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ORIGINAL ARTICLE

Triglyceride-Glucose Index in Parotid Gland Tumours: A Novel Biomarker for Differentiating Warthin Tumour and Pleomorphic Adenoma

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ABSTRACT

Introduction: Pleomorphic adenoma and Warthin tumour are the two most common benign parotid gland tumours with distinct histological and clinical profiles. Recent studies suggest a potential link between metabolic disturbances—particularly insulin resistance—and the development of Warthin tumours. The triglyceride-glucose (TyG) index has emerged as a simple, cost-effective biomarker of insulin resistance. This study aimed to investigate the potential role of the TyG index in differentiating between pleomorphic adenoma and Warthin tumour.

Methods: A retrospective cross-sectional study was conducted on patients histopathologically diagnosed with pleomorphic adenoma ($n=31$) or Warthin tumour ($n=22$), and compared with healthy controls ($n=58$). Fasting glucose and triglyceride levels were used to calculate the TyG index. Statistical analyses included t-tests, ANOVA, and Bonferroni-corrected post hoc comparisons, with a significance threshold of $p<0.05$.

Results: No significant differences were observed in age, sex, BMI or TyG index between the tumour group and controls. However, the TyG index was significantly higher in the Warthin tumour group (4.91 ± 0.28) compared to the pleomorphic adenoma (4.68 ± 0.31, $p=0.006$) and control groups (4.72 ± 0.23, $p=0.033$). No difference was found between the pleomorphic adenoma and control groups.

Conclusion: The TyG index is significantly elevated in patients with Warthin tumours, supporting its potential role as a simple, non-invasive biomarker to aid in the differential diagnosis of benign parotid tumours.

1 | Introduction

Primary neoplasms of the salivary glands are uncommon and account for less than 5% of the annual incidence of head and neck malignancies. Approximately 85% of salivary gland neoplasms originate from the parotid gland. It is estimated that 75% of these tumours are benign, while the remaining 25% exhibit malignant characteristics [1].

Although most parotid tumours are benign, they are predominantly represented by types such as pleomorphic adenoma and Warthin tumour; however, a subset may demonstrate aggressive behaviour and malignant potential [2]. Pleomorphic adenoma is the most common benign tumour of the parotid gland and typically exhibits slow growth. In contrast, Warthin tumour is more frequently observed in older males and individuals with a history of smoking [3].

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> **Highlights**
>
> - The triglyceride–glucose (TyG) index was higher in patients with Warthin tumor compared with pleomorphic adenoma.
> - No significant difference in TyG index was observed between pleomorphic adenoma and healthy controls.
> - The TyG index may serve as a simple, non-invasive complementary parameter to support differentiation between common benign parotid gland tumor subtypes in selected clinical scenarios.

The aetiology of parotid gland tumours remains partially misunderstood. Ionising radiation is a well-established risk factor, while occupational exposure to nitroso compounds and smoking have also been implicated [4]. Recent evidence suggests a potential role for metabolic conditions such as obesity and metabolic syndrome, particularly in Warthin tumour. Additionally, viral agents like EBV and HIV, and a history of other malignancies, may contribute to tumour development [5].

Various studies have demonstrated that metabolic disorders, especially insulin resistance, play a significant role in the development of malignancies. Insulin resistance leads to chronic hyperinsulinemia, which in turn increases the levels of insulin-like growth factor-1 (IGF-1), thereby promoting cellular proliferation and inhibiting apoptosis, ultimately contributing to tumorigenesis [6].

The triglyceride-glucose (TyG) index has been identified as a simple and cost-effective indicator of insulin resistance and has been investigated as a potential biomarker in various malignancies such as colorectal, endometrial, and laryngeal cancers [7, 8].

The relationship between the TyG index and various malignancies has been studied in the literature [8]. However, the role of the TyG index in parotid gland tumours has not yet been clearly established. While there are hypotheses suggesting a link between Warthin tumour and metabolic disorders, particularly insulin resistance, direct evidence in the literature remains limited [3].

Given its accessibility and low cost, the TyG index may serve as a complementary screening tool for early diagnosis, especially in histological subtypes with differing biological behaviours, such as Warthin tumour and pleomorphic adenoma.

