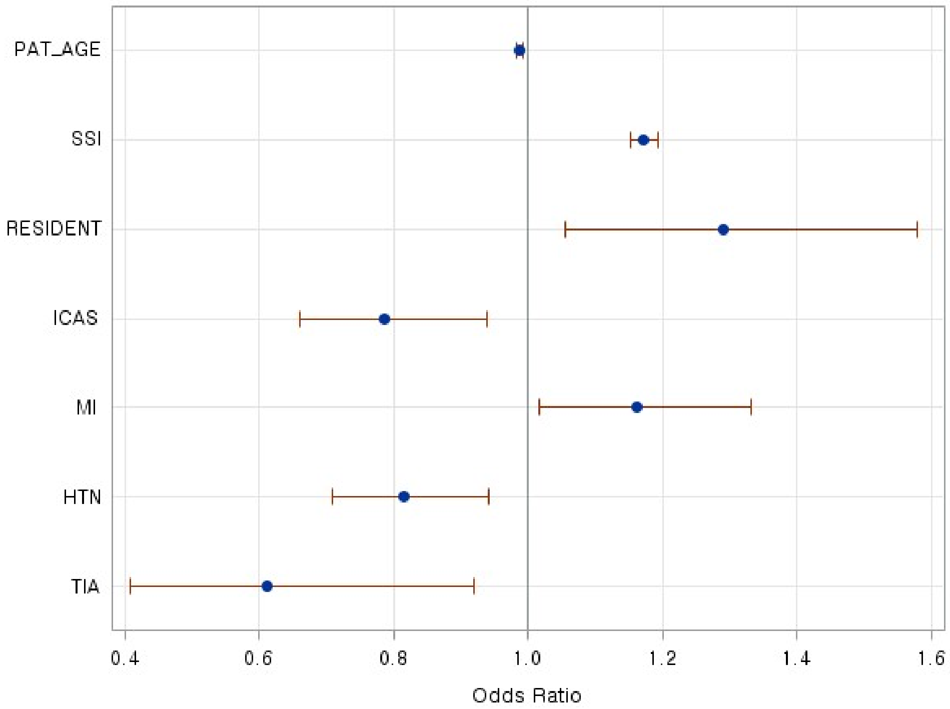

Figure 9. Selected risk adjustment items of symptomatic ICH models with each odds ratios and 95% confidence intervals

PAT_AGE: patient age, SSI: stroke severity index, ICAS: intracranial arterial stenosis, MI: myocardial infarction, HTN: hypertension, TIA: transient ischemic attack.

Table 13. Analysis of maximum likelihood estimates of symptomatic ICH model

Parameter	Estimate	Standard Error	Wald Chi-Square	P value
Intercept	-2.8926	0.2361	150.0609	<.0001
Age	-0.0132	0.00268	24.0105	<.0001
SSI	0.1588	0.0088	325.8385	<.0001
Resident	0.1274	0.0515	6.1081	0.0135
ICAS	-0.1205	0.045	7.1737	0.0074
MI	0.0752	0.0344	4.7757	0.0289
HTN	-0.1021	0.0363	7.8938	0.005
TIA	-0.2451	0.1033	5.6315	0.0176

SSI: Stroke severity index, ICAS: intracranial arterial stenosis, MI: myocardial infarction, HTN: hypertension, TIA: transient ischemic attack.

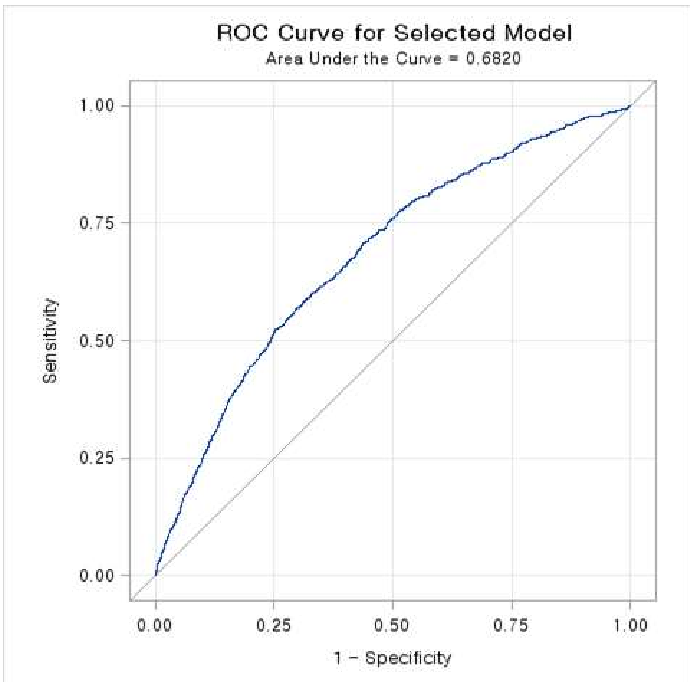

Figure 10. Receiver operating characteristic (ROC) curve for symptomatic intracranial hemorrhage model

3.6. Volume-outcome relationships analyses

For mortality comparison between quartile groups, the odds ratio (OR) showed differences between the 1st and the 3rd quartiles, and between the 1st and 4th quartile in the crude outcome model (*P* value <0.05). However, in the adjustment model, the OR showed differences among the groups from the 2nd quartile to the 4th quartile, and the *P* value for the OR difference of 1st versus 3rd, and 1st versus 4th were found to be more statistically significant (*P* value < 0.005, Table 14).

