OBSERVATIONAL RESEARCH





The impact of histopathological criteria for definite vasculitis in giant cell arteritis: retrospective analysis of temporal artery biopsies

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Abstract

Histopathological findings associated with definite vasculitis in temporal artery biopsy (TAB) defined in 2022 ACR/EULAR classification criteria for Giant Cell Arteritis (GCA) was published in 2022. We aimed to evaluate the TAB of our GCA patients for histopathological findings associated with definite vasculitis. Patients who were diagnosed with GCA by clinicians and underwent TAB between January 2012 and May 2022 were included. Hospital electronic records and patients' files were reviewed retrospectively. A total of 90 patients' pathology reports were evaluated by a pathologist and a rheumatologist. In cases where microscopic findings were not specified in the pathology reports, histopathologic specimens were re-evaluated (n=36). A standard checklist was used for histopathological findings of definite vasculitis. Patients were divided into two groups; (i) definite vasculitis-GCA and (ii) non-definite-GCA group, and the clinical and demographic characteristics for all patients were compared. The mean age of patients was 69.8 (\pm 8.5) years and 52.2% were female. In the first evaluation, 66 (73.3%) patients had a diagnosis of vasculitis according to pathology reports. In the re-evaluation of biopsy specimens, at least one definite finding of vasculitis was observed in TAB of 10/24 (41.6%) patients whose microscopic findings were not specified in the pathology reports. The ROC analysis showed that biopsy length had diagnostic value in predicting the diagnosis of definite vasculitis (AUC: 0.778, 95% CI: 0.65–0.89, p < 0.001). In those with a biopsy length of ≥ 1 cm, sensitivity was 76.5%, specificity was 64.3%, and PPV value was 92. In multivariate analysis, the most significant factor associated with definite vasculitis was biopsy length (OR: 1.18 (1.06-1.31), p = 0.002). Microscopic findings were reported in over 70% of patients. Reinterpretation of results according to a standard check-list improved the impact of TAB in the diagnosis of GCA. A biopsy length ≥ 1 cm was found to contribute towards a definitive histopathological vasculitis diagnosis.

Keywords Definite vasculitis \cdot Giant cell arteritis \cdot Temporal artery biopsy \cdot The Diagnostic and Classification Criteria in Vasculitis (DCVAS) \cdot 2022 ACR/EULAR GCA classification criteria

Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis that affects the elderly and is associated with severe target organ damage such as loss of vision [1]. The 1990 American College of Rheumatology (ACR) classification criteria have been using also for diagnosis, and this criteria emphasizes the importance of temporal artery biopsy (TAB) [2]. Although the gold standard in diagnosing GCA is TAB, a biopsy may not always give definite results, considering parameters such as skipped lesions and biopsy length [3–5]. The 2022 ACR/EULAR GCA classification criteria was published recently and subsequently, histopathological findings suitable with diagnosis with GCA were standardized by Putman et al. [6, 7]. A modified Delphi process involving 13 UK experts achieved consensus on key parameters for standardized reporting of temporal artery biopsy specimens in giant cell arteritis diagnosis. These parameters include presence and extent of inflammation, types of inflammatory cells, presence of giant cells, and changes to the vessel wall structure [8, 9]. Although previous studies have mainly focused on mural inflammation, the 2022 ACR/EULAR GCA classification criteria has defined detailed histopathological findings that may be associated with the diagnosis of definite vasculitis. These findings include fragmentation of the internal elastic lamina, presence of giant cells, and

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mononuclear cell infiltration and these are presented as independent histopathological findings associated with definite vasculitis [7]. In biopsy-proven and suspected GCA patients, the new GCA classification criteria includes a higher sensitivity and specificity in comparison to the 1990 GCA classification criteria (92.6% vs. 66.1%, 85.2% vs. 85.1%, respectively) [10].

Our study investigated the impact of new histopathological findings in a cohort of GCA patients having TAB.

Patients & methods

Study population

This study was approved by the local ethical committee of Hacettepe University (20.09.2022/GO 22/81). Pathology reports of temporal artery biopsies that were available for GCA patients between January 2012 and May 2022 from Hacettepe University, Gazi University, Ankara University and Bilkent City Hospital were examined and included in the study. The histopathological findings in the pathology reports of 90 patients were evaluated by an experienced pathologist (ÖG) (with over ten years of experience) and a rheumatology fellow (GSU) (Fig. 1, *phase I; Evaluation of pathology reports*).

