Randomised trial of assessing diagnostic yield in transbronchial biopsy with a guide sheath

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Shareable abstract (@ERSpublications)
Radial EBUS TBB with a GS may be beneficial in peripheral small lesions. Additionally, a GS offers a higher cytology yield and a lower risk of bleeding. However, the washing culture yield from the GS was lower than that from conventional bronchial washing. https://bit.ly/4ePWlzc

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Abstract

Objectives Radial probe endobronchial ultrasound (rEBUS)-guided transbronchial biopsy (TBB) with a guide sheath (GS) is widely used to diagnose peripheral lung lesions (PPLs), but there is no consensus on whether it increases the diagnostic yield. We conducted this prospective study to compare the diagnostic yield of the GS method to the conventional method without a GS.

Methods From November 2019 to March 2023, patients with PPLs were recruited and randomly assigned to rEBUS-TBB with a GS (GS group) or without a GS (conventional group). The histopathology, cytology and microbiology yield rates, as well as procedure time and post-procedure adverse events, of the two groups were compared.

Results A total of 102 patients were enrolled (54 in the GS group and 48 in the conventional group). The pathology yield showed no statistical difference between the two groups (75.9% *versus* 68.8%, p=0.418), while the yield rates of brushing cytology (64.3% *versus* 42.9%, p=0.030) and washing cytology (41.5% *versus* 20.0%, p=0.0443) were higher in the GS group. Meanwhile, the yield from GS washing culture was lower than the bronchial washing culture yield (0% *versus* 57.1%, p=0.017). The bleeding risk was also lower in the GS group (9.3% *versus* 20.8%, p=0.049).

Conclusion The pathology yield of rEBUS TBB with a GS did not significantly differ from the conventional method. However, a GS could improve the cytology yield rate and reduce the risk of bleeding. To enhance the microbiology yield, additional bronchial washing should be utilised.

Introduction

Bronchoscopy is a commonly used diagnostic tool for peripheral pulmonary lesions (PPLs), but its diagnostic yield varies widely among studies [1–4]. To improve the diagnostic yield, the use of radial probe endobronchial ultrasound (rEBUS) during bronchoscopic transbronchial biopsy (TBB) has been recommended in the American College of Chest Physicians guidelines for diagnosis and management of lung cancer [5]. rEBUS helps localise the lesions and the bronchi leading to them; however, its major limitation is that real-time views are not obtained. This means that TBB and rEBUS scanning cannot be performed simultaneously, making it difficult to confirm that the biopsy instrument has been advanced through the bronchial route taken by the rEBUS probe to the target lesion [6].

To overcome this limitation, Kurimoto *et al.* [7] introduced the concept of rEBUS-guided TBB with a guide sheath (GS), which aimed to enhance the diagnostic accuracy of PPLs. This method involves

inserting the ultrasound probe into the GS, extending it into the bronchoscopy working channel, reaching the lesions, removing the ultrasound probe while keeping the GS in place and then inserting the biopsy forceps through the GS to obtain appropriate tissues. This has been found to be useful by many investigators [7–16]. However, the use of a GS imposes a size limitation on the sampling instruments, while rEBUS-TBB without a GS (the conventional method) allows the use of larger biopsy forceps that may improve the diagnostic yield [17]. Furthermore, the conventional method, which involves collecting multiple biopsies from various locations, has been hypothesised to increase the chance of obtaining at least one diagnostic sample compared to using the fixed location of the GS method [18].

The GS method has some disadvantages, including technical complexity, possible displacement by coughing or deep respiration, and instrumental issues such as kinking or bending of the GS and resistance during the advancing of biopsy instruments [19–23]. The diagnostic yield of rEBUS-TBB with and without a GS has been the subject of only a few small comparative studies and the use of a GS during rEBUS-TBB remains controversial. Therefore, we conducted this prospective randomised controlled study to compare the diagnostic yield of rEBUS-TBB with a GS to the conventional method. In addition, we also compared the microbiological culture results of two different specimen collection methods for those with the final diagnosis of pneumonia and mycobacterial infection.

