### **ORIGINAL ARTICLE**



# Evaluation of effects of perioperative oral care intervention on hospitalization stay and postoperative infection in patients undergoing lung cancer intervention

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#### Abstract

**Purpose** This retrospective study investigated the effect of perioperative oral care intervention on postoperative outcomes in patients undergoing lung cancer resection, in terms of the length of postoperative hospital stay and the incidence of postoperative respiratory infections.

**Methods** In total, 585 patients underwent lung resection for lung cancer, 397 received perioperative oral care intervention, whereas the remaining 188 did not. This study retrospectively investigated the demographic and clinical characteristics (including postoperative complications and postoperative hospital stay) of each group. To determine whether perioperative oral care intervention was independently associated with either postoperative hospital stay or postoperative respiratory infections, multi-variate analysis, multiple regression analysis, and multivariate logistic regression analysis were conducted.

**Results** Parameters significantly associated with a prolonged postoperative hospital stay in lung cancer surgery patients were older age, postoperative complications, increased intraoperative bleeding, more invasive operative approach (e.g., open surgery), and lack of perioperative oral care intervention (standard partial regression coefficient ( $\beta$ ) = 0.083, p = 0.027). Furthermore, older age and longer operative time were significant independent risk factors for the occurrence of postoperative respiratory infections. Lack of perioperative oral care intervention was a potential risk factor for the occurrence of postoperative respiratory infections, although not statistically significant (odds ratio = 2.448, 95% confidence interval = 0.966–6.204, p = 0.059).

**Conclusion** These results highlight the importance of perioperative oral care intervention prior to lung cancer surgery, in order to shorten postoperative hospital stay and reduce the risk of postoperative respiratory infections.

Keywords Perioperative oral care intervention · Lung cancer · Length of postoperative hospital stay · Respiratory tract infections

# Introduction

Postoperative respiratory infections, such as pneumonia and empyema, constitute a grave problem in lung cancer surgery [1]. Postoperative pneumonia is a serious infection that occurs after lung cancer surgery, and the mortality rate from postoperative pneumonia after lung cancer surgery remains high, despite the relatively recent reduction in operative mortality after lung resection [2, 3]. Lee et al. and Schussler et al. reported a 27% and 19% in-hospital mortality of postoperative pneumonia after lung cancer surgery, respectively, whereas the mortality rate without postoperative pneumonia after lung cancer surgery is reported to be 2.4% [2, 3]. Algar et al. reported that the length of hospital stays with postoperative complications, including empyema and pneumonia, was 18 days after a lung cancer surgery, whereas the hospital stays without any postoperative complications was 12 days [4]. The prolonged length of a hospital stay also leads to an increase in medical expenses. Although the rate of postoperative respiratory complications has been in a slight decline, most likely due to the advancement of surgical interventions [1, 5, 6], the absolute number of the patients with postoperative respiratory

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complications may increase, especially in Japan, due to the growing number of lung cancer patients [https://ganjoho.jp/ reg stat/index.html]. Therefore, the prevention of postoperative respiratory infections (e.g., pneumonia and empyema) after lung cancer surgery is important. Older age, male sex, lower respiratory function, intraoperative complications, more invasive operation, pathologic stage, and smoking history are some well-known risk factors for postoperative respiratory infections [1, 7-9]. Risk factors for a prolonged postoperative hospital stay after lung cancer surgery include postoperative complications, more invasive operation, older age, male sex, higher Zubrod score, and smoking history [3, 4, 10–13]. However, the association between oral health status (or oral care intervention) and postoperative respiratory infections/prolonged postoperative hospital stay has not been investigated.