Electronic hospital medical records and hard paper copies of patients' medical charts were reviewed for the data collection of demographics, imaging methods details, clinical characteristics and final diagnoses of patients.

Histopathological findings at temporal artery biopsy

All biopsies were reviewed using a standard check-list for the following histopathological findings, including the; presence of giant cells, fragmentation in the internal elastic lamina, mononuclear cell infiltration, increased intimal thickness, vascular thrombosis, presence of granulomas, medial calcinosis, myxoid degeneration, and perivascular inflammation. The presence of at least one of these findings determined according to DCVAS (fragmentation of the internal elastic lamina/presence of giant cells/mononuclear cell infiltration) was deemed as definite vasculitis in GCA patients.

The pathologists re-evaluated the paraffin blocks of 36 (40%) patients whose microscopic findings were not specified/missing in the pathology reports (Fig. 1, *phase II; Re-evaluation of pathology specimens according to DCVAS criteria*).

The biopsy length of TAB were recorded. Glucocorticoid usage and commencement dates of medications taken prior to the TAB procedure was obtained from patients medical records. Comorbidity diseases (such as diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), hyperlipidemia, cerebrovascular disease (SVH), thrombosis history) at the time of TAB were recorded.

Additionally, the patients were divided into two groups (i) definite vasculitis-GCA and (ii) non-definite-GCA, based on the features emphasized by DCVAS [7]. Clinical data and imaging characteristics were compared between both groups.

Statistical analyses

Statistical analysis was performed with <u>SPSS</u> version 26.0 (SPSS Inc., Chicago, USA). The variables were investigated using visual (histogram and probability plots) and analytical methods (Kolmogorov–Smirnov, skewness, and kurtosis) to test normality of data. Normally distributed variables were expressed as mean and standard deviation (SD) and non-normally distributed variables were expressed as median and interquartile range (IQR). Categorical variables were presented as absolute frequencies and percentages and were compared using the Chi-square test or Fisher's exact test, when appropriate. The student's *t*-test and the Mann–Whitney U-test were used to compare normally- and



Fig. 1 Sankey flowchart of patients with a temporal artery biopsy. 36 pathology specimens (4: Normal, 20: Consistent but not diagnostic for vasculitis, 12: Diagnostic for vasculitis with microscopic findings not specified) were re-evaluated by pathologists

non-normally distributed continuous variables, respectively, between two groups. Associated factors of definite vasculitis were examined for the entire population. These possible factors, which were identified in univariate analyses (p < 0.20), were further integrated into the Cox regression analysis with backward selection. The capacity of temporal artery biopsy length in predicting presence of definite vasculitis were analyzed using ROC (Receiver Operating Characteristic) curve analysis. When a significant cut-off values were observed, the sensivity, specifiticy, positive and negative values were presented. While evaluating the area under the curve, a 5% type-I error level was used to accept a statistically significant predictive value of the test variables.

Results

The mean age at diagnosis for the total of 90 GCA patients was 69.8 (\pm 8.5). 52.2% were female and 80.9% of patients was found to have at least one cranial symptom. Clinical and imaging characteristics of all GCA patients are summarized in Table 1. A total of 59/90 patients had a Temporal Doppler USG result available, where 23/59 (38.9%) patients had a halo finding reported. Vascular PET imaging was completed for 65/90 patients, of which 12/65 (16.9%) had vascular involvement reported. Vascular vasculitis CT/MR angio was identified in 64/90 patients where 12/64 (18.5%) had vascular involvement reported.

In the first evaluation, 66/90 (73.3%) patients were deemed to have diagnosis of GCA vasculitis according to the available pathology reports. The histopathological findings of 36 patients were re-evaluated (included 4 normal cases, 20 non-specific but not definite cases, 12 cases with consistent with vasculitis but unspecified microscopic findings). 10/24 ((41.6%) patients were identified to have had at least one histopathological finding of definite vasculitis after re-evaluation was completed (Fig. 1). With regards to histopathological findings, in order of frequency, the following was identified; 52 (57.7%) cases displayed mononuclear cell infiltration, 44 (48.8%) cases had fragmentation in the internal elastic lamina present, and 37 cases (41.1%) had giant cells present (Fig. 2). According to our findings, we deemed that there were 76/90 (84.4%) patients with definite vasculitis-GCA. Definite vasculitis-GCA was noted to occur in the elderly patients within our study population (74 (7.2))vs 69.9 (11.3) years, p = 0.06).

