European Thyroid Journal (2024) **13** e230255
https://doi.org/10.1530/ETJ-23-0255

Received 14 January 2024
Accepted 28 August 2024
Available online 28 August 2024
Version of Record published 3 October 2024

RESEARCH

The association between BMI and *BRAFV600E* mutation may differ by primary tumor size

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Abstract

Objective: Previous reports suggest that a high body mass index (BMI) increases the risk of thyroid carcinoma. However, it remains unclear whether a high BMI is associated with the risk of the *BRAFV600E* mutation. We aimed to assess whether a high BMI is associated with an increased risk of the *BRAFV600E* mutation.

Design and Methods: We screened 6558 PTC patients who had undergone *BRAFV600E* mutation testing between January 2009 and December 2017. After exclusion, 6438 PTC patients were enrolled. We used logistic regression, and restricted cubic spline plots of the adjusted odds ratios (ORs) were illustrated to model the relationship between BMI and the *BRAFV600E* mutation.

Results: Of the 6438 patients, 5102 (79.2%) had the *BRAFV600E* mutation, and 4954 (76.9%) were female. The median BMI was 23.8 (21.6–26.2) kg/m^2. The primary tumor size was ≤1 cm in 4226 patients (65.6%) and >1 cm in 2212 patients (34.4%). The *BRAFV600E* mutation was significantly associated with high BMI only in patients with a primary tumor size >1 cm (OR: 1.034; 95% CI: 1.003–1.065; $P = 0.029$), whereas no clear association was found in patients with a primary tumor size ≤1 cm (OR: 1.007; 95% CI: 0.984–1.030; $P = 0.570$). Gender was not a significant factor in either group.

Conclusions: Our study found that a higher BMI was positively associated with the *BRAFV600E* mutation in patients with a primary tumor size >1 cm. These results suggest that the association between BMI and the *BRAFV600E* mutation status differs depending on primary tumor size.

Significance Statement

Obesity has been suggested as a potential risk factor for thyroid carcinoma. The aim of this study was to assess the association between BMI and the *BRAFV600E* mutation. In this study, the *BRAFV600E* mutation was significantly associated with a high BMI only in a primary tumor size >1 cm (OR: 1.034; $P = 0.029$). No clear association was found in patients with a primary tumor size ≤1 cm (OR: 1.007; $P = 0.570$). The association between BMI and the *BRAFV600E* mutation status differs depending on the primary tumor size.

Keywords: body mass index; BRAFV600E mutation; papillary thyroid carcinoma; primary tumor size

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Introduction

The incidence of thyroid carcinoma has rapidly increased in many countries over the past few decades (1, 2, 3), but there have been no substantial changes in the mortality rate (4, 5). The use of more sensitive diagnostic techniques, such as ultrasonography, computed tomography, and magnetic resonance imaging, combined with increased medical surveillance, is thought to be primarily responsible for over-diagnosis (6). However, the incidence has been increasing in all tumor sizes (7). Thus, over-diagnosis and early detection cannot fully explain the increasing incidence of thyroid carcinoma, and there may have been a true increase in disease incidence (6). In previous reports, obesity has been suggested as a potential cause of the increasing incidence of thyroid carcinoma. Although the relationship between obesity and thyroid carcinoma is controversial, most studies suggest that obesity is positively associated with thyroid carcinoma risk in both men and women (8, 9, 10, 11).

Recently, Rahman *et al.* demonstrated a positive association between body mass index (BMI) and B-type Raf kinase (*BRAFV600E*) mutation in both men and women based on a large population-based study in Australia (12). de Biase *et al.* reported that the *BRAFV600E* mutation occurs in the early stages of cancer progression preceding histological changes (13) and may function as an initial transforming event during thyroid carcinoma development (14). Based on previous reports, obesity is a potential risk factor for thyroid carcinoma through mechanisms such as DNA damage from oxidative stress (15), and it has a positive association with higher BMI. Therefore, obesity might be a risk factor for the *BRAFV600E* mutation. Additionally, the prevalence of the *BRAFV600E* mutation in papillary thyroid carcinoma (PTC) ranges from 30% to greater than 80% (16, 17), varying by geographic region and dietary components such as iodine intake (18). Thus, we conducted this study to investigate the association between BMI and the *BRAFV600E* mutation in a large East-Asian cohort of a tertiary referral center in Korea.