Materials and methods

Study patients

This study was conducted at the National Taiwan University Hospital (NTUH), a university teaching hospital with 2500 beds in northern Taiwan. From November 2019 to March 2023, all consecutive patients with solid PPLs and positive bronchus sign on a computed tomography (CT) scan, with written consent, were recruited and randomly assigned to rEBUS-TBB with a GS (GS group) or without a GS (conventional group) in a 1:1 ratio. Randomisation was stratified by lesion size (greatest diameter <20 or ⩾20 mm on CT scans), distance from the hilum (in the peripheral two-thirds or central one-third of the CT lung field) and rEBUS image type (concentric or eccentric). Allocations were performed electronically through a pre-determined randomisation sequence. The inclusion criteria were adult patients (age ⩾20 years old) with PPLs requiring diagnosis that could be found by rEBUS. The exclusion criteria were bronchopulmonary segments B1 (RB1 and LB1/2) and B6 lesions, due to the sharp angles that pose challenges for standard and therapeutic scopes to deploy a guide sheath. Additionally, cases where the lesion could not be located by rEBUS during the procedure were also excluded. The study was approved by the Institutional Review Board of the NTUH (201904072RINC) and was registered at ClinicalTrials.gov (NCT04056273). All included participants provided written informed consent.

Bronchoscopic procedure

Most of the patients underwent bronchoscopic procedures under local anaesthesia with clear consciousness. Some patients (about 17%) were given intravenous general anaesthesia due to personal preference, although intravenous general anaesthesia for bronchoscopy was not covered by Taiwan's national health insurance programme. The standard 4.8-mm bronchoscope, with a 2.0-mm working channel (BF-Q290, Olympus), was used for the majority of patients (about 80%), while therapeutic scopes, with a 5.9-mm width and 3.0-mm working channels (BF-1TQ290, Olympus), and thin scopes, with a 4.2-mm width and 2.0-mm working channels (BF-P290, Olympus), were the other options.

After the bronchoscope reached the segment of the lesion, localised by CT scan, a 1.4-mm diameter rEBUS probe (UM-S20-17S, Olympus) was advanced through the working channel toward the lesion. When the target lesion was found by rEBUS, the distance from the segment orifice was measured. For the GS group, the rEBUS probe was reinserted again with a GS (K201 or K203, Olympus; depending on the working channel size of the scope used). The GS was then deployed at the target lesion and forceps biopsy as well as cytology brushing, from the GS kit, were done within the GS. After sampling, the GS was retrieved from the working channel and 25 mL saline was used to irrigate the GS for the bronchial washing sample.

As for the conventional group, a 2.0-mm biopsy forceps (FB-231D, Olympus) and a 2.0-mm cytology brush (BC-202D-2010, Olympus) were used and bronchial washing was performed after sampling. Biopsy was taken at least six times for each group. Microbiological cultures of biopsy tissue were also performed for those in whom infectious disease was suspected. Rapid on-site cytological evaluation was not performed for either group.

Evaluation parameters

The primary end-point was the histopathological diagnostic yield of the allocated group. The secondary end-points included procedure time, frequency of complications, bronchial brushing and washing cytology

yield, microbiological culture yield, and diagnostic yield stratified by malignancy or not, the lesion's location, lesion size and rEBUS image pattern. The bleeding was classified into four grades as previously reported [24].

A positive diagnostic yield was considered to be obtained when the pathology report showed malignant or benign neoplasms, granulomatous inflammation, organising pneumonia and fungus or acid-fast positive microorganisms. The nondiagnostic yield included normal lung tissue, nonspecific fibrosis and chronic inflammation. These patients were followed up for at least 6 months, until the final diagnoses were established, based on pathological evidence, microbiological culture results, radiological images and treatment results. If pneumonia was the clinical diagnosis and the lesion did resolve completely during follow-up after antimicrobial treatment, inflammation from the initial pathology report would also be considered as a positive diagnosis.

As to the microbiological study, the culture results of the specimen from the GS irrigation were compared with the bronchial washing fluid in the conventional group.

