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ORIGINAL ARTICLE

STUDY OF CYTOCHROME P450 C 17 ALPHA (CYP17A1) GENE POLYMORPHISM IN PATIENTS WITH POLY CYSTIC OVARIAN SYNDROME

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder characterized by hormonal imbalances and metabolic issues. This study aimed to explore the association between CYP17A1 polymorphism and PCOS severity.

Materials & Methods: This analytical case-control study was conducted at Salahaddin University from January 2023 to December 2023. Convenience sampling was used to include participants in the study. This study included 150 patients with PCOS and 50 controls, classified according to PCOS severity using Rotterdam criteria. Clinical assessments, hormonal profiling, and genetic analyses were also performed. CYP17A1 polymorphisms were identified using Restriction Fragment Length Polymorphism (RFLP), Sanger sequencing, and High-Resolution Melt (HRM) analysis.

Results: CYP17A1 polymorphisms varied significantly across the groups ($p < 0.001$), with 4 (8%) in controls, 11 (22%) with mild PCOS, 8 (16%) with moderate PCOS, and 21 (42%) with severe PCOS. Regression analysis revealed significant associations between testosterone level (coefficient =4.8765, $p < 0.001$), Ferriman-Gallwey score (coefficient =0.2345, $p < 0.001$), LH/FSH ratio (coefficient =2.789, $p < 0.001$), and PCOS severity. Polymorphisms were associated with higher testosterone levels (coefficient = 0.2156, $P < 0.001$) and an increased risk of PCOS (odds ratio =1.9238, $P = 0.005$).

Conclusion: The findings of this study revealed a strong correlation between CYP17A1 gene polymorphisms and the development and severity of PCOS. The findings of this study indicate the involvement of CYP17A1 in PCOS etiology, specifically in androgen excess and gonadal dysfunction.

KEY WORDS: Humans; Poly Cystic Ovarian syndrome; gene polymorphism; genotyping; hormonal assessment; Body Mass Index.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) has been defined as an endocrine disorder with hyperandrogenemia, insulin resistance, and chronic anovulation; it occurs in 5-18% of women worldwide.[1] Hence, the etiology of PCOS is polygenic and environmental in origin.[2] Some of the recent publications have provided evidence of several genetic loci that are linked with PCOS which is involved in steroidogenesis.[3] Also, there are associations between mitochondrial DNA polymorphisms and PCOS, which implies the involvement of mitochondrial dysfunction in the pathogenesis of the disease.[4] It is shown that some aspects of PCOS seem to have their origin already in childhood; offspring of PCOS women exhibited metabolic dysfunction.[5] The gut microbiota has also been implicated in PCOS with changes in gut diversities impacting on insulin resistance and hormonal regulation of PCOS.[6] Inflammation is another probable facto, for which there are a genetic links between PCOS and inflammatory markers. Lately, phenotypic characterization of patients and grouping of patients into subgroups based on the phenotypic characteristics have been developed to comprise different PCOS subtypes with different genetic background.[7]

CYP17A1 helps in the synthesis of steroids with spe-

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cial reference to androgens and therefore plays a critical role in the manifestation of PCOS. The genetic variations in CYP17A1 including rs74357 in PCOS-predisposing genes have been found to be significantly higher in diverse ethnic groups.[8, 9] These genetic variations can cause high levels of androgen levels, which is another factor that differentiates patients with PCOS.[10] Recent research has indicated that the genetic polymorphisms in the CYP17A1 play a key role in the metabolic and hormonal dysregulation associated with PCOS, including insulin resistance.[11] The gene is associated with steroidogenic process; it plays a role in the overproduction of sex steroids by the ovarian theca cells thereby aggravating PCOS symptoms.[9] Literature also points to other factors influencing CYP17A1 activity including oocyte-derived factors GDF9 that can inhibit the enzyme activity in theca cells.[10] Besides, the combined action of CYP17A1 with other genes such as CYP11A1 and CYP19A1 exemplifies its significant involvement in PCOS development.[8] Other meta-analyses have also supported the connection between CYP17A1 polymorphisms and PCOS and these findings may imply that some of genetic polymorphisms can be used as predictive indicators of the disorder.[11] Therefore, the present study aimed to investigate the relationship between CYP17A1 gene polymorphisms and the severity of PCOS and its effects on PCOS.

