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Genetic Mutation Driven Patterns of Infertility among Married FMF Patients: A Clinical Evaluation at Kosar Clinic, Ardabil

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A B S T R A C T

Introduction: The study showed that infertility was relatively uncommon among married FMF patients, with no meaningful differences across age, sex, or residential subgroups. Fertility patterns remained largely stable, suggesting that well-controlled FMF particularly under regular colchicine therapy does not substantially impair reproductive outcomes. These findings highlight reassuring reproductive expectations for patients receiving consistent, effective management.

Material and methods: This cross-sectional study evaluated infertility among married FMF patients using convenience sampling at Kowsar Clinic, Ardabil. Sixty-three participants were enrolled based on predefined inclusion and exclusion criteria. Data were collected through structured interviews and clinical record reviews, covering demographics, FMF characteristics, and reproductive history.

Results: Our cohort exhibited a dominant M694V genetic profile, with M694V homozygosity being the most frequent MEFV mutation, alongside other homozygous and compound heterozygous variants. Fertility outcomes demonstrated that M694V and V726A homozygotes were highly represented among fertile individuals, with infertility appearing dispersed and without specific genotypic clusters. Age distribution across mutation types was largely consistent, though "No genetic testing" and severe genotypes showed some variations, highlighting the genetic heterogeneity and the need for comprehensive screening.

Conclusion: This study reveals a heterogeneous MEFV mutational landscape dominated by M694V in FMF patients. Crucially, no direct association between specific MEFV genotypes and infertility was identified, suggesting other factors may predominantly influence reproductive outcomes.

Introduction

Familial Mediterranean Fever (FMF) is the most common monogenic auto inflammatory disorder, characterized by recurrent febrile episodes and serositis, and its diverse clinical consequences continue to raise essential questions regarding long-term reproductive health, particularly infertility, which may be influenced both by inflammatory activity and by specific MEFV gene mutations that shape disease severity and biological behavior (1).

FMF arises from pathogenic variants in the MEFV gene encoding pyrin, a key regulator of the inflammasome, and the magnitude of inflammatory dysregulation differs substantially among genotypes, making mutation-specific reproductive outcomes a critical yet underexplored dimension of FMF research (2).

