Journal Pre-proof

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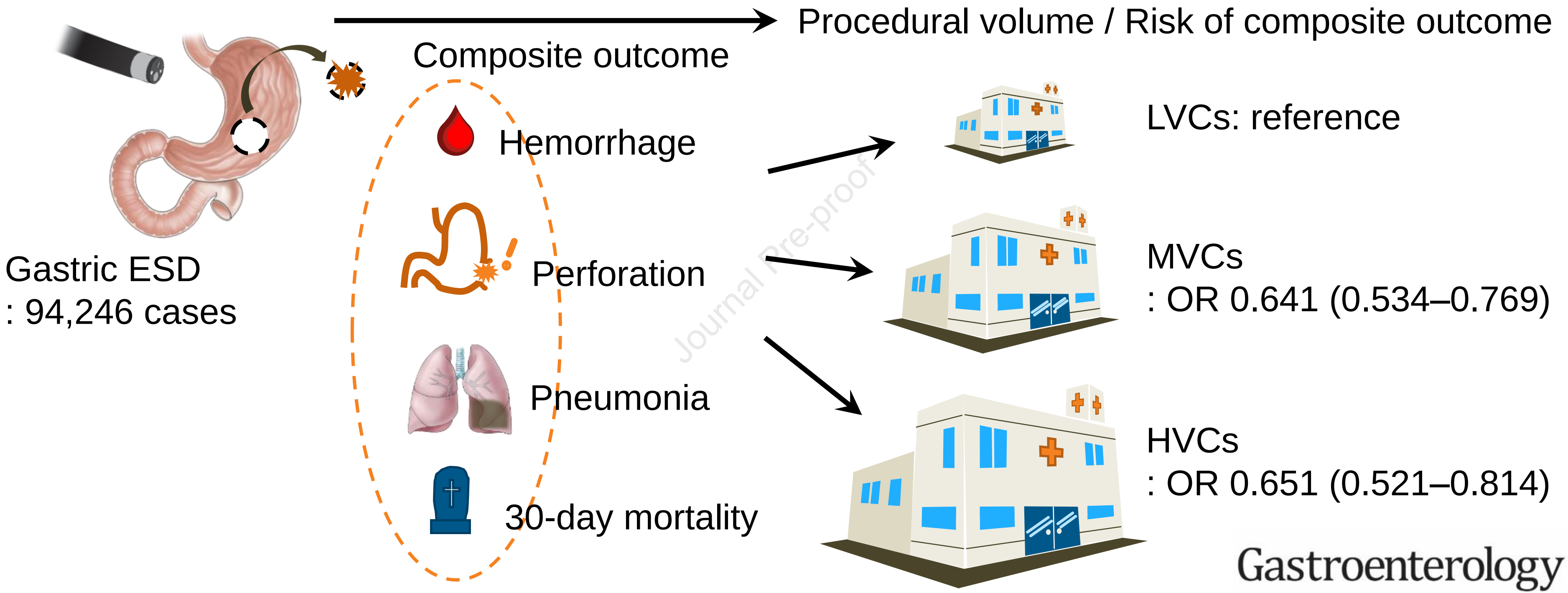
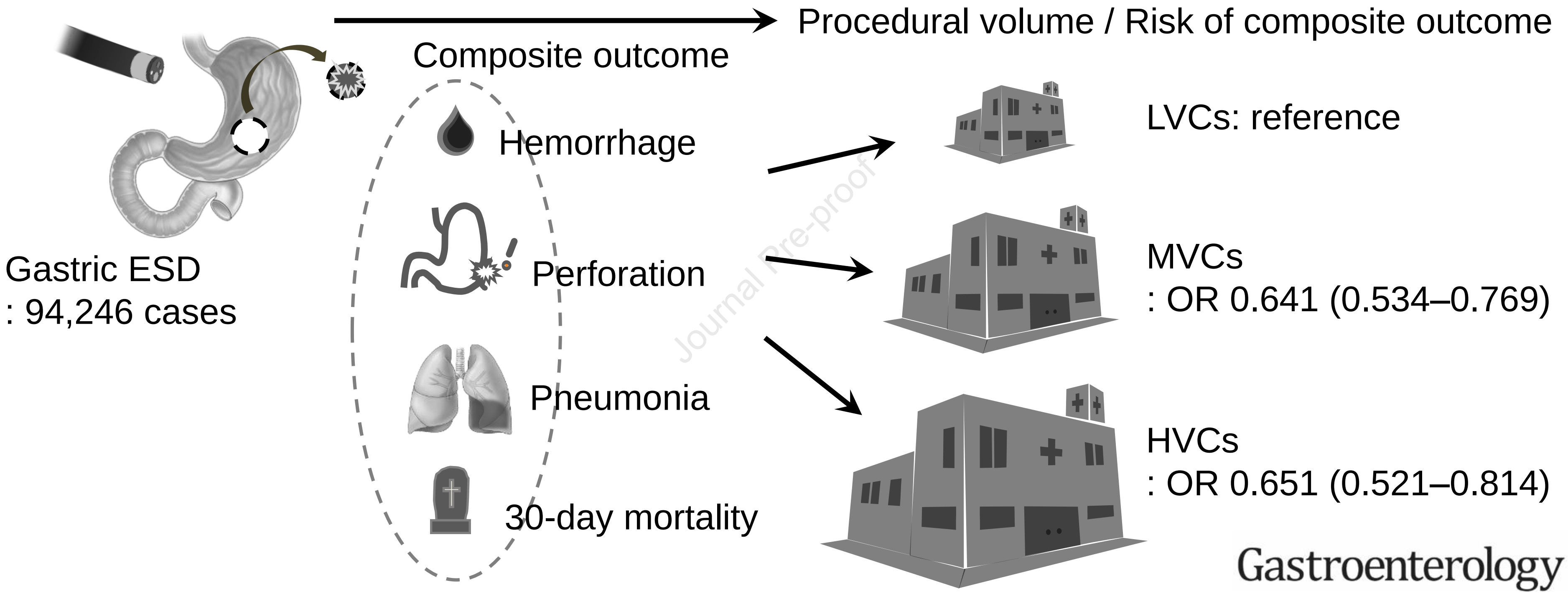
PII: S0016-5085(23)05606-8
DOI: https://doi.org/10.1053/j.gastro.2023.12.010
Reference: YGAST 66053

To appear in: *Gastroenterology*
Accepted Date: 4 December 2023

Please cite this article as: Park JY, Kim M-S, Kim BJ, Kim JG, Influence of procedural volume on the outcome of gastric endoscopic submucosal dissection: A nationwide population-based study using administrative data, *Gastroenterology* (2024), doi: https://doi.org/10.1053/j.gastro.2023.12.010.


Procedural volume / Risk of composite outcome
Composite outcome
Hemorrhage
Perforation
Pneumonia
30-day mortality
Gastric ESD
: 94,246 cases
LVCs: reference
MVCs
: OR 0.641 (0.534–0.769)
HVCs
: OR 0.651 (0.521–0.814)



Gastroenterology

Influence of procedural volume on the outcome of gastric endoscopic submucosal dissection: A nationwide population-based study using administrative data

Running title: Volume–outcome association in gastric ESD

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Grant support

This work was supported by the Korean College of Helicobacter and Upper Gastrointestinal Research Foundation Grant (Grant Number: KCHUGR-201902502).

