RESEARCH ARTICLE

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# Association of *P53* Codon 72 Polymorphism with Ovarian Cancer: An Institutional Study

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## Abstract

**Background:** Polymorphism of *P53* gene has been explored worldwide to know the genetic predisposition of ovarian cancer, however.literature reports inconsistent association between codon 72 polymorphism and ovarian cancer risk. Several studies have reported a higher incidence of ovarian cancer associated with the Pro variant, while others found non-significant association. Present study has been conducted to investigate the association of codon 72 polymorphism of p53 gene with ovarian cancer risk in Asian population and to correlate them with clinicopathological characteristics of patients. **Methodology:** The study was conducted on 60 ovarian cancer patients and 60 healthy women..Single-nucleotide polymorphism (SNP) G>C (Arg>Pro) transition at codon 72 of exon 4 (rs1042522) in the *P53* gene Has been analysed.DNA was extracted by using the DNA Sure Blood Mini Kit (GeNei TM).The genetic polymorphism in *P53* genes was assessed by Allele-specific polymerase chain reaction(ASO-PCR).X2,Fisher exact test and odds ratio[0R] at 95% confidence interval [CI]) were used for statistical analysis. **Results:** The distribution of Arg/Arg, Arg/Pro and Pro/Pro genotype of codon 72 of the*P53* gene was 30%,50%, and 20% in the ovarian cancer patients and 60%,31.6%, and 8.3%, respectively in healthy individuals. Increased frequency of Pro/Pro allele. was associated with the risk of ovarian cancer as revealed by statistically significant values at p-0.003.(OR=4.8;95%CI 1.46-15.72). Patients who expressed *P53* proline allele might be at higher risk of developing ovarian cancer as compared with those who expressed *P53* Arg allele (p= 0.003).However small sample size is the limitation of present study.Analysis of bigger group of ovarian cancer patients may robust the genetic predisposition of *P53* codon 72 in ovarian carcinogenesis. **Conclusion:** Genetic predisposition of proline allele of *P53* gene in ovarian carcinoma might be explored as early diagnostic marker of ovarian cancer and to go ahead towards gene-targeted drug therapy for better clinical outcome as well as to reduce mortality.

**Keywords:** Ovarian Carcinogenesis- *p53*gene- ASO-PCR- Polymorphism- genetic predisposition

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## Introduction

Ovarian cancer is a significant global health concern for women.In India, it is the third leading site of cancer among women after breast and cervix uteri [1]. It continues to be the deadliest gynaecologic malignancy, largely because of the absence of reliable early detection methods, insufficient screening strategies, and the limited effectiveness of therapies for late-stage metastatic disease [2]. Ovarian cancer is usually asymptomatic in its early stages; by the time of diagnosis, the malignancy often metastasizes to the abdominal and pelvic regions, with reduced treatment efficacy and increased mortality [3].

Women of any age group can develop ovarian cancer, but its incidence increases with age and make it most prevalent among the age group between 50 and 80 [1, 4]. It has been estimated that lifetime chance of a woman developing ovarian cancer is one in seventy-eight, while the probability of dying from invasive ovarian cancer is approximately 1 in 108 (https://shorturl.at/kmxC0). American Cancer Society statistics have reported 19710 new cases and 13270 mortalities related to ovarian cancer in 2023.More than 90%of ovarian cases have been reported of epithelial ovarian cancer,and majority with high-grade serous tumoursof the worst prognosis [5]. The geographic pattern affects the incidence rate of ovarian cancer. India has a comparatively higher incidence of ovarian cancer than Western countries [6].

*P53* is a tumour suppressor gene with 11 exons and 10 introns involved in several biological processes. It is found on chromosome 17p13.1 [7]. Dysfunctional *P53* is a hallmark of many cancers, including ovarian cancer that harbors mutation in more than 50% of ovarian tumours and leads to the onset and spread of ovarian cancer [8]. According to cancer genome-sequencing studies, of high-grade serous ovarian carcinomas, *P53*gene mutations have