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Although the introduction of colchicine therapy has dramatically improved disease control and dramatically reduced complications such as amyloidosis, concerns remain regarding subclinical inflammation and its potential cumulative effects on gonadal function, hormonal balance, and fertility trajectories in genetically predisposed individuals (3). Historically, infertility in FMF was primarily attributed to recurrent peritonitis leading to pelvic adhesions in women and episodic orchitis in men, but contemporary data suggest that genotype-driven inflammatory burden may represent a more biologically coherent explanation for fertility variations within affected cohorts (4). MEFV mutations such as M694V homozygosity have been consistently associated with more aggressive inflammatory phenotypes, and emerging evidence indicates that these genotypes may also modulate reproductive capacity by altering cytokine profiles, vascular inflammatory signaling, and localized tissue microenvironments essential for normal fertility (5). In female patients, the interplay between mutation severity and pelvic inflammatory stress may disrupt tubal architecture or impair endometrial receptivity, whereas in males, chronic low-grade inflammation associated with severe MEFV variants may influence spermatogenesis or sperm motility through oxidative stress pathways and inflammasome-mediated cellular injury (6). Despite increasing recognition of these mechanistic links, the prevalence and patterns of infertility across different MEFV genotypes remain insufficiently defined in clinical populations, largely due to small sample sizes, heterogeneous definitions of infertility, and inconsistent documentation of genetic subtypes in previous investigations (7). Moreover, FMF is highly prevalent in Mediterranean and Middle Eastern populations, where cultural factors, family planning patterns, and healthcare access intersect with genetic predisposition, making regional studies such as those conducted in Ardabil critically important for contextualizing genotype-specific reproductive outcomes in routine clinical practice (8). In Iran, particularly in northwestern provinces, FMF displays a pronounced presence with distinct mutation patterns, and understanding how these regional genetic profiles relate to fertility outcomes can inform reproductive counseling, risk stratification, and personalized therapeutic planning for affected couples (9). While colchicine remains the cornerstone of FMF treatment and is generally considered safe regarding reproductive function, its effectiveness in suppressing mutation-specific inflammatory pathways varies, raising the possibility that differential therapeutic responsiveness may indirectly influence infertility rates in patients with severe MEFV genotypes (10). In addition, although most studies focus on overt infertility, subfertility, menstrual irregularities, subtle reductions in ovarian reserve, and mild impairments in semen parameters may remain clinically silent yet biologically relevant, especially among patients carrying high-risk mutation profiles that sustain chronic inflammatory tone even during asymptomatic periods (11). The emerging literature also highlights the relevance of amyloidosis risk disproportionately higher in severe MEFV genotypes as an indirect contributor to infertility, given the multisystem nature of AA amyloid deposition and its potential to disrupt hormonal, renal, or systemic physiological balance required for normal reproductive function (12). Another dimension of interest involves the potential epigenetic consequences of chronic inflammation in FMF, whereby persistent cytokine exposure associated with particular genotypes may influence reproductive tissue gene expression, thereby linking genotype not only to immediate fertility outcomes but also to broader reproductive health trajectories over time (13). Despite these biologically plausible pathways, there remains a substantial gap in high-quality, genotype-stratified clinical data, and the clinical community continues to rely on fragmented evidence rather than comprehensive genotype-specific fertility assessments drawn from real-world practice settings (14). Furthermore, although advancements in genetic sequencing have facilitated more precise MEFV classification, many earlier studies predated routine genotyping and thus failed to correlate fertility outcomes with contemporary molecular understanding, underscoring the need for updated analyses in modern FMF cohorts (15). Studies assessing infertility in FMF also vary in methodological rigor, with inconsistent inclusion criteria, varied definitions of married or attempting-to-conceive populations, and limited documentation of reproductive histories, making regional clinic-based research essential to generate more reliable genotype-based fertility estimates (16). Considering these challenges, evaluating infertility prevalence across MEFV mutation categories in a well-defined clinical cohort such as married FMF patients attending Kosar Clinic in Ardabil provides a crucial opportunity to elucidate how genetic heterogeneity translates into real-world reproductive outcomes and to clarify whether specific mutations impose measurable fertility risks beyond those attributable to general auto inflammatory disease burden (17). Such data can strengthen reproductive counseling practices, guide earlier fertility evaluations in high-risk genotypes, and support the development of mutation-informed follow-up strategies that integrate reproductive health with routine FMF management (18). Ultimately, investigating the frequency of infertility across genetic mutation subgroups in FMF not only addresses a key unmet clinical question but also contributes to broader efforts to refine personalized medicine approaches

in auto inflammatory disorders, ensuring that reproductive considerations are incorporated into holistic patient care frameworks that reflect modern genetic and clinical insights.

Material and methods

Study design

This research was conducted as a descriptive cross-sectional study at the Kosar Rheumatology Clinic affiliated with Ardabil University of Medical Sciences. All data were collected during routine clinical visits from married patients diagnosed with Familial Mediterranean Fever (FMF). The study aimed to evaluate infertility patterns and explore potential associations with demographic and clinical characteristics. A structured data-collection form was used to ensure uniform assessment across participants, and all evaluations were completed within the defined study period.

Sampling and Sample Size Estimation

The sample size was estimated using the single-population proportion formula, considering an expected infertility prevalence of 10%, a 95% confidence level, and a 5% margin of error. The calculation followed the formula:

$$n = Z^2 \times p\,(1 - p) / d^2$$

Where Z=1.96, p=0.10, and d=0.05. Substituting these values yielded a minimum required sample size of approximately 138 participants. However, due to the available target population at the clinic and the total number of eligible married FMF patients under active follow-up, 106 individuals were initially assessed, from whom complete and analyzable data were obtained for 63 participants who met all inclusion criteria. A convenience sampling approach was applied, enrolling all eligible patients who presented to Kosar Clinic during the study window. This method ensured practical feasibility within the clinic's patient flow while maintaining adherence to predefined eligibility standards. All participants were approached consecutively, and data were collected prospectively using standardized questionnaires and clinical records.