Abbreviations

CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Cox-2, cyclooxygenase-2; DOAC, direct oral anticoagulant; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; HVCs, high-volume centers; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LVCs, low-volume centers; MVCs, medium-volume centers; NHIS, National Health Insurance Service; OR, odds ratio; SD, standard deviation; SES, socioeconomic status; SMD, standardized mean difference; SSLR, stratum-specific likelihood ratio.

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Disclosures

The authors declare that they have no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Author contributions

Jae Yong Park (Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review

& editing)

Mi-Sook Kim (Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing)

Beom Jin Kim (Conceptualization, Writing – review & editing)

Jae Gyu Kim (Methodology, Project administration, Supervision, Writing – review & editing)

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files or are available from the corresponding author on reasonable request.

Abstract

Background & Aims: Endoscopic submucosal dissection (ESD) is a well-established treatment modality for gastric neoplasms. We aimed to investigate the effect of procedural volume on the outcome of ESD for gastric cancer or adenoma.

Methods: In this population-based cohort study, patients who underwent ESD for gastric cancer or adenoma from November 2011 to December 2017 were identified using the Korean National Health Insurance Service database. Operational definitions to identify the target population and post-procedural complications were created using diagnosis and procedure codes and were validated using hospital medical record data. Outcomes included hemorrhage, perforation, pneumonia, 30-day mortality, a composite outcome comprising all these adverse outcomes, and additional resection. Hospital volume was categorized into three groups based on the results of the threshold analysis: high-, medium-, low-volume centers (HVCs, MVCs, and LVCs, respectively). Inverse probability of treatment (IPT) weighting analysis was applied to enhance comparability across the volume groups.

Results: There were 94,246 procedures performed in 88,687 patients during the study period. There were 5,886 composite events including 4,925 hemorrhage, 447 perforation, and 703 pneumonia cases. There were significant differences in ESD-related adverse outcomes among the three hospital volume categories, showing that HVCs and MVCs were associated with a lower risk of a composite outcome than LVCs (IPT-weighted odds ratio (OR), 0.651, 95% confidence interval (CI), 0.521–0.814; IPT-weighted OR, 0.641, 95% CI, 0.534–0.769). Similar tendencies were also shown for hemorrhage, perforation, and pneumonia; however, these were not evident for additional resection.

Conclusion: Procedural volume was closely associated with clinical outcome in patients undergoing ESD for gastric cancer or adenoma.

Keywords: Gastric cancer, Endoscopic submucosal dissection, Procedural volume, Outcome, Big data

Introduction

Thanks to the National Cancer Screening Program introduced in Korea since 1999, which provides biennial gastric cancer screening for adults aged 40 years or more, new gastric cancer cases are increasingly detected in the early stages.[1] The prognosis of early gastric cancer (EGC) is excellent, with a 5-year survival rate of over 90%.[2]

For EGC with a negligible risk of lymph node involvement, endoscopic submucosal dissection (ESD) is recommended as the first-line treatment modality in recent guidelines.[2, 3] Likewise, endoscopic resection is also actively recommended for visible gastric dysplasia, which is a well-known precursor of gastric cancer.[4, 5] ESD is a minimally invasive procedure, demonstrating a comparable long term outcome to surgery.[6] Since it does not require an abdominal incision, ESD has the advantage of a shorter hospital stay and faster recovery time than surgery.[7] Patients can also maintain a good quality of life after the procedure since the stomach is preserved.[8] Recently, ESD is actively and widely performed in Korea for the treatment of EGC and gastric dysplasia.

Although ESD is a very efficient and effective treatment modality, it inevitably harbors some risk of complications such as hemorrhage, perforation, and other procedure-related adverse events.[9] It is a procedure that requires a learning curve, demanding quite a high level of technique and experience.[10] Although ESD is widely performed in many institutions in Korea, the current nationwide status of ESD and the differences in procedural results in various institutions are not well investigated.

In general, there is a well-known clear association between the treatment volume and outcome if the surgery or procedure is more complex and difficult.[11, 12] The results from one study on the volume-outcome relationship are used as recommendations within the expert group. Indeed, these findings could be used as a reference data for the recommendation criteria for the number of procedures performed by practitioners or institutions to maintain a quality level of medical services.[13] Therefore, investigating whether gastric ESD differs in outcome depending on the procedural volume of individual institutions might be helpful to manage and improve the quality of the procedure, which is related to patient safety.

Studies on the clinical outcomes of gastric ESD have often been limited by low generalizability due to their retrospective nature or single-center study design. Although gastric ESD is performed in many institutions of various types and sizes nationwide, big data research using national data is essential to comprehensively elucidate the current status and clinical outcomes. Furthermore, this could be an important systematic dataset that could be used to improve the quality of gastric ESD. The aim of this study was to investigate the relationship between the hospital procedural volume and clinical outcomes after ESD for gastric cancer or dysplasia using the Korean National Health Insurance Service (NHIS) database.

Materials & Methods

1) Data sources

We conducted a population-based retrospective cohort study using NHIS data from January 2002 to December 2018. Korea has a mandatory universal health insurance system that has aimed to provide comprehensive medical care since 1999. The NHIS is responsible for operating a health insurance program and manages the eligibility of the insured and all inpatient and outpatient medical claims for providing insurance benefits and reimbursement. Some of these data including information on patient demographics, diagnoses, prescribed drugs, non-surgical and surgical treatments, diagnostic tests, and medical institutions for claims made are extracted and de-identified for research purposes. The research protocol of this study was approved by the Institutional Review Board of Chung-Ang University Hospital (IRB No. 1772-001-290), and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived as the NHIS database is a publicly available anonymized dataset.

2) Study population

This study included patients who underwent ESD for gastric cancer (ICD-10, C16.x) or adenoma (ICD-10, D00.2, D13.1, D37.1), between November 1, 2011 and December 31, 2017. We exclusively enrolled gastric ESD cases performed from November 2011 onward, since the insurance coverage of gastric ESD by the NHI was implemented in November 2011 in South Korea. Consequently, accurate analysis using NHIS data became feasible from this point onward. Information preceding this date was utilized only for the purpose of confirming eligibility criteria, medical history, and medication usage. The classification of ESD was based on specific procedural codes: QZ933, QX704, or QX701. In addition, cases coded for EMR

(Q7652), along with the concurrent use of material codes for ESD knives, were also categorized as ESD.[14, 15] This was based on the notice that ESD conducted in a piecemeal resection manner should be billed as EMR, in accordance with the reimbursement guidelines outlined in the Regulation for Criteria for Providing Reimbursed Services in the NHI. Patients who underwent index ESD more than one year after their diagnosis of gastric cancer or gastric adenoma, patients missing eligibility information, and patients who were under 19 years of age at the time of ESD were excluded. Furthermore, to classify patients according to the procedure volume of the medical institution where they were treated, patients who underwent procedure at two or more institutions on the same day were excluded.