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been identified in over 96% cases [9-13]. The majority of the *P53* gene mutation occurred in exons 4–9, which code for the protein's DNA-binding domain [13]. A particular *TP53* gene variant known as the codon 72 polymorphism is of peculiar interest as reported in certain studies [13-18] due to its links to ovarian cancer. Exon 4 codon 72 *P53* R72P G>C(rs1042522) is a single-nucleotide polymorphism that causes expression of either proline (CCC)orarginine (CGC).Differences in transcriptional activity, apoptotic induction, and susceptibility to malignant transformation are possible outcomes of this amino acid shift [14-16]. The arginine(Arg72)allele enhances *P53*capability to target mitochondria and trigger cellular death. On the other hand, proline allele (Pro 72) has been linked to decreased cellular mortality and cellular arrest during the G1 phase of the cell cycle [17]. Literature reviews have indicated inconsistent association between codon 72 polymorphism and ovarian cancer risk [18-22]. Several studies have reported a higher incidence of ovarian cancer associated with the Pro variant [18, 19], while others found non-significant association [20-22]. Present study has been conducted to know the possible role of *P53* codon 72 polymorphism in ovarian carcinogenesis.

## Materials and Methods

*Location of the study*

Present case-control study included 60 ovarian cancer patients and 60 age-matched healthy females from the tertiary care hospital of Rohtak, Haryana (North India). The study was conducted in Human Molecular and Cytogenetics lab, Department of Genetics, Maharshi Dayanand University Rohtak-, Haryana(India) in collaboration with Department of Obstetrics and Gynecology and Department of Pathology, Pt. B. D. S. University of Health Sciences, Rohtak, Haryana.The study was conducted in accordance with the Declaration of Helsinki with ethical approval from the Institutional Human Ethical Research Committee, Maharshi Dayanand University, Rohtak (Ref no-IHEC/19/07).All procedures were followed in compliance withprescribed guidelines and regulations.Before recruitment, informed consent was obtained from all the participants. All the relevant information, such as clinical history, including the type of tumor and stage of ovarian cancer, and histological grade, was collected with the help of a clinician.All ovarian cancer patients were staged according to the International Federation of Obstetricsand Gynaecologycriteria.Out of 60 ovarian cancer cases,there were 42(70%) advanced stage(FIGO stageIII and IV), while 18(30 %) in earlier stages (FIGO stage I and II).

*Sample Collectionand DNA Isolation*

The blood sample was collected from 60 ovarian cancer patients and 60age-matched normal female individuals after procuring informed consent.The sample size was calculated using the sample size estimation formula: Sample size: $N= Z^2p(1-p)/d^2$ , where N=sample size; p=expected prevalence or proportion (%);d=precision(0.05) for 95% level of confidence; Z=1.96 (for 95% level of confidence).

The study has been conducted with specific exclusion and inclusion criteria.

*Inclusion criteria*

* Patients with reported cases of ovarian cancer or cancer of reproductive tract were included.

* Females of any age with reported ovarian cancer were included.

*Age-matched healthy female individuals without a history of any cancer/disease were recruited as the control group.(from Department of Obstetrics and Gynecology, who came for routine checkup at Pt. B. D. S. University of Health Sciences, Rohtak, Haryana).

*Exclusion criteria*

* Patients reported to have any other cancer were excluded.

* Congenital lesions, unusual tumor types, and inadequate samples were excluded from the study.

After obtaining informed consent, 3 mL of blood samples from patients and the control group was collected and stored at 4 ºC in EDTA vacutainer until use. Extraction of genomic DNA was done using the DNA Sure Blood Mini Kit (GeNei TM).Optimization of the protocol resulted in 80ng to 100ng of DNA. Purity of DNA sample was checked at the OD 260/OD 280. All the samples were found in a desirable reference ratio of 1.65 to 1.85. The samples not in the reference range were purified again by RNAse and Protienase K treatment. DNA of 20-50 kb in size was used as a template in PCRs. The purified DNA was stored in the TE buffer (pH 7.6) at -20ºC.Purity of DNA was checked byNano-400Amicro-spectrophotometer as well as with the help of electrophoresis.

*Genotyping for polymorphism analysis of codon 72 in P53*

DNA amplification was carried out to know codon 72 polymorphism by allele-specific primers.Two set of primers were used for Arginine 72 allele and proline 72 allele as per available literature[18] (Table 1).

