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# Temporal alterations in P-wave electrocardiographic metrics post patent foramen ovale closure: a retrospective study

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## ABSTRACT

**Aims**: This study aimed to analyze the electrocardiograms (ECG) of 69 patients before and after patent foramen ovale (PFO) closure, specifically investigating novel ECG parameters, over a 6-month post-procedure period.

**Methods**: ECGs from 69 patients undergoing PFO closure were examined at three time points: before the procedure, and at 1st and 6th months post-procedure. A comprehensive set of ECG parameters, including P-wave (PW) maximum (PWmax), PW minimum (PWmin), PR interval, PW dispersion (PWdis), PW peak time in lead D2 (PWPTD2), PW peak time in lead V1(PWPTV1), P-axis, PW terminal force in the V1 (PWTF) and heart rate, were analyzed using a generalized linear mixed model (GLMM).

**Results**: The GLMM analysis revealed significant changes in novel ECG parameters at 1-month post-procedure compared to baseline values. Parameters including PWmax (OR=8.898, 95% CI 7.521-10.275, p<0.001, PWmin (OR=6.579, 95% CI 5.611-7.548, p<0.001), PR (OR=4.159,95% CI 3.031-5.288, p<0.001), PWdis (OR=2.594, 95% CI 1.607-3.581, p<0.001), PWPTD2 (OR=4.261, 95% CI 2.928-5.593, p<0.001), PWPTV1 (OR=5.261, 95% CI 4.529-5.992, p<0.001), and PWTF (OR= 5.781, 95% CI 2.083-16.044, p<0.001) exhibited notable alterations, indicating a transient impact on cardiac conduction. However, these changes returned to baseline values by the 6-month follow-up. No statistically significant differences were observed in P-axis and heart rate across all time points.

**Conclusion**: The analysis of ECG in patients undergoing PFO closure highlighted dynamic changes in novel ECG parameters in the early post-procedural period, with subsequent normalization by 6 months. Further research is warranted to elucidate the clinical implications of these dynamic electrocardiographic shifts and their potential association with long-term cardiovascular outcomes.

**Keywords**: Atrial fibrillation, patent foramen ovale, p-wave, stroke

## INTRODUCTION

Stroke continues to pose a substantial global health challenge, with 15% to 30% of cases classified as cryptogenic stroke despite advances in technology.[1] A major contributor to cryptogenic strokes is the presence of patent foramen ovale (PFO), which has been identified in a significant number of cases.[2,3] Recent prospective studies indicate that PFO closure reduces the recurrence of strokes. However, some large-scale studies have observed an increase in atrial tachycardias post-closure when compared to patients undergoing medical monitoring.[4] While this rate was observed to be 4-6% in follow-ups of symptomatic patients and ambulatory Holter analyses, it was reported to be much higher in intracardiac recording studies. Among these atrial tachycardias, atrial fibrillation (AF) is of particular importance.[4,5] While most cases resolve spontaneously without causing ischemic events, some may progress to permanent AF and lead to recurrent ischemic events.[6,7] Although the underlying pathophysiology has not been fully elucidated, regardless of the cause, identifying the factors predictive of AF is crucial for early diagnosis and meticulous patient management.[8] Silent forms of AF, which traditional methods cannot detect, pose a challenge in the diagnosis and treatment of this condition.[9] Although AF detection proved more accurate in implantable cardiac recording studies with a limited number of patients in previous research, its widespread use was hindered by the high cost and complications associated with invasive interventions. Consequently, there is a demand for robust predictive parameters capable of anticipating the risk of development.

P-wave (PW) changes observed on electrocardiogram (ECG) have begun to be used as the latest strong atrial

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arrhythmia predictors. As it is known, atrial arrhythmias are closely related to the PW on ECG.[10-12] PW terminal strength (PWTF), abnormal PW, PW dispersion (PWdis), and a much more specific parameter, PW peak time (PWPT), provide undeniable information about the risk of developing atrial arrhythmia.[11-13]

In this study, we aimed to examine the effect of PFO closure on atrial arrhythmia predictors by examining PW changes before and after the procedure.