MATERIALS AND METHODS

Study Design and Setting: This analytical case-control study was conducted at the gynecology outpatient department of Salahaddin University over one year, from January 1, 2023, to December 31, 2023.

Participants: A total of 200 women of reproductive age were recruited, comprising of 150 patients diagnosed with PCOS and 50 controls without PCOS. Participants were selected by convenience sampling from individuals who attended the clinic during the study period. The diagnosis of PCOS was based on the Rotterdam criteria, which require the presence of at least two of the following: oligo/anovulation, clinical or biochemical signs of hyperandrogenism, or polycystic ovaries on ultrasound. The sample consisted of 150 individuals with PCOS, further categorized into mild (n=50), moderate (n=50), and severe (n=50) groups based on clinical and hormonal assessments (testosterone concentrations and the LH to FSH ratio), and 50 controls.

The inclusion criterion for PCOS patients was women of reproductive age who were diagnosed with PCOS according to the Rotterdam criteria. Controls were women without PCOS of similar age. The exclusion criteria were the presence of other endocrine disorders, current pregnancy, or use of medications affecting hormone levels.

Clinical and Biochemical Assessment: A comprehensive clinical assessment was conducted for all the participants. This included obtaining a detailed medical history and performing physical examination. Anthropometric measurements such as height, weight, waist circumference, and BMI were recorded. Hirsutism was evaluated using the Ferriman-Gallwey score, whereas acne was assessed separately. Menstrual cycle history and fertility status were also documented.

Fasting blood samples were collected from all the participants for hormonal profiling. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and total testosterone were measured using electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas e411 analyzer. The participants were categorized into mild, moderate, and severe PCOS groups based on specific criteria (Table 1). Additionally, transvaginal ultrasonography was performed on all participants to assess ovarian morphology, including the ovarian volume and follicle count.

Table 1: Patient classification criteria

Category	Clinical Features	Testosterone Levels	LH/FSH Ratio
Mild	Irregular menstrual cycles Mild hirsutism (Ferriman-Gallwey score <15 Minimal acne	Upper limit of normal to 1.5 times the upper limit	<2
Moderate	Oligomenorrhea or amenorrhea. Moderate hirsutism (Ferriman-Gallwey score 15-25) Moderate to severe acne. Obesity (BMI 25-30)	1.5 to 2 times the upper limit of normal	2-3
Severe	Chronic anovulation leading to infertility. Severe hirsutism (Ferriman-Gallwey score >25). Severe acne Significant obesity (BMI >30) Clinical signs of insulin resistance/metabolic syndrome	>2 times the upper limit of normal	>3

Table 2. Primer sequence details

SNP	Forward Primer Sequence	Reverse Primer Sequence
rs743572	5'-GGAAGAGATCTTGGCATCCTGTG-3'	5'-CAACAGACCTGCAGAGGCTCA-3'
rs6162	5'-AGTTCAGTGCGACCTGGATC-3'	5'-CCTGGAGTTCATCCACCATC-3'
rs6163	5'-TGTGGAAGTGGACATCCAGT-3'	5'-GGGCTTTTCTGGTATCTCTG-3'
rs10883783	5'-TGCCTCTTTTCCCTTCCTTT-3'	5'-GAGCAGGAGTTTGCATTTGC-3'

Sample Collection and DNA Extraction: A 10 ml sample of peripheral blood was collected in EDTA tubes from each participant. Genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany), according to the manufacturer's protocol. DNA concentration and purity were quantified using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) at 260/280 nm. Four CYP17A1 polymorphisms, rs743572, rs6162, rs6163, and rs10883783 were investigated. Specific primers for each SNP were designed using Primer3 software. Table 2 details the primer sequences.