Comparing the re-admission rates between the quartile groups, the OR showed differences between the 1st and 3rd quartiles, and the 1st and the 4th quartiles in the crude outcome model (*P* value <0.05.) However, in the adjustment model, the readmission rate decreased in the low volume center quartile groups, and statistically insignificant results were found (Table 15).

In comparison, the ICH rate OR between the quartile groups, the crude outcome model and adjustment model showed a statistically significant increase in ICH rate between the 1st and 4th quartile group (*P* value <0.05, Table 16).

Table 14. Relationship between the Hospital Volume Quartile and the Odds ratio of 30-day mortality rate of endovascular recanalization therapy in acute ischemic stroke (N = 111)

Quartile	cOR	95% CI	PV	aOR	95% CI	PV
1st (> 61 / y)	1	-	-	1	-	-
2nd (31 ~ 60 / y)	1.07	0.91-1.27	0.385	1.18*	1.00-1.39	0.048
3rd (19 ~ 30 / y)	1.17*	1.00-1.38	0.047	1.27**	1.08-1.50	0.003
4th (< 18 / y)	1.36**	1.16-1.60	<0.001	1.37**	1.16-1.61	<0.001

cOR: crude odds ratio, CI: confidence interval, PV: *P* value, aOR: adjusted OR

* *P* value < 0.05

** *P* value < 0.005

Table 15. Relationship between the Hospital Volume Quartile and the Odds ratio of 30-day readmission rate of endovascular recanalization therapy in acute ischemic stroke (N = 111)

Quartile	cOR	95% CI	PV	aOR	95% CI	PV
1st (> 61 / y)	1	-	-	1	-	-
2nd (31 ~ 60 / y)	1.07	0.83-1.39	0.567	0.94	0.74-1.20	0.649
3rd (19 ~ 30 / y)	1.38**	1.08-1.76	0.009	0.91	0.71-1.16	0.469
4th (< 18 / y)	1.24*	0.96-1.59	0.089	0.94	0.74-1.20	0.640

cOR: crude odds ratio, CI: confidence interval, PV: *P* value, aOR: adjusted OR

* *P* value < 0.05

** *P* value < 0.005

Table 16. Relationship between the Hospital Volume Quartile and the Odds ratio of intracranial hemorrhage rate of endovascular recanalization therapy in acute ischemic stroke (N = 111)

Quartile	cOR	95% CI	PV	aOR	95% CI	PV
1st (> 61 / y)	1	-	-	1	-	-
2nd (31 ~ 60 / y)	0.98	0.81-1.19	0.892	1.08	0.90-1.30	0.379
3rd (19 ~ 30 / y)	1.08	0.89-1.29	0.458	1.12	0.93-1.34	0.223
4th (< 18 / y)	1.26*	1.06-1.57	0.009	1.21*	1.01-1.45	0.034

cOR: crude odds ratio, CI: confidence interval, PV: *P* value, aOR: adjusted OR

* *P* value < 0.05

The analysis of the distribution showed a significant negative correlation with the crude 30-day mortality rate, with a Pearson correlation coefficient of −0.21 (*P* value 0.03). However, in the risk-adjusted 30-day mortality model, the correlation coefficient was −0.03 (*P* value 0.71), and Spearman correlation coefficient of 0.02 (*P* value 0.844), indicating no statistical significance (Figure 11).