## METHODS

### Study Design and Patient Selection

This study is a retrospective, single-centre investigation involving patients referred to our facility for PFO closure following cryptogenic stroke, between March 2020 and January 2023. The study focused on patients aged over 18 years who underwent closure due to high-risk PFO following a cryptogenic cerebrovascular event (CVE). Exclusion criteria involved patients not meeting cryptogenic stroke criteria[10] and those meeting any of the following criteria: AF, atrial flutter, atrioventricular and interventricular block, pacemaker rhythm, severe valve dysfunction, segmental movement disorder, mechanical prosthetic valve, or use of antiarrhythmic or rate-limiting drugs. Demographic, laboratory, and clinical data were extracted from the hospital automation system. ECGs were recorded before PFO closure and at 1st and 6th months post-closure. The study adhered to the ethical principles specified in the Declaration of Helsinki and obtained approval from the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 13.12.2023, Decision No: 2023-12-666). Given the retrospective nature of the study, the requirement for written informed consent was waived for each participant.

### Definitions and Risk Factors

The study collected information on several patient factors, including age, smoking status, and comorbidities. To determine the presence of Diabetes mellitus (DM), patients were considered positive if they were using blood glucose-lowering medications, if their fasting plasma blood glucose levels were greater than or equal to 126 mg/dL, or if their postprandial blood glucose levels were greater than or equal to 200 mg/dL.[14] Hypertension (HT) was defined as systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg or if patients were taking antihypertensive medication.[15]

Ischemic stroke was defined as a sudden focal neurological deficit lasting 24 hours or longer or associated with a related infarction on brain magnetic resonance imaging. The definition of cryptogenic stroke included an extensive search to exclude other identifiable stroke mechanisms such as large artery atherosclerotic disease (defined by patients with at least 50% stenosis in one main vessel or one main vessel occlusion), lacunar stroke (defined by small deep infarction) an established cardioembolic source, small vessel occlusive disease, hypercoagulation disorder requiring anticoagulants, or arterial dissection. All patients underwent computed tomography angiography, magnetic resonance angiography, or ultrasonography to rule out stroke of vascular origin. Holter or long-term cardiac rhythm monitoring was performed to exclude paroxysmal atrial fibrillation.

### PFO Closure Procedure

Percutaneous PFO closure was performed under local or sedation anaesthesia, according to the physician's decision and the patient's convenience. The interatrial defect was assessed before the procedure through transthoracic and transesophageal echocardiography to facilitate the selection of prosthesis size and type. The procedure was performed via the femoral venous route. Prosthesis was positioned under fluoroscopic control and transesophageal echocardiography in case of local anaesthesia. Two types of prosthesis were implanted: the Amplatzer PFO Occluder (Abbott Vascular, United States of America) and the Occlutech PFO Occluder (Occlutech, Sweden). Intravenous injections of unfractionated heparin (5000 international units) and 300 mg of aspirin, associated with antibiotic prophylaxis were, administered before the procedure. In the absence of contraindication, a dual antiplatelet therapy, including aspirin (between 75-100 mg) and clopidogrel 75 mg was initiated for 3 months followed by long-term aspirin. Transthoracic echocardiography was conducted the following day to verify the positioning of the prosthesis and ensure the absence of complications. Hospital discharge was planned for day 1.

### ECG Analysis

**P-wave indices:** The longest (PWmax) and shortest (PWmin) PW were assessed by measuring the PW across all 12 leads from the onset of the deflection on the isoelectric line to the point of deflection returning to the isoelectric line. PWdis denoted the disparity between PWmax and PWmin. The PR interval spanned from the initiation of the PW (atrial depolarization) to the commencement of the QRS complex. PWPT represented the duration between the onset of the PW and its zenith, calculated from leads D2 (PWPTD2) and V1 (PWPTV1). In V1, housing negative and biphasic PW, the duration from the origin of the PW to the peak of the negative PW was measured. Negative waves for assessment were deemed biphasic if they exceeded or were equal to 0.1 mV; those falling below this threshold were excluded. PWTF was computed by multiplying the depth and duration of the terminal negative component of the PW in V1. An abnormal PWTF was defined as PWTF ≥ 40 mm × ms. An abnormal PW axis was characterized by values less than 0 or exceeding a 75 PW axis. In cases where the PW morphology consisted solely of positive or negative bias, the bias was calculated for the mean value. In instances of biphasic bias, the absolute sum of biases was computed and analyzed. Both intraobserver and interobserver variations were maintained at less than 5%.