3) Study outcomes

The primary outcome was the occurrence of post-procedural complications (hemorrhage, perforation, pneumonia, and 30-day mortality) as a composite event. The secondary outcomes included the individual components of post-procedural complications and additional endoscopic resection or gastric surgery within 180 days after the initial ESD procedure. If any of the following conditions within 30 days after the procedure were met, we considered a hemorrhage event to have occurred: transfusion, endoscopic bleeding control, high-dose intravenous proton pump inhibitor therapy, or emergency endoscopy conducted during off-hours (Supplementary Table 1). A perforation event was defined as a perforation- or peritonitis-related diagnosis code during admission or perforation-related procedure codes within 30 days after the procedure. Pneumonia was defined as having diagnosis codes for pneumonia within the hospital stay following the procedure. Due to the small number of events, 30-day mortality was not analyzed separately and was instead grouped with other complications as a composite outcome for the analysis. The ICD-10 codes and detailed operational definitions for defining primary and secondary outcomes are listed in Supplementary Table 1. To ensure the accuracy of operational definitions in identifying target subjects and outcome events, the validity of these operational definitions was confirmed through a retrospective analysis of medical records from a specific medical institution. A thorough retrospective review of medical records was conducted for patients who underwent gastric endoscopic resections at Chung-Ang University Hospital over a span of 6 years. We compared the case identification results obtained using the algorithm from electronic medical record data with a reference standard (chart-based diagnosis). The validation results for the operational definition of composite events showed a sensitivity of 71.4%, a specificity of 97.1%, a positive predictive value of 68.2%, and a negative predictive value of 97.5%.

4) Threshold analysis and categorization of procedure volume

The annual average procedure volumes were calculated by dividing the total number of ESD procedures performed at each medical institution by the number of months in which the medical institution had been operated and multiplying by 12. Threshold analyses were performed to identify procedure volume thresholds at which differences in complication rates become evident. Medical institutions were categorized into different volume groups based on the results from these threshold analyses. The stratum-specific likelihood ratio (SSLR) analysis was applied to determine meaningful volume thresholds at which statistically significant changes in the risk of post-procedural complications (composite events) occur. Initial volume strata were defined using 10-unit intervals based on the annual procedure volume. We subsequently calculated the likelihood ratio for post-procedural complications within each stratum. These strata were merged into larger ones until a significant difference in the likelihood ratio between adjacent groups was observed. As a result, the SSLR analysis yielded three volume categories based on the likelihood of complication. The detailed description of the analysis method can be found in the Supplementary Methods.

5) Covariates

Baseline demographics such as age, sex, and socioeconomic status (SES) at the date of procedure were captured. Comorbidities including hypertension, diabetes mellitus, other cancer, angina, chronic obstructive pulmonary disease (COPD), liver cirrhosis, renal failure, heart failure, and stroke were evaluated using the admission and outpatient diagnosis for one year prior to the procedure. The ICD-10 codes for defining the comorbidities are listed in Supplementary Table 1. The Charlson Comorbidity Index (CCI) was calculated by summing up the weights assigned to 17 comorbidities based on Quan's algorithm. The use of aspirin, P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor), other antiplatelet agents (ticlopidine, cilostazol, beraprost, sarpogrelate, triflusal), warfarin, direct oral anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (Cox-2) inhibitors, or steroids for 90 days prior to the procedure was evaluated, and medication use was defined only if treatment lasted for at least 30 days. The number of lesions treated and the total number of procedures during the observation period were assessed.

6) Statistical analysis

Inverse probability of treatment weighting (IPTW) method was employed to enhance comparability across the volume categories of the medical institutions where each patient underwent the ESD procedure. The propensity scores, which represent the probability of belonging to each group under given an individual's characteristics, were calculated using a multinomial logistic regression model that includes all measured demographics. We used stabilized IPTW weights, which were calculated as the reciprocal of each individual's probability of their actual group assignment multiplied by the marginal probability of their group membership. Using the standardized mean difference (SMD), we assessed the balance in each covariate before and after applying IPTW. An SMD of less than 0.1 was deemed indicative of a well-balanced distribution.

To examine the association between hospital volume categories and study outcomes, mixed-effects logistic regression models with a 2-level (patient and hospital) hierarchical structure were developed. In the models, the unique identifiers of each patient and hospital were considered random effect variables to account for clustering of outcomes within each patient and hospital. Analyses were repeated after both adjustments for all measured covariates and IPTW weighting. The associations between hospital volume and study outcomes are expressed as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). A p-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC).

Results

1) Study population

From November 2011 to December 2017, 108,302 ESD cases performed for gastric cancer or dysplasia were initially identified in the NHIS dataset. After applying the exclusion criteria, a total of 94,246 ESD cases were finally included for analysis (Figure 1). The mean age of enrolled subjects was 64.8 years, with males accounting for 70.4% of the total population.

2) Clinical outcomes of ESD procedures

Composite events (hemorrhage, perforation, pneumonia, or 30-day all-cause mortality) were identified in 5,886 cases (6.25%). When analyzed for each complication, post-procedural hemorrhage was identified in 4,925 cases (5.23%), perforation in 447 cases (0.47%), and pneumonia in 703 cases (0.75%). The 30-day all-cause mortality was very low (52 cases, 0.06%). For the analysis of additional resection within 180 days after the initial ESD procedure, only index ESD cases (88,687) were included. Among them, additional resection was performed in 6,615 cases (7.46%); surgery in 4,000 cases (4.51%); and endoscopic resection in 2,686 cases (3.02%).

3) Threshold analysis and procedure volume categorization of medical institutions

Threshold analyses identified procedure volume levels at which differences in composite event rates became apparent, leading to the categorization of medical institutions into volume-based groups: 1- 169 (low-volume centers, LVCs), 178-319 (medium-volume centers, MVCs), and 334-1175 (high-volume centers, HVCs) for ESD procedures performed per year. Medical institutions were subsequently classified into these three volume categories.

Among the total ESD cases, 30,479, 27,949, and 35,818 procedures (32.3%, 29.7%, and 38.0%, respectively) were performed at LVCs, MVCs, and HVCs, respectively. Of the total 280 institutions, there were 242 LVCs (86.4%), 24 MVCs (8.6%), and 14 HVCs (5.0%). The mean annual number of procedures was 26.9, 235.7, and 509.6 cases at LVCs, MVCs, and HVCs, respectively (Table 1). Patients who underwent ESD at institutions with a larger procedural volume had a clear tendency of a higher SES quartile. There was a significant difference in the various comorbidities among the groups, and the CCI score increased significantly as the procedure volume increased. After applying IPTW, the variables were generally well-balanced among the three volume groups (Table 2).

4) Volume–outcome relationship of post-procedural complications: composite events

The incidence of a composite event was 7.9%, 5.4%, and 5.6% in LVCs, MVCs, and HVCs respectively. The crude ORs for a composite event were significantly lower in MVCs (0.636, 95% CI 0.530–0.763) and HVCs (0.649, 95% CI 0.520–0.810) compared to LVCs (Table 3). These clinical significances were also maintained in the multivariable analysis and the IPT-weighted analysis. On the other hand, there was no significant difference in the risk of a composite event between MVCs and HVCs (Supplementary Table 2).

