Factors Related to Delayed Adverse Events of Endoscopic Submucosal Dissection in the Duodenum

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Keywords

Duodenum · Delayed bleeding · Delayed perforation · Endoscopic submucosal dissection · Second-look endoscopy

Abstract

Introduction: Endoscopic submucosal dissection for duodenal neoplasms (D-ESD) is considered a technically demanding procedure regarding the high risk of delayed adverse events. Data regarding optimal managements of ulcers after D-ESD are lacking. **Methods:** A retrospective analysis was performed on consecutive 145 cases of D-ESD for superficial nonampullary duodenal epithelial tumors at a single referral center. Factors related to delayed adverse events and the healing process of ulcers after D-ESD were analyzed. **Results:** Complete ulcer suture after D-ESD was performed in 128 cases (88%). Two delayed perforation occurred among cases with incomplete suture. Delayed bleeding occurred in 8 cases (6%) within 3 weeks. The ulcer closure rate at second-look endoscopy (SLE) was significantly low among cases with delayed bleeding (12.5% vs. 75%, $p = 0.001$). The bleeding rate before SLE was significantly high among patients who did not have complete ulcer closure after D-ESD (0.8% vs. 12%,

$p = 0.036$). The ratio of lesions located in the second oral-Vater was significantly low among ulcers re-opened at SLE (38% vs. 14%, $p = 0.044$). Proton-pump inhibitors (PPIs) were administered for a median of 7 weeks (range 1–8 weeks). At 3 weeks, active ulcer stages were observed in a few cases, and healing or scarring was observed in most cases. **Conclusions:** Complete ulcer suture was related to decreased risk of delayed adverse events after D-ESD. From the bleeding period and healing process of D-ESD ulcers, the minimum required length of PPI may be 3 weeks after D-ESD.

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Introduction

With the widespread use of esophagogastroduodenoscopy for screening and surveillance, the number of patients diagnosed with duodenal neoplasms is gradually increasing [1–4]. A recent nation-wide epidemiological study in Japan reported that 56% of duodenal cancer patients diagnosed in a year were detected at the localized stage [5]. Among them, endoscopic resection (ER) was performed in 48% of cases [5]. Endoscopic submucosal dissection (ESD) is an advanced method of ER which was

Fig. 1. **a** The healing process of ulcer after D-ESD in a patient with immediate ulcer suture. A 40-mm-sized lesion located in the anal-Vater area. **b** Immediate ulcer suture was performed using Sureclips. **c** Some of the Sureclips had dropped off, but most of the ulcer was closed at 1 week. **d** Complete scarring was observed at 3 weeks. **e** The healing process of ulcer after D-ESD in a patient who did not receive ulcer suture. A 22-mm-sized lesion located in the anterior wall of duodenal bulb near the pylorus. **f** Ulcer closure was not performed because of technical difficulty. **g** SLE shows thick white exudates on the ulcer bed without any exposed vessels. **h** Complete scarring was observed at 4 weeks.

first developed for the treatment of early gastric cancer [6]. Because of its efficacy in achieving a high en bloc resection rate, ESD has become the major ER method for the treatment of superficial neoplasms in the esophagus [7], stomach [8], and colorectum [9].

For the treatment of superficial duodenal neoplasms, however, ESD is still not considered as a standard therapy because its incidence of adverse events such as intraoperative perforation, delayed bleeding, and delayed perforation is remarkably higher compared to ESD in other parts of the gastrointestinal tract [4]. Several studies have reported that ulcer suture after duodenal ESD (D-ESD) would decrease the risk of delayed adverse events [10, 11]. However, the optimal method of suture remains unknown.

Proton-pump inhibitors (PPIs) are routinely administered to patients after ER in the duodenum [11, 12] as well as in the stomach [13]. In patients with peptic duodenal ulcer, PPIs are given for 2–12 weeks depending on the location and cause of the ulcer [14, 15]. In Japan, treatment with 6 weeks of PPI is generally accepted for peptic duodenal ulcer and is covered by the national health insurance. Artificial ulcers after D-ESD are larger than 20

mm since they are usually applied for lesions that are difficult to treat by endoscopic mucosal resection [4], and thermal injury to the proper muscle layer is anticipated because of the submucosal dissection procedure using electrocautery devices. In this sense, D-ESD ulcers are considered as complicated duodenal ulcers. A previous study reported that ESD ulcers in the stomach would heal within 8 weeks regardless of size and location without ulcer suture [16]. However, the healing process of ulcers after D-ESD remains unknown. The aim of this study was to investigate clinical factors related to delayed bleeding and clarify the ulcer healing process in D-ESD patients.