**Reproducibility:** Intraclass correlation coefficients were computed to assess both intraindividual and interobserver variation. A subset of ECGs from ten randomly selected patients underwent reanalysis by the same observer. For interobserver variability, the identical patients and images were subjected to analysis by a second observer (Ö.G). The intra-observer correlation coefficients for PR, PWmax, PWmin, PWPTD2, PWPTV1, and PWTF were 0.907, 0.901, 0.890, 0.917,0.923 and 0.950, respectively. The inter-observer correlation coefficients were 0.880, 0.936, 0.925, 0.922, 0.912, and 0.937 for the same parameters.

### Statistical Analysis

R statistical software, version 4.1.2, from the Institute for Statistics and Mathematics in Vienna, Austria, was used to perform the statistical analyses. The distribution of the variables was checked using the Kolmogorov-Smirnov test. The continuous variables were expressed as mean (SD) for normal distributions and median (interquartile range (IQR25-75)) for non-normal distributions. The categoric data were displayed using numbers (n) and percentages (%). Generalized linear mixed models (GLMM), using "lmer" for continuous and "glmer" for categoric dependent variables in the lme4 package, were created to detect the significance of the change of ECG parameters on follow-up. Age, device type, device size, DM, HT, smoking, body mass index, left ventricular end-diastolic diameter, left atrial area, gender, and baseline systolic blood pressure were used as covariates in GLMM models. Estimates (OR) and 95% confidence intervals (CI) were reported. Plots were created to demonstrate the changes in the ECG variables during follow-up using ggplot2 in R. Statistical significance was defined at $p < 0.05$ for the study analyses.

## RESULTS

This study consisted of 69 consecutive patients who underwent PFO closure. The mean age was 40.3±8.9 years and 47.8 % of the population were male. Of the patients, 31.9% had HT, 24.6% had DM, and 44.9% were smoking. Occlutech PFO Occluder device was used in 56.5 % of patients and the device size was 25.3 ± 2.4 in the overall population (**Table 1**). GLMM model showed that PWmax (OR=8.898, 95% CI 7.521-10.275, p<0.001), PWmin (OR=6.579, 95% CI 5.611-7.548, p<0.001), PR (OR=4.159, 95% CI 3.031-5.288, p<0.001), PWdis (OR=2.594, 95% CI 1.607-3.581, p<0.001), PWPTD2 (OR=4.261, 95% CI 2.928-5.593, p<0.001), PWPTV1 (OR=5.261, 95% CI 4.529-5.992, p<0.001), and PWTF (OR= 5.781, 95% CI 2.083-16.044, p<0.001) significantly got longer in 1-month after the procedure when compared to baseline values. But all the above-mentioned variables decreased around the basal values again in 6 months. There were no statistically significant differences between all time points regarding the P-axis and heart rate (**Figure**)( **Table 2**).

**Table 1.** Baseline characteristics of study population.

| | |
|---|---|
| Age, years; mean±SD | 40.3±8.9 |
| Male gender, n (%) | 33 (47.8) |
| Body mass index, kg/m2; ±SD | 26.8±4.5 |
| Hypertension, n (%) | 22 (31.9) |
| Diabetes mellitus, n (%) | 17 (24.6) |
| Cigarette smoking, n (%) | 31 (44.9) |
| SBP, mm Hg; median (IQR) | 130 (125-134) |
| DBP, mm Hg; median (IQR) | 73 (70-80) |
| WBC,103/dL; mean±SD | 7.8 (6.4-9.7) |
| Hemoglobin , mg/dl; mean±SD | 13.1+0.9 |
| Platelet, 103/dL; median (IQR) | 224 (193-257) |
| Creatinine, mg/dL; median (IQR) | 0.88 (0.75-0.95) |
| Sodium, mEq/l; mean±SD | 137.1 ± 3.6 |
| Potassium, mEq/l; mean±SD | 4.2 ± 0.2 |
| LVDD, mm, mean±SD | 45.6±2.8 |
| LVSD, mm, mean±SD | 25.4±3.9 |
| LAA, mean±SD | 34.2±2.4 |
| Occlutech PFO Occluder , n (%) | 39 (56.5) |
| Device size, mm; mean±SD | 25.3±2.4 |

