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Original Article

Physical Function and Health-Related Quality of Life after Surgery for Nontuberculous Mycobacterial Pulmonary Disease: A Prospective Cohort Study

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Purpose: To investigate the exercise capacity and health-related quality of life (HRQOL) of surgical patients with nontuberculous mycobacterial pulmonary disease (NTM-PD) preoperatively versus 6 months postoperatively.
Methods: This prospective observational study included patients with NTM-PD and was conducted at a single center. The intervention was surgical resection plus perioperative and post-discharge physical therapy. The physical function was assessed preoperatively and 6 months postoperatively using the 6-minute walk test (6MWT). HRQOL was assessed preoperatively and 6 months postoperatively using the Short-Form 36 (SF-36) health survey questionnaire and St. George's Respiratory Questionnaire. The postoperative HRQOL was compared between patients with and without preoperative clinical symptoms.
Results: In total, 35 patients were analyzed. The preoperatively symptomatic group had significantly lower preoperative HRQOL than the preoperatively asymptomatic group ($p < 0.05$). Compared with preoperatively, there were significant improvements at 6 months postoperatively in the 6MWT ($p < 0.01$) and HRQOL, mainly in the SF-36 mental component summary ($p < 0.01$). The SF-36 mental component summary in the preoperatively symptomatic group was very significantly improved from preoperatively to 6 months postoperatively ($p < 0.05$).
Conclusion: The combination of surgical treatment and physical therapy for NTM-PD contributes to improvements in physical function and HRQOL.

Keywords: nontuberculous mycobacterial pulmonary disease, surgical treatment, physical therapy, exercise capacity, health-related quality of life

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Introduction

Nontuberculous mycobacterial pulmonary disease (NTM-PD) is a progressive lung disease that causes airway destruction and respiratory failure.[1] The incidence of NTM-PD is increasing worldwide and is rapidly increasing in Japan.[2–4] NTM-PD causes chronic cough and sputum production and is characterized by exercise intolerance, respiratory dysfunction, and impaired health-related quality of life (HRQOL).[5–7] The treatment of NTM-PD is primarily medical therapy with a focus on multidrug regimens, although surgical treatment is sometimes required.[1] Surgical treatment is aimed at cure, palliation, and control of disease activity.[8,9] An increasing number of patients are undergoing pulmonary surgery for NTM-PD in the United States and Japan.[10,11] The HRQOL of such patients is assessed using a respiratory illness questionnaire at baseline and postoperatively.[8,12] In addition, the presence or absence of symptoms is of great importance in selecting the treatment strategy for NTM-PD.[13] For patients undergoing surgery for lung cancer, the performance of pre- and postoperative physical therapy contributes to the prevention of postoperative complications and the improvement of HRQOL.[14,15] Several studies have reported the changes in physical function and HRQOL over time after surgery for lung cancer,[15–17] but only one study has examined the physical function and HRQOL outcomes after surgery for non-cystic fibrosis bronchiectasis, including NTM-PD.[18] Furthermore, there are no reports on the effects of combined surgical treatment and physical therapy for patients with only NTM-PD. The purpose of this study was to investigate the pre- and postoperative exercise capacity and HRQOL of patients who underwent surgery for NTM-PD.

Methods

Study population

This prospective study was conducted from August 2018 to April 2020 in a single hospital in Japan. The study was approved by the Institutional Review Board of Human Research of Fukujuji Hospital (approval number 18022), and all patients provided informed consent for study participation. At our institution, the indications for surgery for patients with NTM-PD were failure of drug therapy to eliminate the bacteria, remnant cavitary lesions and/or severe focal bronchiectasis, or evidence of rapid disease progression.[7,19] All 35 consecutive patients who underwent anatomical lung resection for NTM-PD combined with pre- and postoperative chemotherapy were prospectively enrolled in this study and met the diagnostic criteria of the 2007 American Thoracic Society and the Infectious Diseases Society of America guidelines.[1] Of the 35 patients who survived surgery, 32 patients were assessed preoperatively and at 6 months postoperatively (**Fig. 1**). High-resolution CT was used to identify the affected lung segments and the area requiring resection, with a discussion of the findings taking place at a multidisciplinary meeting. The presence or absence of preoperative clinical symptoms was assessed by questioning at the time of physical therapy assessment. The study exclusion criteria were comorbidities or lung function and cardiopulmonary capacity that precluded the planned resection, musculoskeletal impairment that interfered with exercise performance, inability to understand the HRQOL questionnaires, active hemoptysis, two-staged bilateral lung resection, and age younger than 18 years.