To consider the differences according to gastric lesions, subgroup analyses were further performed by separately analyzing gastric cancer and adenoma. The risk of composite events was significantly higher in the cancer group than in the adenoma group, with a crude OR of 1.528 (95% CI 1.444-1.616), an adjusted OR of 1.380 (95% CI 1.299-1.465), and an IPT-weighted OR of 1.517 (1.436-1.604). The overall tendency of a volume–outcome association was similar in both groups, showing the highest risk of composite events in LVCs (Table 4).

5) Volume–outcome relationship of post-procedural complications: hemorrhage

The incidence of hemorrhage was 6.2%, 4.5%, and 5.0% in LVCs, MVCs, and HVCs, respectively. The crude ORs for hemorrhage were significantly lower in MVCs (0.725, 95% CI 0.596–0.882) and HVCs (0.788, 95% CI 0.622–1.000) compared to LVCs (Table 3). These clinical significances were also maintained in the multivariable analysis and the IPT-weighted analysis. On the other hand, there was no significant difference in the risk of hemorrhage between MVCs and HVCs (Supplementary Table 2).

6) Volume–outcome relationship of post-procedural complications: perforation

The incidence of perforation was 0.8%, 0.4%, and 0.3% in LVCs, MVCs, and HVCs, respectively. The crude ORs for perforation were significantly lower in MVCs (0.364, 95% CI 0.222–0.597) and HVCs (0.319, 95% CI 0.177–0.575) compared to LVCs (Table 3). These clinical significances were also maintained in the multivariable analysis and the IPT-weighted analysis. On the other hand, there was no significant difference in the risk of perforation between MVCs and HVCs (Supplementary Table 2).

7) Volume–outcome relationship of post-procedural complications: pneumonia

The incidence of pneumonia was 1.3%, 0.7%, and 0.4% in LVCs, MVCs, and HVCs, respectively. The crude ORs for pneumonia were significantly lower in MVCs (0.382, 95% CI, 0.265–0.552) and HVCs (0.247, 95% CI 0.158–0.387) compared to LVCs (Table 3). These clinical significances were also maintained in the multivariable analysis and the IPT-weighted analysis. On the other hand, there was no significant difference in the risk of pneumonia between MVCs and HVCs (Supplementary Table 2).

8) Volume–outcome relationship of additional treatment

Additional treatment occurred within 180 days in 7.1%, 7.0%, and 8.1% of cases in LVCs, MVCs, and HVCs, respectively. The ORs of additional treatment were not significantly different among the groups on all occasions in the univariable and multivariable analyses, as well as in the IPT-weighted analysis (Table 5, Supplementary Table 3).

Discussion

In this study, we investigated the relationship between the procedural volume and clinical outcomes in patients who underwent ESD for gastric cancer or adenoma using the NHIS database. The results showed that the procedural volume was associated with the short-term clinical outcomes after ESD. To our knowledge, this is the first study to investigate the volume–outcome relationship of gastric ESD at a nationwide level using the Korean NHIS database. Korea has the highest incidence of gastric cancer in the world and is one of the countries where gastric ESD is performed most frequently.[14] The national health insurance system is also very well established and covers approximately 97% of the whole population. Considering these factors, the research on this topic using the NHIS database has great strengths in Korea. To date, nationwide population-based studies regarding the clinical outcomes of ESD for gastric neoplasms have rarely been conducted. Although there have been many reports on the outcome after gastric ESD, most of them were multicenter retrospective studies or short-term follow-up studies involving a small number of large institutions.[6, 14, 16] In particular, studies on the clinical outcomes of gastric ESD targeting almost the entire population, including all grades of medical institutions from clinics to tertiary hospitals, and analyzing the volume–outcome relationship are very rare.

Our study demonstrated that the procedural volume was closely associated with adverse clinical outcomes such as hemorrhage, perforation, pneumonia, and 30-day mortality after ESD for gastric cancer or adenoma. There was a tendency of negative association between the procedural volume and the risk of these adverse outcomes. In particular, the risk of adverse clinical outcomes was significantly higher in LVCs than in other centers. One nationwide

Japanese study evaluated complications after gastric ESD and reported a significant association between high hospital volume and a lower post-ESD complication rate for upper gastric cancers.[17] In another previous study conducted in the UK using an administrative database, Markar et al. showed that endoscopic mucosal resection performed by high-volume endoscopists was associated with lower adverse outcomes, such as requirement of emergent intervention or death.[18] In line with these studies, the findings from the present study also showed that there is a close association between the procedural volume and adverse outcomes after ESD for gastric neoplasms. In particular, our study has advantages over previous research in that it covered both gastric cancer and adenoma, included an analysis by individual complications, and tried to improve the accuracy of the analyses through the validation of outcome measures. Categorizing volume groups based on threshold analysis results and applying IPTW to enhance comparability between groups further contributed to the overall reliability of the analyses.

According to studies on the volume–outcome relationship, hospitals that treat patients with a specific disease or perform certain surgery/procedure in large numbers have lower mortality rates.[19] In particular, there is a volume–outcome relationship in surgical procedures with higher procedural risk and complexity.[20] This tendency is even more evident for procedures that are infrequently performed and have high procedure-related risks.[21] Gastric ESD is a technically demanding procedure that requires a high degree of training.[10] Hemorrhage and perforation are representative complications after ESD that sometimes require intensive care and surgical intervention. Sedation-related adverse events should also be considered during the procedure, especially when the procedure time is prolonged. To prevent and properly cope with these clinical situations, the proficiency of the operating team as well as the medical resources of the institution are important. The hospital volume or procedural volume is a meaningful indicator since it comprehensively reflects the experience of the operators, capacity of the hospital, availability of multidisciplinary approach, response to emergency situation, etc.[22] The reason why the risk of adverse events of gastric ESD was lower in institutions with larger procedural volumes may be due to the abovementioned factors. Additionally, the procedure volume metric is highly advantageous for assessing service quality due to its ease of measurement and clarity compared to other quality indicators. Our study implies that procedure volume could be used as one of the quality indicators in gastric ESD.

In the subgroup analyses, the volume-outcome association for the composite outcome showed similar patterns in both the cancer and adenoma groups, with LVCs having the highest risk. Interestingly, there was a significantly higher risk of composite events in the cancer group compared to the adenoma group. The characteristics of gastric lesions are major risk factors associated with post-procedural complications. It is well-known that the risk of post-procedural hemorrhage is higher in gastric cancer than in adenoma.[23] Angiogenesis and neovascularization are necessary for tumor growth, which are key findings of cancer. Gastric cancer tends to form a hypervascular environment even in its early stages,[24] and increased vascularity in EGC might partially explain the higher bleeding risk after ESD in cancer than in adenoma. Along with obscured visual field due to bleeding, deep invasion of the tumor or submucosal fibrosis could also make the procedure difficult and occasionally lead to perforation. These factors might have increased the technical difficulty of ESD and widened the variance in complication risk by procedural volume.

This volume–outcome association was not evident in additional treatment after initial ESD. Since the purpose of additional treatment was not included in the dataset, a related analysis was not possible. The need for additional surgeries or endoscopic resections can be attributed to various factors, such as non-curative resection, local recurrence, metachronous lesions, and complications. Therefore, it is important not to exclusively attribute the need for additional treatment to technical limitations. Factors such as proper pathologic evaluation and subsequent decision making for additional treatment are important issues for further analysis. Additional research using medical data from individual institutions is required for this subject.