Each set of primers was added to a different tube with a reaction volume containing 6µlof 50–100ng/µl of template DNA, a working concentration of 25 pm for each primer, and a total volume of 25µl.The PCR procedure was conducted using an Applied Biosystems Thermocycler 2720, initiating with denaturation phase at 95°C for 3 minutes, followed by denaturation up to 35 cycles (95°C for 30 seconds), then annealing (60°C for 45 seconds) for the arginine allele, (62°C for 45 seconds) for the proline allele, and extension (72°C for 1 minute) with 10 minutes extension time at 72°C. Amplified PCR products wererun along with negative and positive controls.These werevisualized on a 2.5% Agarose gel along with ethidium bromide using gel documentation (Figure 1).

*Statistical analysis*

The statistical analysis was performed with MEDCALC Software and GraphpadPrism version 8.0.2.Thecorrelation between the *P53*codon 72Arg/Pro polymorphism and clinicopathological characteristics was investigated using the Fisher exact test and Chi-square Hardy-

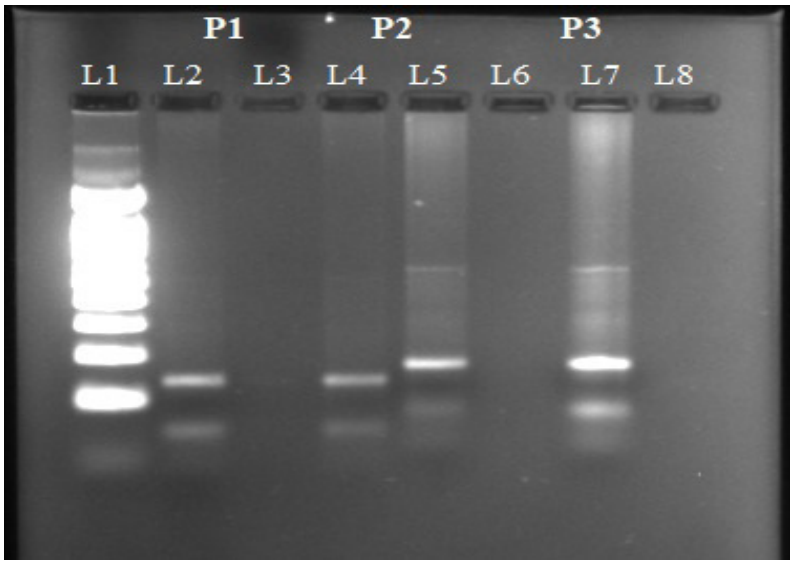


Figure 1. Agarose Gel Electrophoresis for Different Variants of *TP53* codon 72. (L1:100bp DNA MARKER; Lane L2-L3(P1): Homozygous arginine(Arg/Arg); Lane L4-L5(P2): Heterozygous Arginine/proline(Arg/Pro); Lane L6-L7(P3): Homozygous proline(Pro/Pro); L8: Negative control(Non template control )

Weinberg equilibrium. The correlation between the *P53* polymorphism and ovarian cancer was evaluated utilizing the multivariate logistic regression method.Odd ratio was calculated to find the strength of association of genotypes with the occurrence of diseases.All the p-values were two-sided,and the significance level was p≤0.05.

## Results

Ovarian cancer patients & their age-matched 60 normal female (control group) were evaluated for various clinicopathological features as well as codon 72 polymorphism. The ovarian cancer patients were divided into two groups: ≤ 45 years (26.67%) and >45 years (73.33%). Among 60 ovarian carcinoma,there were75% were serous histological subtype,10% mucinous,5%endometrioid, 1.6% clear cell, and 8.3% mixed subtypes. Highest number of cases were observed in stage III (53.33%), followed by stage II (18.33%), stage IV (16.5%) and stage I (11.6%) (Table 2). PCR amplification of the *P53* gene exon 4by ASO-PCR was successful in all ovarian cancer cases and healthy individuals. The *P53* gene codon 72 alleles in exon 4 showed amplimer sizes of 141 bp for arginine andamplimer size of177 bp for proline (Figure 1).Arg/Pro genotype distribution of *P53* codon 72 among ovarian cancer patients and healthy individuals depicted maximum cases in Arg/Progenotype. In the ovarian cancer cases,the distribution of Arg/Arg, Arg/Pro,and Pro/Pro genotype of codon 72 of the *P53* gene was 30%, 50%, and 20%, respectively, whereas in healthy individuals, it was 60%, 31.6 %, and 8.3%.