Physical therapy

As part of standard perioperative care, all patients received an in-hospital physical therapy consultation 3 to 4 days prior to surgery. Patients were encouraged to meet the aggressive postoperative early mobilization recommendations for the prevention of postoperative complications and were given instructions on deep breathing and coughing exercises for airway clearance. After discharge from the hospital, exercise and respiratory care included the maintenance of physical activity levels using a pedometer, a home exercise program for the upper and lower extremities, airway clearance, nutrition

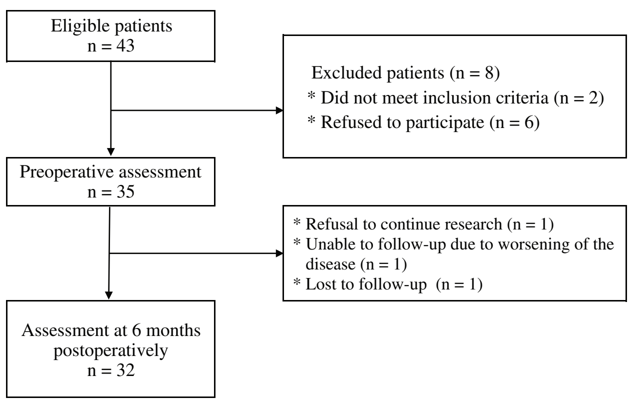

Fig. 1 Study flowchart illustrating patient inclusion and exclusion.

support, mental health care, and routine hospital visits to see a physical therapist.

Follow-up assessments of physical function and HRQOL

Patients performed the 6-minute walk test (6MWT) and underwent a HRQOL evaluation preoperatively (usually 2 to 3 days before surgery) and 6 months postoperatively. The main outcomes were the improvements in the 6-minute walk distance (6MWD) and HRQOL after resection. The 6-MWT was performed in accordance with the published guidelines.[20] We assessed the HRQOL using the Short-Form 36 (SF-36) health survey questionnaire and St. George's Respiratory Questionnaire (SGRQ), both of which are general questionnaires with validated self-reported versions translated into Japanese. The SF-36 is a generic HRQOL instrument with 36 items that assesses eight health concepts (physical functioning, role limitation caused by physical problems, body pain, general health perception, vitality, social functioning, role limitation caused by emotional problems, and mental health).[21] Scores standardized to norms and weighted averages are used to create a physical component summary (PCS) and mental component summary (MCS) on a standard scale. In functional scales with multiple items, higher scores indicate a higher level of health status.

The SGRQ is a disease-specific tool comprising 50 items that provide an individual score for each of three domains (symptoms, impact, and activity), as well as a total score.[22] The score for each domain ranges from 0 to 100, with lower scores indicating better HRQOL. Permission to use the Japanese version of the SGRQ was obtained from Dr. Koichi Nishimura.

Statistical analysis

Data were expressed as means with standard deviation or medians with interquartile ranges for continuous variables, and as counts with percentages for categorical variables. Normal distribution of the data was tested by the Shapiro–Wilk normality test. The 6MWD and HRQOL scores before and after lung resection were compared using the Student's t test or Wilcoxon rank-sum test. Furthermore, due to the recognized importance of the presence or absence of symptoms in the treatment of NTM-PD,[13] a comparative study was conducted of patients with and without preoperative symptoms. A p value <0.05 was considered significant, and Statistical Package for the Social Sciences version 26.0 software was used for all statistical analyses.

Results

Patients

The characteristics of the enrolled patients are shown in **Table 1**. The following data were collected: age, sex, body mass index, smoking status, diseases duration, current disease duration, preoperative sputum culture, disease type, disease extent, preoperative clinical symptoms, pulmonary function tests, and modified Medical Research Council dyspnea scale. Preoperative assessment revealed pulmonary bacterial infection in all patients, and *Mycobacterium avium* complex was detected in the preoperative sputum of 27 patients (77%). 20 patients (57%) had preoperative clinical symptoms such as cough, sputum, and chest pain. The baseline SGRQ and SF-36 scores were compared between the patients with and without preoperative clinical symptoms; the baseline SGRQ symptom subscale score, total SGRQ score, and SF36v2 PCS score were significantly worse in the patients with preoperative symptoms than in those without preoperative symptoms ($p < 0.05$).