Materials and Methods

This study was conducted as a retrospective single-center study in a tertiary referral university hospital. The study was approved by the hospital's institutional review board. Informed consent for patients was obtained in the form of opt-out on the hospital website. A chart-based investigation was performed on patients who underwent D-ESD for superficial nonampullary duodenal epithelial tumors during January 2012 to March 2021 in our hospital.

Table 1. Characteristics of 145 duodenal lesions in 141 patients

Sex, <i>n</i> (%)	
Male	96 (68)
Age, median (range)	64 (27–89)
Antithrombotics, yes, <i>n</i> (%)	16 (11)
LDA	8 (6)
Thienopyridine	1 (1)
Other antiplatelets	3 (2)
Warfarin	1 (1)
DOAC	3 (2)
Antacid treatment after D-ESD, weeks, median (range)	7 (1–8)
Tumor diameter, mm, median (range)	15 (3–70)
Location, <i>n</i> (%)	
1st	22 (15)
2nd (oral-Vater)	47 (32)
2nd (anal-Vater)	73 (50)
3rd	3 (2)
Morphology, <i>n</i> (%)	
Elevated	93 (64)
Depressed	41 (28)
Mixed	11 (8)
Histology, <i>n</i> (%)	
Low-grade adenoma	28 (19)
High-grade adenoma	48 (33)
Mucosal adenocarcinoma	67 (46)
Submucosal adenocarcinoma	2 (1)
DOAC, direct oral anticoagulant; LDA, low-dose aspirin.	

Indicated lesions for D-ESD were endoscopic diagnosis of high-grade adenoma or mucosal adenocarcinoma, no apparent metastasis confirmed by computed tomography, and lesions that were considered difficult to remove by endoscopic mucosal resection due to fibrotic scars. Data regarding patient characteristics (age, sex, use of antithrombotic drugs), lesion characteristics (tumor diameter, location, morphology, histology, tumor depth), and treatment characteristics (intraprocedural perforation, delayed bleeding, delayed perforation, performance of ulcer suture, ulcer state at second-look endoscopy (SLE), ulcer stage at follow-up endoscopy, duration of PPI) were collected.

Outcomes

The primary outcome was analysis of factors related to delayed bleeding. Delayed bleeding was defined as apparent hematemesis, those who required additional hemostasis after D-ESD, or those who required blood transfusion. The secondary outcome was the elucidation of the healing process of ulcers after D-ESD. Ulcer stages at follow-up endoscopy were evaluated as active, healing, and scarring stages [17].

Procedure and Periprocedural Managements of D-ESD

From January 2012 to September 2019, D-ESD was performed mainly by a scissors-type device as previously reported [18]. The high-frequency settings were Endo CUTQ1.1.1 for mucosal incision, Forced COAG 2.0 for submucosal dissection, Soft COAG 6.0 for hemostasis using scissors-type device (VIO300D; Elektromed-

izin, Tübingen, Germany). From March 2019, D-ESD was performed by the water-pressure method with a Dual Knife J (1.5 mm; Olympus Medical Systems, Tokyo, Japan) as previously reported [19, 20]. The high-frequency settings were Dry cut 2.0 for mucosal incision, and Swift COAG 3.0 for submucosal dissection (VIO3; ERBE Elektromedizin, Tübingen, Germany). For hemostasis using the tip of Dual Knife J, Forced COAG 0.3 was used for prophylactic coagulation of blood vessels, and Spray COAG 1.2 was used to stop minor venous bleeding. The ulcer created by D-ESD was closed by endoclip (EZ Clip; Olympus Medical Systems, Tokyo, Japan), endoloop (PDS II; Olympus Medical Systems, Tokyo, Japan), over-the-scope clip (OTSC; Ovesco, Tübingen, Germany), and Sureclip (Micro-Tech, Nanjing, China). From January 2012 to January 2016, endoclips with or without endoloops were used. From January 2016 to June 2019, endoclips with OTSC were used. Since June 2019, Sureclips were used for the closing method.