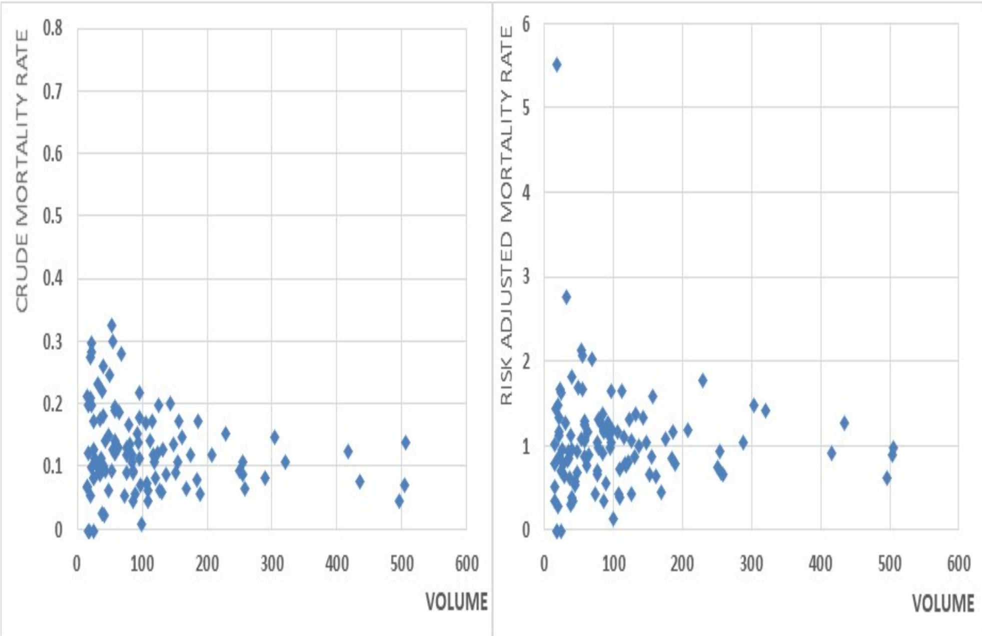

Figure 11. Plotted graphs of hospital crude (left) and risk adjusted (right) 30-day mortality rate and endovascular recanalization therapy volumes for 5 years (N=111)

In the analysis of 30-day readmission rate, both crude (-0.13) and risk-adjusted(-0.15) models showed a negative correlation. Both models showed statistically insignificant values (*P* value 0.20 and 0.14, Figure 12).

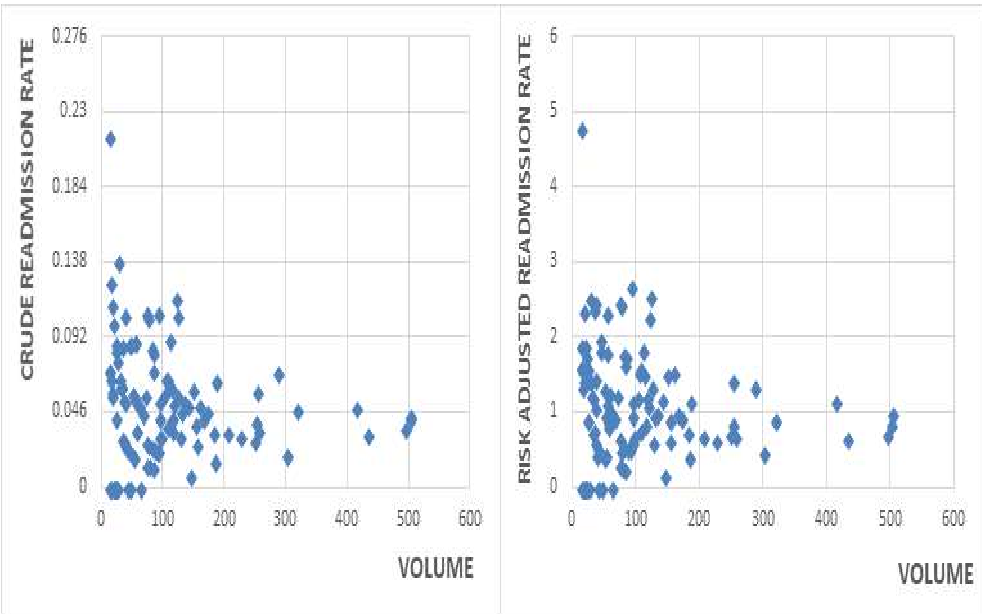

Figure 12. Plotted graphs of hospital crude (left) and risk adjusted (right) 30-day readmission rate and endovascular recanalization therapy volumes for 5 years (N=111)

In ICH rate, both crude and risk-adjusted model showed a negative correlation (-0.16 and −0.03) and were statistically insignificant (*P* value 0.11 and 0.73) result (Figure 13).

