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Predictors of Successful Radiofrequency Ablation of Benign Thyroid Nodules: A Single Centre Analysis

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Abstract

Objective: To assess the predictors of successful inactivation of benign thyroid nodules using radiofrequency ablation (RFA) and the hormonal responses thereafter. **Methods:** A retrospective study conducted at Zhongnan Hospital of Wuhan University (January 2022 to January 2024) analysed thyroid tumor characteristics using B-mode ultrasound, colour Doppler imaging, and CEUS post-RFA. Thyroid hormone levels were also assessed before RFA and at 1, 3, and 6 months after the procedure. **Results**: The study involved 72 patients with benign thyroid nodules, comprising 13 males and 59 females, with a mean age of 45.8 ± 12.1 years. Complete inactivation was achieved in 70.8% of nodules, while 29.2% showed partial inactivation. Nodules with complete inactivation exhibited more calcification ($p = 0.040$), whereas those with partial inactivation demonstrated higher vascularity ($p < 0.001$). Hormonal levels remained within normal ranges, with no significant differences between the groups. Multivariate logistic regression identified nodular vascularity ($p < 0.001$) as an independent predictor of nodule inactivation after RFA. **Conclusion:** In conclusion, this study found that therapeutic RFA effectively achieves high rates of complete inactivation in benign thyroid nodules, with the degree of inactivation mainly influenced by nodule vascularity and calcifications.

Keywords

Predictors, Radiofrequency Ablation, Benign, Thyroid Nodules

1. Introduction

Thyroid nodules are distinct lesions found within the thyroid parenchyma [1]. Most thyroid nodules are asymptomatic and are often discovered incidentally through ultrasound imaging, with prevalence rates ranging from 33% to 60% in adults, particularly in Asia and Europe [2] [3]. Other studies suggest that up to 65% of adults may have thyroid nodules detected via high-resolution ultrasound, with prevalence increasing with age and being more common in females than in males [4]. While the majority of thyroid nodules are benign, such as follicular adenomas, cysts, and colloid nodules, approximately 5% - 15% are malignant, including papillary, medullary, follicular, and anaplastic carcinomas [4] [5]. Although surgical intervention remains the standard treatment for malignant tumors, it is associated with complications like hypothyroidism, voice changes, hypocalcemia, and scar formation. As a result, radiofrequency ablation (RFA) has emerged as a minimally invasive and effective alternative for treating thyroid tumors [2].

RFA utilizes thermal energy to induce coagulative necrosis within targeted tissue, thereby causing inactivation or destruction of the tumor and leading to a reduction in nodule volume and symptom relief. This approach offers several advantages, including faster recovery, preservation of normal thyroid function, and cost-effectiveness [6]. The procedure is guided by ultrasound imaging. Grayscale ultrasound is employed to assess RFA efficacy by evaluating B-mode sonographic characteristics to determine either complete or partial inactivation [7]. This is further supported by color Doppler and Contrast-Enhanced Ultrasound Scan (CEUS), which assess nodule viability. These imaging techniques improve diagnostic accuracy, facilitate comprehensive post-treatment monitoring, and support effective clinical management [8] [9]. RFA avoids many of the risks associated with traditional surgery, such as hypothyroidism and permanent voice changes, making it a more attractive option for patients [10].

Thyroid hormones, including free thyroxine (FT4) and free triiodothyronine (FT3), are essential for growth, development, and metabolic regulation. Their production and release are controlled by thyroid-stimulating hormone (TSH). Changes in these hormones following RFA of benign and malignant thyroid tumors can offer valuable insight into the procedure's impact on thyroid function and overall endocrine health [11] While benign thyroid nodules typically maintain normal hormonal levels after RFA, indicating preserved thyroid function, malignant nodules may exhibit alterations in hormone levels due to the extensive tissue destruction required to eliminate malignant cells [11] [12].

Understanding the predictors of inactivation of thyroid nodules following RFA and the hormonal dynamics thereafter is imperative in leading to more effective patient management strategies and better clinical outcomes for benign thyroid nodules. Therefore, this study evaluated the predictors of inactivation of benign thyroid nodules using RFA through assessing the nodule sonographic characteristics and the post-RFA hormonal response.