Materials and methods

Study population and clinicopathological assessments

We screened the 6558 patients with PTC confirmed by pathology who underwent *BRAFV600E* mutation testing at the Samsung Medical Center from January 2009 to December 2017. Of them, we excluded 120 patients due to incomplete data or due to being younger than 18 years old.

Anthropometric factors, such as height and weight, were measured on the first day of thyroid surgery. The body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters (kg/m^2). Age at diagnosis, gender, *BRAFV600E* mutational status, final pathology reports, alcohol consumption status, and smoking status were obtained from the electronic medical record system. The primary tumor size was determined as the maximum tumor diameter in centimeters on the pathological report. Alcohol consumption status and smoking status were assessed using a structured questionnaire on the first day of thyroid surgery.

We categorized patients into two groups based on primary tumor size: ≤1 cm (T1a) and >1 cm. This study was approved by the Institutional Review Board of Samsung Medical Center (IRB no. 2023-02-132), and informed consent was waived by the committee due to the retrospective nature of the study.

Detection of the BRAFV600E mutation

We performed a dual-priming oligonucleotide (DPO)-based multiplex polymerase chain reaction (PCR) to identify the *BRAFV600E* mutation. Detailed methods were described in a previous report (19).

Statistical analysis

Continuous variables were presented as median with interquartile range (IQR), and categorical variables were presented as number and frequency. The Kruskal–Wallis test was used to compare continuous variables, while the chi-square test or Fisher's exact test was used to compare categorical variables. A logistic regression model was used to identify risk factors for BRAFV600E mutation, and odds ratios (ORs) and 95% CIs were presented. Multivariable regression was performed using backward elimination, and we set the *P*-value to enter the model at $P < 0.10$. A *P*-value less than 0.05 was considered statistically significant. Restricted cubic spline plots of the adjusted ORs were illustrated to model the relationship between BMI and the *BRAFV600E* mutation. The association between BMI and the *BRAFV600E* mutation was adjusted for age, alcohol consumption status, and smoking status. Statistical analysis was executed using SPSS version 25.0 for Windows (IBM), SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and R 3.6.1 (Vienna, Austria; http://www.R-project.org/).

Results

Baseline characteristics

The clinicopathological characteristics of the 6438 patients are presented in Table 1. Among them, the median age was 47 years (39–55 years), and 4954 (76.9%) were female. The median (IQR) height and weight were 160.3 (155.6–166.1) cm and 60.8 (54.4–69.4) kg, respectively. The median BMI was 23.8 (21.6–26.2) kg/m^2. Of the enrolled patients, 336 (5.2%) were current smokers,

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Table 1 Clinicopathological characteristics of the 6438 enrolled patients.

Characteristics	Values
Age, years (median, IQR)	47 (39–55)
Gender (*n*, %)	
Female	4954 (76.9)
Male	1484 (23.1)
Height, cm (median, IQR)	160.3 (155.6–166.1)
Weight, kg (median, IQR)	60.8 (54.4–69.4)
BMI, kg/m^2 (median, IQR)	23.8 (21.6–26.2)
Primary tumor size, cm (median, IQR)	0.8 (0.6–1.2)
Primary tumor size, cm (*n*, %)	
≤1 cm	4226 (65.6)
1 cm	2212 (34.4)
N stage	
N0/Nx	3732 (58.0)
N1a	1984 (30.8)
N1b	722 (11.2)
Smoking status (*n*, %)	
Never smoker	5644 (87.7)
Current smoker	336 (5.2)
Former smoker	458 (7.1)
Alcohol consumption status (*n*, %)	
Nondrinker	4633 (72.0)
Current drinker	1464 (22.7)
Former drinker	341 (5.3)
BRAFV600E mutational status (*n*, %)	
Wild type	1336 (20.8)
Mutant	5102 (79.2)
Surgical extent	
Less than total thyroidectomy	2527 (39.3)
Total thyroidectomy	3911 (60.7)

BMI, body mass index; *BRAF*, B-type Raf kinase; IQR, interquartile range.

and 1464 (22.7%) were current drinkers. *BRAFV600E* mutation was detected in 5102 (79.2%) patients.