The mean value of biopsy length for our GCA patient population was 19.7 (13.4) mm. Biopsy length was noted to be longer in definite vasculitis-GCA patients (21.2 mm (14.8) vs 10.4 (6.6) p = 0.005). The sensitivity and specificity of biopsy length was examined for those GCA patients deemed to have definite vasculitis. Accordingly, when the TAB length ≥ 1 cm, the sensitivity was 76.4, while the specificity was 92.9 when it was ≥ 2 cm. The ROC analysis completed showed that biopsy length has a diagnostic value in predicting the diagnosis of definite vasculitis (AUC: 0.778, 95% CI: 0.65–0.89, p < 0.001) (Fig. 3).

Thirty-five (38.9%) of all patients had glucocorticoid usage before TAB. The duration from initiation of glucocorticoid therapy to TAB was found to be longer in the nondefinite-GCA patients when compared with definite-GCA patients. However, there was no statistical difference (the median duration of treatment was 12 days (3–39) vs 16 days (5–65) p=0.7). We compared the histopathological findings in all patients treated with glucocorticoids and those not treated. The frequency of fragmentation in the internal elastic lamina (34.5%) and definitive vasculitis (71.7%) was lower in the presence of glucocorticoid usage before TAB (Table 2).

We completed univariate analysis using the following data including; age at the time of biopsy, gender, C-reactive protein and sedimentation level, glucocorticoid usage prior to TAB, duration from glucocorticoid initiation to biopsy, and the biopsy length was examined for definite vasculitis cohort. In multivariate analysis, biopsy length was found to be the most important factor to contribute towards having adequate items for definite vasculitis (OR; 1.18 (1.06–1.31) p = 0.002) (Table 3).No differences were observed in the clinical and physical examination findings between the two groups of patients. A Halo finding on temporal artery USG was less commonly observed in the definite-GCA patient group (30.4% VS 61.5% p = 0.044).

Discussion

The objective of this study was to evaluate TAB reports from four tertiary care centers in order to examine the definitive vasculitis criteria emphasized in the newly updated 2022 ACR/EULAR GCA classification criteria. A review of the biopsy reports revealed that microscopic findings were not reported in 36 out of 90 patients (40%). Following the reevaluation of histopathological specimens in 24 of these patients, the percentage of patients fulfilling the criteria for definitive vasculitis increased from 73 to 84%. A biopsy length greater than 1 cm was found to be particularly useful in aiding the diagnosis of definitive vasculitis.

The updated 2022 ACR/EULAR GCA classification criteria place a strong emphasis on the inclusion of histopathological findings. In a sub-study of the Diagnostic Criteria for Vasculitis (DCVAS), Putman et al. reported histopathological findings in 705 GCA patients, identifying vasculitis findings in 69% of their patient population [7]. The most prevalent findings were those of giant cells (51%), mononuclear cell infiltration (32%), and internal elastic lamina (IEL) fragmentation (41%). In our study, the corresponding