2. Materials and Methods

2.1. Study Design and Population

This retrospective analysis examined data from benign thyroid nodule patients treated at Zhongnan Hospital of Wuhan University between January 2022 and January 2024. The study included 72 adult participants aged 18 years or older (mean age: 45.8 ± 12.1), all of whom underwent therapeutic RFA. The inclusion criteria were as follows: patients with symptomatic thyroid nodules, cytologically confirmed benign thyroid nodules based on two separate US-guided biopsies, the absence of malignant features on ultrasound, and nodules classified as solid (≥50% solid components) or predominantly cystic (10% < solid components <50%). Additionally, all participants had normal serum thyroid hormone and thyrotropin levels. Excluded were those with follicular neoplasms, primary thyroid cancer, a history of neck radiation therapy, pregnancy, and cystic nodules (<10% solid components).

2.2. Radio Frequency Ablation and Ultrasound Procedure

All radiofrequency ablations (RFAs) were conducted following established protocols [13]. A SIEMENS ultrasound machine equipped with a 6 - 16 MHz linear probe was utilized for both standard ultrasound and contrast-enhanced ultrasound (CEUS) examinations post-RFA. Certified senior sonographers and radiologists, each with 10 - 20 years of experience in thyroid imaging, performed these examinations. Patients were positioned supine with their necks extended and supported by a soft sponge to optimize imaging clarity.

During the ultrasound evaluation, key nodule characteristics, including size, composition, echogenicity, margins, shape, and calcification, were assessed and recorded using B-mode (grayscale) imaging. Vascularity was evaluated via color Doppler, while enhancement was assessed using CEUS. Color Doppler examinations were performed with standard settings, adjusting amplification just below the threshold where background noise disappeared.

For CEUS, the contrast agent Sono-Vue, containing inert gas (SF6) stabilized with lecithin, was employed. The Sono-Vue microbubble suspension was prepared by mixing the agent with saline. The ultrasound machine's contrast mode was activated with a mechanical index of 0.06. After shaking the solution for 20 seconds, 2.4 mL of the suspension was rapidly injected into an elbow vein, followed by a 5 mL saline flush. Dynamic contrast images were then captured and stored over a period of more than three minutes.

The success of the RFA was determined by the absence of significant color Doppler flow or contrast enhancement in the ablated nodule. CEUS served as the confirmatory test when color Doppler results were inconclusive. In cases where partial inactivation or viable nodule tissue remained detectable, additional RFA procedures were recommended.

2.3. Data Collection

Demographic information, ultrasound reports, cytological findings, and laboratory test results were retrieved from the Hospital Management Information System (HMIS) and the Picture Archiving and Communication System (PACS).

Ultrasound image data were acquired directly from the AX SIEMENS 3000 ultrasound machine, while additional imaging data were accessed via PACS in Digital Imaging and Communication in Medicine (DICOM) format.

The levels of FT3, FT4, and TSH were measured using a radioimmunoassay analyzer, following the procedural guidelines provided by the kit manufacturers. The reference ranges were as follows: FT3: 3.21 - 6.5 pmol/L, FT4: 10.20 - 21.88 pmol/L, and TSH: 0.3 - 4.6 μIU/mL. Deviations from these ranges were classified as either abnormally low or high.

2.4. Data Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS), Version 27 by IBM, Inc. Continuous variables were expressed as means with their respective standard deviations, while categorical variables were presented as counts and percentages. Group comparisons were conducted using the chi-square test and Fisher's exact test for categorical variables, and independent sample t-tests for continuous variables. To identify factors independently associated with complete or partial remission following RFA, a multiple logistic regression analysis was performed. Statistical significance was defined as a p-value less than 0.05.

3. Results

Records of 375 nodules from 373 patients with benign thyroid masses were retrieved from January 2022 to January 2024. After excluding 85 patients who had no cytology results, 25 who underwent mass resection and 193 with no thyroid hormone results, 72 were eligible and so included in the analysis. **Figure 1**. Demographic characteristics of all enrolled patients (n = 72) are summarized in **Table 1**. Before RF ablation, the mean largest diameter of the thyroid nodules was 1.3 ± 1.1 (range 0.2 - 5.4) cm, with a mean volume of 1.1 ± 1.9 (range 0.002 - 8.675) cm^3. Majority of the nodules were regular in shape (59.7%), had clear margins (51.4%) and were solid in composition (91.7%). All patients tolerated RF ablation and none underwent surgery after ablation.