The volume–outcome relationship can be explained through the practice-makes-perfect hypothesis and the selective-referral theory.[25] According to the practice-makes-perfect hypothesis, adverse events are theoretically reduced by accumulated case volume of a hospital through technical improvement, better standardization, and more efficient organization.[26] Then, once the learning process is established, large volume hospitals can maintain their quality of process by performing procedures more regularly. This concept includes the course of maintaining practice and routines as well as the process of obtaining practice itself. The selective-referral theory, on the other hand, suggests that the reason there is a volume–outcome relationship is that more patients are attracted to high-quality providers. Initially, primary physicians or patients may randomly choose hospitals. However, they change their referral strategies and choose hospitals with better outcomes as they gain access to information about the clinical outcomes of individual hospitals. In short, outcome is the driving factor for higher volumes in this theory.[19] In fact, the evidence is mixed for the direction of the volume–outcome relationship and could also be different depending on the conditions. Both explanations might be plausible, and considering the complex aspects of various clinical settings and patient categories, the relative importance of each explanation varies by diagnosis or type of procedure.[19] However, considering the very low mortality rate, indifference in the additional treatment between groups, and omission of long-term outcome analysis, caution is needed before concluding that the outcome of gastric ESD depends only on the treatment volume. It is also clear that the results of this study do not necessarily mean that the results of all gastric ESD procedures performed at lower volume centers are suboptimal. This is because the factors that influence the treatment outcome are very complex and multifactorial, and it is very difficult to include all the related variables in such an analysis. In addition, despite these post-procedural complications, the 30-day all-cause mortality was 0.06%, and in most cases, it was estimated to be an event unrelated to the procedure. Moreover, incidents of hemorrhage or perforation are often managed through conservative or endoscopic treatment. From this, it can be inferred that ESD is a relatively safe procedure with a very low mortality rate. Therefore, a cautious approach seems necessary when considering centralization of ESD for gastric cancer. Since our study did not include cost evaluation, mortality rates, or cancer-associated outcomes, comprehensive consideration is essential when addressing this issue, particularly given the variations in gastric cancer epidemiology, endoscopic procedure volumes, and healthcare capabilities across countries.

There were some limitations in our study. First, there was an inborn limitation of the administrative database. This database does not include either detailed characteristics of gastric lesions, such as size, location, or differentiation, or procedural information, such as procedure time. These factors could affect the occurrence of complications after ESD. Nevertheless, we performed a multilevel analysis to account for the clustering of ESD procedures within patients and within hospitals to reduce the bias and improve the accuracy of estimates. In addition, by including both individual-level and group-level predictors in the model, we minimized the effect of potential confounding factors. Second, there may be an accuracy issue in identifying the outcome events. Since they were extracted through an algorithm using combinations of codes, there should be some discrepancies between the analysis results and real events. However, we tried to improve the accuracy compared with existing studies by using operational definitions after validation with individual hospital data. In addition, our study has the advantage of being able to detect outcome events that include patient transfer to another hospital for treatment of a complication, which could have been missed in chart review-based retrospective studies. Third, we could not verify the purpose of additional treatment due to the limitations of the database. This should be addressed in a future study. Finally, the differences between individual operators or proficiency gain over time were not considered in the analysis. However, we can assume that other complex factors are integrated in the procedural volume of individual institutions, such as experiences, the presence of procedural expertise, medical resources, and multidisciplinary approaches. Therefore, analysis according to individual operators may not always be superior to our approach.

In conclusion, the procedural volume at an institutional level was closely associated with adverse clinical outcomes, such as hemorrhage, perforation, pneumonia, and a composite outcome, in patients treated with ESD for gastric cancer or adenoma. The outcomes of gastric ESD should be closely and systemically monitored at a nationwide level to ensure the quality of procedures and the safety of patients.

Acknowledgements

We are grateful to Professor Bo Ram Yang (College of Pharmacy, Chungnam National University) and Researcher Jinhee Kim for her assistance in the process of applying for data use to the NHIS and for the informative support for data extraction.

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Author names in bold designate shared co-first authorship.

Figure legends

Figure 1. Flowchart of selection of the study population.

Table 1. The average annual number of ESD procedures according to the procedural volume

	Total (n=280)	Procedural volume		
		LVCs (n=242)	MVCs (n=24)	HVCs (n=14)
Mean ± SD	69.0 ± 134.0	26.9 ± 37.2	235.7 ± 47.2	509.6 ± 249.4
Median (IQR)	13 (4, 65.5)	9 (3, 36)	216 (196, 282)	413.5 (337, 600)
Min	1	1	178	334
Max	1175	169	319	1175

LVCs, low-volume centers; MVCs, medium-volume centers; HVCs, high-volume centers; SD, standard deviation; IQR, interquartile range.

Table 2. Baseline characteristics of the enrolled ESD cases before and after matching

