Endoscopic submucosal dissection to treat gastric neoplasms in elderly patients 80 years old or older -safety and effectiveness

Naohiro Nakamura, Koichiro Abe, Takayuki Okamura,Hitoshi Aoyagi, Akari Isono, Shinya Kodashima, Takatsugu Yamamoto

Department of Medicine, Teikyo University School of Medicine

Abstract

Background: Endoscopic submucosal dissection is one of the standard therapies for gastric neoplasms that present with a low probability of lymph node metastasis. However, the validity of the therapy for elderlies has not been fully elucidated. We performed the present retrospective study to clarify the safety and the effectiveness of endoscopic submucosal dissection in elderly patients 80 years of age or older. **Methods**: The study subjects included 275 patients (≥80 years old, n=54; <80 years old, n=221) who underwent endoscopic submucosal dissection for the treatment of gastric tumor between August 1, 2010 and July 31, 2017. From the medical records of the study patients, background factors, lesion factors, and clinical course factors were examined and were compared between patients who were 80 years old or older compared to those who were younger than 80 years old. Additionally, factors related to postoperative bleeding were examined. **Results**: Clinical outcomes such as successful resection rate, rate of adverse events, mortality, or days of hospital stay were similar between the two groups. The most common adverse effect in perioperative period was postoperative bleeding, which was significantly related to two factors of whether heparin was used or not and comorbid chronic kidney disease. **Conclusion**: The present study indicated that the safety and effectiveness of endoscopic submucosal dissection for elderly patients 80 years old or older is comparable to that for younger patients. Perioperative heparin usage and chronic kidney disease were significant factors related to postoperative bleeding.

keywords: elderly, gastric neoplasm, endoscopic submucosal dissection, heparin, chronic kidney disease

Introduction

The aging of the population is rapidly progressing in East Asian countries including Japan, with a high percentage of the elderly population being at least 65 years old and this percentage is projected to increase in the future[1]. With such changes, there is also an aging trend among patients receiving medical treatment. In elderly patients, we often experience cases in which highly invasive treatments are difficult to perform due to reasons such as decreased physical function, oral intake of antithrombotic drugs, and presence of comorbid dementia.

Gastric cancer is highly frequent in East Asian countries as well, and is a malignant disease with a high mortality[2,3]. Although surgical resection had previously been the primary mode of treatment for gastric tumors, endoscopic treatment has rapidly become more widespread in recent years. In particular, endoscopic submucosal dissection (ESD), which can resect the lesion "en-bloc," is one of the standard therapies for tumors that present with a low probability of lymph node metastasis; namely, gastric tumors that primarily exist in the mucosa[4,5]. ESD is less invasive compared to surgical treatment and is known to result in better quality of life, including fewer or milder postoperative complications[6-9]. For this reason, the election of ESD is increasing among elderly patients, in whom it is preferable to avoid the invasiveness of a surgical procedure, even when the lesions are beyond the conventional indications for treatment. On the other hand, since anticipated accidental symptoms such as hemorrhage, perforation, and pneumonia can be fatal to elderly patients, clarifying the kinds of clinical factor that affect the treatment course of ESD is extremely important in elderly patients for advancing safer gastric tumor treatments[10-23].

In Japan, "early elderly" is defined as an individual 65 to 74 years old, and "late elderly" is defined as an individual 75 years old or older. However, one recent proposal was that those 75 years old or older should be defined as "elderly," indicating extensions in life and health expectancy. In actual clinical practice, when notable complications are absent, there is typically no age-related reluctance for treatment among patients in their 70s. However, various risks increase once patients are in their 80s, such as comorbidities, and there is an increasing trend to avoid treatments that involve higher invasiveness.

With the purpose of investigating the validity of ESD in treating gastric tumors in elderly patients, we retrospectively examined the background factors, treatment

outcomes, and post-treatment (postoperative) course in patients who underwent ESD treatment at our department for gastric tumors and compared the effectiveness and safety of treatment between patients ≥80 years old compared with patients <80 years old.