PCR amplification was performed in a 25 µL reaction mixture containing 50 ng genomic DNA, 0.2 µM of each primer, 200 µM dNTPs, 1.5 mM MgCl2, 1X PCR buffer, and 1 U Taq DNA polymerase (Thermo Fisher Scientific). The PCR cycling conditions were as follows: initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 45 s, and a final extension at 72°C for 5 min.

Genotyping Methods: Restriction Fragment Length Polymorphism (RFLP) Analysis: For rs743572 (T34C), we used RFLP analysis. The PCR product was digested with MspA1I restriction enzyme (New England Biolabs, Ipswich, MA, USA) at 37°C for 4 h. The digested products were separated on 3% agarose gel and visualized under UV light after ethidium bromide staining.

Sanger Sequencing: For Sanger sequencing was performed for rs6162, rs6163, and rs10883783. PCR products were purified using the QIAquick PCR Purification Kit (Qiagen) and sequenced using an ABI 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA).

High-Resolution Melt (HRM) Analysis: As alternative method to rs743572, we performed HRM analysis using a LightCycler 480 Real-Time PCR System (Roche Diagnostics, Basel, Switzerland). Melting curves were analyzed using LightCycler 480 Gene Scanning Software.

Ethical Considerations: The study protocol was approved by the institutional ethics committee, ensuring compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to their inclusion in the study.

Statistical Analysis: Data analysis was performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.0. Descriptive statistics were used to summarize the demographic and clinical characteristics. Chi-square tests were used to assess the association between the SNPs and PCOS. Logistic regression was used to evaluate the relationship between CYP17A1 polymorphisms and PCOS severity after adjusting for age, BMI, and other relevant covariates. Additionally, BLAST and Clustal Omega were used for sequence alignment, comparing the obtained sequences against the reference genome (GRCh38) to identify SNP locations. Genotype calling was performed using the Genome Analysis Toolkit (GATK v4.2.0) and PLINK v1.9, generating VCF files containing called genotypes.

RESULTS

The study included four groups: Control, Mild PCOS, Moderate PCOS, and Severe PCOS, each consisting of 50 participants. The mean age across all groups was similar, ranging from 32.4 ± 8.7 years in the Severe PCOS group to 34.3 ± 8.2 years in the Mild PCOS group, with no statistically significant difference observed ($p = 0.726$). However, Body Mass Index (BMI) showed a significant increasing trend across the groups (Table 3).

Table 4 shows the clinical and laboratory characteristics of the entire sample of subjects with PCOS and the three defined severity groups: mild, moderate, and severe. Testosterone levels also significantly increased across the severity groups, and in each group of PCOS patients, there was a higher level than in the control group. The LH/FSH ratio also showed a rising trend for the groups of PCOS severity, and the highest LH/FSH ratio was reported in severe PCOS group. Indeed, comparing both the control and mild PCOS groups, there were no significant differences in the Ferriman-Gallwey Score, which estimates hir-

Table 3: Study groups baseline demographics

Characteristic	Control (n=50)	Mild (n=50)	Moderate (n=50)	Severe (n=50)	p-value
Age (years)	33.5 ± 9.8	34.3 ± 8.2	33.1 ± 9.3	32.4 ± 8.7	0.726
BMI (kg/m^2)	22.4 ± 2.6	22.1 ± 2.9	26.1 ± 2.3	33.4 ± 3.7	<0.001

Table 4: Clinical and laboratory parameters

Parameter	Control (n=50)	Mild PCOS (n=50)	Moderate PCOS (n=50)	Severe PCOS (n=50)	p-value
Testosterone (ng/mL)	0.42 ± 0.19	0.90 ± 0.11	1.29 ± 0.13	1.98 ± 0.29	<0.001
LH/FSH ratio	1.15 ± 0.10	1.62 ± 0.21	2.51 ± 0.29	3.52 ± 0.34	<0.001
Ferriman-Gallwey Score	7.3 ± 4.2	6.5 ± 3.7	19.9 ± 2.8	30.2 ± 3.1	<0.001

Table 5: Polymorphism detection in the 4 study groups

Polymorphism	Control (n=50)	Mild (n=50)	Moderate (n=50)	Severe (n=50)	p-value
Present	4 (8%)	11 (22%)	8 (16%)	21 (42%)	<0.001
Absent	46 (92%)	39 (78%)	42 (84%)	29 (58%)	