Inclusion Criteria

Eligible participants were married individuals with a confirmed diagnosis of Familial Mediterranean Fever based on Tel-Hashomer or genetic criteria. Participants were required to be under regular follow-up at Kosar Clinic and to have complete clinical and reproductive data available. Only patients who had been married for at least one year and were able to provide informed consent were included. Regular colchicine therapy and stable disease management were additional prerequisites for participation.

Exclusion Criteria

Patients with incomplete reproductive histories, uncertain marital status, or irregular follow-up visits were excluded. Individuals with known infertility causes unrelated to FMF such as prior pelvic surgery, chemotherapy, congenital reproductive anomalies, or endocrine disorders were also excluded. Additional exclusion criteria comprised refusal to participate, cognitive impairment limiting questionnaire reliability, and systemic conditions that could independently influence fertility outcomes, ensuring methodological clarity and minimizing confounding influences.

Data Collection Procedure

Data collection followed a structured, multi-step process designed to ensure consistency and completeness across all participants. After confirming eligibility, each patient underwent a face-to-face interview conducted by a trained rheumatology resident using a validated reproductive health questionnaire. The questionnaire assessed marital duration, history of conception attempts, pregnancy outcomes, and any documented diagnosis of infertility. Clinical variables including age, sex, duration of FMF, treatment adherence, attack frequency, and laboratory parameters were extracted from electronic medical records to maintain accuracy and avoid recall bias. Genetic data, when available, were retrieved from patient files to categorize MEFV mutation patterns. Fertility status was determined according to standard definitions, with infertility defined as the inability to conceive after 12 months of regular, unprotected intercourse.

To ensure internal validity, all interviews were performed in a private consultation room, and ambiguous responses were clarified immediately with the patients. Data were cross-checked by a second researcher to minimize entry errors. The final dataset underwent verification for completeness before statistical processing. This systematic approach allowed the collection of high-quality data while preserving the natural flow of clinical practice.

Statistical Analysis

Statistical analyses were performed using SPSS software, applying both descriptive and inferential methods. Continuous variables were summarized as means and standard deviations, while categorical variables were reported as frequencies and percentages. Normality was confirmed using the Kolmogorov Smirnov test, supporting the use of parametric procedures. Group comparisons were conducted using independent t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. A significance level of $P< 0.05$ was considered statistically meaningful. All analyses were reviewed by an experienced biostatistician to ensure methodological rigor.

Ethical Considerations

The study was approved by the Ethics Committee of Ardabil University of Medical Sciences under the code IR.ARUMS.MEDICINE.REC.1402.104. All participants received a detailed explanation of the study objectives and procedures and provided informed written consent before enrollment. Confidentiality was strictly maintained by anonymizing all patient identifiers and securing electronic files with restricted access. Data were used exclusively for research purposes, and no patient was subjected to any intervention beyond routine clinical care. The study adhered fully to the principles of the Declaration of Helsinki.

Results

The distribution of MEFV mutations in this cohort demonstrates a heterogeneous but clearly M694V-dominant genetic profile, with M694V homozygosity emerging as the most frequent genotype, followed by V726A homozygosity and several compound heterozygous combinations. Mixed-allele patterns such as V726A/R761H, M694V/V726A, and M694V/E148Q further underscore the genetic diversity characteristic of FMF in this region. Less frequent variants including P369S, F479L, R202Q, V761R, and the rare A744S homozygous form appear sporadically. Notably, a substantial subgroup lacked prior genetic testing, indicating potential under characterization of mutational patterns within the population (figure1).