Table 1	Demographic and	histopathological	characteristics	of patients
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Variables	All patients $(n=90)$	Definite vasculitis	Non-definite vasculitis	р
	- · · ·	(<i>n</i> =76)	(n = 14)	
Age, mean (SD)	69.88 (+8.6)	74 (12)	69.9 (11.3)	0.06
Gender, female, n (%)	47 (52.2)	39 (50)	10 (69.2)	0.16
Clinical symptoms, n (%)				
at least one cranial symptom (vision loss, scalp, headache, jaw)	68/86 (79)	55/72 (76.3)	13/14 (92.8)	0.19
• Vision loss	27/84 (32.1)	21/72 (29.1)	6/12 (50)	0.27
Scalp tenderness	15/84 (17.2)	12/72 (16.6)	2/12 (16.6)	0.65
New/worse headache	64/84 (71.1)	53/72 (72.2)	11/12 (91.6)	0.56
Jaw claudication	35/84 (41.6)	29/72 (40.2)	3/12 (25)	0.2
Limb claudication	4 /84 (4.7)	3 /72 (4.1)	0	NA
• Fever	16/84 (19.0)	14/72 (19.4)	2/12 (16.6)	0.5
• Weight loss	22/84 (26.0)	19/72 (26.3)	3/12 (25)	0.4
Musculoskeletal symptoms	34/84 (40.4)	24 /72 (33.3)	8/12 (66.6)	0.09
Coexistent PMR. n (%)	35/84 (43.2)	30/72 (41.6)	5/12 (42)	0.71
Physical examination findings, n (%)				
• Abnormality in the temporal artery	24/81 (29.6)	21 (28.8)	3 (23.1)	0.3
• Other vascular abnormalities	3/81 (3.7)	3 (4.1)	0	NA
Comorbid diseases, n (%)	0,01(0,0)		0	1.1.1
Hypertension	42/84 (50)	34 /72(47.2)	8/12(66.6)	0.48
Diabetes mellitus	20/84 (23.8)	15/72 (20.8)	5/12 (42)	0.25
Coronary Artery Disease	19/84 (22.6)	15/72 (20.8)	4/12 (33.3)	0.18
• Hyperlipidemia	37/84 (44)	24 /72 (33.3)	10 / 12 (83.3)	< 0.001
Cerebrovascular disease	3/84 (3.5)	2/72 (2.7)	0	NA
• Thrombosis (4 of them, deep vein thrombosis + pulmonary thromboembolism; 3 of them deep vein thrombosis)	8/84 (9.5)	7 /72 (9.7)	1/12 (7.7)	NA
Laboratory findings *				
• Anemia, n (%)	63 (70)	54 (72.6)	9 (69.2)	0.57
• Hemoglobin, g/L mean (SD)	11.4 (1.8)	11.2 (1.9)	12.3 (1.2)	
• Leukocytosis, n (%)	21(23.3)	16 (25.1)	6 (46.2)	0.1
○ leukocyte count, median (min–max)	9850 (5100-21950)	9.600 (5100-21950)	10,700 (5500–16800	
• Abnormal ESR, <i>n</i> (%)	76/89 (85.5)	65 (94)	11 (84.6)	0.09
• ESR, median (SS)	73.8 (3.9)	77.6 (34.2)	55.6 (33.3)	0.01
• Abnormal CRP, n (%)	81/89 (91)	66 (95.5)	11 (91.7)	0.49
• CRP, median (min-max)	6.8 (0.17–36.6)	8.1 (7.1)	4.2 (3.1)	0.03
Imaging findings, <i>n</i> (%)		· · ·	~ /	
• Halo sign on temporal USG	23/59 (38.9)	14/46 (30.4)	8/13 (61.5)	0.044
• Vascular involvement in PET	12/65(16.9)	10/52(19.2)	1/13 (7.6)	
Abnormal angiography findings on MRI	12/64 (18.5)	10/51(19.6)	2/13 (15.3)	0.54
Glucocorticoid usage before TAB	35/77 (38.9)	25/63 (41.3)	10 (71.4)	0.03
Duration of glucocorticoid usage, day, median (min-max)	15 (3-65)	12 (3-39)	16 (5-65)	0.7
Biopsy length > 1 cm. n (%)	63 (70)	58 (76.3)	5 (35.7)	0.004
Biopsy length, mean (SD)	19.7 (13.4)	21.2 mm (14.8)	10.4 mm (6.6)	0.005
Presence of giant cells, <i>n</i> (%)	37 (41.1)	37 (48.6)	NA	
Fragmentation in the internal elastic lamina. n (%)	44 (48.8)	44 (57.8)	NA	
Mononuclear cell infiltration, n (%)	52 (57.7)	52 (68.4)	NA	
Intimal thickness, <i>n</i> (%)	47 (52.2)	42 (55.2)	5 (35.7)	
At least one histopathological finding. $n(\%)$	76 (84.4)	76	NA	
At least two histopathological findings. <i>n</i> (%)	46 (52.8)	46 (60.5)	NA	
Vascular thrombosis, <i>n</i> (%)	2 (2.2)	1 (1.3)	1 (7.1)	
Granuloma, n (%)	1 (1.1)	-	1 (7.1)	