*Allele and genotype distribution*

Allele frequencies of *P53* Arg and *P53* Pro werecalculatedas0.55 and 0.45 in patients and 0.76 and 0.24 in healthy individuals, respectively. The result showed Pro/Pro allele as more frequent in ovarian cancer cases (0.45) as compared to Arg/Arg allele (0.76) in healthy individuals. The evaluation by odd ratio with 95%CI indicated Pro/Pro genotype as a high-risk factor for ovarian carcinoma patients with an odd ratio of 4.8(1.46-15.72) (Table 3).

*P53 codon 72 polymorphism and its association with age at diagnosis*

The *p53* codon 72 polymorphism and its association with age at diagnosishave been analysed.Data was categorized into two groups: ≤45 years and >45 years. Heterozygous Arg/Pro genotypes was found more in the age group >45 years old,prevalent (56.25% and 47.72%, respectively). However,statistically non-significant correlation was observed between the *P53* polymorphism and age.(p=0.85) (Table 2).

*P53 codon 72 polymorphism and its association with stage and histological grade*

The *p53* codon 72 polymorphism & its association with stage of ovarian cancer revealed that hetrozygous Arg/Pro

Table 1. Primer Sequence Used for *P53* codon 72 Polymorphism R72PG>C (rs1042522)

| | Primer | Product size |
|---|---|---|
| Exon4 | Arginine 72 allele<br>Forward-5'TCCCCCTTCCCGTCCCAA-3'<br>Reverse-5'CTGCTGCAGGGGCCAGGC-3'" | 141 bp |
| | Proline 72 allele<br>Forward-5'GTCCTCTGACTGCTGCTGTTATCACCCATCTAC-3'<br>Reverse 5'-GGGATACGGCCAGGCATTGAAGTCTC-3'" | 177 bp |

Table 2. *P53* Gene Polymorphism and Clinicopathological Features in Ovarian Cancer Patients and Control Group

| Parameters | | Arg/Arg | Arg/Pro | Pro/Pro | Arg | Pro | Chi- square | p- value |
|---|---|---|---|---|---|---|---|---|
| Cases | | 18 (30) | 30 (50) | 12 (20) | 0.55 | 0.45 | 11.35 | 0.003 |
| Control group | | 36 (60) | 19 (31.6) | 05 (8.3) | 0.76 | 0.24 | | |
| Age | ≤45 yrs | 4 (25) | 9 (56.25) | 3 (18.75) | 0.53 | 0.46 | 0.36 | 0.85 |
| | >45 yrs | 14 (31.8) | 21 (47.72) | 9 (20.45) | 0.55 | 0.44 | | |
| Stages | I | 2 (28.57) | 3 (42.85) | 2(28.57) | 0.5 | 0.5 | 3.36 | 0.76 |
| | II | 5 (45.45) | 4(36.36) | 2 (18.18) | 0.6 | 0.4 | | |
| | III | 9 (28.12) | 16 (50) | 7 (21.8) | 0.53 | 0.46 | | |
| | IV | 2 (20) | 7 (70) | 1(10) | 0.55 | 0.45 | | |
| Histological subtype | Serous | 15 (33.33) | 23 (51.11) | 7 (15.56) | 0.59 | 0.41 | 2.49 | 0.29 |
| | Non serous | 3 (20) | 7 (46.66) | 5 (33.33) | 0.43 | 0.57 | | |
| Menopausal status | Premenopausal | 6 (30) | 11 (55) | 3 (15) | 0.58 | 0.42 | 0.52 | 0.76 |
| | Postmenopausal | 12 (30) | 19 (47.5) | 9 (22.5) | 0.54 | 0.46 | | |

P values represented in table are chi-squared p values;p<0.05

Table 3. Percentage Frequency of *TP53* exon 4 Codon 72 Polymorphism in Ovarian Cancer Patients

| Genotype | Ovarian Cancer Patients (n=60) | | Control Group (n=60) | | OR (95%CI) | Chi-square |
|---|---|---|---|---|---|---|
| | Genotype (%) | Proline allele frequency | Genotype (%) | Proline allele frequency | | |
| Arg/Arg | 18 (30) | 0.45 | 36(60) | 0.24 | 1 (ref) | 11.35 |
| Arg/Pro | 30 (50) | | 19(31.6) | | 3.158(1.4- 7.07 | |
| Pro/Pro | 12 (20) | | O5(8.3) | | 4.8(1.46- 15.72) | |