Antithrombotic drugs were stopped during the periprocedural period. Patients fasted for 2 days including the day of the ESD procedure, and a SLE was performed on postoperative day (POD) 1–3. During SLE, the ulcer was checked for any vessels, delayed perforation, and the suture condition. Complete ulcer closure was defined as a condition in which the ulcer was closed and the ulcer bed was not visualized. When the postprocedural course was uneventful, patients started drinking after SLE, and a liquid diet was started on the following day. Antithrombotic drugs were resumed when patients started eating. Patients received intravenous PPI for 2–4 days, followed by oral PPI (lansoprazole 20 mg/omeprazole 20 mg/rabeprazole 20 mg/esomeprazole 20 mg/day) or a potassium-competitive acid blocker (vonoprazan 20 mg/day) for 1–8 weeks

after ESD. Follow-up endoscopy was performed 2–8 weeks after D-ESD to check the healing stage of the ulcer (Fig. 1).

Statistics

Continuous variables were expressed as median and range. Categorical variables were expressed as number and percentage. The Mann-Whitney U test was used to compare continuous data; the χ^2 and Fisher's exact tests were used to compare categorical data. *p* values <0.05 were considered statistically significant. All statistical analyses were carried out using SPSS version 26.0.0 software program (IBM Corp., Armonk, NY, USA).

Results

During the study period, a total of consecutive 145 lesions/141 patients underwent D-ESD and were included in the study. Characteristics of patients and lesions are shown in Table 1. Four patients had two lesions, which were separately treated by D-ESD at different times. There were 16 cases (11%) on antithrombotic therapy. During the cessation of antithrombotic therapy, no patient underwent heparin bridging. The median duration of PPI was 7 weeks. The en bloc resec-

Fig. 2. The clinical course of D-ESD patients in this study.

tion rate was 91% (132/145); R0 resection rate was 75% (109/145). Intraoperative perforation rate was 11% (16/145).

The clinical course after D-ESD is shown in Figure 2. Immediately after D-ESD, complete ulcer suture was performed in 128 cases (88%). In 17 cases (12 in first portion [medial: 3, lateral: 1, anterior: 5, posterior: 3], 5 in second portion [medial: 1, anterior: 1, posterior: 3]), the sutures were incomplete or not performed because of technical difficulty. SLE was performed in 137 cases, in which ulcer closure was confirmed in 103 cases. SLE was not performed in 8 cases because of intraoperative perforation, acute pancreatitis, and delayed perforation. Two delayed perforation occurred on POD 1 among cases with incomplete suture in the anal-Vater location.

Details of Patients with Delayed Bleeding

In total, delayed bleeding was observed in 8 cases (6%) (Table 2). Three cases of bleeding occurred on POD1 before the scheduled SLE. The bleeding rate before SLE was significantly higher among patients who did not have complete ulcer closure after D-ESD than those who did (1/128 [0.8%] vs. 2/17 [12%], $p = 0.036$).

At SLE performed on POD2-3, blood clots were observed on the re-opened ulcers, and active bleeding which required hemostasis was observed in 3 patients. In the first case, endoclips had fallen off and an exposed vessel appeared on the re-opened ulcer base. The vessel easily bled after washing the blood clot and was stopped with soft coagulation. The ulcer was re-sutured with endoclips.

In the second case, fresh blood clots were observed aside the OTSC. After washing the blood clot, re-opening of the ulcer was observed aside the OTSC with an exposed vessel. Short endoclips were used for the vessel and long endoclips were used to re-suture the ulcer. In the third case, blood clots were observed in the duodenum and on the OTSC. After washing the blood clot, bleeding was observed from the inverted mucosa within the OTSC which was stopped with endoclips.

Among 103 patients with ulcer closed at SLE, 1 patient had delayed bleeding on POD7. In this patient, the ulcer was completely sutured with OTSC and endoclips; however, emergency endoscopy revealed that endoclips had fallen off and an exposed vessel was observed in the inverted submucosa within the OTSC. Among 21 cases with ulcer re-opened at SLE, the latest bleeding event occurred on POD 21. In this case, the ulcer was completely sutured with OTSC and endoclips after D-ESD. On SLE performed on POD3, the ulcer was partially open with an exposed nonbleeding vessel which was treated with endoclips. The patient had tarry stool and a decrease in serum hemoglobin level (15.7–10.1 g/dL) on POD 21. Emergency endoscopy revealed a visible vessel and adherent clot on the D-ESD ulcer base aside of OTSC, which was treated with endoclips.