Variables	Before IPTW				After IPTW			
	LVCs (n=30,479)	**MVCs (n=27,949)**	**HVCs (n=35,818)**	**SMD**	**LVCs (n=30,449)**	**MVCs (n=27,948)**	**HVCs (n=35,865)**	**SMD**
Total number of procedures	1.06 ± 0.27	1.07 ± 0.28	1.06 ± 0.26	0.0218	1.06 ± 0.27	1.06 ± 0.27	1.07 ± 0.27	0.0034
Age	65.11 ± 10.11	64.92 ± 10.00	64.31 ± 10.02	-0.0794	64.83 ± 10.24	64.75 ± 10.04	64.80 ± 9.88	-0.0075
Male sex	21,339	19,457	25,580	0.0395	21,449	19,662	25,233	-0.0020
Inpatient on index date	30,444	27,863	35,815	0.0754	30,417	27,862	35,861	0.0744
Socioeconomic status								
Top 25%	10,877	10,821	15,451	0.1529	11,991	11,013	14,081	-0.0029
Middle 50%	12,270	10,945	13,373	-0.0600	11,818	10,850	13,926	0.0003
Bottom 25%	5,269 (17.29)	4,495 (16.08)	5,417 (15.12)	-0.0587	4,918 (16.15)	4,504 (16.12)	5,805 (16.19)	0.0019
Medical aid	1,483 (4.87)	1,087 (3.89)	804 (2.24)	-0.1419	1,094 (3.59)	1,002 (3.59)	1,317 (3.67)	0.0045
Missing	580 (1.90)	601 (2.15)	773 (2.16)	0.0181	628 (2.06)	579 (2.07)	737 (2.05)	-0.0012
Multiple site procedure	4,149 (13.61)	3,350 (11.99)	3,319 (9.27)	-0.1369	3,524 (11.57)	3,207 (11.48)	4,119 (11.48)	-0.0031
CCI	3.02 ± 2.49	3.07 ± 2.33	3.34 ± 2.31	0.1326	3.17 ± 2.57	3.16 ± 2.40	3.17 ± 2.27	0.0021
Comorbidities								
Hypertension	15,748	14,018	16,996	-0.0844	15,137	13,876	17,828	0.0012
Diabetes mellitus	9,526 (31.25)	8,247 (29.51)	9,887 (27.60)	-0.0802	8,969 (29.46)	8,201 (29.35)	10,532	-0.0025
Other cancer	2,032 (6.67)	1,994 (7.13)	3,289 (9.18)	0.0932	2,383 (7.83)	2,176 (7.78)	2,812 (7.84)	0.0021
Angina	3,406 (11.17)	2,822 (10.10)	3,539 (9.88)	-0.0422	3,169 (10.41)	2,890 (10.34)	3,730 (10.40)	-0.0022
COPD	3,976 (13.05)	3,597 (12.87)	4,489 (12.53)	-0.0153	3,886 (12.76)	3,574 (12.79)	4,594 (12.81)	0.0014
Liver cirrhosis	2,583 (8.47)	2,431 (8.70)	2,835 (7.92)	-0.0284	2,551 (8.38)	2,324 (8.32)	2,995 (8.35)	-0.0023
Renal failure	818 (2.68)	608 (2.18)	824 (2.30)	-0.0330	734 (2.41)	666 (2.38)	858 (2.39)	-0.0016
Heart failure	1,705 (5.59)	1,343 (4.81)	1,568 (4.38)	-0.0559	1,509 (4.96)	1,370 (4.90)	1,778 (4.96)	0.0026
Stroke	1,766 (5.79)	1,512 (5.41)	1,611 (4.50)	-0.0587	1,593 (5.23)	1,452 (5.20)	1,879 (5.24)	0.0019
Medication								
Aspirin	4,617 (15.15)	3,999 (14.31)	5,005 (13.97)	-0.0333	4,397 (14.44)	4,043 (14.47)	5,165 (14.40)	-0.0018
P2Y12 inhibitor	1,698 (5.57)	1,517 (5.43)	1,706 (4.76)	-0.0365	1,606 (5.27)	1,457 (5.21)	1,892 (5.28)	0.0028
Other antiplatelet agents	1,495 (4.91)	1,333 (4.77)	1,388 (3.88)	-0.0503	1,371 (4.50)	1,250 (4.47)	1,639 (4.57)	0.0047
Warfarin	228 (0.75)	182 (0.65)	266 (0.74)	-0.0116	223 (0.73)	198 (0.71)	262 (0.73)	-0.0027
DOACs	115 (0.38)	94 (0.34)	137 (0.38)	0.0077	111 (0.37)	101 (0.36)	132 (0.37)	0.0010
NSAIDs	2,704 (8.87)	2,295 (8.21)	2,476 (6.91)	-0.0727	2,430 (7.98)	2,225 (7.96)	2,885 (8.04)	0.0030
Cox-2 inhibitors	618 (2.03)	492 (1.76)	586 (1.64)	-0.0292	556 (1.82)	506 (1.81)	652 (1.82)	-0.0011
Steroids	780 (2.56)	631 (2.26)	721 (2.01)	-0.0366	693 (2.27)	632 (2.26)	826 (2.30)	0.0029

Values are shown as the mean ± SD or number (%).
IPTW, Inverse probability of treatment weighting; LVCs, low-volume centers; MVCs, medium-volume centers; HVCs, high-volume centers; SD, standard deviation; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; Cox-2, cyclooxygenase-2.

Table 3. Risk of post-procedural complications according to procedural volume

Complications	LVCs (n=30,479)	MVCs (n=27,949)	HVCs (n=35,818)	Total
Composite event				
Numbers (%)	2,394 (7.85%)	1,500 (5.37%)	1,992 (5.56%)	5,886 (6.25%)
Crude OR (95% CI)	1 (ref)	0.636 (0.530, 0.763)	0.649 (0.520, 0.810)	
Adjusted OR† (95% CI)	1 (ref)	0.609 (0.507, 0.733)	0.622 (0.496, 0.780)	
IPT-weighted OR (95% CI)	1 (ref)	0.641 (0.534, 0.769)	0.651 (0.521, 0.814)	
Hemorrhage				
Numbers (%)	1,873 (6.15%)	1,252 (4.48%)	1,800 (5.03%)	4,925 (5.23%)
Crude OR (95% CI)	1 (ref)	0.725 (0.596, 0.882)	0.788 (0.622, 1.000)	
Adjusted OR† (95% CI)	1 (ref)	0.700 (0.578, 0.847)	0.760 (0.602, 0.959)	
IPT-weighted OR (95% CI)	1 (ref)	0.728 (0.597, 0.888)	0.788 (0.619, 1.003)	
Perforation				
Numbers (%)	248 (0.81%)	99 (0.35%)	100 (0.28%)	447 (0.47%)
Crude OR (95% CI)	1 (ref)	0.364 (0.222, 0.597)	0.319 (0.177, 0.575)	
Adjusted OR† (95% CI)	1 (ref)	0.365 (0.223, 0.598)	0.320 (0.178, 0.575)	
IPT-weighted OR (95% CI)	1 (ref)	0.364 (0.222, 0.597)	0.319 (0.177, 0.575)	
Pneumonia				
Numbers (%)	382 (1.25%)	186 (0.67%)	135 (0.38%)	703 (0.75%)
Crude OR (95% CI)	1 (ref)	0.382 (0.265, 0.552)	0.247 (0.158, 0.387)	
Adjusted OR† (95% CI)	1 (ref)	0.357 (0.242, 0.527)	0.234 (0.145, 0.377)	
IPT-weighted OR (95% CI)	1 (ref)	0.384 (0.266, 0.554)	0.251 (0.161, 0.393)	

† In the multivariable model, adjustments were made for all the variables listed in Table 2.
LVCs, low-volume centers; MVCs, medium-volume centers; HVCs, high-volume centers; OR, odds ratio; CI, confidence interval; IPT, inverse probability treatment.

Table 4. Subgroup analysis for volume–outcome association regarding the occurrence of composite events after ESD