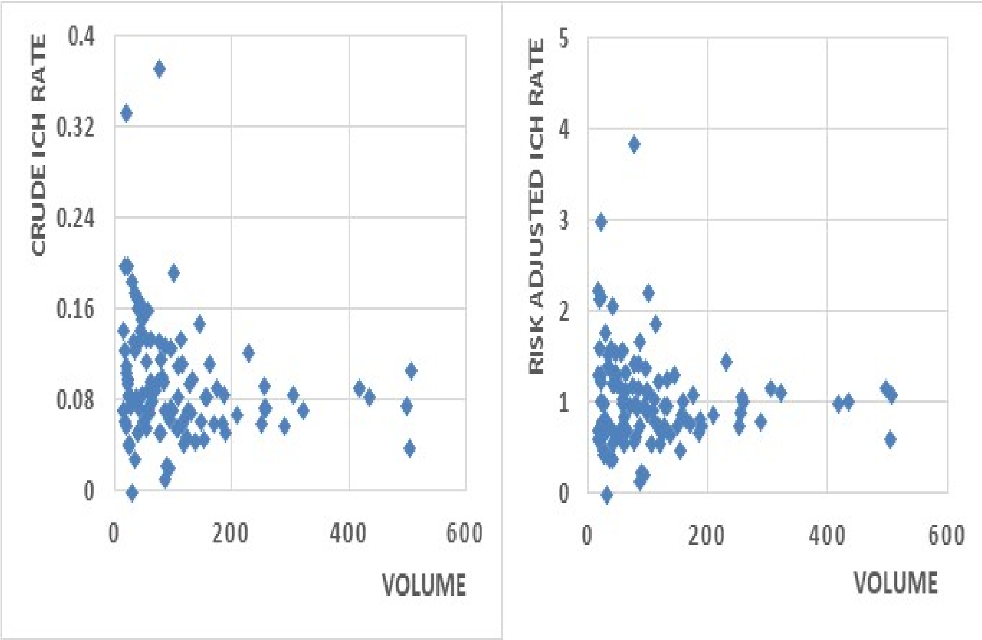

Figure 13. Plotted graphs of hospital crude (left) and risk adjusted (right) symptomatic intracranial hemorrhage rate and endovascular recanalization therapy volumes for 5 years (N=111)

3.7. Estimation of volume threshold and evaluation of modifiable 'structures and processes'

In the comparison of quartile groups according to the amount of hospital volume, there was statistical significance in OR between the 1st and 2nd quartiles for risk-adjusted mortality rate, and it was also significantly different between 1st and 4th quartiles for symptomatic ICH rate. Based on this, we concluded that a VOR existed in ERT of AIS, and we decided to estimate the point where the threshold exists.

It was assumed that a threshold would be exist between the volume of the boundary point between the 2nd quartile (below 60 cases per year) and the boundary point of the 4th quartile (above 19 cases per year) review. Between 60 and 19 cases per year, a modified method of assessing volume threshold presented in a paper[32] was chosen.

In this process, a J-shaped curve was created, and the threshold was set to the point at which the odds for mortality approaches "1.0" as the total volume falls. Thus, at the lowest value of the J curve, 22 cases per year (110 cases per 5 years) corresponding to the inflection point, and 24 cases per year (120 cases per 5 years) corresponded to where the odds fell below 1. Based on this, we set 24 cases per year as the VOR threshold of ERT for AIS (Figure 14).

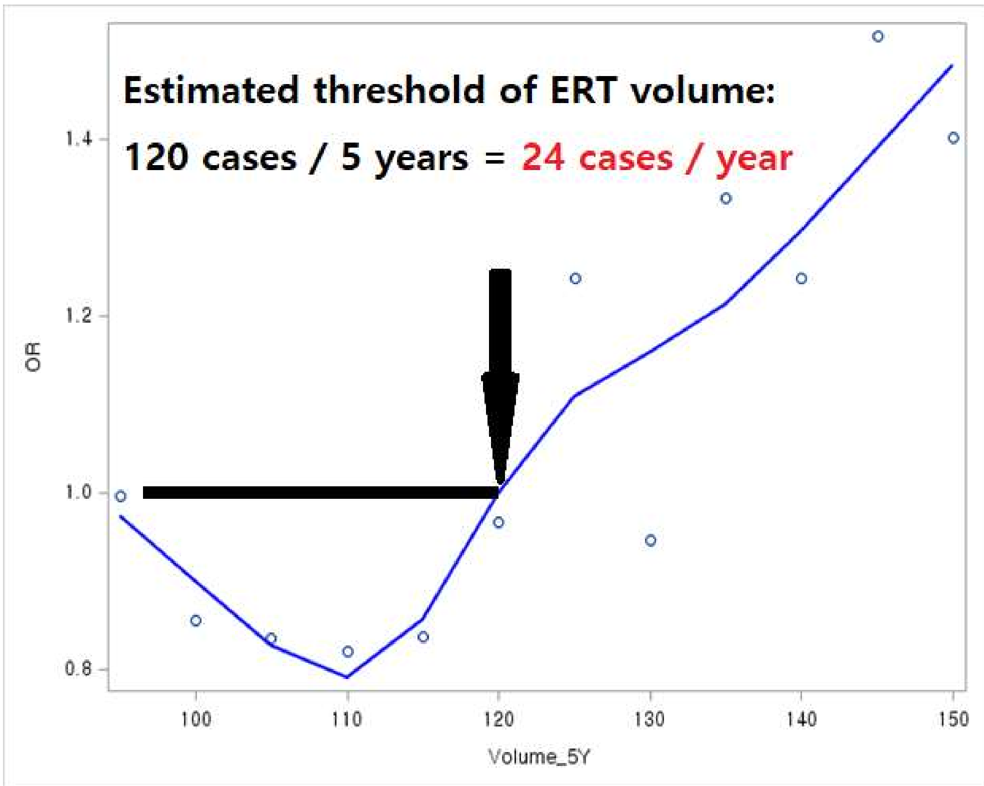

Figure 14. Predicted effect of an increase of 10 patients in annual procedure volume on the adjusted odds of mortality in Korea, 5 years ERT: Endovascular recanalization therapy, OR: odds ratio, Volume_5Y: 5 year total volume