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Table 1 (continued) Variables Definite vasculitis All patients (n = 90)Non-definite vasculitis p (n = 76)(n = 14)Presence of perivascular inflammation, n (%) _ Medial calcinosis, n (%) 6 (6.6) 4 (5.2) 2 (14.2) Myxoid degeneration, n (%) 7 (7.7) 4(5.2)3 (21.4)

The data was given based on what is currently available

CT Computed Tomography, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *COPD* Chronic Obstructive Pulmonary Diseases, *MRI* Magnetic resonance imaging, *PET* positron emission tomography, *PMR* polymyalgia rheumatica, *SD* Standard deviation, *USG* ultrasonography *Reference ranges of laboratory findings: hemoglobin level; male: (13.5 - 17.5), female=(12.5 - 15.5); leukocyte count=between (4,000–11,000); CRP, (0–0.8) mg/dL; ESR, (0–25) mm/h



Biopsy length Reference line

Fig. 2 Histological section of the temporal artery biopsies (Hematoxylin and eosin stain, $\times 100$ magnification). **a** Arrow (\Rightarrow): Fragmentation of the internal elastic lamina. **b** Asterisk (*): Transmural

lymphohistiocytic inflammation, indicative of vasculitis. **c** Asterisk (*): Transmural lymphohistiocytic inflammation. Triangle (Δ): Giant cells. Arrow (\Rightarrow): Fragmentation of the internal elastic lamina



Biopsy length Sensitivity (%) Specificity (%) PPV (%) NPV (%) >1 cm 76.4 64.2 92.0 33.3 >1.5 cm 56.6 78.6 94.4 30.5 >2 cm 43.4 92.9 97.0 32.0 PPV: Positive predictive value; NPV: Negative predictive value

Fig. 3 Receiver Operating Characteristic (ROC) curve assessing the predictive capacity of temporal artery biopsy length for diagnosing definite vasculitis. The accompanying table presents diagnostic per-

formance matrics, including sensitivity, specificity, positive predictive value, and negative predictive value

findings were giant cells (41.1%), mononuclear cell infiltration (57.7%), and IEL fragmentation (48.8%). The cohort and ot

discrepancies in the histopathological findings between our cohort and other studies may be attributed to variations in

Table 2 Comparison of histopathological changes according to glucocorticoid usage before temporal artery before temporal		Glucocorticoid usage* before TAB (+), n=35	Glucocorticoid usage* before TAB (-) n=42	р
biopsy	Fragmentation in the internal elastic lamina, <i>n</i> (%)	10 (28.5)	28 (66.6)	0.005
	Mononuclear cell infiltration, n (%)	15 (42.8)	27 (64.2)	0.053
	Intimal thickness, n (%)	14 (40)	26 (61.9)	0.08
	Presence of giant cells, n (%)	11 (31.4)	19 (45.2)	0.06
	Definite vasculitis <i>n</i> (%)	25 (71.4)	38 (90.4)	0.03

TAB Temporal artery biopsy

*Out of 77 patient in which data was available, 35 were using glucocorticoids

Table 3 Factors associated with the diagnosis of histopathological definite vasculitis of GCA

Risk factors	OR	RR (%95 CI)	р
Age at the TAB	1.04	(0.96–1.12)	0.26
Gender	1.68	(0.4–7.1)	0.47
CRP	1.44	(0.7–12)	0.81
ESR	0.74	(0.5–9.8)	0.7
Glucocorticoid usage before TAB	0.56	(0.13–2.4)	0.4
Biopsy length, mean (SD)	1.18	(1.06–1.31)	0.002

CRP C-reactive protein. ESR Ervthrocyte sedimentation rate. TAB Temporal artery biopsy, SD Standard deviation, OR Odds ratio, RR Relative risk, CI Confidence interval

the stage of GCA, the use of glucocorticoids before biopsy, and differences in the fixation properties of pathology specimens [11-13].

Initially, 66 patients (73.3%) were diagnosed with vasculitis based on pathology reports. After re-evaluation of the histopathology specimens, approximately half of the 24 patients (46%) with initially negative TAB results were subsequently determined to have definitive vasculitis. This finding underscores the importance of including detailed histopathological criteria, as specified by the 2022 ACR/ EULAR classification criteria, in order to provide a more accurate and standardized evaluation of TAB.