DBP, diastolic blood pressure; IQR, interquartile range, LVDD, left ventricular end diatolic diameter; LVDD, left ventricular end sistolic diameter; LAD, left atrial area ; SD , standard deviation ; SBP, systolic blood pressure; WBC, white blood cell

**Table 2.** Generalized lineer mixed model regression for detecting the significance of the change of variables on follow-up

| | Estimate | 95% CI | p-value |
|---|---|---|---|
| PW max | | | |
| 1 month | 8.898 | 7.521-10.275 | **<0.001** |
| 6 month | 0.724 | -0.651-2.101 | 0.304 |
| PW min | | | |
| 1 month | 6.579 | 5.611-7.548 | **<0.001** |
| 6 month | 0.246 | -0.722-1.214 | 0.619 |
| PR | | | |
| 1 month | 4.159 | 3.031-5.288 | **<0.001** |
| 6 month | -0.001 | -1.128-1.129 | 0.999 |
| PW dis | | | |
| 1 month | 2.594 | 1.607-3.581 | **<0.001** |
| 6 month | 0.261 | -0.726-1.247 | 0.605 |
| PWPTD2 | | | |
| 1 month | 4.261 | 2.928-5.593 | **<0.001** |
| 6 month | -0.711 | -2.042,0.622 | 0.298 |
| PWPTV1 | | | |
| 1 month | 5.261 | 4.529-5.992 | **<0.001** |
| 6 month | 0.289 | -0.441,1.021 | 0.439 |
| P axis | | | |
| 1 month | 0.439 | -0.601-1.478 | **0.409** |
| 6 month | 0.621 | -0.417-1.661 | 0.243 |
| Heart Rate | | | |
| 1 month | -0.188 | -2.103-1.726 | 0.847 |
| 6 month | 0.536 | -1.378-2.451 | 0.584 |
| V1TF | | | |
| 1 month | 5.781 | 2.083-16.044 | **0.001** |
| 6 month | 2.446 | 0.873-6.852 | 0.089 |

PWmax, maximum P wave; PW min, minimum P wave, P wave dispersion (PW dis) was determined as the difference between the maximum and minimum P wave; PR, interval spanned from the initiation of the P wave (atrial depolarization) to the commencement of the QRS complex.PWPTD2, from the beginning of P wave to peak in lead D2. PWPTV1 from the beginning of P wave to peak in lead V1; V1TF, P wave terminal force in lead 1.

- Reference group was basal time point.
- Age, device type, device size, diabetes mellitus, hypertension, cigarette smoking, body mass index, left ventricular end-diastolic diameter, left atrial area, male gender, and baseline systolic blood pressure were used as covariates in GLMM model.
- Estimate and 95 % CI values for V1TF reflect odds ratio and 95 % CI for odds ratio.