This study aims to investigate whether there is a significant difference in the TyG index between patients diagnosed with pleomorphic adenoma or Warthin tumour and healthy individuals, and to evaluate the potential utility of this parameter as a screening tool across these two histological subtypes.

2 | Methods

2.1 | Design

This was a retrospective cross-sectional observational study.

2.2 | Setting

The study was conducted at the Department of Otorhinolaryngology, Tertiary University Hospital, between January 2019 and July 2024.

2.3 | Participants

During the chart review conducted between July and October 2024, patients diagnosed with parotid tumours between January 2019 and July 2024 and who had available blood test data suitable for TyG index calculation were included in the study. The parotid tumour group (Group 1) consisted of patients whose histopathological diagnoses were confirmed as either pleomorphic adenoma (Group 1A) or Warthin tumour (Group 1B). Group 1A included 31 patients, while Group 1B included 22 patients.

For each patient, if fasting triglyceride and glucose values allowing for the calculation of the TyG index were available within 1 year prior to diagnosis, these data were used. In cases where no adequate pre-diagnosis data were available, blood test results obtained within 1 year after the diagnosis were utilised. For patients who had not yet completed 1 year since diagnosis, blood samples were obtained during routine follow-up visits to allow for TyG index calculation.

In the control group (Group 2), 58 healthy individuals were evaluated. Fasting blood samples were obtained, and triglyceride and glucose levels were measured to calculate the TyG index. Inclusion in the control group required the absence of any known malignancy or systemic disease.

2.3.1 | Inclusion Criteria

Age between 18 and 70 years; histopathologically confirmed diagnosis of pleomorphic adenoma or Warthin tumour (for the patient group); absence of systemic disease and malignancy (for the control group); availability of fasting blood triglyceride and glucose values.

2.3.2 | Exclusion Criteria

Diagnosis of diabetes mellitus or use of antidiabetic medication; treatment for hyperlipidaemia; history of advanced liver, cardiac, or renal disease; pregnancy; history of surgery or radiotherapy involving the head and neck region.

2.4 | Main Outcome Measures

The primary outcome was the TyG index, calculated for each subject using the following formula [7]:

$$\text{Ln}\left[\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)}/2\right].$$

Secondary variables included age, sex, and body mass index (BMI).

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2.5 | Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed by the Kolmogorov–Smirnov test. Continuous variables were compared using the independent samples *t*-test, while categorical variables were analysed by the chi-square test. In subgroup analyses, one-way analysis of variance (ANOVA) was performed, followed by Bonferroni-corrected post hoc pairwise comparisons. Multiple linear regression analysis was used to determine whether differences in TyG index between groups persisted after adjusting for age, with tumour type as a categorical predictor and age as a covariate. Statistical significance was defined as $p < 0.05$.

2.6 | Ethics

The study protocol was approved by the local Clinical Research Ethics Committee (Ethics Committee Decision No: 11/5, Date: 3 July 2024, Document No: E.163209) and conducted in accordance with the Declaration of Helsinki.

2.7 | Reporting Guideline

This manuscript was prepared in accordance with the STROBE guidelines for observational studies.

3 | Results

This study included a total of 53 patients histopathologically diagnosed with pleomorphic adenoma (Group 1A, $n = 31$) or Warthin tumour (Group 1B, $n = 22$), and 58 healthy individuals in the control group (Group 2). The mean values for age, sex distribution, BMI, and TyG index were compared among the participants.

There were no statistically significant differences between the tumour group (Group 1) and the control group (Group 2) in terms of age (Group 1: 54.8 ± 11.2 years; Group 2: 52.1 ± 10.7 years; $p = 0.161$), sex distribution ($p = 0.177$), or BMI (Group 1: 27.5 ± 4.1 kg/m^2; Group 2: 26.8 ± 3.8 kg/m^2; $p = 0.441$). The TyG index was also similar between these two groups (Group 1: 4.75 ± 0.31; Group 2: 4.72 ± 0.23; $p = 0.538$), indicating only a modest difference between tumour patients and healthy controls (see Table 1 and Figure 1).