3.1. Treatment Outcomes

The primary outcome of this study was nodule inactivation following RFA. Of the 72 patients, 51 (70.8%) had complete nodule inactivation, while 21 (29.2%) had partial inactivation. **Figure 2** shows nodule images of 2 patients before and after RFA. The two groups of patients had no significant differences in terms of age, gender, nodular diameter and volume (all $p > 0.05$). Those with complete inactivation had more calcification ($p = 0.040$), while those with partial inactivation had more vascularity ($p < 0.001$). **Table 2**. Analysis of changes in thyroid hormone levels between the two groups over a 6-months period showed no significant difference, although slight increase in TSH levels were seen within groups over the same period. **Table 3**. **Figures 2-4** show sonographic images of a benign nodule pre RFA, a partially inactivated nodule and a completely inactivated nodule respectively.

3.2. Predictors of Nodule Inactivation

To determine factors associated with nodule inactivation, we conducted multiple logistic regression analysis. Included on the model were age, sex, nodular diameter, initial volume, nodular number, calcification, and nodular vascularity. Results of the regression analysis are summarized in Table 4, which revealed that only nodular vascularity ($p < 0.001$) was an independent predictor of nodule inactivation following RFA.

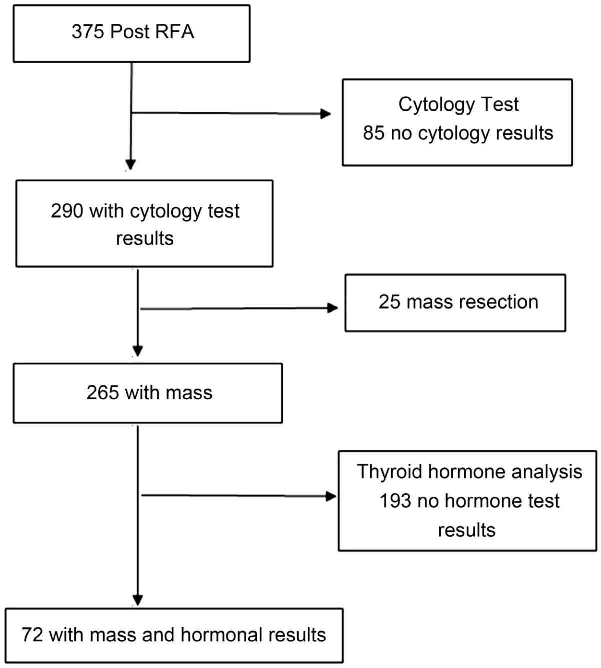

Figure 1. Participants' selection flowchart.

Table 1. Demographic characteristics of enrolled patients.

Characteristics	RF ablation (n = 72)
Sex (Male: Female)	13:59
Age (Years)	45.8 ± 12.1 (28 - 65)
Nodular diameter (cm)	1.3 ± 1.1 (0.2 - 5.4)
Nodular Volume (cm^3)	1.1 ± 1.9 (0.002 - 8.675)
Shape (Regular: irregular)	43:29
Margins (Clear: unclear)	37:35
Composition (Solid: mixed)	66:6

Note: Values represent mean ± SD; numbers in parenthesis represent range. RF = radiofrequency, SD = standard deviation.