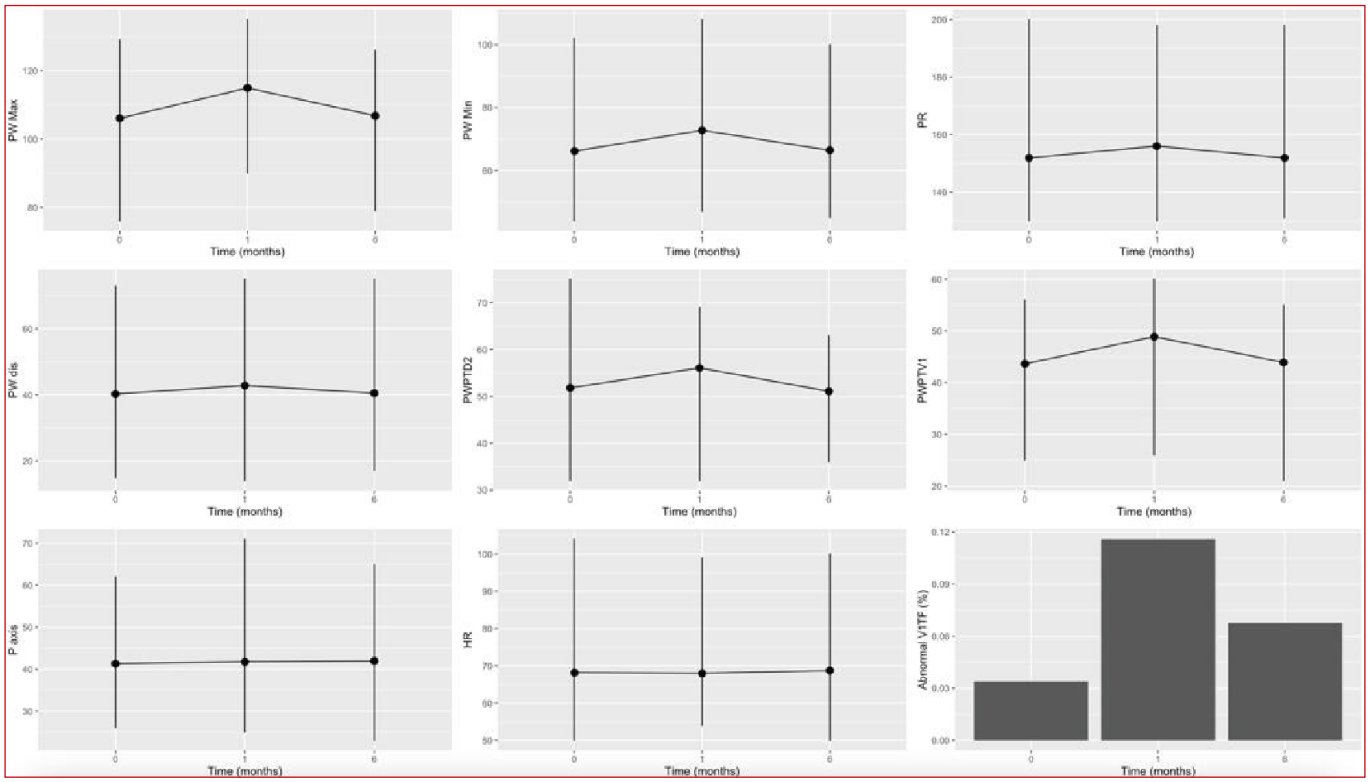


**Figure 1.**

## DISCUSSION

We observed that changes in PW, which are robust predictors of atrial arrhythmia, shifted in favour of arrhythmia during the early period in patients monitored following PFO closure. These findings underscore the importance of exercising caution regarding the risk of atrial arrhythmia in the initial period after PFO closure.

Prestigious studies and meta-analyses indicate an increase in atrial tachycardias following PFO closure.[4,16] Especially in studies conducted with 72-hour Holter and event recorder, it was observed that the incidence of atrial arrhythmias, especially AF, was much higher than the incidence of AF detected in symptom-based evaluations and analyses performed only with ECG.[16-18] This underscores the need for a comprehensive understanding of the arrhythmic picture after PFO closure and its potential effects on patient care. AF, the major contributing factor to the observed increase in atrial arrhythmias, is a significant clinical problem due to its association with stroke and other adverse cardiovascular outcomes.[19] Serious CVEs can be observed during AF attacks; therefore, it is vital to predict the risk of AF development.[19,20] In our study, we observed a significant increase in PW durations, a strong predictor of AF, during the first month. However, these durations gradually approached the baseline level over time. In the study conducted by Elgendy et al.[21] the rate of forgiveness development was found to be higher in the first month, which supports our findings. Understanding this early phase after closure is crucial for clinicians to effectively predict and manage potential arrhythmic events.

There are several theories regarding early arrhythmias. Atrial remodelling and heightened sensitivity following PFO closure may be linked to factors such as tissue inflammation, particularly in the vicinity of the PFO closure device. Inflammation within the tissue surrounding the PFO closure device could potentially predispose to atrial arrhythmias.[7,22,23] It may also play a pivotal role in AF by contributing to the barrier macro-reentry cycle induced by the closure device. Additionally, studies have indicated that the utilization of larger-sized devices and the presence of atrial septal aneurysms are correlated with AF.[6,24] Further research is necessary to reveal the specific mechanisms that underlie this phenomenon and explore potential strategies for mitigating the risk of arrhythmias following PFO closure.