Surgical procedure

The types of anatomic lung resections performed for NTM-PD are shown in **Table 1**. Of the 35 patients who underwent surgery, 32 (91%) and 3 (9%) were scheduled to undergo video-assisted thoracoscopic surgery and thoracotomy, respectively; however, one patient was subsequently excluded due to postponement of the scheduled surgery and another was excluded because she underwent two-stage bilateral surgery. Three patients had adverse events that required only clinical treatment: prolonged air leak (>7 days) in two patients and tachycardia requiring medication in one. There was no operative mortality. All patients were ambulating with or without a gait aide in the intensive care unit with the assistance of a physical therapist on the first postoperative day. All patients were finally discharged home with no adverse events. One patient was difficult to follow-up after 3 months postoperatively due to worsening disease.

Primary outcomes

Table 2 shows the results of the repeated measures analyses of variances comparing physical function and HRQOL from preoperatively to 6 months postoperatively. The exercise capacity (based on the 6MWD) was significantly improved at 6 months postoperatively compared with preoperatively. The mean change in the 6MWD at 6 months postoperatively (38.1 m) far

Table 1 Demographics of the 35 patients who underwent lung resection

Variable	Value
Age (years)	54.8 ± 14.5
Female, sex	29 (83%)
BMI (kg/m^2)	19.4 ± 2.4
Smoking status (never/former)	26/9
Disease duration[a] (months)	25 (12–82)
Current treat duration[b] (months)	11 (5–21)
Sputum culture	
Mycobacterium avium complex	27 (77%)
Mycobacterium abscessus complex	5 (14%)
Mycobacterium kansasii	2 (6%)
Mycobacterium paraense	1 (3%)
Preoperative sputum culture positive	16 (46%)
Disease type	
Nodular-bronchiectatic	17 (49%)
Fibrocavitary	4 (11%)
Nodular-bronchiectatic with cavity	14 (40%)
Affected segments[c]	3 (1–5)
Disease extent	
Limited	20 (57%)
Extensive	15 (43%)
Clinical symptoms	
Hemoptysis	1 (2%)
Cough	14 (40%)
Sputum	13 (37%)
Fever	1 (2%)
None	15 (43%)
Preoperative pulmonary function test	
FEV_1 (L)	2.2 ± 0.5
FEV_1 % predicted	89 ± 16
FVC (L)	2.7 ± 0.6
FVC % predicted	90 ± 15
mMRC	0 (range 0–1)
Surgical procedure	
Lobectomy	17 (49%)
Segmentectomy	8 (23%)
Bilobectomy	2 (6%)
Combined resection	7 (20%)
Right upper lobe + right S6	1
Right middle lobe + right S6	1
Left lower lobe + lingulectomy	4
Right upper and middle lobe + right S6	1
Pneumonectomy	1 (2%)
Surgical approach	
Video-assisted thoracic surgery	32 (91%)
Thoracotomy	3 (9%)
Postoperative hospital stay (days)	11 (9–17)

Data are reported as mean ± standard deviation, n (%), and median (interquartile range)
[a]Interval between the diagnosis of the disease and the time of surgery
[b]Interval between the start of the current treatment and the time of surgery
[c]Number of segments with irreversible lung damage
BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: modified Medical Research Council dyspnea scale

exceeded the minimum clinically important difference (MCID) of 25 m.[23] In addition, the 6MWD at 6 months postoperatively was significantly improved in both the patients with preoperative clinical symptoms and those without preoperative clinical symptoms (**Fig. 2**). The SGRQ activity score and the SF-36 PCS score were significantly worse at 6 months postoperatively compared with preoperatively. In contrast, the SF-36 MCS score was significantly better at 6 months postoperatively than preoperatively. There were no significant differences in the pre- and postoperative HRQOL by preoperative disease type (nodular bronchiectatic versus other). **Table 3** shows the HRQOL score preoperatively and at 6 months postoperatively in the patients with and without preoperative clinical symptoms. Both groups had significantly decreased postoperative SGRQ activity scores compared with preoperatively. The SF-36 MCS score was significantly improved at 6 months postoperatively compared with preoperatively in the group with preoperative symptoms but did not show such improvement in the group without preoperative symptoms.