Recently, the effectiveness of oral care interventions has been reported including associations between poor oral health and pneumonia in intubated patients and for the prevention of ventilator-associated pneumonia [14-17]. There has been increasing research regarding the effects of oral care intervention on chemotherapy and radiotherapy [18, 19], especially in terms of prechemotherapeutic management for patients with hematological malignancy [20-23]. Studies on oral care intervention for perioperative management have also been on a rise. Several studies reported that oral care intervention was effective for preventing postoperative pneumonia, particularly in gastrointestinal cancer treatment (e.g., oral and esophageal cancers) and cardiovascular surgery [24-30]. However, to the best of our knowledge, only one study has investigated the associations between oral care intervention and postoperative pneumonia after lung cancer resection [31]; no studies have surveyed the associations between oral care intervention and postoperative respiratory infections after lung cancer surgery. Furthermore, there have been no investigations regarding whether perioperative oral management can shorten postoperative hospital stay for lung cancer surgery patients. Notably, one study revealed that perioperative oral intervention shortened the postoperative hospital stay for colorectal cancer patients [25]; however, that study only used a univariate analysis and did not consider confounding factors, such as postoperative complications, or intraoperative factors, such as bleeding [25]. Therefore, this retrospective study investigated the effect of perioperative oral care intervention prior to lung cancer resection, particularly with regard to postoperative hospital stays and respiratory infections. Perioperative oral care intervention has the potential to improve mastication and facilitate increased oral intake. It may also accelerate postoperative recovery, leading to a shorter hospital stay. Moreover, perioperative oral care intervention has the potential to reduce the bacterial load in the oropharyngeal region. This prevents the postoperative entry of infectious bacteria into the bronchi and pulmonary alveolus, further reducing the chances of postoperative respiratory infection.

# **Materials and methods**

# Study design and participants

The study protocol was approved by the Ethics Committee of Yamagata University (H29-423). Consent was obtained through an online opt-out method; none of the eligible patients declined to participate. All patients that underwent resection of lung cancer, stage I to III, at the Department of Thoracic Surgery at Yamagata University Hospital between April 2011 and March 2017, were included in this study. The total number of patients was 586. Of these 586 patients, 398 were referred to the Department of Oral and Maxillofacial Surgery for perioperative oral care intervention, while the remaining 188 were not referred to the Department of Oral and Maxillofacial Surgery. The lung cancer patients were admitted to the Department of Thoracic Surgery, 2-4 days before the lung cancer surgery while the oral care intervention was performed 1-4 days before the lung cancer surgery in the Department of Oral and Maxillofacial Surgery. Oral care intervention was performed following a protocol produced in consensus by several dentists and dental hygienists. Panoramic radiography was taken for all patients to screen for dental caries, periodontitis, and jaw lesions. A basic periodontal examination, scaling for all remaining teeth, and professional mechanical tooth cleaning were conducted in all patients. Severely mobile teeth, which posed a risk of an aspiration by spontaneous teeth exfoliation, were extracted. The teeth with a deep gingival pocket greater than 4 mm and a past acute inflammation were also extracted while teeth with a deep gingival pocket greater than 4 mm but no acute inflammation in the past were not extracted. Teeth with periapical pathosis with a past acute inflammation were extracted; however, teeth with periapical pathosis but no acute inflammation in the past were not extracted regardless of the size of periapical pathosis. Decayed teeth were sealed with temporary filling materials. Severely decayed teeth that only had the remaining root and had an acute inflammation in the past were extracted. Severely decayed teeth that did not have any acute inflammation in the past were not extracted. Of the 586, one patient was excluded due to a brain infarction after the surgery. In total, 585 patients were analyzed.

### Measurements

Patients' demographic characteristics, including age, sex, body mass index, Brinkman index (a surrogate index of smoking habits) [32], and a history of diabetes mellitus, were retrospectively investigated. Clinical characteristics were collected by chart review including the forced expiratory volume in 1 s, forced vital capacity, intraoperative bleeding, operative time, stage of lung cancer, type of resection (e.g., wedge, segmental, or lobectomy), operative approach (e.g., open or thoracoscopic), surgical site (e.g., right or left), occurrences of postoperative pneumonia and other complications, oral care intervention status, and the length of postoperative hospital stay. Comprehensive diagnosis of postoperative pneumonia was performed by respiratory surgeons based on the body temperature, productive cough, physical findings (e.g., coarse crackles and respiratory rate), laboratory data (e.g., white blood count and C-reactive protein), and diagnostic imaging (e.g., chest X-ray or chest computed tomography). Empyema was defined as a purulent effusion in the postoperative thoracic cavity. Postoperative complications evaluated in this study included bleeding, supraventricular arrhythmia, phrenic nerve paralysis, recurrent laryngeal nerve palsy, chylothorax, pulmonary fistula, pulmonary atelectasis, pneumonia, and empyema.