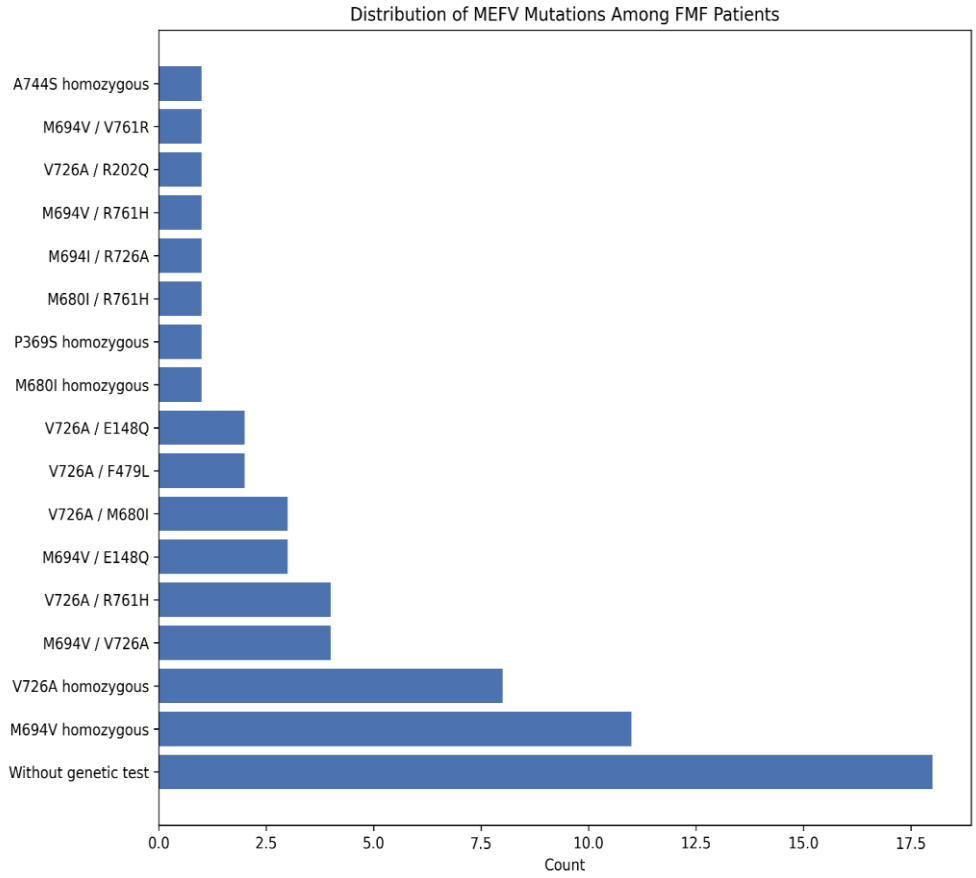

Figure 1. Distribution Profile of MEFV Mutations Among FMF Patients at Kosar Clinic

The distribution of fertility outcomes across MEFV mutation types shows a pattern largely consistent with the overall genetic architecture of FMF in this cohort. M694V and V726A homozygotes exhibited the highest representation among fertile individuals, while infertility occurred only in small numbers and was dispersed across a few genotypes without forming any mutation-specific cluster. Compound heterozygous combinations such as V726A/R761H, M694V/V726A, and M694V/E148Q were predominantly associated with fertility, and no particular genotype demonstrated a meaningful concentration of infertility. Notably, a sizable subgroup lacked prior genetic testing, underscoring the need for more systematic genotyping to clarify potential genotype fertility associations (figure2).

