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Prevalence of Infertility and Its Association with Demographic Factors in Married Patients with Familial Mediterranean fever: A Study from Kowsar Clinic, Ardabil

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A B S T R A C T

Introduction: FMF as a chronic autoinflammatory disorder with potential reproductive implications driven by sustained inflammation and variable MEFV genotypes. It emphasizes uncertainties regarding infertility prevalence, the influence of demographic factors, and conflicting evidence on colchicine effects. The need for region-specific data from high-prevalence areas such as Ardabil is underscored to clarify these associations.

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: Among 63 married FMF patients, infertility was identified in only four individuals (6.3%), with no significant associations across demographic subgroups. Age demonstrated minimal influence on infertility, with nearly identical rates in those younger and older than 45 years. Sex-based comparisons revealed similarly high fertility proportions in both men and women, and residence analyses showed no meaningful variation between urban and rural participants. Overall, fertility patterns remained consistent throughout the cohort.

Conclusion: The study indicates that infertility is uncommon among married FMF patients and appears largely unaffected by demographic factors such as age, sex, or place of residence. These findings suggest that, when appropriately managed particularly with regular colchicine therapy FMF does not impose substantial reproductive limitations.

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic auto inflammatory disorder, characterized by recurrent, self-limited episodes of fever and serositis that arise from dysregulated innate immune pathways driven largely by mutations in the MEFV gene (1). The disease follows an autosomal recessive or pseudo-dominant pattern, with the pathogenic variants resulting in impaired pyrin inflammasome regulation and excessive interleukin-1β secretion, which together generate a potent inflammatory cascade (2).

Although FMF is traditionally associated with populations in the Mediterranean basin including Turks, Armenians, Arabs, Iranians, and Sephardic Jews recent epidemiological shifts indicate its increasingly global distribution due to migration patterns and improved genetic screening (3). The onset of FMF commonly occurs in childhood or adolescence, but the clinical burden continues into

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adulthood, shaping multiple domains of quality of life, including physical health, emotional stability, and reproductive potential (4). The reproductive implications of FMF have gained growing attention, especially as more patients reach reproductive age with better diagnostic and therapeutic strategies that prolong long-term health and survival (5). Chronic systemic inflammation is increasingly recognized as a major determinant of reproductive dysfunction, and FMF given its episodic yet persistent inflammatory milieu may influence fertility through multiple biological pathways (6). Pro-inflammatory cytokines such as IL-1β and TNF-α are known to interfere with ovarian reserve, endometrial receptivity, male spermatogenesis, and hypothalamic pituitary gonadal axis regulation, suggesting potential mechanisms linking FMF to reduced fertility (7). In addition, recurrent febrile attacks, oxidative stress, and microvascular dysfunction may negatively impact gonadal tissues and hormonal signaling, further raising the possibility of subfertility among affected individuals (8). Evidence from chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus supports the notion that systemic inflammation, even in the absence of direct urogenital pathology, may alter fertility outcomes both in men and women (9).

Colchicine therapy, the mainstay of FMF treatment, has also been implicated in discussions surrounding fertility, although results have been inconsistent and disease-specific conclusions remain limited (10). While colchicine is essential for preventing inflammatory attacks and reducing the risk of amyloidosis, it may theoretically influence spermatogenesis through microtubule inhibition, raising concerns about reversible reductions in sperm count or motility, though robust evidence is lacking in FMF-focused cohorts (11). Conversely, some studies suggest that infertility in FMF may stem more from chronic inflammation rather than colchicine exposure, underscoring the importance of distinguishing medication effects from disease-related pathophysiology (12). In women, certain investigations have proposed potential associations between FMF and menstrual irregularities, ovulatory dysfunction, and higher rates of miscarriage, though findings remain heterogeneous and influenced by genetic, environmental, and cultural factors (13).