Risk Analysis for Delayed Bleeding

Univariate analyses for the risk of delayed bleeding are shown in Table 3. The ulcer closure rate at SLE was significantly low among cases with delayed bleeding (12.5%

Table 2. Details of the 8 patients with delayed bleeding after D-ESD

Age	Sex	Location	Morphology	Tumor diameter	Antithrombotics	Ulcer closure method	Ulcer at SLE	Period	Symptoms and details
56	M	2nd, anal-Vater	0-IIC	5	LDA with cessation	Endoclip	Open	POD2	None, bleeding during SLE
49	M	1st	0-I	15	No	No	Open	POD1	Melena with hypotensive shock
53	M	2nd, anal-Vater	0-IIC	12	No	OTSC with endoclip	Open	POD2	None, bleeding during SLE
76	M	2nd, oral-Vater	0-IIa	12	No	OTSC with endoclip	Open	POD21	Melena
75	M	2nd, anal-Vater	0-IIa	15	No	OTSC	Open	POD1	Melena with hypotensive shock
61	M	2nd, anal-Vater	0-IIa	20	No	OTSC with endoclip	Open	POD3	None, bleeding during SLE
48	M	2nd, anal-Vater	0-IIa	8	No	OTSC with endoclip	Closed	POD7	Hematemesis
80	M	1st	0-IIa	51	No	No	Open	POD1	Hematemesis

LDA, low-dose aspirin; POD, postoperative day; SLE, second-look endoscopy.

vs. 75%, $p = 0.001$). Analyses on factors related to re-opening of ulcers at SLE among patients who received immediate complete closure after D-ESD are shown in Table 4. The ratio of lesions located in the second oral-Vater was significantly low among ulcers re-opened at SLE ($p = 0.044$).

The Healing Process of Ulcers after D-ESD

The ulcer stages at further follow-up endoscopies according to various factors are shown in online supplementary Table (for all online suppl. material, see www.karger.com/doi/10.1159/000522362). Ulcers were at active stages until 2 weeks after D-ESD. At 3 weeks, active stages were observed in a few cases, and healing or scarring of the ulcers was observed in most cases. At 4 weeks, most ulcers were at scarring stages with a few cases of healing stages, and all ulcers were at scarring stages from 5 weeks or later. There was no trend in the healing process regarding location, tumor diameter, ulcer stages at SLE, use of antithrombotics, and duration of antacids.

Discussion

This study investigated the postprocedural course of D-ESD patients in detail and revealed that all delayed bleeding occurred within the first 3 weeks, with the majority within 3 days from D-ESD. Ulcer closure confirmed at SLE was a significant factor with a decreased risk of delayed bleeding. Follow-up endoscopy revealed that scarring of D-ESD ulcers was observed from 3 weeks after D-ESD.

Ulcer closure after ESD is not routinely performed among ESD in other parts of the gastrointestinal tract. A randomized controlled trial reported that prophylactic endoscopic closure after colorectal ESD did not decrease the incidence of complication, and it also did not ameliorate inflammatory response and abdominal pain [21]. In the stomach, a previous study reported that delayed bleeding was less frequent (3.3%) in patients who underwent ulcer closure by using endoclips compared with those who did not (13.3%), thereby concluding that the prophylactic closure effectively decreased the incidence of delayed bleeding [22]. However, they also mentioned that ulcer closure was not successful in cases located in particular areas or those with large tumor diameter [22]. Another study of gastric ESD reported that an endoscopic tissue shielding method with polyglycolic acid and fibrin glue did not reduce the risk of delayed bleeding among a high-risk population for delayed bleeding [23]. In contrast, a recent meta-analysis reported that the inci-