Table 2 shows the comparison of the clinicopathological characteristics according to primary tumor size. *BRAFV600E* mutational status significantly differed by primary tumor size ($P = 0.003$) and was detected in 3395 (80.3%) and 1707 (77.2%) patients with a primary tumor size ≤1 cm and >1 cm, respectively. Additionally, age, gender, height, weight, BMI, smoking status, and alcohol consumption status significantly differed by primary tumor size.

The association between BMI and BRAFV600E mutational status by primary tumor size

As the baseline characteristics between primary tumor size ≤1 cm and >1 cm were significantly different, we examined the association between BMI and the *BRAFV600E* mutation in each group. In the primary tumor size ≤1 cm group, BMI, gender, and age did not significantly affect the *BRAFV600E* mutation risk. However, in the primary tumor size >1 cm group, BMI was significantly associated with the *BRAFV600E* mutation (OR: 1.034, $P = 0.029$) (Table 3). There was no significant difference between female and male genders in either group.

Figure 1 shows the associations between BMI and the *BRAFV600E* mutation risk through the use of a restricted cubic spline function. The OR plots were adjusted for age, alcohol consumption status, and smoking status. In the entire cohort, the OR plot showed a positive association between BMI and the *BRAFV600E* mutation risk. However, after dividing patients into two groups based on primary tumor size, the OR plot was flat in the primary tumor size ≤ 1 cm group. On the other hand, the OR plot showed a strong positive association between BMI and the *BRAFV600E* mutation risk in the primary tumor size > 1 cm group.

Figure 2 shows OR plots stratified by primary tumor size and gender. The pattern was similar between female and male genders in the primary tumor size > 1 cm group but differed slightly in the primary tumor size ≤ 1 cm group. The OR plot showed a reverse U shape for male patients. However, gender was not a significant factor in logistic regression (OR: 1.220; 95% CI: 0.946–1.573, $P = 0.125$).

Discussion

This study aimed to assess the association between BMI and the *BRAFV600E* mutation risk in a large cohort in an iodine-sufficient area. A positive association was found between BMI and the *BRAFV600E* mutation among patients with a primary tumor size >1 cm. On the other hand, no significant association was seen among patients with a primary tumor size ≤1 cm. Gender was not a significant factor in either group.

Previous studies have demonstrated that a high BMI is associated with an increased risk of thyroid carcinoma (9, 20, 21). Several potential mechanisms have been proposed to explain this association, including overweight, oxidative stress, hyperinsulinemia, inflammation, and the effects of adipokines, such as leptin and adiponectin (22, 23, 24, 25). While a high BMI appears to be related to an increased likelihood of thyroid carcinoma, inconsistent results have also been reported. Recently, Shin *et al.* reported a nonlinear association between BMI and thyroid carcinoma risk in an Asian cohort (26). BMI was found to have a linear association with thyroid carcinoma risk in men but not women.

Obesity appears to be modestly associated with thyroid carcinoma risk, but the relationship between obesity and the *BRAFV600E* mutation is different. Recently, Rahman *et al.* reported that a high BMI was associated with an increased risk of *BRAF*-positive thyroid cancer compared

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Table 2 Clinicopathological characteristics according to primary tumor size.