In order to identify modifiable 'structures and processes', additional analyzes were conducted with regard to the two hypothesized hospital-related variables; stroke unit and teaching status. Of the 111 hospitals included in the analysis, the hospitals with stroke units were 50 (45%), and teaching status hospitals accounted for 79% of the total hospitals (Table 17). Both the proportion of hospitals with stroke units and the teaching status decreased from 1st to 4th quartile group, and was statistically significant in the fourth quartile group. Due to dichotomization of the classification according to the value determined by volume threshold, statistically significant differences were found in both stroke unit and teaching hospital between two groups.

Table 17. Relationship between the hospital volume group and the presence of stroke unit & teaching status

Group		no.	Stroke Unit (%)	*P* Value	Teaching status (%)	*P* Value
by Quartile group	1st (> 61 / y)	7	7 (100)	-	7 (100)	-
	2nd (31 ~ 60 / y)	14	10 (71)	0.255	14 (100)	1
	3rd (19 ~ 30 / y)	25	14 (56)	0.066	21 (84)	0.552
	4th (< 18 / y)	65	19 (29)**	<0.005	46 (70)	0.178
by volume threshold group	high volume (> 24 / y)	31	23 (74)	-	31 (100)	-
	low volume (< 23 / y)	80	27 (34)**	<0.005	57 (71)**	<0.005
Total		111	50 (45)	-	88 (79)	-

** *P* value < 0.005

4. Discussion

4.1. Baseline characteristics of administrative database

In this study, the trends of most ERT procedures performed in Korea for the past 5 years, demographic information of patients, and patient history were obtained. The stroke version modified version of the Charlson comorbidity index was also derived, which is frequently used as a correction index of mortality in the studies using the claims data, and we found a distribution similar to that of the previous studies.[28] Other studies that have focused on only patients with ERT are prospective randomized controlled trials rather than retrospective observational studies, and this study seems to produce a different result from previous studies.[2-8] To our knowledge, there have been no study investigating every case of ERT in the nation.

Almost 50% of all patients received ERT in the top 21 hospitals (18.9%). In the comparison between the groups, the frequencies of the other comorbidities except SSI were higher in the 2nd, 3rd, and 4th quartiles. 68% had diabetes, 61% had atrial fibrillation, and compared to the results of other studies, this was higher. There seems to be selection bias of patients with atrial fibrillation. It is presumed that there many patients with large arterial disease (LAD in TOAST classification) without atrial fibrillation. In these cases, the I65 code is not probably diagnosed during acute phase treatment, and the process of coding would be delayed in this period.

Percentage of patients with hyperlipidemia was high; 79%. This is because of the nature of health insurance system in Korea. There is large evidence on statin therapy in acute phase treatment producing good outcomes in AIS patients' prognosis. However, in Korea, when statins are prescribed without detection of a diagnosis of hyperlipidemia, the hospital information system automatically blocks the prescription of the drug. From our literature search, there have been no similar cases in other studies.

4.2. Comparative analysis of administrative and clinical databases

In comparison between DAUH and PNUYH, there was some difference between the total number of patients (3,176 vs 1,756). Overall patients' age were younger in DAUH, and shorter LOS in DAUH. These results seems to reflect the difference between the private and the public hospital, and the geographical difference (the metropolitan city in DAUH, and the rural area in PNUYH). However, there was no significant difference in patients' severities. Sensitivity, specificity, and positive predictive value are somewhat different, but overall sensitivity and positive predictive value are 83.2% and 80%.

This seems to be the matter of difference of hospital management strategy between public and private hospitals. Many other hospitals were enrolled in the administrative database, and there also will be differences, certainly. It would have been good if there was some study of the coincidence rate between the coding information and the actual clinical database in Korea in the preliminary study. However, this is beyond a scope of this study's purpose. If we can do research in this style in the future, it will be helpful in research using administrative data. The reason for the difference between high and low sensitivity is that, when false negative is low, which means that there is no missing claim data due to good and robust system. High false negative, it is suspected that there are some this missing claim data. If the positive predictive value is low, it means that there are many false positives. It is necessary to analyze more detailed discrepancies about the point at which this type of error actually occurs.

In-depth analysis of PNUYH cases (Table 9) showed the influence of Korean medical insurance system. Before 2013 in Korea, the ‘stentrievers’ were not covered by health insurance, subsequently, many hospitals could not use them properly. It is assumed that other hospitals have used similar methods, such as making claims for other devices or adding another diagnosis (e.g. intracranial arterial stenosis).