Although several validation studies have implemented the new 2022 ACR/EULAR criteria [14, 15] our study is the first to report the use and inclusion of histopathological items in aiding the diagnosis of definitive vasculitis in GCA biopsies. Furthermore, our analysis identified that age, CRP/sedimentation level, gender, and pre-biopsy glucocorticoid treatment were associated with definitive vasculitis. The results of the multivariate analysis indicated a significant correlation between biopsy length and the diagnosis of definitive vasculitis.

Previous studies have established that longer biopsy lengths increase the diagnostic accuracy of TAB for GCA [5, 16, 17]. Currently, there is no consensus in the literature with regards to the biopsy length, however, several studies have shown that more positive results are obtained in biopsies that measure longer than 15 mm [18, 19]. For example, Grejve et al. found that among 141 patients who underwent TAB, biopsy length was statistically significant in those with positive biopsy results, particularly when TAB length exceeded 1 cm [20]. In another study, Breuer et al. reported a positivity rate of 89% in patients with a biopsy length greater than 2 cm, where positive biopsy was defined as mononuclear cell infiltration in the vessel wall [21]. In our study, longer biopsy lengths correlated with definitive vasculitis findings according to DCVAS. We categorized biopsy lengths as 1 cm, 1.5 cm, and greater than 2 cm, with corresponding specificities of 64%, 78%, and 92%, respectively.

Glucocorticoid (GC) use prior to TAB can influence biopsy results. This effect is more pronounced in patients with non-definitive GCA. Data on the timing of GC administration before biopsy are inconsistent, with studies reporting treatment periods ranging from two weeks to twelve months [13]. A study of 78 GCA patients found that TAB positivity decreased over time, with biopsies performed after more than two weeks of glucocorticoid initiation demonstrating lower sensitivity [22]. Similarly, Mehta et al. reported a positivity rate of only 20% in patients who underwent TAB two weeks after starting glucocorticoids [23].

In our study, 35 (38.8%) patients received GC treatment before biopsy. Notably, GC use prior to biopsy was less frequent in our cohort, and the median time to biopsy was shorter (12 days) in patients with definite vasculitis-GCA. Our analysis revealed no significant difference in glucocorticoid use duration between patients with definite and non-definite GCA. However, limited existing literature and our own study's limitations, including a small sample size and missing data, hinder definitive conclusions. These limitations also restrict our ability to comment further on the relationship between temporal artery abnormalities on physical examination, vision loss, and fulfillment of definite GCA criteria.

Gonzales-Gay et al. reported lower frequencies of jaw claudication, abnormal temporal artery examination findings, and constitutional symptoms in GCA patients, with headache and PMR being more prevalent [24]. Conversely, non-definite patients in our study were more likely diagnosed based on ultrasound findings. This aligns with the recently published 2022 ACR/EULAR GCA classification criteria, which acknowledge ultrasound as a diagnostic tool even in the presence of a negative TAB for suspected GCA [6]. Our study differed from a previously published report [25] in that definite vasculitis was less frequently diagnosed in patients with halo findings. This discrepancy might be attributable to our retrospective design, which limited access to complete ultrasound reports for all patients. Additionally, some patients underwent ultrasound examinations while already receiving treatment, potentially affecting the results.

Our study has several limitations. The retrospective design restricted access to complete clinical and imaging data for some patients. Furthermore, the small sample size limited our ability to explore the relationship between clinical features, Doppler US findings, and TAB histopathology.

A key strength of our study lies in the re-evaluation of TAB preparations according to the DCVAS cohort recommendations, thereby contributing to a more comprehensive understanding of biopsy results. Additionally, the 2022 ACR/EULAR GCA classification criteria promote standardized evaluation of temporal artery pathology. The updated criteria provide valuable guidance for defining a positive TAB in clinical practice.

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Author contribution Conceived and designed the analysis: GSU,OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK. Collected the data: GSU, OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK. Contributed data or analysis tools: GSU, OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK. Performed the analysis and interpretation of results: GSU, OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK. Draft manuscript preparation: GSU, OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK. Other contribution: GSU, OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK. Other contribution: GSU, OG, BO, AH, SG, RCK, MAO, EU, AA, BA, AO, LK, OK.

Data availability The datasets gathered during the preparation of this manuscript are available from the corresponding author upon reasonable request.

Declarations

Confict of interest The authors have declared no conflicts of interest regarding the publication of this manuscript.

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