Discussion

The present study evaluated the changes in exercise capacity and HRQOL after surgery plus perioperative and post-discharge physical therapy for NTM-PD. The findings demonstrated that lung resection significantly improved the exercise capacity and HRQOL of patients with NTM-PD.

The MCID of the 6MWD after exercise training is 25 m in patients with bronchiectasis.[23] In our study, the 6MWD at 6 months postoperatively was significantly improved by the MCID compared with baseline. Previous studies of people with lung cancer have shown that better mobilization adherence during hospitalization is significantly related to a higher 6MWD postoperatively.[17] Therefore, in our study, physical function was also expected to improve by encouraging aggressive mobilization during hospitalization and after discharge. It is often assumed that ventilation/perfusion (V_A/Q) mismatch occurs or exaggerates during exercise in patients with chronic respiratory impairment and causes reduced exercise capacity.[24] Similarly, NTM-PD results in V_A/Q mismatch that shows as a focal defect of perfusion in the affected area on technetium perfusion scintigraphy.[8] In the present study, lung resection may have improved V_A/Q impairment and contributed to the improvement in exercise capacity. Patients who have undergone lung resection for cancer still have impaired

Table 2 Physical function and HRQOL from preoperatively to 6 months postoperatively for the 32 patients who completed the follow-up

Variable	Preoperative	Six months postoperative	p value
6MWD, m	545.4 ± 51.8	583.5 ± 57.5[a]	<0.01
Dyspnea – Borg scale	2 (0.5–4)	3 (2–4)	0.02
Leg fatigue – Borg scale	1 (0.5–3)	2 (2–4)	0.59
SGRQ score			
Symptom	23.6 (16.2–43.7)	27.0 (11.8–47.3)	0.46
Activity	17.5 (5.3–35.6)	32.6 (11.5–48.3)	<0.01
Impact	16.8 (8.4–29.3)	12.1 (7.0–23.4)	0.28
Total	20.7 (9.6–28.8)	20.6 (12.3–32.5)	0.56
SF36v2			
Physical functioning	50.6 (39.8–54.2)	47.0 (33.5–54.2)	0.2
Role physical	55.7 (39.1–55.7)	45.8 (39.1–55.7)	0.24
Bodily pain	61.7 (44.7–61.7)	54.6 (44.7–54.6)	0.11
General health	44.2 (36.2–52.2)	46.9 (39.5–51.5)	0.01
Vitality	49.8 (43.4–59.5)	53.0 (46.6–59.5)	0.1
Social functioning	50.6 (31.2–57)	57.0 (44.1–57.0)	0.02
Role emotional	56.1 (43.6–56.1)	56.1 (40.5–56.1)	0.54
Mental health	51.8 (43.8–57.2)	55.8 (46.5–59.9)	0.03
PCS	53.0 (38.9–55.5)	46.1 (37.7–54.0)	0.04
MCS	52.8 (41.5–57.2)	55.3 (49.5–59.6)	<0.01

Data are reported as mean ± standard deviation and median (interquartile range)
[a]Thirty-one patients did complete the functional test at 6 months postoperatively
HRQOL: health-related quality of life; 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire; SF36v2: Short-Form 36 Health Survey Questionnaire; PCS: physical component summary; MCS: mental component summary

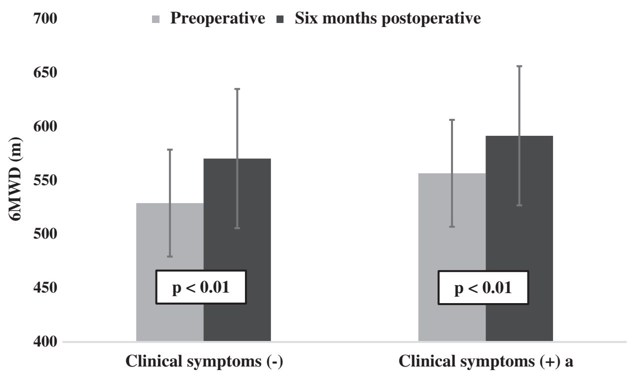

Fig. 2 Changes in the 6MWD from baseline to 6 months postoperatively for patients with versus without clinical symptoms. Data were compared using the Student's t test. 6MWD, 6-minute walk distance. a: patients with cough, sputum, hemoptysis, and fever preoperatively. 6MWD: 6-minute walk distance