	Primary tumor size		
	≤1 cm (*n* = 4226)	**>1 cm (*n* = 2212)**	***P***
Age, years (median, IQR)	47 (39–54.3)	46 (36–55)	0.001
Gender (*n*, %)			
Female	3332 (78.8)	1622 (73.3)	<0.001
Male	894 (21.2)	590 (26.7)	
Height, cm (median, IQR)	160 (155.6–165.4)	161 (155.9–167.4)	0.001
Weight, kg (median, IQR)	60.3 (54.3–68.5)	61.9 (55.0–71.1)	0.001
BMI, kg/m^2 (median, IQR)	23.7 (21.6–26.0)	24.0 (21.7–26.4)	0.003
Primary tumor size, cm (median, IQR)	0.6 (0.5–0.8)	1.5 (1.2–2.0)	<0.001
N stage			
N0/Nx	2898 (68.6)	834 (37.7)	<0.001
N1a	1111 (26.3)	873 (39.5)	
N1b	217 (5.1)	505 (22.8)	
Smoking status (*n*, %)			
Never smoker	3740 (88.5)	1904 (86.1)	<0.001
Current smoker	228 (5.4)	108 (4.9)	
Former smoker	258 (6.1)	200 (9.0)	
Alcohol consumption status (*n*, %)			
Nondrinker	3073 (72.7)	1560 (70.5)	<0.001
Current drinker	965 (22.8)	499 (22.6)	
Former drinker	188 (4.4)	153 (6.9)	
BRAFV600E mutational status (*n*, %)			
Wild type	831 (19.7)	505 (22.8)	0.003
Mutant	3395 (80.3)	1707 (77.2)	
Surgical extent			
Less than total thyroidectomy	2224 (52.6)	303 (13.7)	<0.001
Total thyroidectomy	2002 (47.4)	1909 (86.3)	

BMI, body mass index; *BRAF*, B-type Raf kinase; IQR, interquartile range.

Table 3 The association between body mass index and BRAFV600E mutation risk according to primary tumor size. Multivariate results for primary tumor size ≤1 cm were not shown because there was no significant factor.

	Primary tumor size					
	≤1 cm		**>1 cm**			
	Univariate	***P***	**Univariate**	***P***	**Multivariate**	***P***
Age (years)	0.995 (0.988–1.003)	0.214	1.007 (0.999–1.016)	0.083	1.008 (0.999–1.016)	0.068
Gender						
Female	Reference		Reference		Reference	
Male	1.220 (0.946–1.573)	0.125	1.393 (1.033–1.878)	0.030	1.284 (0.983–1.677)	0.066
BMI, continuous (kg/m^2)	1.004 (0.980–1.028)	0.740	1.035 (1.004–1.066)	0.025	1.034 (1.003–1.065)	0.029
Smoking status						
Never smoker	Reference		Reference			
Current smoker	0.886 (0.722–1.088)	0.248	0.701 (0.429–1.145)	0.156		
Former smoker	1.183 (0.772–1.814)	0.441	0.872 (0.580–1.312)	0.511		
Alcohol consumption status						
Nondrinker	Reference		Reference		Reference	
Current drinker	1.177 (0.786–1.762)	0.428	0.762 (0.584–0.994)	0.045	0.738 (0.569–0.958)	0.023
Former drinker	1.049 (0.710–1.550)	0.811	0.758 (0.493–1.165)	0.206	0.751 (0.496–1.138)	0.177

BMI, body mass index.

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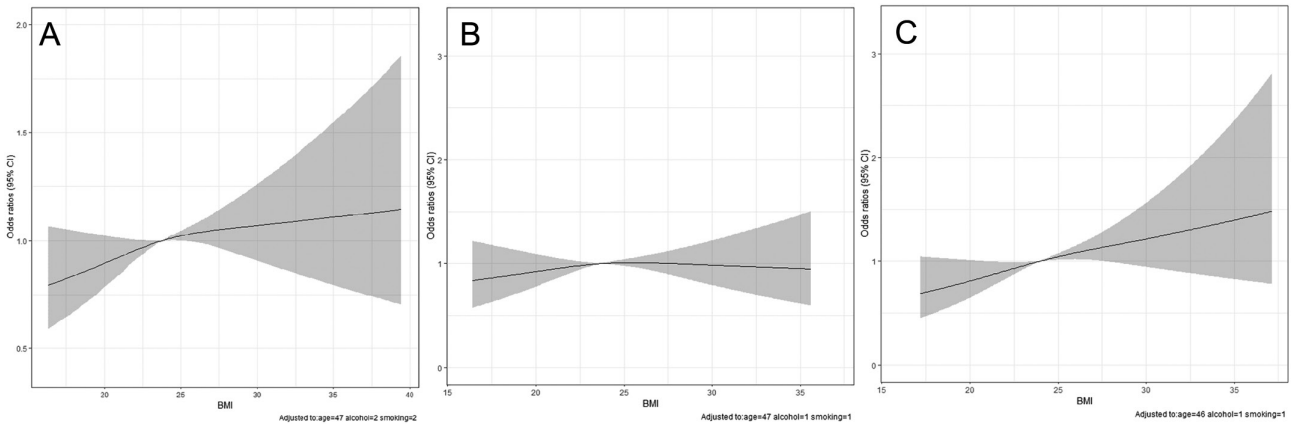