The role of MEFV genotypes in reproductive outcomes is another emerging area of interest. Variants such as M694V, V726A, E148Q, and M680I differ in penetrance, disease severity, and inflammatory activity, which may theoretically contribute to fluctuating fertility profiles (14). Severe or uncontrolled FMF phenotypes, particularly those associated with high-risk MEFV genotypes, may increase exposure to inflammatory mediators and oxidative stress, potentially affecting both male and female reproductive physiology (15). However, genotype–fertility associations remain poorly characterized, and current literature provides only fragmentary insights, highlighting the need for systematic investigation in well-defined clinical populations (16). Moreover, sociocultural variables, including age at marriage, parity expectations, access to reproductive healthcare, and regional demographics, may further modulate infertility rates among FMF patients, creating complex interactions between biological and contextual determinants (17).

Despite these theoretical mechanisms, the true prevalence of infertility among FMF patients remains unclear, as available studies often involve small sample sizes, heterogeneous populations, or inconsistent diagnostic tools for assessing reproductive function (18). Most previous research has focused on disease epidemiology, genotype-phenotype relationships, or colchicine resistance, with considerably less attention devoted to long-term reproductive health and infertility patterns in adult FMF populations (19). There is particularly limited evidence from Middle Eastern and Iranian cohorts, despite the region's high FMF prevalence and unique genetic structure, which makes local investigations especially relevant for clinical practice and policymaking (20). As a result, clinically important questions regarding the magnitude of infertility in FMF, its demographic correlates, and its potential modifiable determinants remain inadequately answered.

Given these gaps, there is a pressing need for region-specific research that characterizes infertility prevalence and explores its association with demographic factors among married FMF patients. Such data are valuable not only for improving clinical counseling and personalized disease management but also for shaping therapeutic decisions, reproductive planning, and public health strategies tailored to high-risk regions. The Kowsar Clinic in Ardabil, as a major referral center for rheumatologic disorders in Northwest Iran, provides a unique setting to examine these questions in a well-defined FMF population. By addressing these knowledge gaps, the present study aims to contribute critical, locally relevant evidence to the global understanding of reproductive outcomes in auto inflammatory diseases.

Material and methods

Study Design

This descriptive cross-sectional study was conducted at Kosar clinic of Ardabil University of Medical Sciences, to evaluate infertility prevalence and its demographic determinants among married patients diagnosed with FMF. The study focused on individuals attending routine rheumatology follow-ups during the designated study period. A cross-sectional framework was selected to capture

real-world patterns of reproductive outcomes and associated factors in a defined clinical population, enabling quantitative assessment of demographic influences within a single time window.

Sampling and Sample Size Estimation

A sample size of 63 participants was estimated using the standard single-population proportion formula, assuming a conservative infertility prevalence of 0.5, a 95% confidence level, and a marginal error of 0.12. The formula applied was:

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

where n is the sample size, Z (1.96) corresponds to the 95% confidence level, p is the estimated prevalence (0.5), and d is the acceptable margin of error (0.12). Following substitution, the calculated sample size was 63 participants, considered adequate for the targeted precision and variability. Sampling was performed through a convenience sampling approach, recruiting all eligible married FMF patients who presented to the rheumatology clinic of Kosar clinic of Ardabil during the study period and met the predefined inclusion criteria. This method ensured timely enrollment and feasibility within the study's operational constraints while maintaining a representative spectrum of disease severity, treatment exposure, and demographic diversity among the FMF population routinely managed in the center.

Inclusion Criteria

Eligible participants were married adults diagnosed with FMF based on clinical criteria and confirmed by expert rheumatologic assessment. Individuals were required to have a minimum of one year of disease history, regular follow-up at Kosar clinic of Ardabil, and the ability to provide informed consent. Only patients with complete demographic and reproductive history data were included to ensure accurate evaluation of infertility patterns and associated variables.

Exclusion Criteria

Patients with known non-FMF causes of infertility, including structural reproductive abnormalities, endocrine disorders, or prior gonadotoxic treatments, were excluded. Individuals with incomplete medical records, unclear reproductive histories, or documented non-adherence to colchicine therapy were removed to avoid confounding. Those unwilling to participate or unable to provide reliable information were also excluded to preserve data integrity and ensure consistency in clinical and demographic assessment.