In the three-group comparison, a statistically significant difference was found in terms of age ($p < 0.001$). The mean age of patients with Warthin tumour (63.1 ± 8.4 years) was significantly higher than that of patients with pleomorphic adenoma (49.7 ± 10.2 years) and healthy controls (51.2 ± 9.8 years). No significant difference in BMI was found among the three groups ($p = 0.741$).

Regarding the TyG index, the mean value was 4.91 ± 0.28 in the Warthin tumour group, 4.68 ± 0.31 in the pleomorphic adenoma group, and 4.72 ± 0.23 in the control group. Statistical

TABLE 1 | Comparison between Group 1 (benign parotid tumour group) and Group 2 (control group).

	Group 1 (Benign parotid tumour)	Group 2 (Control)	
	(*n* = 53)	(*n* = 58)	Statistic[a,b]
	Mean ± SD	Mean ± SD	*p*
Sex (male/female)	35M/18F	31M/27F	$p = 0.177$[b]
Age (years)	52.58 ± 14.32	49.76 ± 2.28	$p = 0.161$[a]
TyG	4.75 ± 0.31	4.72 ± 0.23	$p = 0.538$[a]
BMI (kg/m^2)	27.85 ± 5.20	27.15 ± 4.20	$p = 0.441$[a]

Abbreviations: BMI, body mass index; F, female; M, male; SD, standard deviation; TyG, triglyceride–glucose index.
[a]Independent *t*-test was used to compare the groups. $p < 0.05$ significant accepted.
[b]Ki-kare was used to compare the groups. $p < 0.05$ significant accepted.

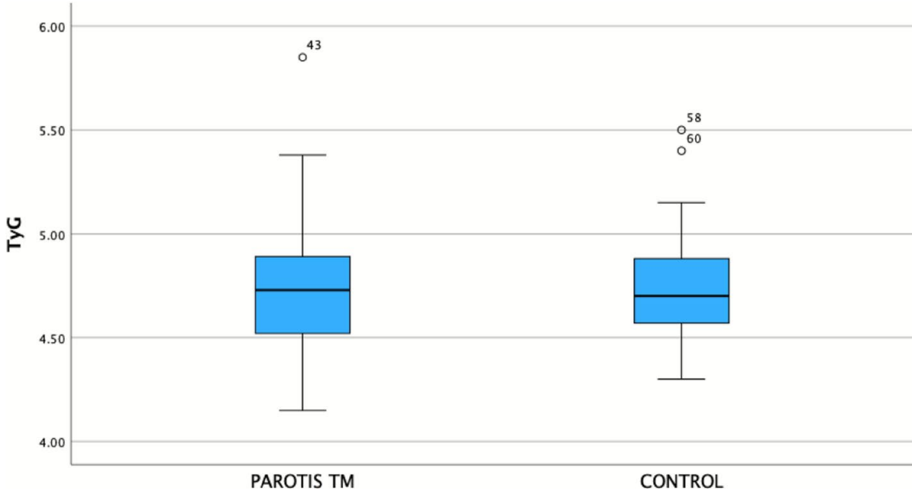

FIGURE 1 | TyG index comparison between tumour and control groups.

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analysis revealed that the TyG index was significantly higher in the Warthin tumour group compared to both the pleomorphic adenoma group ($p=0.006$) and the control group ($p=0.033$), although this difference was smaller in magnitude compared with the difference between Warthin tumour and pleomorphic adenoma (see Table 2 and Figure 2). No significant difference was observed between the pleomorphic adenoma group and the control group ($p=0.521$).

In the post hoc analysis for differences in the TyG index among the three groups, Bonferroni correction was applied, with the significance threshold set at $p<0.0167$. According to this correction, the difference between the Warthin tumour and pleomorphic adenoma groups remained statistically significant, while the difference between the Warthin tumour and control groups was of borderline significance ($p=0.033$), consistent with the modest overall difference observed between tumours and controls (see Table 2 and Figure 2).

Multiple linear regression analysis demonstrated that the difference in TyG index between the Warthin tumour and pleomorphic adenoma groups remained at the threshold of statistical significance after adjusting for age ($p=0.053$ for group effect), while age itself was not a significant independent predictor ($p=0.704$). This suggests that the higher TyG index observed in Warthin tumour patients is not solely attributable to their older age.