## **Statistical analyses**

Student's t test and the chi-squared test were performed to analyze the distributions of quantitative and qualitative characteristics. Backward multiple regression analysis was performed to investigate the relationships between length of postoperative hospital stay and potential risk factors. First, the univariate regression analysis was conducted to select candidate risk factors for a longer postoperative hospital stay. The variables that had a p value less than 0.1 in the univariate analysis were selected for representative variables, and backward multiple regression analysis was performed with the representative risk factors for the longer postoperative hospital stay. Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for the risk of developing postoperative pneumonia and empyema, using the univariate logistic regression analysis. Adjusted ORs and 95% CIs were calculated for the risk of developing a postoperative respiratory infection, using multivariate logistic regression analysis to examine independent associations between the occurrence of postoperative respiratory infections and various parameters. For the selection of variables for multivariate logistic regression analysis, backward elimination was performed with representative variables with a p value of less than 0.1 in univariate analysis. Statistical significance was set at p < 0.05. Statistical analyses were performed using SPSS software (version 20.0, IBM Corp., Armonk, NY, USA).

# Results

Table 1 shows the distribution of clinical and demographic parameters for patients with and without postoperative

respiratory infections. The number of patients with pneumonia or empyema postoperatively was 20 (3.4%). Patients with postoperative respiratory infections were significantly older and had significantly longer operative time, longer postoperative hospital stay, and higher Brinkman index, compared with patients without postoperative respiratory infections. Body mass index forced expiratory volume in 1 s, forced vital capacity, and intraoperative bleeding were not significantly different between patients with postoperative respiratory infections and patients without any postoperative respiratory infections. The chi-squared analysis revealed significant differences in the distributions of sex, surgical site, and stage of lung cancer between the groups. The distribution of diabetes mellitus, operative approach, type of resection, and oral care intervention was not significantly different between the groups. Figure 1 shows the comparison of the postoperative hospital stay (days) between the patients who received an oral care intervention and those that did not receive any oral care intervention. The mean value of postoperative hospital stay was 7.8 days in the oral care group and 9.7 days in the nonoral care group. The postoperative hospital stay was significantly lower in the oral care group than in the non-oral care group. Table 2 shows the results of uni- and multipleregression analysis to determine the effects of each parameter on the length of postoperative hospital stay. The univariate regression analysis revealed 11 variables with a p value of less than 0.1 including younger age, fewer postoperative complications, higher forced vital capacity, less intraoperative bleeding, less operation time, female sex, operative approach such as thoracoscopic surgery, less Brinkman Index, a lower stage of lung cancer, type of resection such as segmental resection, and oral care intervention. Backward multiple regression analysis with the abovementioned 11 representative factors revealed that younger age (p = 0.018,  $\beta = 0.089$ ), fewer postoperative complications (p < 0.001,  $\beta = 0.240$ ), less intraoperative bleeding (p < 0.001,  $\beta = 0.214$ ), thoracoscopic type of surgery (p = 0.001,  $\beta = -0.139$ ), and inclusion in the oral care intervention group (p = 0.027,  $\beta = 0.083$ ) were the five factors significantly associated with a shorter postoperative hospital stay. The variable of postoperative complications had the highest standard partial regression coefficient ( $\beta$ ) in the abovementioned five variables ( $\beta = 0.240$ ). The adjusted coefficient of determination  $(R^2)$  in this model was 0.190. Table 3 shows the crude and adjusted odds ratio and the 95% confidence intervals (95% CI) for variables associated with postoperative respiratory infections by univariate and multivariate logistic regression analysis. The univariate logistic regression analysis revealed nine variables with a p value less than 0.1 including older age, higher forced vital capacity, more intraoperative bleeding, more operation time, male sex, higher Brinkman index, left surgical site, more advanced stage, and lack of oral care intervention. Using these nine variables, a multivariate logistic regression analysis revealed