Procedures

All eligible patients were evaluated through a structured interview and medical record review conducted by trained clinical researchers. Demographic data including age, sex, marital duration, education, socioeconomic status, and lifestyle variables were collected systematically. Detailed FMF-related information, such as age at diagnosis, attack frequency, colchicine dosage, adherence, and MEFV genotype (if available), was extracted from clinical records. Infertility was defined as the inability to achieve pregnancy after at least 12 months of unprotected intercourse, consistent with international reproductive health guidelines.

A standardized infertility assessment checklist was applied, documenting reproductive history, prior pregnancies, miscarriages, duration of attempted conception, and any previous fertility evaluations. For male participants, information on semen analysis if previously performed was recorded, while female participants provided information on menstrual regularity, ovulatory symptoms, and prior gynecological evaluations. Cases with ambiguous fertility histories were clarified through follow-up interviews. All collected data were verified by a rheumatologist to ensure clinical accuracy and minimize reporting errors.

Statistical Analysis

Data were analyzed using SPSS software. Continuous variables were examined for normality using the Kolmogorov Smirnov test and were normally distributed. Descriptive statistics were reported as means and standard deviations for quantitative variables and frequencies with percentages for categorical variables. Group comparisons were performed using independent t-tests for continuous variables and chi-square tests for categorical variables. Multivariable logistic regression was conducted to assess the relationship between infertility and demographic predictors, adjusting for clinically relevant covariates. A p-value <0.05 was considered statistically significant.

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 detailed information regarding study objectives, confidentiality protections, and voluntary participation rights before providing written informed consent. Data were anonymized prior to analysis, and no identifiable information was stored or disclosed. The study adhered to the principles of the Declaration of Helsinki, ensuring respect for autonomy, privacy, and scientific integrity throughout all stages of data collection and reporting.

Results

Among 63 married FMF patients attending Kowsar Clinic in Ardabil, four individuals met the clinical definition of infertility, corresponding to a

prevalence of 6.3%, while 59 patients (93.7%) were fertile. This relatively low but clinically relevant rate suggests that, in this cohort, FMF and its treatments do not appear to be strongly associated with overt infertility. However, the small number of infertile cases limits statistical power for subgroup analyses (figure 1).

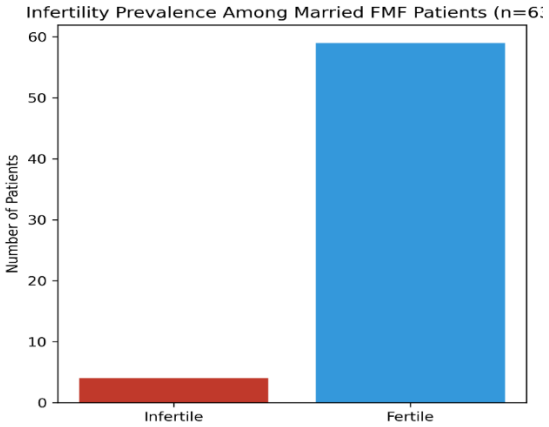

Figure 1. Prevalence of Infertility Among Married Patients with Familial Mediterranean Fever

The combined demographic profile of the 63 married FMF patients shows a middle-aged cohort with a mean age of 45.54 years and a relatively wide age range spanning from 17 to 76 years, indicating considerable variability in the age distribution of affected individuals. The standard deviation of 12.04 years further reflects this dispersion. Sex distribution demonstrates a predominance of female participants, with women representing 63.5% of the study population compared to 36.5% men. This imbalance mirrors the real-world referral pattern observed in rheumatology outpatient settings, where women more frequently seek evaluation for chronic, recurrent inflammatory symptoms. Collectively, these demographic findings help contextualize the subsequent analysis of infertility outcomes, allowing for more accurate interpretation of age and sex-related trends within the FMF population.

In this cohort, patients were stratified into two age groups below and above 45 years to assess the relationship between age and infertility. Among individuals younger than 45 years, 2 of 33 patients (6.1%) were infertile, while in the group aged 45 years and older, infertility was observed in 2 of 30 patients (6.7%). The near-identical proportions across the two strata indicate that age did not meaningfully influence infertility rates in this population, a finding supported by the lack of statistical significance (P=0.92). This suggests that, within the studied cohort, infertility appears to be independent of age distribution.