respiratory function postoperatively; however, their exercise capacity is almost completely recovered by 12 months postoperatively.[16] There is a need for more detailed objective evaluation of the ventilation patterns of the respiratory system during cardiopulmonary exercise testing, including pulmonary function.

A previous study of preoperatively symptomatic patients reported that lung resection results in a significant improvement in HRQOL.[18] In our series, the HRQOL was improved at 6 months postoperatively compared with preoperatively, especially regarding the mental component. About 43% of patients in the present series had no preoperative clinical symptoms, which may explain why lung resection did not affect the non-mental components of HRQOL. Postoperative management of NTM-PD generally requires continuation of the same multidrug regimen used preoperatively, and it is recommended that patients receive chemotherapy for at least 1 year after conversion to a negative culture.[19] The continuation of chemotherapy may contribute to a lack of improvement in HRQOL after lung resection. In patients who undergo lung resection for cancer, HRQOL does not recover to the preoperative level by 1 year postoperatively,[25,26] and lower HRQOL is associated with continued postoperative chemotherapy.[25] Thus, it is also conceivable that continued chemotherapy could cause the impairment of HRQOL in patients who undergo surgery for NTM-PD. In the present study, the exercise capacity was improved at 6 months postoperatively, but the physical HRQOL did not improve

Table 3 Relationship between the change in HRQOL and preoperative clinical symptoms at 6 months postoperatively

	Clinical symptoms (−) n = 14			Clinical symptoms (+)[a] n = 18		
Variable	Preoperative	Six months postoperative	p value	Preoperative	Six months postoperative	p value
SGRQ score						
Symptom	15.2 (8.5–19.9)	16.0 (10.5–35.1)	0.55	38.2 (23.6–58.3)	32.6 (16.2–52.4)	0.18
Activity	9.0 (0–29.8)	24.2 (6.0–43.2)	0.03	21.4 (10.4–43.3)	36.1 (11.9–55.6)	0.03
Impact	12.2 (7.7–21.1)	8.7 (7.1–18.1)	0.92	22.9 (9.5–34.5)	16.6 (3.9–27.5)	0.2
Total	12.1 (6.7–22.8)	14.6 (7.3–28.0)	0.25	27.7 (12.0–35.2)	26.9 (16.1–37.9)	0.88
SF36v2						
Physical functioning	52.4 (47.0–57.8)	50.6 (47.0–57.8)	0.75	47.0 (36.2–55.1)	41.6 (31.7–54.2)	0.2
Role physical	55.7 (51.6–55.7)	54.1 (42.4–55.7)	0.12	44.1 (31.7–55.7)	42.4 (31.7–55.7)	0.65
Bodily pain	61.7 (61.7–61.7)	54.6 (52.1–61.7)	0.23	51.5 (44.7–61.7)	47.0 (44.6–54.6)	0.17
General health	50.9 (40.5–55.5)	46.9 (38.6–56.7)	0.42	41.0 (35.1–46.1)	45.6 (40.9–49.5)	<0.01
Vitality	49.8 (43.4–60.3)	54.7 (45.8–59.5)	0.1	49.8 (39.4–57.1)	51.4 (46.6–59.5)	0.09
Social functioning	57.0 (37.7–57.0)	57.0 (50.6–57.0)	0.06	37.7 (24.8–57.0)	50.6 (37.7–57.0)	0.09
Role emotional	56.1 (49.8–56.1)	56.1 (46.7–56.1)	0.93	49.8 (39.4–56.1)	43.6 (35.3–56.1)	0.35
Mental health	53.2 (46.5–59.9)	57.2 (46.5–57.9)	0.29	51.8 (43.1–55.2)	53.2 (46.5–59.9)	0.04
PCS	54.0 (50.2–55.6)	48.8 (43.3–56.0)	0.18	47.4 (33.2–54.8)	38.0 (28.1–51.5)	0.09
MCS	55.1 (46.0–58.9)	55.3 (48.9–58.5)	0.16	47.2 (40.0–54.2)	55.3 (49.0–59.7)	<0.01