Materials and Methods

Subjects

This study investigated 275 patients (≥80 years old, n=54; <80 years old, n=221) who underwent ESD at our department for the treatment of gastric tumor (adenocarcinoma, adenoma) between August 1, 2010 and July 31, 2017. All patients were definitively diagnosed based on histopathological examination. The study also included patients who underwent submucosal dissection with snaring as a resection method. Since the evaluation variables included the durations of the procedure and hospital stay, patients who simultaneously underwent resection of multiple lesions and patients for whom the purpose of hospitalization was not tumor resection were excluded from the study.

Methods

From the medical records of the study patients, background factors (age, gender, comorbidities, presence/absence of *Helicobacter pylori* (*H.pylori*) infection, status of oral antithrombotic intake), lesion factors (site, histological type, operation time, diameter of resected specimen, status of curative resection), and course factors (days of hospital stay, complications, death) were examined and were compared between patients who were 80 years old or older compared to those who were younger than 80 years old. Additionally, factors related to postoperative bleeding, the most common complication, were examined using univariate or multivariate logistic regression analysis. For statistical analysis *t*-test or x^2 test was used to compare the two groups, where $p<0.05$ was considered statistically significant. Statistical software SPSS Statistics version 24 (IBM Japan, Tokyo, Japan) was used for all analyses. This study was approved in advance by the ethics committee of Teikyo University (TU-17-046).

Results

Table 1 shows the comparison of patient background factors by age group. The rate of hypertension, chronic kidney disease (CKD) and ischemic heart disease

comorbidities were significantly greater in the ≥80-year-old group. There was no significant difference of concomitant medicines between two groups.

Table 2 shows treatment outcomes and postoperative course. Regarding the resected lesions, no differences were seen in lesion site, size, proportions of cancer and adenoma, curative resection rate, although curative resection rate seemed a little lower in the ≥80-year-old group. Duration of hospital stay and rate of accidental symptoms did not differ significantly between groups. Deaths related to gastric tumor or endoscopic procedure were not observed.

Table 3 shows the result of univariate analysis regarding postoperative bleeding. Three factors of perioperative heparin usage, regular use of antithrombotic agents and comorbid CKD were significantly associated with the occurrence of postoperative bleeding. On the multivariate analysis using logistic regression analysis (compulsory methods) for 5 factors with p-value below 0.1 (diabetes, malignancy, antithrombotic agent, CKD, heparin usage), two factors of heparin usage and CKD were significant (Table 4).

Discussion

In East Asian countries including Japan, the incidence of gastric cancer has been high since before and its treatment has been a significant clinical challenge for many years. *H. pylori* was discovered in 1982, and was revealed as the primary cause of gastric inflammation and tumors, and eradication treatment has become widely known as effective in suppressing carcinogenesis[24]. In advance of other countries, the Japanese government instituted a regulation in 2013 for the national health insurance system to cover eradication treatment with the vision to prevent gastric cancer. Since then, eradication treatment has been performed proactively. Endoscopic examination is necessary for this treatment and, coupled with the increase in endoscopic checkups in recent years, the impression is that the number of discovered cases of gastric tumor is increasing. Most of these cases are early cancer or adenoma that is the target of endoscopic treatment. Endoscopic treatment results in similar or better outcomes as surgical resection in guideline-indicated lesions (indicated lesions) that meet specific criteria or in lesions that fit the criteria for expanded indications, and has become the standard therapy for treating early gastric cancer at the present time[4-9].

The purpose of this study was to evaluate the safety and the effectiveness of ESD for

not only carcinoma but also adenoma in elderly patients. The effectiveness measured by curative resection rate did not differ between age groups significantly. Whether ESD contributed to a better life prognosis is unclear based on our study results alone. However, because no deaths were seen related to gastric tumor or endoscopic procedure, we think the effectiveness of this treatment in elderly patients was partly demonstrated. Regarding surgical gastrectomy for early gastric cancer, Choi et al. have reported that older age of patients was one of significant factors associating recurrence and survival after treatment[25], which might indicate the difference of effectiveness between surgical and endoscopic treatment. Moreover, because no age differences were found in intraoperative/postoperative accidental symptoms and complications and because no deaths occurred in relation to the procedure, the safety of this treatment for elderly patients was verified. Previous papers regarding gastric cancer investigated the effectiveness and safety of ESD in patients with early gastric cancer and reported that both were non-inferior compared to that in non-elderly patients[10-23], consistent with our findings.