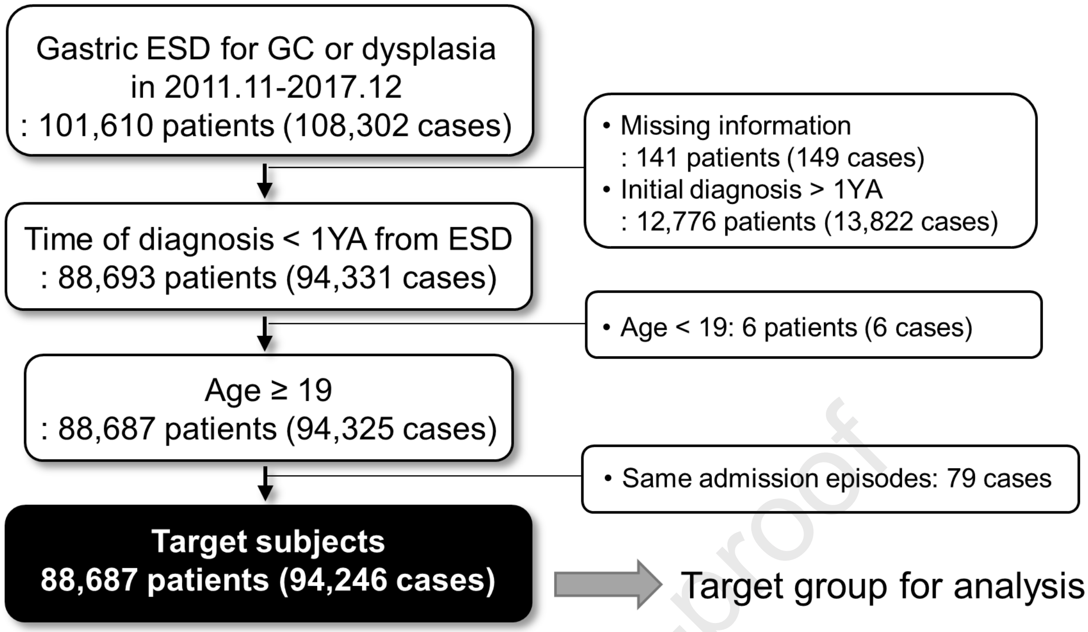
Volume classification criteria	Crude OR (95% CI)	P-value	Adjusted OR† (95% CI)	P-value	IPT-weighted OR (95% CI)	P-value
Gastric cancer						
MVCs vs. LVCs	0.617 (0.507-0.752)	<.0001	0.647 (0.531-0.789)	<.0001	0.649 (0.534, 0.790)	<.0001
HVCs vs. LVCs	0.565 (0.447-0.713)	<.0001	0.608 (0.480-0.769)	<.0001	0.610 (0.483, 0.771)	<.0001
HVCs vs. MVCs	0.915 (0.697-1.201)	0.5208	0.939 (0.714-1.234)	0.6523	0.940 (0.715, 1.236)	0.6579
Gastric adenoma						
MVCs vs. LVCs	0.560 (0.460-0.682)	<.0001	0.566 (0.465-0.690)	<.0001	0.585 (0.479, 0.714)	<.0001
HVCs vs. LVCs	0.618 (0.489-0.782)	0.0001	0.652 (0.515-0.826)	0.0004	0.665 (0.526, 0.841)	0.0007
HVCs vs. MVCs	1.103 (0.834-1.460)	0.4910	1.151 (0.869-1.524)	0.3258	1.137 (0.861, 1.502)	0.3659

† In the multivariable model, adjustments were made for all the variables listed in Table 2.
OR, odds ratio; CI, confidence interval; IPT, inverse probability treatment; LVCs, low-volume centers; MVCs, medium-volume centers; HVCs, high-volume centers.

Table 5. Risk of additional treatment according to procedural volume

Additional treatment	LVCs (n=28,749)	MVCs (n=26,199)	HVCs (n=33,739)	Total
Numbers (%)	2040 (7.10)	1845 (7.04)	2730 (8.09)	6615 (7.46)
Crude OR (95% CI)	1 (ref)	1.121 (0.921, 1.365)	1.230 (0.967, 1.565)	
Adjusted OR[†] (95% CI)	1 (ref)	0.871 (0.738, 1.029)	0.897 (0.734, 1.096)	
IPT-weighted OR (95% CI)	1 (ref)	1.022 (0.844, 1.239)	0.994 (0.785, 1.257)	

[†] Multivariable models were adjusted for volume classification, age, sex, Charlson Comorbidity Index, hospitalization, multiple site procedure, comorbidities, and drugs.
LVCs, low-volume centers; MVCs, medium-volume centers; HVCs, high-volume centers; OR, odds ratio; CI, confidence interval; IPT, inverse probability treatment.


Gastric ESD for GC or dysplasia
in 2011.11-2017.12
: 101,610 patients (108,302 cases)
• Missing information
: 141 patients (149 cases)
• Initial diagnosis > 1YA
: 12,776 patients (13,822 cases)
Time of diagnosis < 1YA from ESD
: 88,693 patients (94,331 cases)
• Age < 19: 6 patients (6 cases)
Age ≥ 19
: 88,687 patients (94,325 cases)
• Same admission episodes: 79 cases
Target subjects
88,687 patients (94,246 cases)
Target group for analysis

What You Need to Know

Background and Context: There is often an association between the treatment volume and outcome for complex procedures, and research on this topic is lacking for gastric endoscopic submucosal dissection.

New Findings: In this nationwide population-based study, there were significant differences in post-procedural adverse events such as hemorrhage, perforation, and pneumonia according to procedural volume.

Limitations: Detailed characteristics of gastric lesions or procedure information were not included due to the inborn limitation of the dataset, which might have affected the study results.

Clinical Research Relevance: The significant association between the procedural volume and clinical outcomes suggests that the outcomes of gastric endoscopic submucosal dissection should be systemically monitored in a nationwide level to ensure the quality and safety of procedures.

Basic Research Relevance: N/A

Lay summary

The risk of adverse outcomes of endoscopic resection of stomach neoplasms varied per hospital depending on the volume of procedures. These data could be important in terms of patient safety.

The influence of procedural volume on the outcome of gastric endoscopic submucosal dissection: a nationwide population-based study using administrative data

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Threshold analysis and categorization of procedure volume

The stratum-specific likelihood ratio (SSLR) analysis was applied to determine meaningful volume thresholds at which statistically significant change in the risk of post-procedural complications (composite events) occur. Initial volume strata were defined using 10-unit intervals based on the annual procedure volume. We subsequently calculated the likelihood ratio for post-procedural complications (composite events) within each stratum. These strata were merged into larger ones until a significant difference in the likelihood ratio between adjacent groups was observed. The data were initially divided into five groups, as shown in the table below. To minimize the impact of a specific institution on the overall volume-outcome association, we conducted additional grouping to ensure that a minimum of a certain number (at least 10) of institutions were assigned within each group. Subsequently, the SSLR analysis yielded three volume categories based on likelihood of complication. We evaluated the discriminatory ability of a 3-group model compared to the 5-group model. The result indicated an AUC of 0.604 in both models, demonstrating no significant difference in outcome discrimination between the 5-group and simplified 3-group models, which also offers advantages in terms of analysis convenience. Accordingly, medical institutions were categorized into three volume categories: 1-169 (low-volume centers, LVCs), 178-319 (medium-volume centers, MVCs), and 334-1175 (high-volume centers, HVCs) ESD procedures performed per year (Figure).

Table. The stratum-specific likelihood ratio analysis to determine meaningful volume thresholds