4 | Discussion

Parotid gland tumours represent approximately 80% of all salivary gland neoplasms and are the most common major salivary gland tumours in the head and neck region [9]. Approximately 75%–80% of these tumours are benign, with pleomorphic adenoma and Warthin tumour being the most frequently encountered subtypes. Pleomorphic adenoma accounts for around 60% of parotid neoplasms, while Warthin tumours are more frequently seen in older males and are reported to constitute 10%–15% of cases [10].

In our study, no significant difference in the TyG index was observed between the overall tumour group and the healthy control group. However, in the Warthin tumour subgroup, the TyG index was significantly higher than that observed in both the pleomorphic adenoma group and the healthy controls. These findings align with previous studies suggesting a possible role of metabolic factors in the development of Warthin tumours [11]. In our study, the TyG index was assessed as a biochemical marker independent of conventional metabolic parameters.

TABLE 2 | Comparison of benign parotid tumour subgroups and healthy controls.

	Group 1A (pleomorphic adenoma)	Group 1B (Warthin tumour)	Group 2 (control)	Statistic[a]		
	($n=31$)	($n=22$)	($n=58$)			
	Mean ± SD	Mean ± SD	Mean ± SD	1A vs. 1B	1A vs. 2	1B vs. 2
Age (years)	48.16 ± 16.10	58.82 ± 8.23	49.76 ± 2.28	$p \leq 0.001$	$p=0.725$	$p \leq 0.001$
TyG	4.66 ± 0.29	4.89 ± 0.31	4.72 ± 0.23	$p=0.006$	$p=0.521$	$p=0.033$
BMI (kg/m^2)	28.26 ± 6.18	27.29 ± 3.45	27.15 ± 4.20	$p=0.741$	$p=0.547$	$p=0.993$

Abbreviations: BMI, body mass index; SD, standard deviation; TyG, triglyceride–glucose index.
[a]One-way ANOVA test was used to compare the groups. $p<0.05$ significant accepted. Bonferroni correction was applied for multiple comparisons; pairwise group comparisons were performed using the Wilcoxon test, and significance was set at $p<0.0167$.

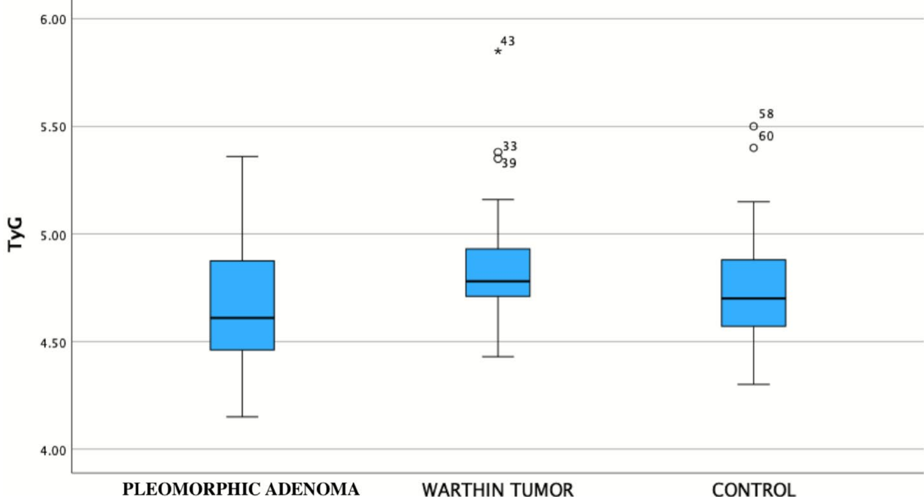

FIGURE 2 | Comparison of TyG index among parotid tumour subgroups and healthy controls.

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Importantly, multivariable analysis showed that the higher TyG index observed in Warthin tumour patients could not be explained by age alone, supporting a tumour-specific metabolic association.