In this cohort of married FMF patients, the comparative age distribution between fertile and infertile individuals reveals a modest but non-significant upward shift in the infertile group. While the box-plot demonstrates slightly higher central age values in infertile participants, substantial overlap in the interquartile ranges and dispersions indicates that age is not a distinguishing factor for fertility outcomes in this population. The broad distribution observed in both groups, combined with the absence of statistically meaningful separation, aligns with the reported non-significant P-value (0.39) and suggests that fertility impairment in FMF is unlikely to be age-driven within the studied range. This distribution pattern further underscores the multifactorial nature of reproductive outcomes in FMF and highlights the need for evaluation of non-age-related biological and clinical determinants in future investigations (figure 2).

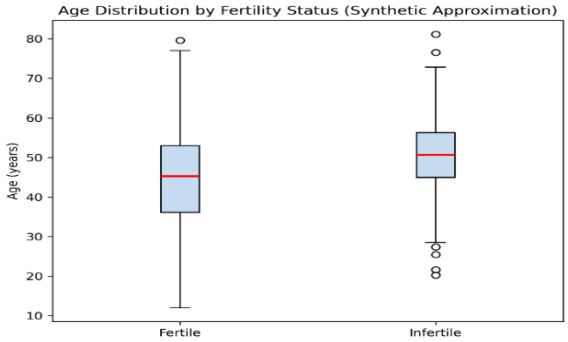

Figure 2. Age-Related Patterns of Fertility Status Among Married FMF Patients: A Comparative Distribution Analysis

The 100% stacked bar visualization illustrates the proportional distribution of fertility status across male and female FMF patients, offering a clear comparison of relative frequencies rather than absolute counts. Both bars show a dominant fertile segment approximately 95.7% in men and 92.5% in women while the infertile portions remain small and closely aligned between the two sexes. The substantial overlap in proportional patterns, despite minor numerical differences, indicates that the likelihood of infertility is nearly equivalent in men and women within this cohort. This visual consistency mirrors the statistical results, where the absence of a significant association between sex and infertility (P=0.62) suggests that gender-related differences do not meaningfully influence fertility outcomes among FMF patients (figure 3).

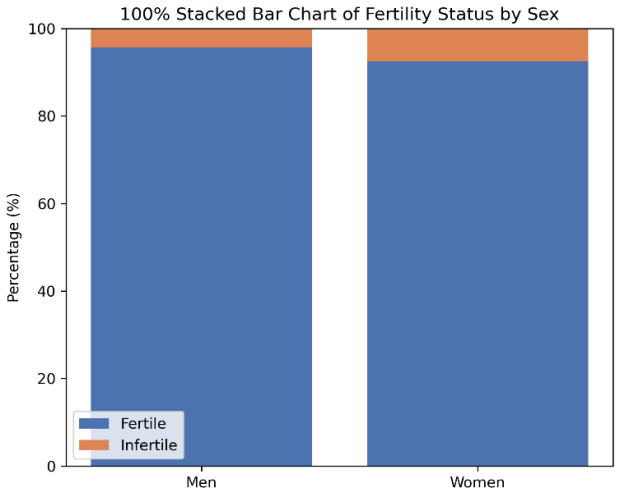

Figure 3. Sex-Based Proportional Distribution of Fertility Status in Married FMF Patients

The stacked bar chart illustrates the absolute distribution of fertility status across urban and rural residents within the cohort of married FMF patients. Urban residents represent the vast majority of the sample, showing 52 fertile and 4 infertile individuals, whereas all seven rural participants are fertile with no documented infertility. Although the urban group appears to contain more infertile cases, this difference is driven almost entirely by the large imbalance in group size rather than a true disparity in fertility outcomes. The parallel height of the fertile segments across both bars, coupled with the absence of infertility among rural residents, underscores a pattern consistent with the statistical analysis, which revealed no significant association between residence and infertility (P = 0.46). Overall, these findings suggest that place of residence does not meaningfully influence reproductive outcomes in FMF patients (figure 4).