Although it did not differ significantly, the number of non-curative lesions tended to be greater in the older elderly patient groups, most likely because the procedure was frequently performed in patients for whom surgery under general anesthesia was considered highly risky; in other words, those in poor general condition. Our results infer that the procedure can be performed safely in these patients since related deaths were not observed, however, its usefulness is unclear because the curative resection rate was not sufficiently high. At the present time, the usefulness of non-curative resection remains unclear. For this reason, when the patient has a strong request to undergo low-invasive treatment and the gastric tumor could become a potential prognosticator, endoscopic treatment is frequently utilized even in cases where curative resection may be difficult. Recent reports have indicated that careful follow-up may be an alternative strategy to gastrectomy in patients treated by non-curative ESD[26,27]. Anyway, it is necessary to collect data and build evidence regarding the utility of such non-curative resection in the future.

Concerning hemorrhage, as one of the primary postoperative complications, perioperative replacement with heparin during discontinuation of antithrombotic agent, as a so-called “heparin bridge,” was shown to be a significant related factor. The guidelines for gastroenterological endoscopy in patients undergoing antithrombotic

treatment pressed in 2012, recommended replacement with heparin in patients using an anticoagulant[28]. However, since many studies have demonstrated contradictory results on the effects of replacement in suppressing embolism and since replacement also significantly increased gastrointestinal hemorrhage[29,30], this recommendation was removed from the 2017 addendum[31]. A rapid increase in the number of patients taking some type of antithrombotic agent has been seen in recent years, and discontinuation is a significant challenge in gastrointestinal endoscopy-related procedures. Regarding anticoagulants, in addition to the existing warfarin, several direct oral anticoagulants are on the market. These are characterized by reduced induction of major hemorrhagic events compared to warfarin, but may increase gastrointestinal hemorrhage through local effects[32-36]. Nevertheless, according to reports on hemorrhage related to endoscopy-related procedure in Japan, such risk is suggested to be similar to or lower than that of warfarin[37]. For patients using warfarin, switching to a direct oral anticoagulant with a shorter half-life, rather than heparin, and promptly restarting it after a short period of discontinuation may thus be an option.

Chronic kidney disease was another factor relating postoperative bleeding. Yoshioka et al. have described that the possible mechanisms of bleeding tendency in patients with CKD include uremic platelet dysfunction, platelet-vessel wall interaction, or abnormalities in blood coagulation[38]. Since renal dysfunction is more common in elderlies than younger patients, we should pay more attention to the risk of bleeding after gastric ESD in patients with impaired renal function.

Limitations of this study include the retrospective study design, small sample size, and involvement of a single center. This study was exploratory in nature, and further investigation of larger samples is necessary.

Conclusions

The present study proved that the safety and effectiveness of endoscopic submucosal dissection for elderly patients 80 years old or older is comparable to that for younger patients. Perioperative heparin usage is a significant factor related to postoperative bleeding.

Data Availability

All the data are available from the corresponding author upon request.

Conflict of Interest and Funding Statement

There is neither conflict of interest nor financial funding regarding the study.

References

1) World Health Organization. World health statistics reports on global health goals for 194 countries. .Available at https://www.who.int/mediacentre/news/releases/2015/world-health-statistics-2015/en/ -. Accessed March 13, 2015.
2) Goh LY, Leow AH, Goh KL. Observations on the epidemiology of gastrointestinal and liver cancers in the Asia-Pacific region. *J Dig Dis* 2014;15: 463–468.
3) Fock KM. Review article: the epidemiology and prevention of gastric cancer. *Aliment Pharmacol Ther* 2014;40: 250–260.
4) Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016; 28: 3-15.
5) Nakamoto S, Sakai Y, Kasanuki J, et al. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. *Endoscopy* 2009; 41: 746–750.
6) Park CH, Lee H, Kim DW, et al. Clinical safety of endoscopic submucosal dissection compared with surgery in elderly patients with early gastric cancer: a propensity-matched analysis. *Gastrointest Endosc* 2014; 80: 599-609.
7) Ryu SJ, Kim BW, Kim BG, et al. Endoscopic submucosal dissection versus surgical resection for early gastric cancer: a retrospective multicenter study on immediate and long-term outcome over 5 years. *Surg Endosc* 2016; 30: 5283-5289.
8) Tanabe S, Ishido K, Matsumoto T, et al.. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a multicenter collaborative study. *Gastric Cancer* 2017; 20(Suppl 1): 45-52.
9) Jeon HK, Kim GH, Lee BE, et al. Long-term outcome of endoscopic submucosal dissection is comparable to that of surgery for early gastric cancer: a propensity-matched analysis. *Gastric Cancer* 2018; 21: 133-143.
10) Kakushima N, Fujishiro M, Kodashima S, et al. Technical feasibility of endoscopic submucosal dissection for gastric neoplasms in the elderly Japanese population. *J Gastroenterol Hepatol* 2007; 22: 311-314.
11) Abe N, Gotoda T, Hirasawa T, et al. Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. *Gastric Cancer* 2012; 15: 70-75.
12) Murata A, Muramatsu K, Ichimiya Y, et al. Endoscopic submucosal dissection for gastric