Figure 1

Association between body mass index and BRAFV600E mutational status: (A) Entire cohort, (B) primary tumor size ≤ 1 cm, and (C) primary tumor size > 1cm.

to *BRAF*-negative cancer (OR 1.17) (12). However, limited evidence has been presented, especially in the Asian population. East Asia is an iodine-sufficient area, and the frequency of the *BRAFV600E* mutation was reported to be approximately 85.1% (27). Considering that the *BRAFV600E* mutation is known to be associated with iodine intake (16), different results might be obtained in studies conducted on the Asian population.

In East Asia, two retrospective cohort studies have reported on the association between BMI and the *BRAFV600E* mutation in PTC. Lee *et al.* reported that a high BMI was significantly associated with advanced stage and *BRAFV600E* mutational status (28). However, advanced stage might be associated with *BRAF*-positive thyroid cancer, rather than high BMI (29, 30). Although they demonstrated that *BRAFV600E* mutation was significantly associated with higher BMI (categorical), the numbers of patients in BMI < 18.5 and BMI ≥ 30 groups were too small. We should consider that dichotomization decreases measurement reliability, and categorization occurs with the loss of reliable information (31). Shi *et al.* reported a positive relationship between BMI and the *BRAFV600E* mutation in 108 PTC patients. *BRAFV600E* mutation was observed in 47.2% of enrolled patients. However, that study was conducted with a relatively small sample size, and they used body weight and height reported by patients at the time of diagnosis. To overcome the limitations of previous studies, we conducted this study with a large sample size and actually measured body weight and height, using BMI as a continuous factor. *BRAFV600E* mutational risk was adjusted for potential confounding factors for cancer, such as alcohol use and smoking.

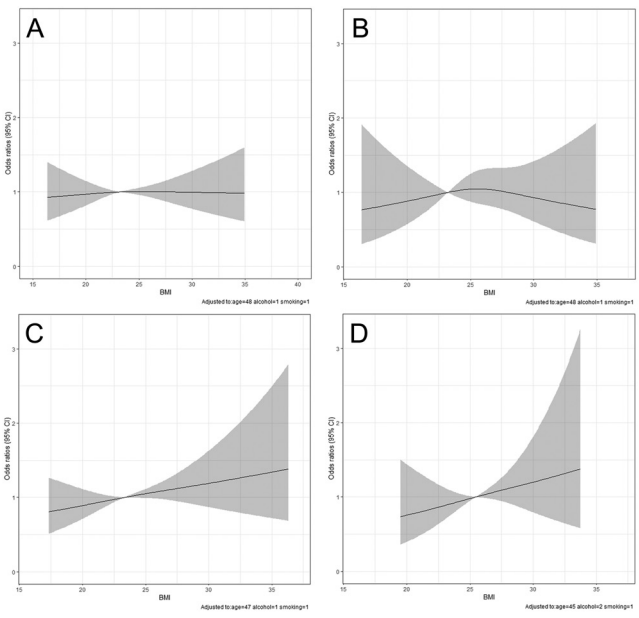

Figure 2

Association with BRAFV600E mutational status according to primary tumor size and gender: (A) for primary tumor size ≤ 1 cm and female gender, (B) primary tumor size ≤ 1 cm and male gender, (C) primary tumor size > 1 cm and female gender, and (D) primary tumor size > 1 cm and male gender.

In this study, we found a positive association between BMI and the *BRAFV600E* mutation among patients with a primary tumor size > 1 cm. However, there was no significant association in patients with a primary tumor size ≤ 1 cm. The reason for categorizing patients into two groups was due to differences in baseline characteristics. In Korea, the incidence of PTC has rapidly increased since 1999, mainly due to cancer screening. Although a decreasing trend has been observed since 2013, most of the enrolled patients were diagnosed before the debates on over-diagnosis in thyroid carcinoma in Korea (3, 32). In this study, 65.6% of the patients had a primary tumor size ≤1 cm. Considering that the proportion of papillary microcarcinoma (PTMC) in other countries is between 35.3% and 47.5 % (2, 33), the proportion of PTMC in this study was much higher.