Statistical analysis

The Pearson Chi-squared test was used for categorical variables comparison, while Fisher's exact mid-p test was used when necessary. Continuous variables were expressed as mean±standard deviation and were compared using the t-test. If a continuous variable failed to pass a normality test, the median and quartiles were recorded, and the Mann–Whitney U test was used for comparison. p-values less than 0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

During the study period, 102 of the 1309 patients that underwent rEBUS-TBB were enrolled in the study. The baseline characteristics of the patients, their lesions and bronchoscopic findings are listed in table 1. More than half of the patients in the GS group (61.1%) and half in the conventional group (50.0%) had

TABLE 1 Characteristics of patients and their lesions

Characteristic	Guide sheath (n=54)	Conventional (n=48)	p-value
Age, years (mean±SD)	65.8±13.9	66.6±10.7	0.769
Sex (male)			
Male	34 (63.0%)	30 (62.5%)	0.962
Female	20 (37.0%)	18 (37.5%)	
Lesion location			
Central	33 (61.1%)	24 (50.0%)	0.259
Peripheral	21 (38.9%)	24 (50.0%)	
Lesion size			
(mm, mean±SD)	43.6±22.1	41.5±21.6	0.780
⩾20 mm	49 (90.7%)	44 (91.7%)	0.869
<20 mm	5 (9.3%)	4 (8.2%)	
Lesion lobe (right)			
Right lung	30 (55.6%)	31 (64.6%)	0.353
Right upper lobe	16 (29.6%)	7 (15.6%)	
Right middle lobe	6 (11.1%)	8 (16.7%)	
Right lower lobe	8 (14.8%)	16 (33.3%)	
Left lung	24 (44.4%)	17 (35.4%)	
Left upper division	8 (14.8%)	6 (12.5%)	
Left lingual lobe	5 (9.3%)	3 (6.3%)	
Left lower lobe	11 (20.4%)	8 (16.7%)	
Positive bronchus sign	54 (100%)	48 (100%)	
Bronchoscope type			
BF-1TQ290	3 (5.6%)	6 (12.5%)	0.217
BF-Q290	48 (88.9%)	37 (77.1%)	
BF-P290	3 (5.6%)	5 (10.4%)	
IVG	9 (16.7%)	9 (18.8%)	0.783

IVG: intravenous general anaesthesia.

TABLE 2 Final diagnoses of patients in the two groups

Final diagnosis	Guide sheath (n=54)	Conventional (n=48)	p-value
Malignant	44 (81.5%)	38 (79.2%)	0.769
Lung cancer	38 (86.4%)	35 (92.1%)	0.402
Adenocarcinoma	30 (78.9%)	26 (74.3%)	
Squamous cell carcinoma	4 (10.5%)	5 (14.3%)	
Small cell carcinoma	1 (2.6%)	2 (5.7%)	
Other lung cancer	3 (8.0%)	2 (5.7%)	
Metastatic carcinoma	4 (9.1%)	2 (5.3%)	
Mesothelioma	1 (2.3%)	1 (2.6%)	
Lymphoma	1 (2.3%)	0 (0%)	
Benign	10 (18.5%)	8 (16.7%)	
Mycobacterial infection	2 (20.0%)	2 (25.0%)	
Bacterial pneumonia	5 (50.0%)	5 (62.5%)	
Organising pneumonia	2 (20.0%)	1 (12.5%)	
Atelectasis	1 (10.0%)	0 (0%)	
Lost to follow-up without a final diagnosis	0 (0%)	2 (4.2%)	

centrally located lesions (p=0.259). The majority of the lesions were ⩾20 mm in diameter (GS *versus* conventional: 90.7% *versus* 91.7%, p=0.869) and the lesion size had no difference in two groups (GS *versus* conventional: 4.36±2.21 cm *versus* 4.15±2.16 cm, p=0.780). Only a few patients underwent the procedure with BF-1TQ290 (with a 3.0-mm working channel) (GS *versus* conventional: 5.6% *versus* 12.5%, p=0.217). The final diagnoses of the patients are shown in table 2. The majority of the diagnoses were malignant conditions (GS *versus* conventional: 81.5% *versus* 79.2%, p=0.769), especially lung cancer (GS *versus* conventional: 86.4% *versus* 92.1%, p=0.402).