$\chi 2$, Pvalues denote chi square test probabilities; OR and 95%CI .*P<,0.05

genotypes were more prevalent in advanced stage (FIGO III&IV) (50% and 70%, respectively),wherase in the early stage (FIGO II), homozygous Arg/Arg genotypes was more(45.45%).)However, a non-significant correlation was observed between the *P53* polymorphism and stage of ovarian cancer(p=0.76).A statistically nonsignificant association was observed between serous and non-serous histological types of ovarian cancer, with a p-value of 0.29.Correlation between *P53* polymorphism and different histological subtypes and menopausal status revealed non-significant association (p=0.29),(p=0.76)(Table 2). Statistically significant differences were observed between allele frequencies of ovarian cancer patients and normal individuals (p= 0.003). Patients who expressed *P53* proline allele showedhigher risk of developing ovarian cancer as compared to patients who exhibited the *P53* Arg allele (p= 0.003)when analyses of using odd ratio.Small sample size is a limitation of the current study. Analysis in larger group will increase robustness of study.

## Discussion

Role of genetic predisposition in the occurrence of ovarian cancer and its application as genetic marker for early diagnosis and efficient surveillance hasgarnered significant attention in recent decades.Normal functioning of *P53* gene is necessary for tumour suppression.Any alteration in gene has been linked to the development and spread of cancer.Because of the important role of *p53* as a tumor suppressor,it is a frequently mutated gene in more than 50% of human cancers [8]. Over 3600 mutations have been reported in *p53*, and the most common mutation is missense mutation with substitution in amino acid [23]. The majority of *P53* gene mutations occurred in exons 4–9, which code for the protein's DNA-binding domain [13]. The most researched *P53* polymorphism in cancer, particularly ovarian carcinoma, is codon 72. Numerous investigations have demonstrated a link between ovarian cancer malignancies and the codon 72 polymorphism. Exon4 codon 72 *P53* R72P G>C(rs1042522)is a single-nucleotide polymorphism that causesexpression of either proline(CCC) or arginine(CGC).Differences in transcriptional activity, apoptotic induction, and susceptibility to malignant transformation are possible outcomes of this amino acid shift [16]. The arginine (Arg72) allele enhances *P53* capability to target mitochondria and trigger cellular death.In addition to forming a complex with GRP75, mitochondrial *p53* has also been reported to associate with heat shock protein 60 (Hsp60), which co-localizes in the mitochondria with several pro-apoptotic factors, including caspase-3, apoptosis-inducing factor (AIF), and Nip [24]. On the other hand, proline alleles have been linked to decreased cellular mortality and cellular arrest during the G1 phase of the cell cycle (Pro 72) [17]. The current investigation assessed the *P53* codon 72 allele and genotype frequencies in 60 ovarian cancer patients and 60 healthy individuals. Statistically non-significant association was observed between *P53* polymorphism and clinical characteristics such as age, FIGO stages, histological subtypes, and menopausal status in concordance with literature reports [18, 20, 25]. On the contrary study by Malisic and associates reported statistically significant differences between histological subtypes ( serous and non-serous)

[20]. In present study, higher frequency of proline homozygotes and proline /argenine heterozygotes was observed in ovarian cancer patients. Pro allele of codon 72 of *P53* gene has revealed highly statistically significant result between ovarian cancer patient and control .In North Indian population, the Pro/Pro genotype in patients with epithelial ovarian cancer had been reported in ovarian cancer progression [18]. A similar study on lung cancer in the north Indian population has reported a strong correlation between the polymorphism of codon 72 Arg/ Pro variants and cancer susceptibility [25]. But, contrary to this, some reports depicted a non-significant correlation between the polymorphism of codon 72Arg/Pro variants and the risk of ovarian cancer [20, 26].Proline allele has been reported as a probable risk factor for the occurrence of ovarian cancer [19, 27], while other studies reported Arginine allele as a probable risk factor for the occurrence of ovarian carcinoma [28, 29]. A meta-analysis on 12 studies comprising of 993 OC Cases and 1264 healthy individuals reported that codon 72 polymorphism may not be significantly associated with ovarian cancer susceptibility [30]. A link between *P53* pro variant with increased risk of CLL, breast cancer, liver cancer as well as esophageal cancer has been reported [31-34], whereas other reports have shown correlation between *P53*Arg 72 variant and increased risk of cancer in lung,breast, and esophagus carcinoma [35, 36].