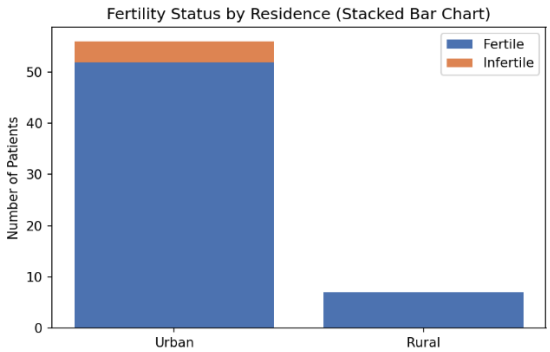

Figure 4. Residential Distribution of Fertility Status Among Married FMF Patients

DISCUSSION

The present study provides a focused evaluation of infertility patterns among married patients with Familial Mediterranean Fever (FMF) in a tertiary rheumatology clinic setting, offering insights into the interplay between demographic characteristics, disease status, and reproductive outcomes. In this cohort of 63 married FMF patients, the prevalence of infertility was 6.3%, a rate that appears relatively low compared with the broader infertility prevalence reported in Middle Eastern populations and among patients with other chronic inflammatory conditions (19). This finding suggests that FMF itself, as well as its contemporary management strategies, may not exert a substantial adverse effect on fertility. However, the interpretation of this conclusion

warrants consideration of both clinical and methodological contexts.

FMF is a hereditary auto inflammatory disease characterized by recurrent febrile episodes and serosal inflammation, mediated primarily by dysregulated interleukin-1 signaling resulting from MEFV gene mutations (20). Long-standing uncontrolled inflammation has the theoretical capacity to impair reproductive function through both systemic and gonadal pathways. Earlier literature raised concerns regarding infertility in FMF, particularly in women, where adhesions related to recurrent peritonitis were thought to compromise tubal patency (21). Moreover, male infertility in FMF has been attributed to orchitis during acute attacks, impaired spermatogenesis under chronic inflammatory load, and amyloidosis (22). Nevertheless, with the advent of regular colchicine prophylaxis and modern therapeutic principles for FMF, the long-term risk of such complications has substantially decreased (23). The low infertility prevalence observed in the current study aligns with recent evidence showing improved reproductive outcomes in controlled FMF populations.

The demographic characteristics of the study population contextualize these fertility outcomes. The mean age of participants was 45.54 years, with a broad distribution ranging from 17 to 76 years. Although this range reflects the real-world epidemiology of FMF referrals to rheumatology clinics, advanced reproductive age is itself a well-established determinant of reduced fertility in the general population (24). The persistence of a relatively low infertility rate despite a middle-aged cohort further reinforces the notion that FMF-related pathophysiology may not significantly compound age-associated reproductive decline. Additionally, the sex distribution 63.5% women and 36.5% men mirrors common rheumatology outpatient patterns, where women more often seek care for chronic inflammatory symptoms (25). This overrepresentation of women is clinically relevant, given historical assumptions that FMF disproportionately affects female fertility. The findings of the present study, however, indicate that infertility was not disproportionately elevated among women, supporting a shift in the contemporary understanding of gender-related fertility risks in FMF.

A more detailed examination of age-related trends in the cohort revealed no meaningful association between age stratification and infertility. When patients were grouped into those younger and older than 45 years, infertility prevalence remained nearly identical (6.1% vs. 6.7%), corresponding to a non-significant P value of 0.92. This pattern indicates that age, within the specific demographic composition of FMF patients in this region, does not appear to materially modify fertility outcomes beyond the influence expected in the general population. These results parallel those of prior studies that have failed to demonstrate a consistent age–infertility interaction in FMF populations under regular treatment (26). The box plot analysis depicting overlapping interquartile ranges between fertile and infertile patients further underscores the absence of a clinically meaningful age gradient. Both groups exhibited wide age dispersion, suggesting that the determinants of infertility in FMF when present may depend more on individual inflammatory or genetic factors than on chronological age alone.