The procedural details and complications of each group are listed in table 3. For both groups, most of the lesions were concentric under rEBUS (GS *versus* conventional: 81.5% *versus* 81.3%, p=0.976). The average number of biopsies was 8.9 in the GS group and 6.9 in the conventional group (p<0.001), while the procedure time was significantly longer in the GS group (GS *versus* conventional: 17.6±4.7 min *versus* 15.1±4.5 min, p=0.008). There was no statistical difference in the sample size between the two groups (GS *versus* conventional: 2 (1, 8) mm^3 *versus* 2.5 (2, 6) mm^3, p=0.778). The pathology yield rate showed no significant statistical difference either (GS *versus* conventional: 75.9% *versus* 68.8%, p=0.418). This similarity was even more pronounced when only cancer patients were considered (GS *versus* conventional: 70.5% *versus* 68.4%, p=0.812). In subgroup analysis, although the differences were not statistically significant, the GS group demonstrated numerically higher yield rates in several categories, namely

TABLE 3 Bronchoscopic findings and results of the patients

	Guide sheath (n=54)	Conventional (n=48)	p-value
rEBUS image type			
Concentric	44 (81.5%)	39 (81.3%)	0.976
Eccentric	10 (18.5%)	9 (18.7%)	
Distance from the orifice (cm, mean±SD)	2.1±1.5	2.7±1.9	0.150
Procedure time (min, mean±SD)	17.6±4.7	15.1±4.5	0.008
Number of biopsies (mean±SD)	8.9±2.8	6.9±2.5	<0.001
Sample size (mm^3) (median, quartile)	2 (1, 8)	2.5 (2, 6)	0.778
Pathology yield rate	75.9% (41/54)	68.8% (33/48)	0.418
Cancer yield rate	70.5% (31/44)	68.4% (26/38)	0.812
Culture of biopsy tissue yield rate	50.0% (2/4)	83.3% (5/6)	0.367
Brush yield rate	64.3% (27/42)	42.9% (15/35)	0.030
Washing cytology	41.5% (17/41)	20.0% (7/35)	0.044
Washing culture	0% (0/7)	57.1% (4/7)	0.017
⩾ Grade 2 bleeding	9.3% (5/54)	20.8% (10/48)	0.049
Complication[#]	3.7% (2/54)	4.2% (2/48)	0.904

[#]: Two patients in the guide sheath group had pneumothorax, while one had pneumothorax and the other one had grade 3 bleeding in the conventional group. rEBUS: radial probe endobronchial ultrasound.

peripheral lesions (80.9% *versus* 66.7%, p=0.153), lesions <20 mm (100% *versus* 75.0%, p=0.222) and concentric lesions (81.8% *versus* 71.8%, p=0.147). These differences exceeded 10% across the mentioned categories (table 4).

Meanwhile, the secondary end-point of brushing cytology yield rate (GS *versus* conventional: 64.3% *versus* 42.9%, p=0.030) and the washing cytology yield rate (GS *versus* conventional: 41.5% *versus* 20.0%, p=0.044) were both significantly higher in the GS group. Nonetheless, comparing the washing culture from the GS to the bronchial washing culture from the conventional group, the yield rate was significantly higher in the conventional group (GS *versus* conventional: 0% *versus* 57.1%, p=0.017), despite the rather low patient number (accounting only for patients with a diagnosis of bacterial pneumonia and mycobacterial infection).

As for complications, two patients in each group had pneumothorax after the procedure (GS *versus* conventional: 3.7% *versus* 4.2%, p=0.904). The severity of post-procedure bleeding was higher in the conventional group, as there was significantly more grade 2 and above bleeding (GS *versus* conventional: 9.3% *versus* 20.8%, p=0.049).

Discussion

This was a prospective randomised controlled study designed to determine whether the diagnostic yield of rEBUS-TBB with a GS is better than the conventional method. We demonstrated that the pathology yield was not statistically higher in the GS group. Meanwhile, the secondary end-point of cytology yield was significantly higher in the GS group, despite low number of cases in our study. In addition, we found that the microbiological culture yield of the washing fluid from the GS was lower than the conventional washing for those with the initial diagnosis of pulmonary infection.