Volume strata	Normals	Abnormals	SSLR (95% CI)	Category (SSLR)	AUC (SE)	**Category (final)**	AUC (SE)
1-10	1612	145	1.50 (1.21-1.87)	Very low	0.604 (0.004)	**Low**	0.604 (0.004)
11-20	1855	129	1.16 (0.92-1.46)				
21-30	1378	62	0.75 (0.54-1.05)				
31-40	1588	118	1.24 (0.97-1.58)				
41-50	1752	123	1.17 (0.92-1.49)				
51-60	3191	261	1.37 (1.16-1.61)				
62-67	1662	120	1.21 (0.95-1.53)				
72-73	1537	126	1.37 (1.08-1.73)				
85-85	808	46	0.95 (0.65-1.40)				
92-97	2343	213	1.52 (1.27-1.82)				
102-108	1042	71	1.14 (0.83-1.56)				
114-120	2237	167	1.25 (1.02-1.53)				
129-130	1223	93	1.27 (0.97-1.67)				
134-138	2633	179	1.14 (0.93-1.38)				
143-144	2053	117	0.95 (0.75-1.21)				
166-169	1477	118	1.33 (1.05-1.70)				
178-180	1701	93	0.91 (0.70-1.20)	Low		**Medium**	
186-188	1328	65	0.82 (0.59-1.13)				
193-199	4864	271	0.93 (0.80-1.09)				
212-219	4150	183	0.74 (0.61-0.89)				
221-221	1123	52	0.77 (0.54-1.11)				
255-255	2415	162	1.12 (0.91-1.38)				
274-280	2390	156	1.09 (0.88-1.34)				
284-284	1351	85	1.05 (0.79-1.40)				
293-299	4222	180	0.71 (0.59-0.86)	Medium			
314-319	3054	104	0.57 (0.44-0.73)				
334-337	6364	354	0.93 (0.81-1.06)	High		**High**	
341-341	1639	82	0.84 (0.63-1.12)				
379-379	1825	87	0.80 (0.60-1.05)				
412-415	4100	198	0.81 (0.67-0.97)				
426-426	1964	92	0.78 (0.60-1.03)				
470-470	2071	95	0.77 (0.59-1.00)				
600-600	2899	164	0.94 (0.77-1.16)	Very high			
728-728	3572	197	0.92 (0.77-1.11)				
849-849	3983	278	1.17 (1.00-1.36)				
1175-1175	5516	338	1.02 (0.89-1.18)				

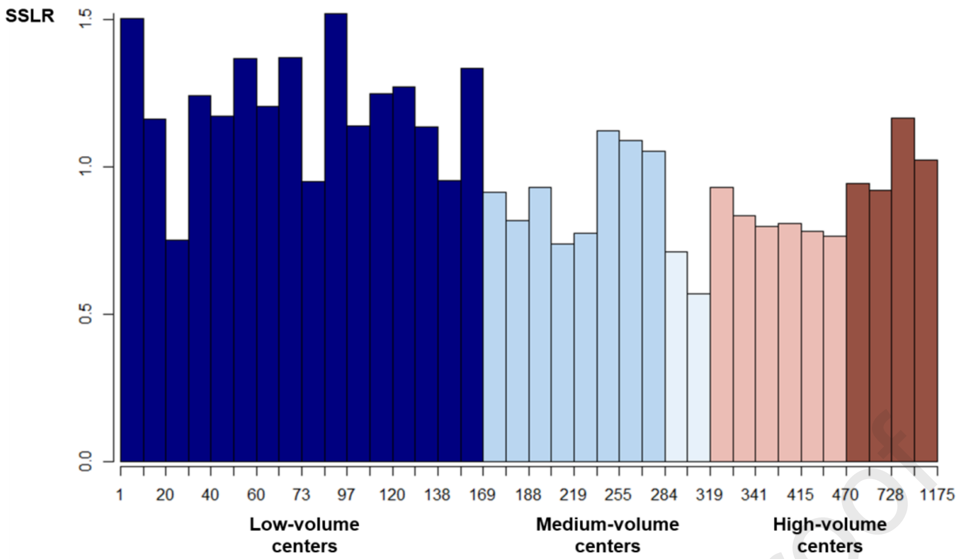

Figure. Categorization of medical institutions according to the threshold analysis result

The influence of procedural volume on the outcome of gastric endoscopic submucosal dissection: a nationwide population-based study using administrative data

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Supplementary Table 1. The ICD-10 codes and detailed operational definitions for defining primary and secondary outcomes

Outcome	Operational definitions
Hemorrhage	- If any of 1)-5) was satisfied within 30 days from the date of ESD: 1) Red blood cell transfusion 2) Endoscopic hemostasis (Q7620) performed 3) Total dose of intravenous proton pump inhibitor (PPI) ≥ 10 vial and PPI use density ≥ 2 vial/day 4) Visit to emergency room and administration of intravenous PPI 5) Emergency (off-hours) endoscopy performed
Perforation	- If any of 1) or 2) was satisfied: 1) Primary or secondary diagnosis codes related to perforation at the time of admission (regardless of rank of the diagnosis) ① Perforated peptic ulcer: K251, K252, K255, K256, K271, K272, K275, K276 ② Peritonitis: K650 ③ Iatrogenic perforation during endoscopic procedures: T812 2) Procedure codes related to perforation within 30 days from the date of ESD ① Endoscopic treatment of upper GI perforation: Q7660 ② Simple closure of perforated stomach and duodenum: Q2540
Pneumonia	- If there was primary or secondary diagnosis codes related to pneumonia at the time of admission (regardless of rank of the diagnosis): ① Pneumonia: J12, J13, J14, J15, J16, J17, J18, J67, J69 ② Postprocedural respiratory disorders, not elsewhere classified: J95
Composite outcome	- If any of hemorrhage, perforation, pneumonia, or 30-day mortality occurs, it was regarded as composite outcome.
Additional treatment	- If any of 1) or 2) was satisfied within 180 days from the date of ESD: 1) Endoscopic resection: QZ933, Q7652, QX704, QX701, Q7653 2) Surgery: Q2533, Q2534, Q2536, Q2537, QA536, Q0259, Q2594, Q0251, Q0252, Q0253, Q0254, Q0255, Q0256, Q0257, Q0258, Q2598

Supplementary Table 2. Association between procedural volume and occurrence of composite events after ESD in HVCs vs. MVCs

Complications (HVCs vs. MVCs)	**Crude OR (95% CI)**	**P-value**	**Adjusted OR† (95% CI)**	**P-value**	**IPT-weighted OR (95% CI)**	**P-value**
Composite event	1.020 (0.784, 1.327)	0.8812	1.021 (0.782, 1.333)	0.8802	1.016 (0.781, 1.323)	0.9032
Hemorrhage	1.087 (0.821, 1.439)	0.5593	1.086 (0.826, 1.427)	0.5538	1.082 (0.814, 1.439)	0.5855
Perforation	0.878 (0.435, 1.772)	0.7155	0.876 (0.435, 1.765)	0.7105	0.878 (0.435, 1.772)	0.7155
Pneumonia	0.647 (0.380, 1.100)	0.1076	0.655 (0.373, 1.153)	0.1424	0.65 (0.386, 1.112)	0.1170

† In the multivariable model, adjustments were made for all the variables listed in Table 2.

HVCs, high-volume centers; MVCs, medium-volume centers; OR, odds ratio; CI, confidence interval; IPT, inverse probability treatment.

Supplementary Table 3. Association between procedural volume and additional treatment after ESD in HVCs vs. MVCs

Additional treatment	**Crude OR (95% CI)**	**P-value**	**Adjusted OR† (95% CI)**	**P-value**	**IPT-weighted OR (95% CI)**	**P-value**
HVCs vs. MVCs	1.097 (0.828, 1.455)	0.5185	1.029 (0.815, 1.298)	0.8103	0.972 (0.738, 1.280)	0.8384

† Multivariable models were adjusted for volume classification, age, sex, Charlson Comorbidity Index, hospitalization, multiple site procedure, comorbidities, and drugs.

HVCs, high-volume centers; MVCs, medium-volume centers; OR, odds ratio; CI, confidence interval; IPT, inverse probability treatment.