Despite these drawbacks, however, trend analysis using administrative data and comparison between hospitals was considered ingenious because it was impossible to study the data in other forms. Future studies will need to find ways to improve the sensitivity and positive predictive values. The basic principle, being the correct coding and billing, is mandated by both the HIRA service and individual medical institutions.

4.3. Analyses of hospital volumes and outcome variables

The total ERT volume of AIS patients in Korea during the past 5 years were obtained. Additionaly, the trends of annual volume change, and the hospital average volume per year were calculated. The outcome also showed the overall mortality rate, how much was re-admitted, and how much ICH was occurred.

ERT volume per hospital was found be increasing, which is likely caused by popularization of ERT due to the success of large randomized controlled trials including MR CLEAN study.[2] In addition to MR CLEAN, six large studies were also considered successful. It is considered that the number of physicians who are practicing ERT and the performance of equipment is increasing.[9-12,30] However, it declined slightly between 2012 and 2013, which is likely due to the failure of the IMS III trial.[54]

The reason why home-time as an functional outcome variables were failed is, too much amount of value '0.' Hopeless discharge was coded as '0 (death)', and good outcome (rehabilitation hospital) was also the same . It is also strange that it is not Gaussian distribution.

4.4. Derivation and validation of risk-adjusted outcome models

3 outcomes were acquired by using multivariable regression modeling for each of them. There were 12, 5, and 6 factors that affect the outcome models of 30-day mortality, 30-day readmission, and symptomatic ICH. Calculating *C*-statistics of each models were done. One looks good with a *C*-statistic of 0.83, but the two are as low as 0.61 and 0.68. The O/E ratio was selected from the risk adjustment method, and used for the VOR analysis based on the these models.

Of the various parameters associated with 30-day mortality, age, NIHSS (SSI as proxy value), and diabetes were found to be influential in both univariate and multivariate analyzes. This might be because the disease entity is a well-known risk factor for acute ischemic stroke. Hypertension and congestive heart failure have OR lower than 1.

If the readmission is high, the prognosis may be poor. However, if the readmission occurred, it may also be due to the need to perform endarterectomy or carotid artery stenting after the acute phase management of stroke. In Korea, If the treatment period is extended, the patient may be discharged from the hospital and re-hospitalized due to technicalities surrounding the insurance system. Therefore, it is possible high readmission rate may not be correlated to prognosis. This is similar to the home-time distribution problem.

Symptomatic ICH can be assumed as a complication of ERT, which, by definition, uses coded data and differs from the theoretical definition. Theoretically, symptomatic ICH had 5 characteristics, 1) intracranial hemorrhage was proved by radiological studies, 2) altered neurological status of the patient, 3) NIHSS altered by more than 4 points, 4) occurred 24 to 36 hours after ischemic event, 5) should be discriminated from hyper-perfusion syndrome.[54] By using administrative database, 4 of 5 conditions (from number 2 to 5) were not met. However, administrative data is not reflected immediately, so 30 days have been applied.

Three outcome models are '30-day all cause mortality', '30-day all cause readmission rate' and '30-day ICH rate.' It is possible that modeling does not reflect actual real information. For example, omission of onset time, long or short time period of the ERT procedure, high or low hospital level were factored into multilevel analysis, but such meaningful factors were not included in the univariate analysis. In the first modeling parameter, the hospital factors were not included in the model, and the ICH model in which the hospital level factor was included, was omitted from the multivariate analysis.

The difference between using O/E ratio and P/E ratio is that there are several controversy. In other studies, P/E ratios are widely used, which is often VOR-free modeling. Therefore, considering the existence of VOR, modeling based on O/E ratio is applied for modeling according to VOR.[40]

4.5. Volume-outcome relationships, volume thresholds, and modifiable 'structures and processes'

In this study, we calculated the minimum volume of ERT in AIS for maintaining the quality as a scientific base. Volume threshold was calculated by using a spline regression and was confirmed as 24 cases per year. In the mortality model, the frequency of 'low-volume good-outcome' hospitals were very high, so it was not easy to get the volume threshold. In the US studies, dichotomous analysis defined 50 cases per year and guidelines (from IMS III[55]) were stated as 10 cases per year. However, these studies were outdated, and the knowledge and equipment used have since changed. Therefore, we suggest that these studies be understood contextually in their relevant time period.

Volume-outcome relationship may not form an ideal inverse straight or curved form. There may be a cut-off pattern or a step-wise pattern. In other studies that have used this type of analysis, cut-off values have been determined by defining them as dichotomous values based on certain cut-off criteria.[20]

By using the threshold value, it is possible to support the healthcare policies concerning ERT, such thresholds can guide the designation of a comprehensive stroke center using the population ratio as an indicator, and setting up the manpower and facilities required for the investment. For example, it is possible to consider placing a center in an area where an overtasked comprehensive stroke center is located, to allow for implementation of more than 25 cases of ERT annually. It may also be useful in the planning of equipment and manpower required for effective maintenance of the center.