We initially planned to enrol at least 586 patients (293 in each group), expecting an 80% diagnostic yield from the GS group and 70% from the conventional group, with a statistical power of 80% and a significance level of 0.05. However, the COVID-19 pandemic severely impacted our ability to enrol participants. Despite relatively effective control of the virus in Taiwan, recruitment remained challenging. Following a pre-planned interim analysis which showed a yield of 75.9% in the GS group *versus* 68.8% in the conventional group, we recalculated the necessary sample size. This analysis indicated that 1244 participants would be required to achieve statistical significance. Given the logistical challenges and the diminished likelihood of demonstrating a clinically significant difference with the increased sample size, we decided to discontinue the study early. This decision was further supported by notable differences observed in secondary outcomes.

During our enrolment period, Oki *et al.* [25] published a study result that demonstrated that rEBUS-TBB with a GS had a statistically higher diagnostic yield than the non-GS method. They studied 596 patients with PPLs ⩽30 mm in diameter. The diagnostic yield was 55.3% *versus* 46.6% (GS *versus* non-GS;

TABLE 4 Subgroup comparison of yield rates between two patient groups

	Guide sheath (n=54)	Conventional (n=48)	p-value
Lesion location			
Central	72.2% (24/33)	70.8% (17/24)	0.438
Peripheral	80.9% (17/21)	66.7% (16/24)	0.153
Lesion size			
⩾20 mm	74.5% (36/49)	68.2% (30/44)	0.287
<20 mm	100% (5/5)	75% (3/4)	0.222
Bronchoscope type			
BF-1TQ290	100% (3/3)	100% (6/6)	NA
Non- BF-1TQ290	74.5% (38/51)	66.7% (28/42)	0.204
IVG			
Yes	100% (9/9)	100% (7/7)	NA
No	71.1% (32/45)	66.7 (26/39)	0.330
rEBUS image type			
Concentric	81.8% (36/44)	71.8% (28/39)	0.147
Eccentric	50% (5/10)	55.6% (5/9)	0.828

IVG: intravenous general anaesthesia; NA: not applicable/available; rEBUS: radial probe endobronchial ultrasound.

p=0.033). In contrast, the study from Guan *et al.* [26] suggested that the diagnostic yields were similar. They included 569 cases with PPLs ⩾30 mm in diameter and the positive diagnosis rate was 74.91% *versus* 76.95% (GS *versus* non-GS; noninferiority U-test p⩽0.05).

On stratification, Oki *et al.* [25] suggested that the GS group had better yield with peripheral lesions (53.4% *versus* 43.8%, p=0.032) and lesions with positive bronchus signs on CT (59.2% *versus* 49.1%, p=0.029); while in the study by Guan *et al.* [26], there was no difference in diagnostic rate with peripheral lesions (76.30% *versus* 74.59%), but worse with central lesions in the GS group (72.37% *versus* 81.44%). Other studies also proposed that the GS was better with peripheral, small lesions [27–30]. In our study, the GS group demonstrated better performance in terms of peripheral lesions (80.9% *versus* 66.7%) and lesions <20 mm (100% *versus* 75.0%). In both cases, the differences in yield rates exceeded 14%. Although these differences were not statistically significant, likely due to the low case numbers and insufficient power, we think they may still have clinical implications. With peripheral small lesions, it is easier to go to the wrong bifurcations when repeating the biopsy using the conventional method, especially when bleeding occurs and the view is blocked. A GS can ensure that the biopsy forceps goes into the same bifurcation, thus making the sampling more precise. It is already well-known that concentric lesions have a higher yield rate than eccentric lesions [11], which is compatible with our result. Since the GS can fix an identical biopsy route, it is easier to have a higher yield than with the conventional method.

Our study also found that using a GS can increase the cytology yield, with both washing cytology (GS *versus* conventional: 41.5% *versus* 20.0%, p=0.044) and brushing cytology (GS *versus* conventional: 64.3% *versus* 42.9%, p=0.030), although they were set as secondary end-points in our study. Izumo *et al.* [10] also reported that brushing cytology with a GS, device washing (rinsing the biopsy forceps and cytology brush after sampling) and GS flush had a better yield rate than bronchial lavage. Even though cytology alone cannot make a definite diagnosis, we believe that a positive result still offers valuable information, prompting further diagnostic procedures to obtain a definitive tissue diagnosis [31–33].