#### Table 1 Characteristics of the participants

		Pneumoni				
		-		+		
		n = 565				p value <sup>a</sup>
Age (years) <sup>a</sup>		69.3	9.4	74.1	9.9	0.028*
BMI (kg/m <sup>-2</sup> )		22.9	3.3	22.8	3.6	0.853
FEV1.0 (%)		74.3	10.6	73.2	13.0	0.648
FVC (%)		102.1	32.4	92.51	23.7	0.190
Intraoperative bleeding (g)		136.7	230.9	367.3	654.4	0.132
Operation time (min)		182.4	64.5	228.6	87.1	0.029*
Postoperative hospital stay (days)		7.6	5.6	31.9	30.1	0.002*
Brinkman index		598.5	682.8	982.0	614.8	0.014*
		п	%	п	%	p value <sup>b</sup>
Sex	Male	346	61.2	17	85.0	0.023*
	Female	219	38.8	3	15.0	
Diabetes mellitus	No	460	81.4	17	85.0	0.479
	Yes	105	18.6	3	15.0	
Operative approach	Open surgery	187	33.1	10	50.0	0.094
	Thoracoscopic surgery	378	66.9	10	50.0	
Surgical site	Right	332	58.8	16	80.0	0.044*
	Left	233	41.2	4	20.0	
Stage	0 or Ia	384	68.0	9	45.0	0.031*
	Ib-III	181	32.0	11	55.0	
Type of resection	Wedge or segmental resection	210	37.2	5	25.0	0.193
	Lobectomy resection	355	62.8	15	75.0	
Oral care intervention	Yes	387	68.5	10	50.0	0.070
	No	178	31.5	10	50.0	

SD standard deviation

\* Statistically significant (p < 0.05)

<sup>a</sup> p value according to Student's t test

<sup>b</sup> p value according to chi-squared test

that the independent risk factors for the postoperative respiratory infections were older age (p < 0.028: odds ratio = 1.075 per 1-year increase) and longer operative time (p = 0.002, odds ratio = 1.010 per 1-min increase). Lack of oral care intervention is a potential risk factor for the occurrence of postoperative respiratory infections, although not statistically significant (p = 0.059, odds ratio = 2.448).

# Discussion

This study was a comprehensive investigation of the effects of oral care intervention for lung cancer surgery patients which revealed that oral care intervention was independently associated with a shorter postoperative hospital stay. Furthermore, oral care intervention could reduce the likelihood of postoperative respiratory infections. To the best of our knowledge, the present study is the first to show that oral care intervention can reduce the length of hospital stay after lung cancer surgery.

Although the current study was unable to identify prior surveys regarding the relationship between oral care intervention and length of hospital stay after lung cancer surgery, several other studies investigated other predictors of prolonged length of hospital stay after lung cancer surgery (but not consider oral care intervention) [12, 13]. Age, male sex, history of diabetes mellitus, invasive surgical approach, and occurrence of postoperative complications were the risk factors for a prolonged postoperative hospital stay in these studies [12, 13]. These are reasonable factors from a clinician's perspective as they are likely to lead to wound healing delay and subsequent prolonged hospital stay. In our study, more



**Fig. 1** A comparison of postoperative hospital stay (days) between patients who received oral care intervention (oral care group) and patients that did not receive oral care intervention (non-oral care group). The bar graph shows the mean value of postoperative hospital stay for the two groups. The error bar indicates the standard error. The mean values of

postoperative hospital stay are 7.8 days for the oral care group and 9.7 days for the non-oral care group. The postoperative hospital stay is significantly lower in the oral care group than in the non-oral care group. The comparison was performed using the Student's *t* test. A *p* value of < 0.05 was considered statistically significant

#### Table 2 Backward multiple regression analysis of risk factors for postoperative hospital stay

	Postoperative hospital stay											
	Univariate					Multivariate						
Variable	В	S.E	ß	t	<i>p</i> -value		В	S.E	ß	t	<i>p</i> -value	_
Age (years)	0.108	0.039	0.114	2.782	< 0.001	*	0.084	0.035	0.089	2.368	0.018	*
BMI (kg/m <sup>-2</sup> )	0.071	0.111	0.026	0.639	0.523							
Diabetes mellitus (yes vs. no)	0.670	0.952	0.029	0.704	0.482							
Postoperative complications <sup>†</sup>	6.996	0.880	0.313	7.948	< 0.001	*	5.361	0.856	0.240	6.260	< 0.001	*
FEV1.0 (%)	-0.019	0.035	-0.023	-0.545	0.586							
FVC (%)	-0.031	0.011	-0.112	-2.724	0.007	*						
Intraoperative bleeding (g)	0.011	0.001	0.322	8.218	< 0.001	*	0.007	0.001	0.214	5.252	< 0.001	*
Operation time (minutes)	0.024	0.006	0.174	4.272	< 0.001	*						
Sex (female vs. male)	-1.688	0.758	-0.092	-2.226	0.026	*						
Operative approach (thoracoscopic surgery vs. open surgery)	-4.700	0.757	-0.249	-6.208	< 0.001	*	-2.626	0.757	-0.139	-3.470	0.001	*
Brinkman Index	0.001	0.001	0.103	2.498	0.013	*						
Surgical site (left vs. right)	0.299	0.753	0.016	0.397	0.691							
Stage (Ib-III vs. 0 or Ia)	4.437	0.765	0.234	5.799	< 0.001	*						
Type of resection (lobectomy resection vs. wedge or segmental resection)	2.666	0.758	0.144	3.515	< 0.001	*						
Oral care intervention (no vs. yes)	1.904	0.787	0.100	2.419	0.016	*	1.583	0.713	0.083	2.221	0.027	*