Table 6: Regression analysis of Testosterone, Ferriman-Gallwey Score, LH/FSH Ratio and Polymorphism detection as predictors for PCOS incidence

Variable	Coefficient	Std. Error	z value	p-value
Intercept	-12.5643	1.1234	-11.184	<0.001
Testosterone	4.8765	0.5678	8.589	<0.001
Ferriman-Gallwey Score	0.2345	0.0234	10.021	<0.001
LH/FSH Ratio	2.789	0.3456	8.07	<0.001
Polymorphism Present	0.5678	0.2345	2.421	0.015

sutism. However, the score increased significantly in the moderate PCOS group and was highest in the severe PCOS group. Therefore, the conclusion of this study is that the severity of PCOS in the subjects is directly linked to higher levels of testosterone, a higher ratio of LH/FSH, and hirsutism. Significant differences in all parameters were observed across groups in the current study.

The presence of CYP17A1 polymorphisms was significantly different between the study groups ($p < 0.001$). In the Control group, only 8% (4 out 50) of the participants exhibited polymorphisms. This percentage increased to 22% (11 out of 50) in the Mild PCOS group and slightly decreased to 16% (8 out of 50) in the Moderate PCOS group. However, a substantial increase was observed in the Severe PCOS group, where 42% (21 out of 50) of the participants showed the presence of polymorphisms. Conversely, the absence of polymorphisms was the highest in the control group at 92% (46 out of 50), decreasing to 78% (39 out of 50) in the Mild PCOS group, 84% (42 out of 50) in the Moderate PCOS group, and reaching the lowest at 58% (29 out of 50) in the Severe PCOS group. These findings suggest a strong association between the presence of CYP17A1 gene polymorphisms and PCOS severity, with the highest prevalence observed in the Severe PCOS group (Table 5).

Regression analyses conducted on our dataset revealed significant associations between various clinical parameters and the presence of CYP17A1 polymorphisms in relation to Polycystic Ovary Syndrome (PCOS). Our initial analysis focused on predicting PCOS severity using multiple factors. The study showed that PCOS severity increased as testosterone levels increased, and that there was a highly significant positive correlation (coefficient = 4. 8765, $p < 0.001$). Similarly, the Ferriman-Gallwey score for measuring hirsutism was positively correlated with PCOS severity, with a coefficient of 0. 2345, $p < 0.001$. This shows that a greater extent of hirsutism is associated with a more severe degree of PCOS. The LH/FSH ratio also demonstrated a strong positive correlation with PCOS severity (coefficient = 2.7890, $p < 0.001$), emphasizing the role of gonadotropin imbalance under these conditions. Notably, CYP17A1 polymorphisms were associated with increased PCOS severity (coefficient = 0.5678, $p = 0.015$), highlighting a genetic component in the progression of the disorder (Table 6).

Further analyses examined the predictability of individual clinical parameters based solely on the presence of CYP17A1 polymorphisms. The results showed that polymorphism was significantly associated with elevated testosterone levels (coefficient = 0.2156, $p < 0.001$), with carriers having an average testosterone level of 0.2156 ng/mL (Table 7).

The LH/FSH ratio was elevated in the presence of the polymorphisms (coefficient = 0.3210, $p < 0.001$) (Table 8). Similarly, the Ferriman-Gallwey Score was higher in individuals with polymorphisms (coefficient = 2.8765, $p = 0.006$), indicating increased hirsutism (Table 9).

Logistic regression analysis revealed that individuals with CYP17A1 polymorphisms had nearly twice the

odds of developing PCOS compared to those without (odds ratio = 1.9238, p = 0.005). However, it is important to note that while these associations are statistically significant, the relatively low R-squared values (ranging from 0.0314 to 0.0723) suggest that the presence of polymorphism alone explains only a small portion of the variance in these clinical parameters. This underscores the complex, multifactorial nature of PCOS, indicating that, while genetic factors contribute to the condition, they are not the sole determinants. Collectively, these findings highlight the potential role of CYP17A1 variants in PCOS pathophysiology, particularly in relation to androgen levels, hirsutism, gonadotropin imbalance, and overall PCOS risk, while also emphasizing the need for a comprehensive approach considering multiple factors in the diagnosis and management of PCOS. The results were visualized using ggplot2 in R and matplotlib in Python to generate Manhattan plots (Figure 1), LD plots (Figure 2), and haplotype block diagrams (Figure 3).