Warthin tumours and pleomorphic adenomas demonstrate distinct differences in clinical behaviours and treatment strategies. Warthin tumours typically occur in older males, may present bilaterally or multifocally, and are strongly associated with smoking [12]. Histologically, they are characterised by a bilayered oncocytic epithelial lining and a prominent lymphoid stroma [13]. The risk of malignant transformation is extremely low, with reported rates below 0.1% [12].

In contrast, pleomorphic adenomas are characterised by a mixed epithelial and mesenchymal composition. Their capsules are often incomplete, allowing for microscopic extension of tumour cells beyond the capsule. As such, insufficient excision carries a high risk of recurrence, and long-standing lesions may rarely undergo malignant transformation to carcinoma ex pleomorphic adenoma [14].

Differential diagnosis between Warthin tumour and pleomorphic adenoma carries significant clinical implications not only histopathologically but also in terms of treatment decisions. Pleomorphic adenomas are typically treated with surgical excision (total or superficial parotidectomy), while more conservative approaches such as microwave ablation, radiofrequency ablation, and sclerotherapy are increasingly used for Warthin tumours. Recent literature supports active surveillance as an appropriate management strategy in elderly and asymptomatic patients with Warthin tumours. In this context, the integration of a simple and non-invasive biomarker like the TyG index into the diagnostic process may offer valuable support in clinical decision-making [15].

Metabolic syndrome, chronic inflammation, and oxidative stress have been implicated as contributing factors in the development of various cancers [6]. The TyG index, as a simple, low-cost, and widely applicable biochemical parameter, offers potential as a non-invasive screening tool that could complement more complex imaging techniques and invasive diagnostic procedures. As the TyG index is calculated from fasting glucose and triglyceride measurements, which are already included in routine biochemical panels, it does not require any additional laboratory procedures. The combined cost of these two tests is low, generally falling within the range of standard metabolic screening fees in most healthcare systems, making TyG a cost-effective complementary parameter [16].

Ultrasound (USG) is commonly used in the diagnosis of parotid tumours due to its accessibility and low cost; however, it has limitations in detecting deep lobe or multifocal lesions [17]. Magnetic resonance imaging (MRI) may be preferred in such cases as it provides more detailed information regarding tumour extent and internal structure [18]. Although fine-needle aspiration biopsy (FNAB) demonstrates high diagnostic accuracy, its sensitivity may be limited in certain benign lesions [17].

Given the limited sensitivity of FNAB in Warthin tumours, the use of additional diagnostic parameters has gained importance. In a study by Fois et al., the sensitivity of FNAB alone in diagnosing Warthin tumours was reported as 68.4%, but this increased to 92.9% when clinical and ultrasonographic findings were evaluated in a multiparametric approach [19]. In this context, the TyG index obtained through a simple blood test may offer a practical advantage as a supplementary diagnostic tool in clinical workflows. However, the TyG index should not be considered a standalone diagnostic test; rather, it serves as a complementary parameter that may enhance diagnostic confidence when conventional imaging or FNAB findings are inconclusive.

Although no universally accepted algorithm exists for the management of non-diagnostic FNAB results in parotid tumours, common clinical practice involves repeating FNAB under USG guidance, as inadequate or acellular aspirates often improve with repeat sampling [20]. When cytology remains inconclusive, subsequent management typically depends on the presumed underlying pathology. While the TyG index can be calculated at any stage of evaluation, its clinical contribution is not universal; TyG values in the overall tumour cohort did not differ significantly from those of healthy controls, indicating limited value during the initial assessment. However, its practical utility becomes more apparent in diagnostically ambiguous situations such as inconclusive or discordant FNAB or imaging findings, where metabolic differences between Warthin tumour and pleomorphic adenoma may meaningfully support decision-making. In this context, a higher TyG value, suggestive of Warthin tumour, may reduce the need for additional sampling and favour a more conservative or surveillance-oriented approach, particularly in older or asymptomatic patients. Conversely, lower TyG values closer to those observed in pleomorphic adenoma may strengthen indications for core needle biopsy or surgical excision, given the recurrence and rare malignant potential associated with pleomorphic adenoma. Thus, the TyG index offers a complementary, low-cost tool that may help clinicians navigate diagnostically challenging cases by aligning management with the most likely tumour subtype (see Figure 3).