Ethnically different populations have reported varied associations of *p53* codon 72 polymorphism with carcinoma, including ovarian carcinoma [18, 20, 28, 31, 33, 35, 37]. Overall pooled result of the meta-analysis in literature showed that codon 72 polymorphism had no influence on decreased or increased risk of ovarian cancer. Studies have indicated an inconsistent association between codon 72 polymorphism and ovarian cancer risk.The conflicting results may be because of ethnicity, different genotype models, and quality scores.

In the present study,*P53* proline allele depicted higher risk of developing ovarian cancer as compared to patients who exhibited the *P53* Arg allele.A subgroup analysis between age, menopausal status, and histological factorsto identify all the factors that contribute to heterogeneity revealed statistically non-significant association between *P53* polymorphism and clinical characteristics.However, HPV infection was not analyzed in the present study. No associationhas been reported in the literature between HPV infection and ovarian cancer risk [20]. However, There has been substantial reports of association of HPV with the risk of cervical cancer [38].

.Significant association between codon 72 polymorphism of *P53* gene and occurrence of ovarian cance rhas been revealed in the present study. In reference to the investigated gene locus, both ovarian cases and control group have followed Hardy-Weinberg equilibrium. Increased frequency of proline homozygote and proline / arginine heterozygote in ovarian cancer cases has revealed statistically significant difference between pro allele and *TP53* codon72 polymorphism associating with occurrence of ovarian carcinom, Studies have shown differential distributions of the proline and arginine alleles among various ethnic groups, which could affect both the predictive value of the allele and the design of equitable screening strategies [18, 20, 26, 34]. Recognizing these differences would help tailor clinical approaches to the genetic background of diverse populations, reducing health disparities and improving the effectiveness of precision medicine initiatives.Small sample size is the limitation of present study. Robustness of study will be revealed by exploring *p53* codon 72 polymorphism cancer on larger sample size, focusing on ethnicity and gene-gene interaction.

Future research should be focussed on large-scale,multicentre studies across diverse ethnic groups to validate association and minimize population-specific bias. After getting validated through large-scale, multi-ethnic studies, this polymorphism could be integrated into genetic screening panels to identify individuals at elevated risk for developing ovarian cancer. It will certainly help the clinician to make decision on clinical outcome . Later on this can be explored for development of gene targeted drug therapy.

In conclusion, present study revealed increased proline homozygote and prolin/ arginine heterozygote in ovarian cancer cases as compared to control group. Presence of proline allele of *P53* gene in ovarian carcinoma might be explored as genetic predisposition towards occurrence of ovarian carcinogenesis. It may lead to develop gene targeted drug therapy and play a role in early diagnosis of ovarian cancer as well.

## Author Contribution Statement

Geeta Bazard:Formal analysis; Investigation; Methodology; Visualization; Writing - original draft. Minakshi Vashist: Conceptualization; Funding acquisition; Investigation; Project administration; Resources; Supervision; Visualization; Writing - review & editing. Reetu Hooda: Data curation; Writing - review & editing. GulshanRohilla: Investigation Data curation; Writing - review & editing.Nidhi Paliwal: InvestigationWriting - review & editing.Rohit Kaushik: Validation, Writing review & editing.Vandana Kalra:Investigation ,Software; Validation;.

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*Ethics approval and consent to participate*

The study was conducted in accordance with the Declaration of Helsinki with ethical approval from the Institutional Human Ethics Research Committee, Maharshi Dayanand University, Rohtak (Ref no-IHEC/19/07). All methods were carried out in accordance with prescribed guidelines and regulations. Written

informed consent prior to enrolment in the study was procured.

*Consent for publication*

All the authors have given consent for the publication of present research article.

*Availability of data and materials*

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

*Declaration of interests*

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests:

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