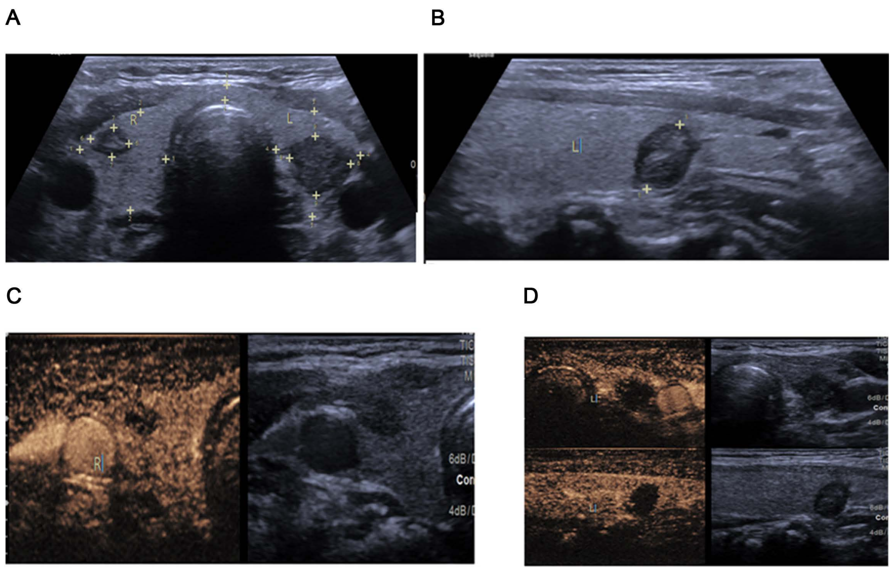

Figure 2. Pre-ablation benign nodules in the right and left thyroid lobes based on the cytological results. The sonographic features included (A, B) hypoechoic solid nodules, with clear margins on grayscale mode (C, D) Application of CEUS shows a scanty enhancement in the right nodule. Thyroid nodule RFA: Radiofrequency Ablation, CEUS: contrast-enhanced ultrasound.

Table 2. Patient characteristics by treatment outcome.

Variables	Complete tumor inactivation (n = 51)	Partial tumor inactivation (n= 21)	P value
Age, mean (SD)	45.5 (12.3)	45.6 (8.6)	0.963
Male, n (%)	10 (19.6)	3 (14.3)	0.594
Nodular diameter (cm) mean (SD)	1.2 (0.8)	1.6 (1.4)	0.170
Nodular volume (cm^3)	0.8 (1.6)	1.7 (2.6)	0.092
Nodule number			0.285
1, n (%)	38 (74.5)	13 (61.9)	
>1, n (%)	13 (25.5)	8 (38.1)	
Calcification			0.040
Yes, n (%)	9 (17.6)	0 (0.0)	
No, n (%)	42 (82.4)	21 (100)	
Vascularity			<0.001
Vascular, n (%)	6 (11.7)	14 (66.7)	
Avascular, n (%)	45 (88.3)	7 (33.3)	

Note: SD: Standard deviation.

Table 3. Thyroid hormone levels over a 6-months follow up post RFA.

Variables	Complete	Partial	P value
Initial			
TSH	0.97 ± 1.1	0.97 ± 1.1	-
FT3	4.80 ± 1.11	4.80 ± 1.11	-
FT4	15.19 ± 4.81	15.19 ± 4.81	-
1 month			
TSH	1.8 ± 2.0	1.7 ± 1.8	0.615
FT3	5.1 ± 0.9	5.1 ± 0.9	0.817
FT4	17.1 ± 3.5	16.9 ± 3.6	0.343
3 months			
TSH	1.9 ± 1.9	1.8 ± 1.7	0.713
FT3	4.6 ± 0.7	4.6 ± 0.7	0.918
FT4	15.3 ± 2.9	15.2 ± 3.0	0.880
6 months			
TSH	2.0 ± 1.9	2.0 ± 1.6	0.872
FT3	4.6 ± 0.8	4.6 ± 0.7	0.921
FT4	14.8 ± 3.1	14.8 ± 3.2	0.861

TSH: Thyroid stimulating hormone. FT3: Free Triiodothyronine. FT4: Free Thyroxine.

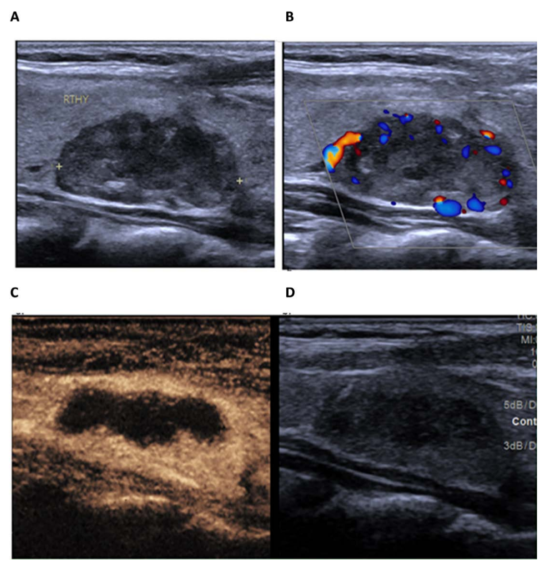

Figure 3. A benign nodule in the right thyroid lobe based on the cytological results. The sonographic features included (A) wider than tall orientation, heterogeneous-hypoechoic solid mass, clear lobulated margins on grayscale mode (B) Addition of color Doppler showing peripheral color flow. (C, D) Application of CEUS shows peripheral enhancement. This was a **partially inactivated** benign thyroid nodule after RFA: Radiofrequency Ablation, CEUS: contrast-enhanced ultrasound.