Data are reported as interquartile range and expressed as Wilcoxon rank-sum test
[a]Patients with cough, sputum, hemoptysis and fever preoperatively
HRQOL: health-related quality of life; SGRQ: St. George's Respiratory Questionnaire; SF36v2: Short-Form 36 Health Survey Questionnaire; PCS: physical component summary; MCS: mental component summary

significantly. This may be characteristic of NTM-PD surgical patients. Our study included a certain number of patients whose disease had become difficult to successfully control with medical therapy; we consider that lung resection in these patients caused shortness of breath during exercise and decreased HRQOL during physical activity. In contrast, for the patients with preoperative symptoms such as sputum and cough, we consider that surgical treatment and physical therapy contributed to the improvement of their mental component of HRQOL. A systematic review suggested that postoperative exercise training contributes to improved exercise capacity and an improved physical component of HRQOL score at 12 months postoperatively.[15] In addition, exercise capacity in surgical patients with NTM-PD is strongly correlated with a reduced HRQOL score for the domain of respiratory symptoms.[7] There are many reports of short-term effects of perioperative physical therapy for patients with lung cancer (specifically, reduced postoperative complications or length of stay), but research on the long-term effects of physical therapy interventions is clearly lacking.[27] Longer term observational studies are needed to determine which patients are more likely to benefit from postoperative physical therapy.

In our study, the group with preoperative clinical symptoms had a significantly lower preoperative HRQOL and a significantly higher rate of improvement in HRQOL (SF-36 MCS) at 6 months postoperatively than the group without preoperative clinical symptoms. Previous studies have reported associations between respiratory symptoms (such as sputum and cough) and HRQOL,[28,29] and an association between the presence of a residual lesion and decreased HRQOL in patients with *M. avium* complex pulmonary disease (MAC-PD).[5] In recent years, the initiation of drug therapy has been recommended in cases with positive acid-fast bacilli sputum smears and/or cavitary lung disease,[13] but the pathogenesis and prognosis of NTM-PD vary depending on the severity of the disease. Previous reports have shown that complete resection of the parenchymal destructive lesions in MAC-PD can prevent recurrence in the long term.[19] However, there are a certain number of patients who are resistant to medical therapy or are unable to undergo complete lung resection, and the effects of combined physical therapy on physical fitness and HRQOL are unclear. The effectiveness of airway clearance in patients with NTM-PD has been reported in several studies,[30] and our study showed that perioperative and post-discharge physical therapy improved the HRQOL of patients with symptomatic NTM-PD. The present findings indicate that surgical treatment and comprehensive physical therapy of patients strongly contributed to exercise capacity and HRQOL improvement.

The present study has several limitations. First, relatively few subjects were recruited due to the limited number of surgical procedures for NTM-PD performed annually in our center. However, our hospital is a representative institution for NTM-PD surgical treatment in Japan. Second, the postoperative follow-up period was relatively short. As NTM-PD is a long-term disease with a prolonged course, physical function and HRQOL need to be investigated over a period of several years. Third, there was no control group. There is a need for a comparison of the patients with a residual disease area versus those without a residual disease area, and a comparison of a surgical group versus a medical therapy-only group.

Conclusion

The present study demonstrated that patients with NTM-PD experience a significant improvement in their exercise capacity and HRQOL after lung resection, especially regarding the mental component of HRQOL. Moreover, preoperatively symptomatic patients achieve very large improvements in HRQOL (SF-36 MCS) after surgical treatment. However, we need to determine which patients will benefit the most from physical therapy. We suggest that appropriate surgical treatment combined with perioperative and post-discharge physical therapy improves the physical function and HRQOL of patients with NTM-PD.

Authors' Contributions

YK, MH, YS, and HS made substantial contributions to study conception and design. YK, MT, and SO contributed to data acquisition. YK, SO, MH, YS, HK, and HS contributed to data analyses and interpretation. MH, YS, HK, and HS contributed to the drafting of the manuscript. YK, MT, SO, MH, YS, HK, and HS critically revised the manuscript. All authors read and approved the final manuscript.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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