The relationship between the TyG index and malignancies has been extensively investigated in the literature. For instance, a study by Kim et al. demonstrated a significant association between an elevated TyG index and the development of gastric cancer [21]. In colorectal cancer, a higher TyG index has been correlated with advanced disease stage and poor prognosis [22]. Similarly, in breast cancer, elevated TyG values have been linked to poorer clinical outcomes in hormone receptor-negative subtypes [23]. In patients with hepatocellular carcinoma, the TyG index has been identified as an independent predictor of recurrence and mortality [24].

In contrast, direct data on the diagnostic value of the TyG index in benign tumours such as fibroadenomas or pleomorphic adenomas remain limited. Therefore, further prospective studies with larger sample sizes are needed to evaluate the potential of the TyG index as a screening or differentiating biomarker in benign parotid tumours.

To the best of our knowledge, this is the first study in the literature to evaluate the potential role of the TyG index in distinguishing between the two most common benign parotid gland tumour subtypes: Warthin tumour and pleomorphic adenoma.

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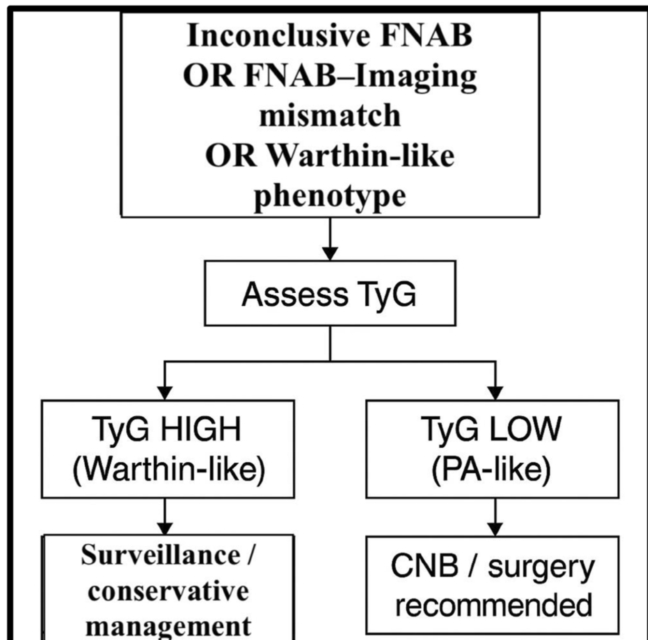

Abbreviations: FNAB: Fine-needle aspiration biopsy, **CNB:** Core needle biopsy, **TyG:** Triglyceride–glucose index, **PA:** Pleomorphic adenoma

FIGURE 3 | Proposed diagnostic algorithm incorporating the TyG index to support differentiation between Warthin tumour and pleomorphic adenoma in diagnostically ambiguous cases.

Our findings provide preliminary evidence that a simple, non-invasive, and cost-effective biochemical marker may be useful in clinical practice.

The main limitations of our study include its retrospective design and relatively small sample size.

5 | Conclusion

This study provides a novel contribution to the literature as one of the pioneering investigations exploring the use of the TyG index in parotid gland tumours. To our knowledge, it is among the first studies to evaluate the potential role of the TyG index in differentiating between Warthin tumour and pleomorphic adenoma, the most common benign tumours of the parotid gland. Our findings demonstrate that the TyG index is significantly elevated in patients with Warthin tumour, suggesting that this simple, non-invasive biochemical parameter may aid in the differential diagnosis of benign parotid neoplasms.

Author Contributions

Remzi Dogan: conceptualisation, methodology, writing – original draft (lead), writing – review and editing. **Ramazan Bahadır Kucuk:** data curation, writing – original draft (supporting), investigation. **Alper Yenigun:** supervision, project administration. **Elif Ece Dogan:** investigation, data curation. **Orhan Ozturan:** conceptualisation, methodology, supervision.

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Funding

The authors have nothing to report.

Ethics Statement

This study was approved by the Clinical Research Ethics Committee of Bezmialem Vakıf University (Ethics Committee Decision No: 11/5, Date: 3 July 2024, Document No: E.163209). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki for research involving human subjects.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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