Although obesity may be associated with thyroid carcinoma risk, the reason why high-BMI patients were more frequently *BRAF*-positive was unclear. If obesity was a predisposing factor for *BRAFV600E* mutation, consistent results should be obtained in other cancers associated with the *BRAFV600E* mutation. However, high BMI was positively associated with *BRAF*-negative cancer, whereas height was positively associated with *BRAF*-positive colorectal cancer (34). This result suggests that BMI may have a potentially different association with *BRAFV600E* mutation due to other factors, such as tumor type and primary tumor size.

This study observed that the association between the *BRAFV600E* mutation and obesity may vary according to primary tumor size. However, the underlying mechanism for these findings remains unclear. Given that various factors likely contribute to genetic alterations, further research is needed to fully understand the results of this study.

In this study, there was a negative association between current drinking and the *BRAFV600E* mutation when the primary tumor size was > 1 cm. The relationship between alcohol consumption and thyroid cancer remains inconclusive, but previous studies have suggested that moderate alcohol consumption may be linked to a reduced risk of thyroid cancer (35, 36, 37). To the best of our knowledge, the association between alcohol consumption and the *BRAFV600E* mutation in thyroid carcinoma has not been established. According to the findings of this study, alcohol consumption might have a protective effect against the *BRAFV600E* mutation, which is the most common oncogene in PTC. However, no significant association was observed in patients with a primary tumor size ≤1 cm, similar to the results for BMI. This result suggests that PTMC and PTC may have different susceptibility to gene-environment interactions or tumor microenvironments.

This study has several limitations. First, our study has the potential for selection bias. Although 6438 patients were enrolled, the study was conducted at a single tertiary referral center. Additionally, this study was conducted in an area with a high prevalence of the *BRAFV600E* mutation. Furthermore, *BRAFV600E* testing was not conducted in consecutive cases. During the study period, 12,867 patients with thyroid carcinoma underwent thyroid surgery at our hospital, of which 6777 patients (52.7%) underwent the *BRAFV600E* testing. Among them, 6558 patients with PTC were included in this study. In Korea, national health insurance does not cover *BRAFV600E* mutation testing, and the cost is about $100–130. Therefore, *BRAFV600E* testing was performed on patients who agreed to cover the cost. Second, only baseline BMI was available, and the longitudinal effect of high BMI on the *BRAFV600E* mutation could not be assessed. Also, other anthropometric measures that may better reflect obesity, such as waist circumference, waist-to-hip ratio, and percent body fat, were not assessed. Third, information on alcohol consumption at baseline was included, but we could not obtain information on the amount of alcohol consumed in the past or the type of alcoholic beverage because the questionnaires only included non-drinkers, current drinkers, and former drinkers. Further evidence is needed to confirm a negative association between alcohol consumption and the *BRAFV600E* mutation. Fourth, potential confounders of cancer incidence and stage, such as socioeconomic status, income, and educational attainment, were not included. Fifth, the exact mechanism underlying the different results obtained for primary tumor size could not be revealed in this study. Further studies are needed to fully understand this result.

Conclusions

A higher BMI is associated with an elevated risk of *BRAFV600E* mutation among those with primary tumor size > 1 cm. On the other hand, no significant association was found between BMI and the risk of the *BRAFV600E* mutation in patients with a primary tumor size ≤ 1 cm.

Declaration of interest
Hyunju Park, Jung Heo, Hyun Jin Ryu, Min-Ji Kim, Young Lyun Oh, Tae Hyuk Kim, Sun Wook Kim, and Jae Hoon Chung declare that there are no conflict of interest to disclose.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Data Availability Statement
The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared upon reasonable request to the corresponding author.

Author contribution statement
JHC, and HP performed study concept and design; HP performed development of methodology and drafted the manuscript; HP and M-JK performed statistical analysis; JH, HJR, THK, and SWK provided acquisition and interpretation of data; JHC reviewed and revised the paper; YLO provided technical and material support. All authors read and approved the final paper.

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