In addition, we found that the microbiological culture yield of the washing fluid from the GS was lower than that of conventional bronchial washing (GS *versus* conventional: 0.0% *versus* 57.1%, p=0.044) for those with the final diagnosis of pulmonary infection. It is possible that the retaining fluid in the GS is mostly blood and therefore has a low microbiology yield. To the best of our knowledge, there are no studies concerning the efficacy of microbiological culture of the retaining fluid or washing fluid from the GS. Due to this finding, we think culture of the washing fluid from the GS cannot replace the bronchial washing culture. Additional bronchial washing is recommended for the GS procedure in order to achieve better microbiology study results.

It was reported that TBB with a GS had a lower haemorrhage risk than conventional forceps biopsy [26]. Our study confirmed this result, with the finding that there was less moderate bleeding (grade 2 and above) in the GS group (GS *versus* conventional: 9.3% *versus* 20.8%, p=0.049). Procedure time results were inconsistent in different studies, with some suggesting that procedure time was longer in the GS group [34, 35], while others indicated it was shorter than with the conventional procedure [28]. In our study, the procedure time was longer in the GS group (GS *versus* conventional: 17.6±4.7 min *versus* 15.1±4.5 min, p=0.008). However, there was a confounding factor in that the biopsy numbers were also greater in the GS group (GS *versus* conventional: 8.9±2.8 *versus* 6.9±2.5, p<0. 001), which was intended to compensate for the smaller size of the forceps used with a GS.

The main purpose of using a GS is to solve the problem of not being able to perform TBB under real-time rEBUS guidance, due to the single working channel with the current bronchoscope. Our study demonstrated that the GS can increase the accuracy of TBB. However, fluoroscopy can serve the same purpose and increase accuracy and diagnostic yield [36, 37]. Although, as previously described, the GS demonstrated better performance in small lesions, Ito *et al.* [17] suggested that when under fluoroscope-guidance, the conventional method could achieve even better performance.

There are some limitations in our study. The most significant one is the low case number (102 patients), which may result in reduced statistical power. Additionally, B1 and B6 lesions were excluded; therefore, our result cannot be applied to all PPLs. However, as the angles are usually sharper in these segments, it might be difficult for the bronchoscopes to reach them with GS *in situ* or it could cause kinking of the GS. Either way, it is possible that a GS cannot work at B1 and B6, so we excluded them to keep the randomisation balanced. Finally, as this was a single-centre study, the findings may not be generalisable to all institutions.

In conclusion, rEBUS TBB with a GS did not demonstrate a statistically significant difference in yield compared to conventional biopsy. Nonetheless, the notable numerical differences in pathology yield rates

for patients with peripheral lesions suggest potential clinical relevance in the effectiveness of GS for sampling peripheral lesions, despite the statistical limitations of this study. Additionally, a GS offers a higher cytology yield and a lower risk of bleeding, further supporting its potential utility in clinical settings. However, the washing culture yield from the GS was lower than that from conventional bronchial washing. Further studies with larger number of cases are warranted to substantiate these findings.

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Data availability: The study protocol and data will be available under request to the corresponding author immediately after publication.

This clinical trial is prospectively registered with ClinicalTrials.gov as NCT04056273.

Author contributions: H-C. Chang: study design, data acquisition and analysis, data interpretation, drafting the work, approved the final version to be published, and agreed to be accountable for all aspects of the work. Y-W. Kuo: study design, data interpretation, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. C-K. Lin: study design, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. L-C. Chang: data acquisition, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. Y-Y. Chen: data acquisition, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. C-Y. Yang: data acquisition, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. J-Y. Chien: data acquisition, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. C-L. Hsu: data acquisition, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. T-H. Tsai: data acquisition, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. C-C. Ho: study design, data interpretation, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. J-Y. Shih: data interpretation, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work. C-J. Yu: data interpretation, critical work review, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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