The available method is likely to improve the quality of hospital that lacks a stroke unit, and takes up about 50% of the total hospitals, by investing in a low volume center. If patients are concentrated in a high-volume center, but can be dispersed, there is increased likelihood of better outcomes. Increasing the number of teaching hospitals and stroke units could be also be done. This is also associated with qualitative improvement in overall stroke management.

Conversely, some studies showed that when patients were transferred to a high-volume center, the results were better than the low-volume center.[33] However, we do not agree with this solution because if patients are concentrated in the hospital, it is likely that surgery or other procedures are only required because of emergencies. There is a possibility of lowering the overall medical system's quality in such situations due to increased transfer time of the patient.

In addition to the ERT volume, there are other factors in a comprehensive stroke center selection or designation. Consideration of geographical location, population size, and prevalence rate relative to population in the region are important as well. In rural areas, where there are many elderly patients, the number of AIS patients is likely to be higher, but there is concurrent inferiority of the social infrastructure including public transportation systems, roads, and traffic culture. Therefore, there would be increased delays in patient discovery and transfer.

Similar studies about correlation of procedure volume and outcome of procedure for similar diseases and other procedures (coil embolization for patients with hemorrhagic stroke due to rupture of an intracranial aneurysm, carotid stenting for patients with carotid stenosis) can be investigated in the future. In addition, since new equipment and techniques are continually being developed and tested, it is expected that the methods applied in this study can be used.

4.6. Limitations

There are two categories of limitations in this study. The first category consists of systematic limitations, (the part that can be predicted from the initial planning stage of the research as weakness), and the second category focuses on limitations of the research process.

The greatest systematic limitation is that of data reliability in hospitals using coded data (administrative data). This limitation was overcome by comparing administrative and clinical databases. Another limitation is that the operational definition of symptomatic ICH was not realistic when taking out variable in research design, and there is no way to recognize other factors such as early neurological deterioration (END), presence of intravenous alteplase, and transference from primary stroke center or not. Because we analyzed hospital levels, we did not analyze the outcomes by individual interventionist.

There are some other limitations of the research process. We did not consider other proxy values such as length of stay (LOS) and total cost of hospitalization, etc. We were unable to create a statistically powerful risk-adjusted models for readmission rate and symptomatic ICH rate (*C*-statistic less than 0.8). In addition, only 2 hospitals were included in the SSI modeling process. Finally, there were no subgroup analyses by year.

4.7. Conclusions

We obtained the entire volume of ERT procedures in AIS patients in Korea within the past 5 years using an administrative database from HIRA service. There was a correlation between hospital volumes and risk-adjusted outcomes of ERT. We estimated the hospital volume thresholds of ERT procedures as, 24 cases per year. The risk adjustment method of using stroke severity index was used from the Taiwan paper and this was customized to the Korean medical environment. The trends of volumes and outcomes were traced and utilized as a quality indicator of ERT procedures. Although the volume thresholds of ERT can be utilized as reference values to guarantee good outcomes, there are other factors affecting the outcome of ERT in AIS patients. Therefore, this value should be used with caution.

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초 록

서론

급성기 허혈성 뇌졸중의 치료기술 중 하나인 혈관내 재개통 치료의 질적 관리를 위하여, 적절한 시술량에 관한 연구는 아직 미흡하다. 복잡하고 위험성이 높은 시술이나 수술에서 시술량-시술결과 연관성(volume-outcome relationship; VOR)이 있다는 연구 결과를 바탕으로, 혈관내 재개통 치료의 경우도 시술량과 시술결과간의 상관성이 존재할 것이란 가설을 검증하고자 한다. 시술결과와 시술량 간의 상관성 여부를 알아보고, 상관성이 존재할 경우 최소 시술량을 산출하고자 하였다.

연구대상 및 방법

분석자료는 건강보험심사평가원에서 제공하는 의료빅데이터, 양산부산대병원과 동아대병원의 청구자료 및 의무기록 등을 이용하였다. 2011년부터 2016년까지, 국내 혈관내 재개통 치료를 받은 급성기 허혈성 뇌졸중 환자들을 대상으로, 시술 결과 항목은 병원 단위에서의 30일 이내 사망률, 30일 이내 재입원율, 합병증으로서 뇌출혈(symptomatic ICH) 여부 등을 선정했으며, 환자의 기능적 상태에 대한 평가항목으로서의 수정 랭킨척도 (modified Rankin Scale; mRS)를 이용하는 것이 바람직하나, 모든 의무기록을 이용할 수 없어서, 이에 대한 대리 변수(proxy variable)로 퇴원 후 1년째 '집에서 보낸 기간' (home-time) 등을 측정하였다.