cancer in elderly Japanese patients: an observational study of financial costs of treatment based on a national administrative database. *J Dig Dis* 2014; 15: 62-70.

13) Zhang Y, Huang L, Li L, et al. Endoscopic submucosal dissection for early gastric neoplasms in elderly patients. *J Laparoendosc Adv Surg* 2014; 24: 391-398.

14) Yang TC, Hou MC, Chen PH, et al. Clinical outcomes and complications of endoscopic submucosal dissection for superficial gastric neoplasms in the elderly. *Medicine (Baltimore)* 2015; 94: 31964.

15) Lin JP, Zhang YP, Xue M, et al. Endoscopic submucosal dissection for early gastric cancer in elderly patients: a meta-analysis. *World J Surg Oncol* 2015; 13: 293.

16) Chinda D, Sasaki Y, Tatsuta T, et al. Perioperative complications of endoscopic submucosal dissection for early gastric cancer in elderly Japanese patients 75 years of age or older. *Intern Med* 2015; 54; 267-272.

17) Nishida T, Kato M, Yoshio T, et al. Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J Gastrointest Endosc* 2015; 7: 524-531.

18) Yoshifuku Y, Oka S, Tanaka S, et al. Long-term prognosis after endoscopic submucosal dissection for early gastric cancer in super-elderly patients. *Surg Endosc* 2016; 30: 4321-4329.

19) Komori K, Nakamura K, Ihara E, et al. Endoscopic submucosal dissection is feasible for very elderly patients with early gastric cancer: comparison of short-term and long-term outcomes in very elderly and non-elderly patients. *Fukuoka Igaku Zasshi* 2016; 107: 72-81.

20) Kato M, Michida T, Kusakabe A, et al. Safety and short-term outcomes of endoscopic submucosal dissection for early gastric cancer in elderly patients. *Endosc Int Open* 2016; 4: E521-E526.

21) Sumiyoshi T, Kondo H, Fujii R, et al. Short- and long-term outcomes of endoscopic submucosal dissection for early gastric cancer in elderly patients aged 75 years and older. *Gastric Cancer* 2017; 20: 489-495.

22) Sekiguchi M, Oda I, Suzuki H, et al. Clinical outcomes and prognostic factors in gastric cancer patients aged over 85 years undergoing endoscopic submucosal dissection. *Gastrointest Endosc* 2017; 85: 963-972.

23) Watanabe K, Hikichi T, Nakamura J, et al. Endoscopic submucosal dissection for early gastric cancer in very elderly patients age 85 or older. *Endosc Int Open* 2017; 5:

E17-E24.

24) Correa P. Helicobacter pylori and gastric carcinogenesis. *Am J Surg Pathol* 1995; 19 Suppl 1: S37-43.

25) Choi HJ, Kim SM, An JY, et al. Risk factors and tumor recurrence in pT1N0M0 gastric cancer after surgical treatment. *J Gastric Cancer* 2016; 16: 215-220.

26) Toya Y, Endo M, Nakamura S, et al. Clinical outcomes of non-curative endoscopic submucosal dissection with negative resected margins for gastric cancer. *Gastrointest Endosc* 2017; 85: 1218-1224.

27) Hatta W, Gotoda T, Oyama T, et al. Is radical surgery necessary in all patients who do not meet the curative criteria for endoscopic submucosal dissection in early gastric cancer? A multi-center retrospective study in Japan. *J Gastroenterol* 2017; 52: 175-184.