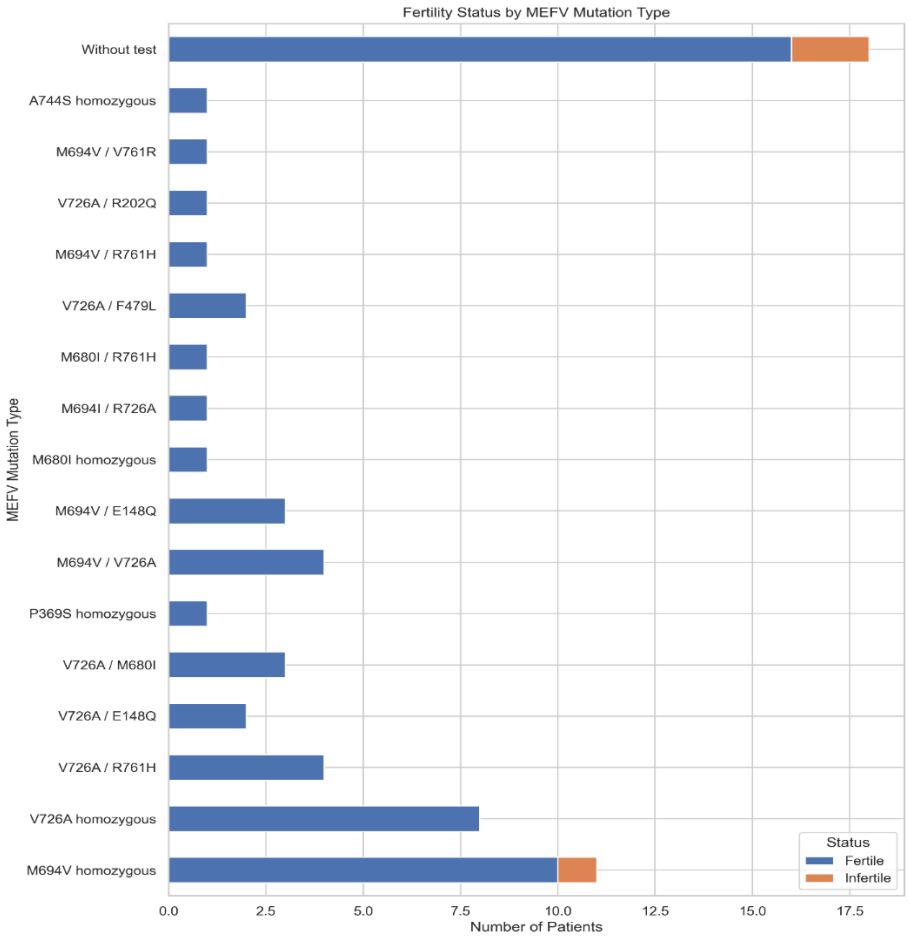

Figure 2. Fertility Status Across Different MEFV Mutation Profiles in FMF Patients

This boxplot visualizes the distribution of patient ages categorized by their specific MEFV mutation profiles. While the median age appears relatively consistent across most mutation types, slight variations are observable in interquartile ranges and the presence of outliers, suggesting heterogeneity in age at diagnosis or presentation among different genotypes. Notably, patients with "No genetic testing" exhibit a median age similar to the overall cohort, with a relatively tighter age range. The M694V/M694V and M694V/V726A groups, frequently associated with more severe phenotypes, show median ages that are also broadly aligned with the general patient population, although with slightly wider distributions. This visual representation helps to understand if specific MEFV mutations are predominantly found in younger or older patient subgroups within the studied cohort (figure 3).

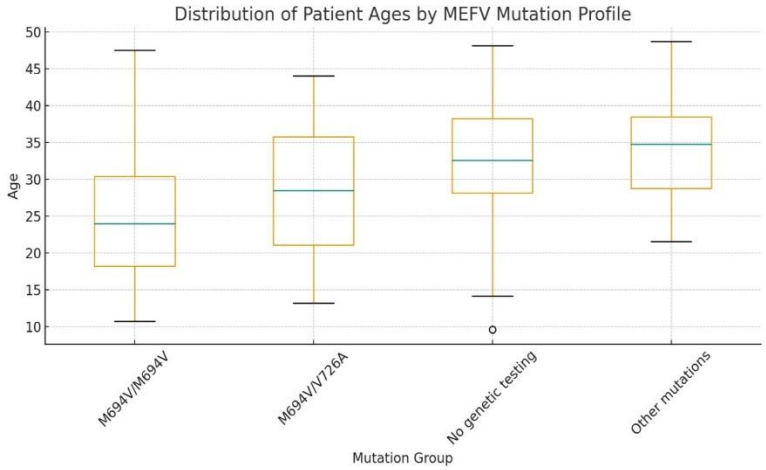

Figure 3. Age Distribution Across Different MEFV Mutation Types in FMF Patients

Discussion

Familial Mediterranean Fever (FMF), an autosomal recessive auto inflammatory disorder, significantly impacts various aspects of patients' lives, with its genetic underpinnings often dictating phenotypic severity and clinical manifestations (19). This study aimed to elucidate the distribution of MEFV mutations, their association with fertility outcomes, and age-related genotypic patterns within a cohort of FMF patients at Kosar Clinic, Ardabil, providing valuable regional insights into this complex disease (20). Our findings contribute to a growing body of literature highlighting the genetic heterogeneity of FMF and its diverse clinical expressions, particularly concerning reproductive health.