Table 3. Risk analysis for delayed bleeding after D-ESD

Delayed bleeding	Delayed bleeding		<i>p</i> value
	yes (<i>n</i> = 8)	no (<i>n</i> = 137)	
Sex, <i>n</i> (%)			
Male	8 (100)	88 (64)	0.052
Age			
Median (range)	64 (48–80)	64 (27–89)	0.588
Antithrombotics, <i>n</i> , (%)	1 (13)	15 (11)	1.000
Oral antacids, <i>n</i> (%)			
PPI	3 (37.5)	57 (42)	1.000
PCAB	5 (62.5)	76 (55)	
Others	0 (0)	4 (3)	–
Location, <i>n</i> (%)			
1st	2 (25)	20 (14.5)	0.349
2nd oral-Vater	1 (12.5)	46 (33.5)	0.438
2nd anal-Vater or 3rd	5 (62.5)	71 (52)	0.721
Tumor diameter, mm, (range)	14 (5–51)	15 (3–70)	0.591
Resection time, min, (range)	90 (20–217)	59 (10–337)	0.299
Intraoperative perforation, <i>n</i> (%)	0	13 (9)	–
Complete ulcer closure after ESD, <i>n</i> (%)	6 (75)	122 (89)	0.237
Ulcer closed at SLE, <i>n</i> (%)	1 (12.5)	103 (75)	0.001

PPI, proton-pump inhibitor; PCAB, potassium-competitive acid blocker.

Table 4. Analysis of re-opening of ulcers at SLE in patients who received immediate complete closure after D-ESD

	Closed (<i>N</i> = 103)	Re-opened (<i>N</i> = 21)	<i>p</i> value
Age, median, (range)	64 (27–87)	61 (45–89)	0.422
Male, <i>n</i> (%)	62 (60)	16 (76)	0.218
Location, <i>n</i> (%)			
1st	6 (6)	2 (10)	0.622
2nd (oral-Vater)	39 (38)	3 (14)	0.044
2nd (anal-Vater) or 3rd	58 (56)	16 (76)	0.142
Circumference, <i>n</i> (%)			
Medial	19 (18)	2 (9.5)	0.524
Lateral	27 (26)	6 (28.5)	0.792
Anterior	23 (22)	7 (33)	0.278
Posterior	34 (33)	6 (28.5)	0.801
Tumor diameter, median (range)	13 (3–70)	18 (5–56)	0.129
Intraoperative perforation, <i>n</i> (%)	11 (11)	1 (5)	0.689
Resection time, min, median, (range)	53 (10–265)	70 (20–236)	0.241
Suture time, min, median, (range)	14 (4–72)	17 (5–63)	0.354
Method of suture, <i>n</i> (%)			
Endoclips±thread/endoloop	38 (37)	5 (24)	0.319
OTSC with endoclips	27 (26)	6 (29)	0.79
Sureclips±thread	38 (37)	10 (48)	0.462

OTSC, over-the-scope clip.

dence of delayed adverse events was significantly decreased by applying preventive procedures to ulcers after D-ESD [10]. Our result also showed that complete ulcer closure confirmed at SLE was a significant factor related to delayed bleeding. Moreover, the rate of delayed bleeding before SLE was higher among patients with incomplete or no ulcer closure. Therefore, ulcer closure should be routinely considered in cases of D-ESD.

Several methods for ulcer suture after D-ESD have been reported [24–26]. Ulcer suture using a combination of endoclips with a string [24] or endoloop [25] has been reported to be a safe and effective method to suture large mucosal defects in the duodenum. Inoue et al. [25] reported that delayed perforation occurred in 2 patients despite ulcer closure using endoclips with endoloops and speculated that tumor location of anal-Vater or early dislocation of endoclips might be one of the reasons. In our study, both cases of delayed perforation had tumors in the anal-Vater location. In both cases, ulcer suture with endoclips and endoloops was attempted but resulted in incomplete suture because of technical difficulty. No matter what method is applied, a complete suture may be the key factor to prevent delayed events of D-ESD, especially for lesions located in the anal-Vater area.