28) Fujimoto K, Fujishiro M, Kato M, et al. Japan Gastroenterological Endoscopy Society. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; 26: 1-14.

29) Jaruvongvanich V, Sempokuya T, Wijarnpreecha K, et al. Heparin-bridging therapy and risk of bleeding after endoscopic submucosal dissection for gastric neoplasms: a meta-analysis. *J Gastrointest Cancer* 2018; 49: 16-20.

30) Kono Y, Obayashi Y, baba Y, et al. Postoperative bleeding risk after gastric endoscopic submucosal dissection during antithrombotic drug therapy. *J Gastroenterol Hepatol* 2018; 33: 453-460.

31) Kato M, Uedo N, Hokimoto S, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment: 2017 appendix on anticoagulants including direct oral anticoagulants. *Dig Endosc* 2018; 30: 433-440.

32) Providencia R, Grove EL, Husted S, et al. A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens. *Thromb Res* 2014; 134: 1253-1264.

33) Desai J, Granger CR, Weitz JL, et al. Novel oral anticoagulants in gastrointestinal practice. *Gastrointest Endosc* 2013; 78: 227-239.

34) Goodman SG, Wojdyla DM, Piccini JP, et al. Factors associated with major bleeding events. *J Am Coll Cardiol* 2014; 63: 891-900.

35) Holster L, Valkhoff VE, Kuipers EJ, et al. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013; 145: 105-112.

36) Hernandez I, Baik SH, Pinera A, et al. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med* 2015; 175: 18-24.

37) Shirai T, Yamamoto T, Kawasugi K, et al. Gastrointestinal bleeding risk of non-vitamin K oral anticoagulants is similar to warfarin –a Japanese retrospective cohort study-. *Int J Clin Pharm Ther* 2016; 54: S41-S46.

38) Yoshioka T, Nishida T, Tsuji M, et al. Renal dysfunction is an independent risk factor for bleeding after gastric ESD. *Endosc Int Open* 2015; 3: E39-E45.

Table 1 Background characteristics of the study patients

	≥80 (n=54)	<80 (n=221)	p-value*
Sex (male:female)	35:19	167:54	0.109
Age (median (range))	82 (80-93)	72 (42-79)	n/a
Comorbidities			
Hypertension	**42 (77.8%)**	**133 (60.4%)**	**0.016**
Diabetes	13 (24.1%)	41(18.6%)	0.360
Dislipidemia	16 (29.6%)	67 (30.5%)	0.922
Chronic kidney disease	**37 (68.5%)**	**81 (36.8%)**	**<0.0001**
Ischemic heart disease	**37 (68.5%)**	**22 (10%)**	**<0.0001**
Liver cirrhosis	0	4 (1.8%)	0.319
Chronic obstructive pulmonary disease	2 (3.7%)	8 (3.6%)	0.977
Antithrombotic agents	17 (31.5%)	44 (19.9%)	0.066
Helicobacter pylori infection**	38/47 (80.9%)	166/198 (83.3%)	0.622

*; The *t*-test or x^2 test is used to compare the two groups, where $p<0.05$ was considered statistically significant. **; The rates of infection are calculated after excluding undifinite cases. Abbreviation: n/a; not available.

Table 2 Treatment outcome and postoperative course of patients underwent endoscopic submucosal dissection for gastric neoplasms

	≥80 (n=54)	<80 (n=221)	p-value*
Lesion factor			
Location (Upper: Middle: Lower)	10: 20: 24	26: 75: 120	0.094
Maximal diameter of resected specimen (mm)	38.4±12.9**	34.3±12.8**	0.079
Operation time (min)	109±78**	102±83**	0.389
Malignancy (rate of carcinoma)	47 (87%)	187 (85%)	0.654
Curative resection rate	46 (85.2%)	206 (93.2%)	0.056
Perioperative heparin usage	11 (20.4%)	19 (8.6%)	**0.013**
Course factor			
Days of hospital stay	11.2±4.6**	10.0±2.8**	0.063
Perforation	1 (1.8%)	3 (0.9%)	0.786
Postoperative bleeding	7 (13.0%)	20 (9.0%)	0.386
Postoperative surgery	0	0	n/a
Pneumonia	1 (1.8%)	0	n/a
Death	0	0	n/a