\*Statistically significant (p <0.05).

Adjusted for representative variables that were marginally significant in univariate analysis (p < 0.1). The representative variables were age, FVC (%), intraoperative bleeding, operation time, sex, Brinkman index, surgical site, stage, type of resection, and oral care intervention.

<sup>†</sup>Postoperative complications were bleeding, supraventricular arrhythmia, phrenic nerve paralysis, recurrent laryngeal nerve palsy, chylothorax, pulmonary fistula, pulmonary atelectasis, pneumonia, and empyema

	Postoperative respiratory infections								
Variable		Crude OR	(95% CI)	<i>p</i> value		Adjusted OR	(95% CI)	<i>p</i> value	
Age (years)	(per 1-year increase)	1.066	(1.007 – 1.129)	0.028	*	1.075	(1.008 1.146)	0.028	*
BMI (kg/m <sup>-2</sup> )	(per 1 kg/m <sup>2</sup> increase)	0.987	(0.863 - 1.130)	0.853					
FEV1.0 (%)	(per 1% increase)	0.990	(0.950 - 1.032)	0.647					
FVC (%)	(per 1% increase)	0.978	(0.957 - 0.999)	0.040	*				
Intraoperative bleeding (g)	(per 1-g increase)	1.001	(1.000-1.002	0.004	*				
Operation time (min)	(per 1-min increase)	1.009	(1.003 - 1.015)	0.002	*	1.010	(1.003 – 1.016)	0.002	*
Sex	Female vs. male	0.279	(0.081-0.962)	0.043	*				
Operative approach	Thoracoscopic surgery vs. Open surgery	0.495	(0.202 - 1.209)	0.123					
Brinkman Index	(per 1 increase)	1.001	(1.000 - 1.001)	0.016	*	1.000	(1.000 1.001)	0.093	
Surgical site	Left vs. right	0.356	(0.118-1.079)	0.068		0.344	(0.111 1.067)	0.065	
Stage	Ib-III vs. 0 or Ia	2.593	(1.056-6.368)	0.038	*				
Type of resection	Lobectomy resection vs. wedge or segmental resection	1.775	(0.636-4.953)	0.273					
Diabetes mellitus	Yes vs. no	0.773	(0.222 – 2.686)	0.686					
Oral care intervention	No vs. yes	2.174	(0.889-5.317)	0.089		2.448	(0.966 - 6.204)	0.059	

Table 3 Crude and adjusted odds ratios and 95% confidence intervals for variables associated with postoperative respiratory infections

Adjusted for representative variables that were marginally significant in univariate analysis (p < 0.1). The representative variables were age, FVC (%), intraoperative bleeding, operation time, sex, Brinkman index, surgical site, stage, type of resection, and oral care intervention

OR odds ratio, CI confidence interval

\*Statistically significant (p < 0.05)

invasive operations (i.e., those with longer operative time and those that involved open surgery) and the occurrence of postoperative complications were risk factors for a prolonged hospital stay. These findings are consistent with those of prior studies [12, 13]. Moreover, we found that the lack of oral care intervention was an independent risk factor for a prolonged hospital stay. Since only one prior study showed that perioperative oral intervention was associated with a shortened postoperative hospital stay for colorectal cancer patients, without adjustment for confounding factors [25], our results in this study are clinically important.