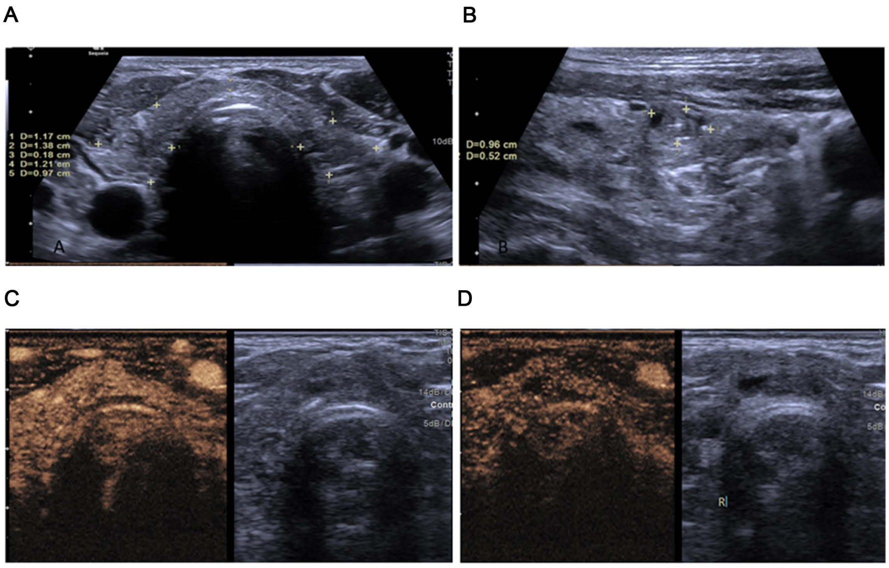

Figure 4. Follow up after 9 months. (A) A coarse and heterogeneous thyroid parenchyma with a small ill-defined lesion solid lesion with tiny linear calcification in the left lobe (B). CEUS shows an enhanced thyroid parenchyma with unenhanced tiny area in the right isthma. (C, D) These changes suggest complete inactivation.

Table 4. Multiple linear regression analysis of factors independently predictive of tumor inactivation.

Variable	B	SE	Wald	Exp(B)	95% CI for Exp(B)	P value
Age (years)	0.018	0.037	0.246	1.019	0.947 - 1,096	0.620
Sex (Male)	1.438	1.129	1.620	4.210	0.460 - 38.519	0.203
Nodular diameter (cm)	−0.492	0.769	0.410	0.611	0.136 - 2.757	0.552
Initial volume (cm^3)	0.397	0.390	1.035	1.488	0.692 - 3.197	0.309
Nodular number	0.476	0.813	0.342	1.609	0.327 - 7.923	0.559
Calcification	−0.81	0.830	0.009	0.922	0.181 - 4.696	0.923
Vascularity	3.820	0.996	14.707	45.625	21.475 - 60.568	0.001*

*Statistical significance. CI: Confidence interval.

4. Discussion

This retrospective study investigated the degree of inactivation in benign thyroid nodules and the hormonal effects following RFA. Existing literature largely supports the efficacy of RFA in managing thyroid tumors, primarily benign nodules and select malignant cases, with minimal or no significant impact on thyroid function [13]-[15]. In our analysis, we examined key sonographic parameters that confirm complete or partial inactivation, as well as factors that may independently predict RFA success in benign thyroid nodules. Our findings highlighted vascularity (presence or absence) and nodule calcification as key determinants of the extent of nodule inactivation.

Our study identified nodule vascularity as a key sonographic finding. Color Doppler imaging revealed that nodules with internal and peripheral blood flow were associated with partial inactivation ($p < 0.001$), while completely inactivated nodules exhibited minimal to no vascularity. In similar studies, Motaghed *et al.* [16] found hyper-vascular benign nodules were 4.1 times more likely to achieve RFA success, while Deandrea *et al.* [17] linked hyper-vascularity to higher volume reduction rates, attributing success to coagulative necrosis and subsequent cell death. These findings contrast with ours, which indicated that partially inactivated nodules exhibited greater vascularity than completely inactivated ones. We attribute this discrepancy to the fact that RFA uses an electrode to generate heat that destroys nodule cells. Hypervascular nodules, however, require more energy for ablation due to the heat sink effect and perfusion-mediated cooling, as described by So Lyung Jung [18] and Navin *et al.* [19]. The cause of this inconsistency remains unclear, and further research is needed to elucidate the underlying mechanisms.