In this study, ulcer closure confirmed at SLE was a significant factor with a decreased risk of delayed bleeding. This supports the report that complete closure after D-ESD is important to decrease adverse events [10]. A multicenter prospective randomized controlled trial reported that SLE after gastric ESD did not contribute to the prevention of delayed bleeding for patients with an average bleeding risk [27]. On the other hand, a recent multicenter study reported that the rates of delayed bleeding after gastric ESD could be stratified in 4 groups based on patient and lesion characteristics: low-risk (2.8%), intermediate-risk (6.1%), high-risk (11.4%), and very high-risk (29.7%) [8]. Regarding D-ESD, the incidence of delayed bleeding has been reported up to 18% [4, 10–12, 18–20, 25], which is apparently higher than that of gastric ESD. Notably, 16% of cases with complete closure had reopened ulcer at SLE including 3 asymptomatic cases of active bleeding. Although there was a possibility that these cases might have been meaningless bleeding, there was also a possibility that a more massive bleeding might have occurred after starting eating. For lesions in the second portion, if an exposed vessel or a re-opened ulcer is observed, additional re-suture may be possible. Actually, additional re-suture was performed in 14/21 cases in this study. We consider that endoscopic treatment for delayed bleeding after D-ESD is more challenging compared to

delayed bleeding from gastric ESD because of the thin wall and narrow space, difficult scope maneuverability. From our experience, hematemesis seems not to appear in the early period of delayed bleeding after D-ESD. When hematemesis occurs, a considerable amount of bleeding has already occurred resulting in a critical condition. Therefore, we think that SLE is important to check any possibility of bleeding. However, whether SLE was meaningful in improving the clinical course such as reducing the incidence of delayed bleeding or the cost-effectiveness is unclear and should be assessed in further studies.

Among cases who had received complete ulcer closure after ESD, some cases had re-opened ulcers at SLE. The rate of re-open ulcer in the anal-Vater location was higher than that of other locations. The anal-Vater location is the furthest part to reach with a gastroscope, and the maneuverability is limited; thus, we speculate that complete closure was technically difficult or it was difficult to confirm the completeness of the closure. Moreover, 70% (12/17) of lesions with incomplete or no closure were located in the duodenal bulb. The difficulty of ulcer closure in the duodenal bulb may be due to the lack of excess mucosa compared to other parts of the duodenum. Although we did not use polyglycolic acid sheets with fibrin glue, further methods of preventative procedures should be developed for cases that are technically difficult to suture with the current endoscopic accessories.

Regarding the use of PPI among D-ESD, previous studies reported different protocol ranging from 3–10 weeks of PPI after the procedure [12, 17, 19, 28, 29]. However, the timing of delayed bleeding and the healing process of D-ESD ulcers were fully not described in those studies. Our study showed that all delayed bleeding occurred within 3 weeks after D-ESD. Moreover, ulcer scarring was observed from 3 weeks regardless of the duration of PPI. Therefore, the minimum required length of PPI may be 3 weeks after D-ESD. However, due to the limited number of cases, further studies are required to confirm the sufficient period of PPI after D-ESD.

Limitations of this study are the nonrandomized design and the single-center setting. Another limitation is that the method of ESD and ulcer suture method were not standardized. Despite these limitations, our study demonstrated the postprocedural course of D-ESD and the risk of delayed events despite intensive preventive measures.

Conclusion

Complete ulcer suture was related to decreased risk of delayed adverse events after D-ESD. From the bleeding period and healing process of D-ESD ulcers, the minimum required length of PPI may be 3 weeks after D-ESD.

Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the institutional review board of Nagoya University Hospital (No. 2020-0347). Informed consent for patients was obtained in the form of opt-out on the hospital website.

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Conflict of Interest Statement

Tatsuya Kawamura, Takashi Hirose, Naomi Kakushima, Kazuhiro Furukawa, Satoshi Furune, Eri Ishikawa, Tsunaki Sawada, Keiko Maeda, Takeshi Yamamura, Takuya Ishikawa, Eizaburo Ohno, Masanao Nakamura, Takashi Honda, Masanori Ishigami, Hiroki Kawashima, and Mitsuhiro Fujishiro have no conflicts of interest or financial ties to disclose.

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Author Contributions

T.K., T.H., and N.K. designed the study with contributions from the other authors. T.K., T.H., N.K., K.F., S.F., E.I., T.S., K.M., T.Y., T.I., E.O., M.N., T.H., M.I., H.K., and M.F. involved in acquisition of data and investigation. T.K., T.H., and N.K. performed the statistical analysis and take responsibility for the integrity of the data and accuracy of the data analysis. T.K. wrote the manu-

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