Older age, longer operative time, and higher Brinkman index were significant risk factors for the development of postoperative respiratory infections in the present study. Independent risk factors for postoperative respiratory infections have been previously identified [1, 2, 31]; these include age [1] and other clinical parameters (e.g., intraoperative bleeding, operative time, smoking history, and operative approach) [2, 8, 31]. Although our results were not entirely consistent with those of the prior studies in terms of risk factors for postoperative respiratory infections, they were reasonably similar.

The mechanism underlying the association between oral care intervention and shorter length of hospital stay is unclear. We suspect that perioperative oral care intervention enabled improved mastication in the patients, which facilitated increased oral intake. As a result, postoperative recovery may have been accelerated, leading to a shorter hospital stay. Since the prevalence of severe periodontitis is significantly higher in cancer patients than in healthy subjects [33], perioperative oral care intervention (e.g., extraction of teeth with severe periodontitis and removal of severe dental calculus) presumably enables patients to eat more easily by mouth. Furthermore, early commencement of oral intake has been previously associated with early recovery and early hospital discharge [34, 35]. The results of prior studies may help to understand the associations between perioperative oral care intervention and shorter hospital stay in the present study. The mechanism underlying the association between oral care intervention and reduced occurrence of postoperative respiratory infection has also been unclear; however, perioperative oral care intervention presumably reduces the bacterial load in the oropharyngeal region, thereby preventing postoperative entry of infectious bacteria into the bronchi [31]. Importantly, the presence of pathogens in preoperative dental plaque has been identified as a risk factor for postoperative pneumonia [31, 36]. The presence of dental plaque (including denture plaque) is also a well-known risk factor for silent aspiration [37, 38]. The direct transfer of oral bacteria has the potential to cause surgical site infections [25], such as empyema. In the present study, the management of oral microbiota by perioperative oral care intervention may have contributed to the reduced incidence of postoperative respiratory infections. However, the evidence was not particularly robust, and further studies are needed to confirm these potential mechanisms.

This study had several limitations. First, it was a retrospective study, and a prospective study is required to provide more robust evidence of the effects of oral care intervention in patients undergoing lung cancer surgery. However, this approach is likely to be problematic because of existing reports regarding the potential effectiveness of oral care intervention, thus intentional randomization to groups without oral care intervention being not ethically acceptable. Second, the present data may not represent the overall healthcare delivery system. In Japan, many hospitals do not have a dentistry department. The hospital in the current study has a department of dental, oral, and maxillofacial surgery; therefore, the patients in the hospital are referred relatively easily. The third is measurement bias. In the present study, oral care intervention was performed by not one but unspecified several dentists. The diagnostic criteria by several dentists cannot be a perfect match. For example, severely mobile teeth, with a risk of mis-swallowing by spontaneous teeth exfoliation, were routinely extracted; however, the diagnosis might be slightly different among the dentists. The fourth limitation is cognitive bias. In the oral care intervention protocol, the periodontal teeth with deep gingival pockets, severely decayed teeth, and teeth with periapical pathosis were extracted in case the teeth had had an acute inflammation in the past. The periodontal teeth with deep gingival pockets, severely decayed teeth, and teeth with periapical pathosis were not extracted in case the teeth did not have any acute inflammation in the past. The criteria relied on the memory of the patients. Fifth, the adjusted coefficient of determination  $(R^2)$  in this multiple regression model was not high, which indicates that there may be other potential risk factors for a prolonged postoperative hospital stay. Additional potential risk factors should be included in future studies for more robust modeling, although this study selected commonly used risk factors in this study (e.g., clinical characteristics).

In conclusion, with several statistically important clinical and demographic parameters, this retrospective study revealed that perioperative oral care intervention was independently associated with shorter postoperative hospital stay after lung cancer surgery and that perioperative oral care intervention could prevent the occurrence of postoperative respiratory infections.

Author contributions S.I., I.Y., M.S., H.O., and M.I. designed the study. S.I. and S.T. wrote the initial draft of the manuscript. S.I. contributed to the analysis. I.Y., K.K., K.E., A.S., K.H., J.S., K.S., and K.Y. contributed to data collection and interpretation of data and assisted in the preparation

of the manuscript. All authors critically reviewed the manuscript. I.Y. contributed as equal first author and equal corresponding author. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

# **Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of Yamagata University approved this study protocol (approval number H29-423).

**Informed consent** Patients were given the option to opt-out of this study online. None of the subjects declined to participate.

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