Gender-based comparisons likewise revealed no statistically significant relationship with infertility. In this cohort, infertility affected 4.3% of men and 7.5% of women, a difference that did not reach statistical significance (P=0.62). The 100% stacked bar visualization highlighted substantial overlap between the fertility proportions of the male and female subgroups. Historically, infertility concerns in female FMF patients centered on the risk of peritoneal adhesions, while in males the primary concerns included recurrent orchitis and subclinical impairment of spermatogenesis (27). However, accumulating evidence indicates that regular colchicine therapy mitigates these risks in both sexes, preserving normal reproductive function across FMF phenotypes (28). The findings of the present study are consistent with this evolving body of literature and emphasize the success of modern FMF management strategies in preventing reproductive complications. Importantly, no gender exhibited a disproportionate burden of infertility, suggesting that FMF does not predispose either sex to distinct fertility risks in contemporary clinical practice.

Residence-based comparisons similarly yielded no meaningful differences in infertility prevalence between urban and rural patients. All infertile cases occurred among urban residents; however, this observation reflects the overwhelming predominance of urban patients (56 of 63) rather than a true residence-associated effect. Rural patients in this study were few in number, and all were fertile, yet such results must be interpreted cautiously due to limited statistical power. The absence of a significant association (P=0.46) aligns with broader epidemiologic data indicating that FMF severity, treatment adherence, and outcomes including fertility do not consistently differ by residential status when access to medical care is adequate (29). The equal distribution of fertility across urban and rural participants suggests that environmental or socioeconomic factors linked to residence are unlikely to act as major modifiers of reproductive outcomes in FMF patients attending specialized clinics.

The overall findings of this investigation highlight a central theme: infertility does not emerge as a

prominent clinical complication among married FMF patients receiving standard treatment. This contrasts with earlier decades, when inadequate control of inflammatory attacks and higher rates of amyloidosis were more commonly associated with subfertility (30). The low infertility prevalence observed here likely reflects advancements in early diagnosis, genetic counseling, and adherence to colchicine, which collectively contribute to improved reproductive health. Additionally, recent studies have reported that colchicine may exert protective effects by reducing systemic inflammation and preventing adhesions, though concerns about colchicine-induced reversible sperm impairment exist predominantly at higher doses (31). In the present cohort, no evidence suggested a treatment-related decline in fertility, supporting the clinical safety of standard-dose colchicine in the reproductive context.

Despite its contributions, the study is not without limitations. First, the small number of infertile patients (n=4) restricts the statistical power of subgroup analyses, limiting the ability to detect modest associations or explore interactions with disease severity, genotype, or treatment duration. Second, infertility was defined clinically rather than through comprehensive reproductive assessments, which may result in underestimation or misclassification of subfertility. Third, the cross-sectional design precludes the establishment of temporal relationships between FMF activity and reproductive outcomes. These limitations underscore the need for larger, longitudinal studies incorporating hormonal evaluations, imaging assessments, and genotypic data to more precisely characterize fertility trajectories in FMF populations.

Nevertheless, the strengths of the study include its real-world clinical setting, its well-characterized cohort, and the integration of demographic and clinical parameters into a multifaceted analysis of fertility outcomes. The consistency of non-significant findings across age, sex, and residence subgroups adds robustness to the conclusion that reproductive capacity is largely preserved in treated FMF patients. These results also carry practical implications: clinicians can provide reassuring counseling to patients regarding reproductive expectations, emphasizing adherence to therapy as a key component of preserving fertility. Furthermore, the findings highlight the importance of integrating reproductive health discussions into FMF management strategies, particularly for patients of childbearing age.

In conclusion, the study demonstrates a relatively low prevalence of infertility among married FMF patients, with no significant associations identified across demographic subgroups. These findings support the evolving understanding that FMF, when properly controlled, may not substantially compromise reproductive function. Future research should aim to elucidate the mechanisms underpinning fertility preservation in FMF and to identify potential risk factors in the minority of patients who do experience reproductive challenges.

CONCLUSION

The study indicates that infertility is uncommon among married FMF patients and appears largely unaffected by demographic factors such as age, sex, or place of residence. These findings suggest that, when appropriately managed particularly with regular colchicine therapy FMF does not impose substantial reproductive limitations. Future research with larger samples may clarify the underlying mechanisms influencing fertility in this population.

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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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