시술 결과 항목에 대한 중증도 보정 모델은, 다변량 회귀분석 모형을 이용하여 개인 수준의 보정 결과변수를 계산한 뒤, 이를 근거로 각각의 병원별 보정된 결과 값을 구했다. 이 병원별 보정 결과 값과 각 병원의 시술량에 대한 산포도를 분석해서 시술량-시술결과 연관성 분석을 시행했다.

중증도 보정 항목은 나이, 성별 등의 인구학적 정보, 허혈성 뇌졸중의 위험인자들 (당뇨병, 고혈압, 심장질환 등)을 포함했다. 그밖에 타 연구에서 강조했던, 허혈성 뇌졸중의 중증도를 반영하는 지수인 미국 국

립보건원 뇌졸중 척도 NIHSS (NIH Stroke Scale)는 임상자료가 아니면 구하기 힘들지만, 이에 대한 대리변수로 청구자료에서 계산할 수 있는 SSI (stroke severity index)도 계산하여 보정에 이용했다. SSI와 실제 NIHSS 간의 회귀식 계산을 위하여, 모델 유도 및 검증을 위한 자료로 양산부산대병원 및 동아대병원의 청구 자료와 임상 자료를 이용했다.

연구 결과

행정 의무기록 데이터베이스 (administrative database)와 병원 임상 데이터베이스 (clinical database) 비교 분석에서, 전체적으로 민감도 79%, 특이도 98.7%, 양성 예측률 80%로 확인되었다. 총 12,013 명이 연구 모델에 선정되었고, 특징적으로 심방세동과 당뇨병이 많았다. 연간 시술 양은 뚜렷하게 증가 추세를 보였으며, 전체 병원 혈관재개통 시술량 평균은 연간 14.8 례임을 확인하였다. ‘집에서 보낸 기간(home-time)’은 비대칭적인 분포를 보여 분석에서 제외했으며, 다른 결과값들 중 모든 원인에 따른 30 일째 조사망률 11.6%, 모든 원인에 따른 재입원비율은 4.6%, 증상이 있는 뇌내출혈의 빈도는 8.6% 였다. 시술량이 극도로 적었던 병원들을 제외한 뒤, 총 111개 병원을 대상으로 SSI 등을 이용한 다중회귀분석을 이용한 시술량-시술결과 연관성 분석을 시행했고, 시술량에 따라 4개 그룹(quartile)을 비교하는 형태로 분석한 결과, 사망률과 뇌출혈 발생률에서, 의미 있는 그룹간의 차이가 확인되었다. 시술량-시술결과 관련성이 있는 것으로 판단해서, 최소 시술량을 계산한 결과, 중등도 보정 사망률 기준으로 연간 24 례가 최소시술량으로 계산되었다.

시술량-시술결과 관련성이 있을때, 이를 설명할 수 있는 '수정가능한 구조와 과정(modifiable structures and processes)'을 확인하기 위해 추가 분석을 실시하였으며, 최소 시술량 기준으로 나눈 2분법 비교에서, 두 집단간에 뇌졸중집중치료실 운영여부(74%:34%)와 수련병원여부(100%:71%)에서 통계적으로 유의한 차이(P value <0.005)를 보였다.

고찰 및 결론

본 연구는 심평원 데이터를 이용하여 국내에서 혈관내재개통 치료를 받은 환자들의 시술량과 그 결과에 대해 추정할 수 있었고, 혈관내재개통 치료를 받았던 환자군에서의 위험인자 (risk factor) 등의 현황을 알 수 있었다. 고지혈증 같은 보험 청구와 관련된 이슈도 알게 되었다. 청구목적의 데이터와 임상 데이터를 비교해서 민감도, 특이도, 양성 예측률을 계산하는 방법을 적용해봤으며, 비교대상이 현재 국내 연구에 없는 상태이다. 또한, SSI 모델 개발과 검증 등이 비교적 만족할만하게 되었다고 판단했으며, 이를 이용한 청구자료 이용연구에, 향후 도움이 될 것으로 판단된다. 위험도 보정 모델의 경우, 사망률은 비교적 모델을 잘 만들었으나 다른 모델은 잘 안된 편이지만, 향후 보완할 수 있을 것으로 판단된다. 시술량-시술결과 관련성이 있다고 판단하여, 4분위 그룹을 나누어 최소 시술량을 계산할 수 있었다. 최소 시술량를 참고치로 잡아서 혈관내 재개통치료술 시행 병원의 관리에 이용할 수 있겠지만, 시술 관련 기술이 계속 발전하고 있고, 시술 결과에 결정적인 다른 임상적 요소들이 중증도 보정 항목에 빠졌으므로, 위 결과는 신중하게 이용하는 것이 바람직하겠다.

주요어: 허혈성 뇌졸중, 혈관내 재개통치료, 시술량, 시술량-시술결과 연관성, 혈전제거술, 혈전용해술

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