Furthermore, the presence of calcification was associated with a reduced likelihood of achieving complete inactivation ($p = 0.040$). This finding aligns with that of Li *et al.* [20] who reported that macro-calcifications were linked to lower VRR in calcified benign nodules compared to non-calcified nodules. This they said could be due to challenges in penetrating dense calcifications, which hinder effective heat conduction to the targeted tissue, as well as the inability to monitor the electrode tip within areas of acoustic shadowing.

Other factors, such as shape (regular or irregular), margins (clear or unclear), and composition, showed no significant impact on complete versus partial inactivation. While regular shapes may distribute ablation energy more evenly, irregular masses are harder to eliminate due to uneven borders and invasive behavior. The inconclusive results in our study could stem from a small sample size or patient similarity. Although RFA is effective for all thyroid nodule types, studies indicate greater volume reduction and lower recurrence rates in predominantly cystic nodules [21]. Conversely, our findings showed that nodule composition (solid versus mixed) did not significantly influence RFA success, likely due to varying ablation energy requirements.

The impact of RFA on thyroid function remains uncertain, despite well-documented evidence of benign nodule inactivation. Theoretically, RFA can alter thyroid function by inducing hyperthyroidism through hormone release from ablated tissue or hypothyroidism due to extensive tissue destruction [21]. Long-term studies have generally shown no significant hormonal changes, with FT3, FT4, and TSH levels remaining normal up to 12 months post-RFA [22] [23]. Wang *et al.* [14] also reported stable thyroid function one month after thermal ablation in low-risk unifocal PTMC cases. However, short-term thyroid function trends are inconsistent. Some reports document temporary hypothyroidism, such as elevated TSH levels immediately after RFA, which typically resolve within a year [21] [24] [25]. Hussain *et al.* [26] observed significant FT4 reductions post-RFA in non-functioning nodules, suggesting a potential indicator of hypothyroidism.

Wang *et al*. [27] further reported increased hormone levels within a week post-RFA, especially in patients with diabetes, alongside cases of overt thyrotoxicosis, subclinical thyrotoxicosis, and long-term subclinical hypothyroidism. In our study, no significant changes in FT3 or FT4 were observed over 6 months, though borderline TSH elevations were noted at 3 and 6 months. These variations may result from unmasked subclinical hypothyroidism or incomplete ablation. Long-term follow-up beyond two years is recommended to ensure patient reassurance and guide future management.

Our study provides valuable insights into key sonographic parameters influencing complete and partial inactivation of benign thyroid nodules post-RFA. It also highlights the importance of hormonal follow-ups to guide patient expectations regarding thyroid function outcomes. However, the study has some key limitations: It was a single-institution retrospective analysis with no pre-RFA nodule data, had a small sample size which may affect statistical power, and had a short follow-up duration (6 months), excluding long-term hormone monitoring. A well-designed, prospective cohort study is needed to further validate these findings.

5. Conclusion

In conclusion, this study demonstrated that therapeutic RFA achieves high rates of complete inactivation in benign thyroid nodules. The extent of inactivation is primarily influenced by nodule vascularity and calcifications. While no significant impact on thyroid function was observed, mild upper borderline TSH changes at 3 and 6 months underscore the need for long-term monitoring. To further substantiate these results, a larger, well-designed prospective multicenter cohort study is essential, particularly exploring combination therapies for malignant thyroid tumors.

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Author Contributions

Conceptualization, WE; methodology, WE and MW; software, WE. Formal analysis, WE. Investigation; WE and JYC; resources, MW. Data curation. WE, Writing—original draft preparation, WE; writing—review and editing, JYC EAS, MP. Visualization, WE. Supervision, JYC; funding acquisition, WE. All authors have read and agreed to the published version of the manuscript.

Statement of Ethics

This study was approved by the Zhongnan Hospital of Wuhan University Research Ethics Committee.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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