The lack of consensus about recurrent CVEs and AF occurring after PFO closure, and the detection of different incidences in follow-ups with ECG, Holter, and event recorder, make it necessary to use simpler and common parameters.[4-6] The electrocardiographic parameters related to PW characteristics—specifically PWmax, PWmin, PWdis, PWPT, and PWPTF —provide valuable insights into their potential associations with AF.[25] These parameters serve as important markers of atrial electrophysiology, offering a window into

the underlying substrate that may contribute to the initiation and maintenance of AF.[11,25] The PW duration, represented by PWmax, and the minimum PW duration are key electrocardiographic parameters that reflect atrial depolarization and are associated with atrial remodelling, and studies suggest that these alterations may be indicative of increased susceptibility to AF. PWdis provides a measure of the heterogeneity of atrial conduction. Increased PWdis may signify irregular conduction patterns, promoting the formation of reentrant circuits and contributing to the substrate for AF.[24] The timing of the peak of the PW, denoted as PWPT, is another parameter that merits attention in the context of AF.[11,26] In addition, The calculation of PWTF involves the multiplication of the depth and duration of the terminal negative component of the PW in lead V1. This index reflects the electromechanical properties of atrial depolarization and provides a quantitative measure that may be indicative of underlying atrial pathology. The identification of PWTF as a potential predictor for AF holds clinical significance.[27] Abnormal values of PWTF may signify alterations in atrial electrophysiology, contributing to an increased susceptibility to AF. Incorporating PWTF into routine electrocardiographic assessments may offer clinicians a non-invasive tool for identifying individuals at risk for AF, prompting further investigation and targeted interventions. Elevated PWTF suggests abnormalities in the terminal phase of atrial depolarization, which may be linked to atrial remodelling. Atrial structural changes and fibrosis, often observed in conditions predisposing to AF, can manifest in the ECG. Monitoring PWTF provides a dynamic assessment of these changes, aiding in the early detection of atrial remodelling and potential AF development.[28,29]

Understanding the relationship between PW parameters and AF has important clinical implications. These electrocardiographic indices, which can be obtained from routine evaluations after PFO closure, provide a non-invasive method for identifying individuals at risk of AF. Integrating these parameters into risk stratification models may improve our ability to predict the development of AF after PFO closure, facilitating targeted interventions and preventive measures.

### Limitation

Our study has several noteworthy limitations that warrant consideration. Firstly, the retrospective nature and the confinement of the study to a single-centre may compromise the generalizability of the findings. Secondly, the study's limitation lies in its relatively small sample size, which may restrict the robustness of statistical analyses; therefore, a larger patient cohort could enhance the validity of the results. Thirdly, the absence of observed AF development after PFO closure within our study population precludes our ability to provide insights into PW changes before and after the procedure in patients who develop AF. Lastly, the absence of a PFO-related stroke group with medical follow-up in our study prevents a direct comparison of PW parameters. Despite these limitations, our study's findings offer crucial insights into the early-period risk of AF post-PFO closure. However, to establish more definitive conclusions regarding the impact of PFO closure on AF across diverse patient groups, further research with larger sample sizes, prospective designs, extended follow-up periods, and varied patient populations is imperative.

## CONCLUSION

The present study contributes valuable information regarding the ECG changes and arrhythmic effects associated with PFO closure. While transient alterations in ECG parameters were observed, the clinical significance lies in the short-lived nature of these changes. The increased risk of abnormal PW warrants further investigation into the mechanisms and potential long-term implications of arrhythmias following PFO closure. Clinicians should consider these findings in the context of patient care, emphasizing the need for ongoing research to refine our understanding of the complex interplay between PFO closure and cardiac electrophysiology.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was conducted following the ethical principles stated in the Declaration of Helsinki and was approved by the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (December 2023 dated 2023-12-666).

### Informed Consent

The need for a written informed consent form from each participant was waived due to the study's retrospective nature.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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