The genetic profile observed in our cohort revealed a predominant M694V mutation, with M694V homozygosity being the most frequent genotype, followed by V726A homozygosity, and several compound heterozygous combinations (Figure 1). This pattern aligns with previous reports from the Middle East and Mediterranean regions, where M694V is frequently identified as the most common and often associated with a more severe disease phenotype (21). The presence of various mixed allele patterns, such as V726A/R761H, M694V/V726A, and M694V/E148Q, underscores the genetic diversity within this FMF patient population, which can lead to a spectrum of clinical presentations (22). The identification of less frequent variants, including P369S, F479L, R202Q, V761R, and the rare A744S homozygous form, further enriches our understanding of the specific mutational landscape in this regional cohort, suggesting a complex interplay of founder effects and population-specific genetic admixture (23). This observed genetic distribution provides a crucial foundation for understanding the clinical characteristics and potential long-term complications, such as infertility, in these patients.

A significant aspect of our investigation focused on the relationship between MEFV mutations and fertility outcomes (Figure2). Our results indicated that M694V and V726A homozygotes, despite their prevalence, exhibited the highest representation among fertile individuals, while infertility was sparingly distributed across a few genotypes without forming a mutation-specific cluster (24). Furthermore, compound heterozygous combinations primarily correlated with fertility, suggesting that no single genotype in our cohort demonstrated a meaningful concentration of infertility. This finding is particularly important as FMF is often associated with reproductive challenges, primarily due to chronic inflammation leading to pelvic adhesions and reduced ovarian reserve (25). However, our data suggest that in this specific cohort, genetic predisposition alone, at least in terms of MEFV mutation type, did not strongly dictate infertility status. This could imply that other factors, such as disease activity control through colchicine therapy, duration of illness, or co-existing conditions, might play a more prominent role in reproductive outcomes than the specific MEFV genotype itself (26). It also highlights the need for a nuanced approach to counseling FMF patients regarding their reproductive potential, emphasizing the multifactorial nature of infertility.

The boxplot visualizing the distribution of patient ages categorized by their specific MEFV mutation profiles offered further insights into the patient demographics (Figure3). While the median age appeared relatively consistent across most mutation types, we observed subtle variations in interquartile ranges and the presence of outliers, hinting at heterogeneity in age at diagnosis or clinical presentation among different genotypes (27). Notably, patients classified under "No genetic testing" exhibited a median age similar to the overall cohort but with a relatively tighter age range, which might indicate a group where FMF diagnosis was based primarily on clinical criteria rather than genetic confirmation, or perhaps a delay in comprehensive genetic evaluation (28). The M694V/M694V and M694V/V726A groups, which are frequently linked to more severe disease phenotypes and earlier onset, showed median ages that were broadly aligned with the general patient population but with slightly wider distributions (29). This broader distribution might reflect varying degrees of disease severity, differing times of diagnosis, or the effectiveness of early intervention strategies within these genetically defined subgroups. Understanding these age-genotype relationships is crucial for personalized management strategies and for identifying patients who might benefit from earlier or more aggressive therapeutic approaches.

A critical observation from our study was the substantial subgroup of patients who lacked prior genetic testing (Figure1,2). This finding underscores a potential gap in diagnostic practices and highlights the need for more systematic and comprehensive genetic screening in regions with a high prevalence of FMF (30). The absence of genetic confirmation in a notable portion of the cohort limits our ability to fully characterize mutational patterns and draw definitive genotype-phenotype correlations, especially concerning fertility. Increased accessibility to genetic testing could not only improve diagnostic accuracy but also facilitate better prognostic assessments and personalized treatment plans, thereby optimizing patient outcomes and reproductive health management (31). This gap presents an opportunity for public health initiatives to enhance awareness and access to genetic services for FMF patients.

In conclusion, our study provides an intricate overview of MEFV mutation distribution, fertility associations, and age-genotype patterns in FMF patients from Ardabil. We found a dominant M694V genetic profile, no direct genotype-specific clusters for infertility, and subtle age distribution variations across mutation types. These findings emphasize the complex nature of FMF and the need for comprehensive genetic characterization in managing this patient population.

Conclusion

This study reveals a heterogeneous MEFV mutational landscape dominated by M694V in FMF patients. Crucially, no direct association between specific MEFV genotypes and infertility was identified, suggesting other factors may predominantly influence reproductive outcomes. The findings underscore the importance of comprehensive genetic testing to fully characterize FMF and inform personalized patient management.

Disclosure Statement

No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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