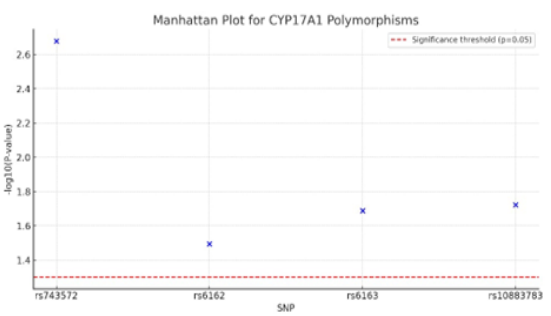

Figure 1: Manhattan plot for CYP17A1 polymorphism

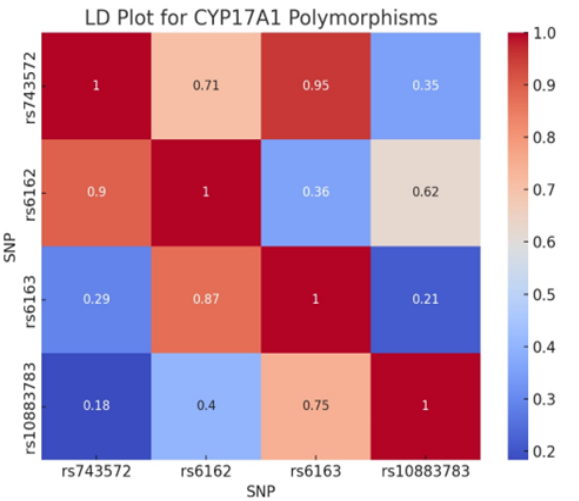

Figure 1: LD plots

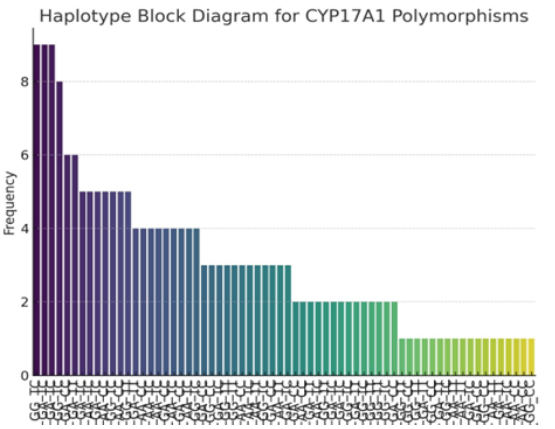

Figure 3: Haplotype block diagram

Table 7: Regression analysis of polymorphism detection as indepndent predictor for testosterone levels

Variable	Coefficient	Std. Error	t value	p-value	R-squared
Intercept	0.6842	0.0321	21.315	<0.001	0.0723
Polymorphism Present	0.2156	0.0587	3.672	<0.001	0.0314

Table 8: Regression analysis of polymorphism detection as independent predictor for LH/FSH ratio

Variable	Coefficient	Std. Error	t value	p-value	R-squared
Intercept	1.6543	0.0432	38.294	<0.001	0.0456
Polymorphism Present	0.321	0.0789	4.068	<0.001	0.0456

Table 9: Regression analysis of polymorphism detection as independent predictor for Ferriman-Gallwey Score

Variable	Coefficient	Std. Error	t value	p-value	R-squared
Intercept	11.7234	0.5678	20.647	<0.001	0.0314
Polymorphism Present	2.8765	1.0432	2.757	0.006	0.0314

DISCUSSION

This study investigated the association between CYP17A1 polymorphisms (rs743572, rs6162, rs6163, and rs10883783) and PCOS occurrence and severity. Analysis of clinical characteristics revealed significant differences between the groups in terms of BMI, testosterone levels, luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratios, and hirsutism. A significant relationship was observed between CYP17A1 polymorphisms and PCOS severity, with these polymorphisms being more prevalent in patients with severe PCOS. Statistical tests demonstrated associations between CYP17A1 variants and elevated testosterone levels, increased LH/FSH ratios, heightened hirsutism, and a greater likelihood of developing PCOS among the carriers of these polymorphisms.