*; The *t*-test or x^2 test is used to compare the two groups, where $p<0.05$ was considered statistically significant. **; Figures are expressed as mean ± standard deviation. Abbreviation: n/a; not available

Table 3 Results of univariate analysis between clinical factors and postoperative bleeding (by logistic analysis)

Factors	Odds ratio	95% confidence interval	P value
Age	1.001	0.954-1.050	0.961
Sex (male)	0.451	0.151-1.352	0.155
Hypertension	0.800	0.356-1.799	0.589
Diabetes	2.256	0.952-5.346	0.065
Dyslipidemia	0.792	0.321-1.952	0.613
Chronic kidney disease	**2.602**	**1.144-5.917**	**0.023**
Ischemic heart disease	2.223	0.769-6.428	0.140
Past GI bleeding	0.485	0.110-2.137	0.339
Size of resected specimen	1.000	0.920-1.118	0.857
Operation time	1.003	0.998-1.007	0.216
Malignancy (carcinoma)	0.439	0.172-1.118	0.084
Non-curative resection	0.430	0.057-3.402	0.430
Antithrobotic agent	**3.869**	**1.707-8.767**	**<0.001**
Perioperative heparin usage	**6.706**	**2.713-16.577**	**<0.001**

Abbreviation: GI; gastrointestinal

Table 4 Results of multivariate analysis between clinical factors and postoperative bleeding (by logistic regression analysis)

Factors	Odds ratio	95% confidence interval	P value
Chronic kidney disease	**2.483**	**1.037-5.941**	**0.041**
Perioperative heparin usage	**4.238**	**1.002-17.916**	**0.050**
Diabetes	2.170	0.848-5.548	0.106
Malignancy	0.468	0.165-1.328	0.154
Antithrombotic agent	1.252	0.329-4.761	0.741

Fig.1

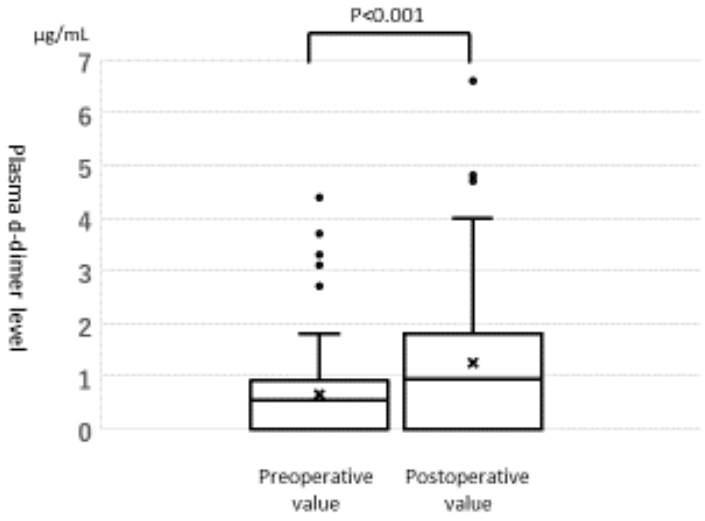
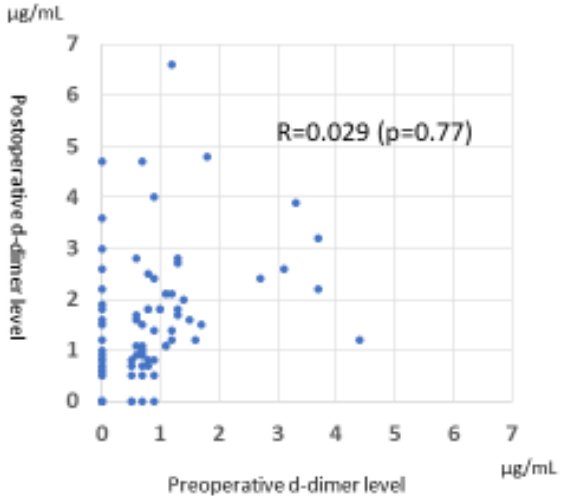

P<0.001
μg/mL
7
6
5
4
3
2
1
0
Plasma d-dimer level
Preoperative value
Postoperative value

Fig.2


μg/mL
Postoperative d-dimer level
R=0.029 (p=0.77)
0
1
2
3
4
5
6
7
Preoperative d-dimer level
μg/mL