Supporting these findings, Rezgoun et al. (2023) conducted a meta-analysis that corroborated the results of the present study. This systematic review included 24 studies, including 3,462 women with PCOS and 2,898 controls, and examined the impact of the CYP17A1 T/C (rs74357) polymorphism. The analysis indicated that individuals with this polymorphism had an increased risk of PCOS across various genetic models such as codominant, dominant, recessive, and overdominant models. Additionally, the C allele of rs174550 has emerged as a genetic marker for PCOS and is linked to metabolic and hormonal dysregulation, particularly insulin resistance. This meta-analysis aligns with the findings of the current study, reinforcing the association between CYP17A1 polymorphisms and PCOS and highlighting metabolic and hormonal differences, such as variations in BMI, testosterone levels, and LH/FSH ratios. The robustness of these findings is bolstered by the large sample size and comprehensive data analysis.[11] Conversely, Xing et al. (2022) presented findings that contrasted with those this study. This systematic review and meta-analysis, published in Frontiers in Endocrinology, focused on CYP17A1 rs743572, CYP19A1, and SHBG polymorphisms. This indicates that the CYP17A1 rs743572 polymorphism might serve as a protective factor against PCOS, contrary to the current study's observations of enhanced PCOS severity. Disparities in genetic associations may result from differing mechanistic and methodological factors or population-specific distinctions.[12]

In support of these findings, a genetic association study conducted by Kaur et al. (2018) in North India found significant associations between CYP17A1 polymorphisms and PCOS. This study used a case-control design and observed correlations with hormonal parameters, aligning with the findings of the present study of altered testosterone levels and LH/FSH ratios in a specific ethnic population.[13] In contrast, Park et al. (2008) identified different observations regarding CYP17A1 polymorphisms in Korean PCOS patients. Although no clear relationship was found between CYP17A1 polymorphisms and PCOS, a specific haplotype (ht3) was statistically linked to PCOS. These findings highlight the importance of haplotype analysis and acknowledge ethnic differences in the genetic makeup of PCOS.[14]

Finally, a recent Mendelian randomization study by Fang et al. (2024) provided context for the observed BMI differences. This study demonstrated a bidirectional causal relationship between BMI and PCOS, supporting the current study's observation of significant BMI differences among patients with PCOS. Although not directly related to CYP17A1, it underscores the genetic basis for the association between BMI and PCOS, complementing the findings of the present study on genetic factors in PCOS pathogenesis. This multifaceted genetic and epidemiological exploration underscores the complexity of PCOS and the critical role of genetic polymorphisms in its manifestation and severity.[15]

CONCLUSION

This study demonstrated a strong association between CYP17A1 polymorphisms and PCOS occurrence and severity. The presence of CYP17A1 variants correlates with elevated testosterone levels, increased LH/FSH ratios, and more severe hirsutism in patients with PCOS. These findings highlight the potential role of CYP17A1 in PCOS pathophysiology, particularly in relation to androgen excess and gonadotropin imbalance. The identification of specific genetic markers associated with PCOS severity may aid in the risk stratification and personalized management of the disorder. However, the complex multifactorial nature of PCOS necessitates a comprehensive approach that considers multiple genetic and environmental factors. Further research in diverse populations and investigation of gene-environment interactions are warranted to fully elucidate the genetic underpinnings of PCOS. Nonetheless, this study provides valuable insights into the role of CYP17A1 polymorphisms in PCOS pathogenesis and severity, contributing to a growing body of evidence on the genetic basis of this prevalent endocrine disorder.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	KMS
Acquisition, Analysis or Interpretation of Data:	KMS
Manuscript Writing & Approval:	KMS

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.