



## Original Article



## Prevalence and Risk Factors of Rheumatoid Arthritis among Women in Sahiwal District of Pakistan: A Cross-Sectional Study

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## ABSTRACT

Rheumatoid arthritis (RA) starts as a chronic autoimmune disease and gradually destroys joints and representing a systemic complication. **Objectives:** To identify the prevalence of RA and to investigate demographic, clinical, and lifestyle-related factors of the disease in the Sahiwal District of Pakistan. **Methods:** 288 patients who had known RA were recruited. Categories such as demographic, socioeconomic, and lifestyle were used to gather data using a structured questionnaire. There was also a review of clinical records and lab parameters such as ESR and anti-CCP. **Results:** The most prevalent seem to be between the ages of 43-48 years, with RA being 38.2% ultimate, which implies that middle age is the riskiest age group. A large percentage of respondents were experiencing coexisting polycystic ovary syndrome (36.1%), and almost half (48.6%) of the respondents had a family history of autoimmune disease. Over 52.8 percent of them were in low-income households. Although 87.5% were on RA treatment, more than half (54.2%) said they had no regular exercise, even though obesity was found in 43.4%. There were high rates of comorbidities, such as diabetes (39.2%), other autoimmune connective tissue disorders (53.1%). The level of inflammatory activity was high, and 82.6% had an elevated level of ESR, and 94.8% an abnormal result of anti-CCP. **Conclusions:** The findings are a confirmation of the multifactorial nature of RA, which is a combination of the impact of age, genetic factors, hormonal imbalance, lifestyle, and socioeconomic status.

## INTRODUCTION

Rheumatoid arthritis (RA) is a combination of various factors, which are mostly categorized as non-modifiable and modifiable factors. These factors are also known as modifiable personal factors, and some of them include tobacco, overweight, and nutrient-deficient diets. These are some of the intrinsic factors, such as age, sex (female), and genetic background/predisposition to RA. Other elements of vulnerability to RA are environmental, including socioeconomic status and infection exposures [1, 2]. The less socioeconomically developed or less

educated people are more vulnerable to RA, especially the antibody-positive type [3, 4]. RA diagnosis depends on clinical manifestation and laboratory tests in accordance with the classification criteria, which were developed by the European League against Rheumatism and American College of Rheumatology. They are categorized by systemic inflammation markers (i.e., high C-reactive protein or high sedimentation rate) and by RA symptoms: joint pain, swelling, and stiffness. Most often, joint damage is examined by means of imaging techniques, including X-ray



and MRI [5]. Rheumatoid arthritis nowadays is treated more with a combination of medication and supportive care. The supportive methods, including physical and occupational therapy, are used to enhance mobility and positively stimulate the work of joints and muscles. Pharmacologically, patients can be treated with a variety of options that include traditional anti-inflammatory medications and the disease-modifying antirheumatic drugs (DMARDs), or more recent agents, including Janus kinase (JAK) inhibitors, used to address the inflammatory pathways to control the symptoms and prevent or slow the progression of the disease [6]. Rheumatoid arthritis (RA) is not new in the world, and its increased prevalence in developed nations could be explained by genetic inclination as well as environment. The prevalence of RA among adults is approximately 1 per cent across the globe, and among women, the disease affects a significantly greater proportion, especially those in the 40 to 60-year-old category. The growing prevalence is likely to result in an aging population, changes in the epidemiology of lifestyle, and improved diagnosis [7]. Lifestyle change is a major component of prevention, and to a certain degree, there exists evidence that breastfeeding is protective. The overall treatment of RA is pegged on the application of the disease-modifying antirheumatic drugs (DMARDs), which selectively attack the underlying inflammatory processes. It seems that the first DMARDs (methotrexate and sulfasalazine) still seem to be the center around which the treatment plans keep rotating, and even the biologic and more modern synthetic agents (the Janus kinase (JAK) inhibitors) have proven to be effective in controlling the disease activity [8, 9]. Although significant progress has been made in efforts to treat rheumatoid arthritis (RA), high inconsistencies in defining treatment and response have still been reported by patients, thus making it worthwhile to understand the biological mechanisms involved to pursue individual management [10]. The more recent forms of treatment include biologic therapies such as interleukin-17 (IL-17) and interleukin-23 (IL-23) and targeted synthetic DMARDs such as Janus kinase inhibitors, which may be useful in the management of symptoms of RA and also in evaluations of the activity of RA [11]. Simultaneously, the improvement of genomics made it possible to identify the polymorphisms related to RA risk, including polymorphisms in human leukocyte antigen (HLA) and other genes related to immunology, which can enhance the risk prediction and provide the possibility of individualized treatment [12]. Even though rheumatoid arthritis is a well-known health issue in the global community, there has been little evidence on the same in Pakistan, particularly in semi-urban areas like Sahiwal. Earlier literature has largely

focused on the urban population, and there is a gap in the literature to comprehend how demographic, lifestyle, and socioeconomic status affect the disease patterns in smaller districts. Clinically, the need to fill this gap can facilitate the earlier diagnosis, risk assessment, and more effective management approaches that help address local needs. The recent years have been marked by the efforts aimed at the implementation of patient-centered care to include shared decision-making with patients in their management to meet the unique needs and preferences [11]. Although rheumatoid arthritis presents a heavy burden, new research and new treatments are being developed, and this will mark the beginning of the era of better care and disease outcome, and improved living [13, 14]. Complementary and alternative medicine (CAM), such as dietary supplements, massage, herbal preparations, and acupuncture, has also elicited interest in addition to standard treatment. Certain literature indicates that some CAM can be of assistance, although findings have been variable even within the same CAM approach, and patients are never forgetting to consult his/her health provider or primary provider before introducing a given approach, taking into account his/her risks and benefits [15]. Exercise is also part of RA treatment. For some people, individualized programs that include aerobic activity, strength exercises, or stretching can also be useful in relieving pain and enhancing normal functioning in everyday life. It is indicated that medical staff or exercise specialists are also to cooperate with the persons on how to properly organize safe activity [16]. Rheumatoid arthritis (RA) may severely affect the quality of life of a person, as it may not only be physical, but also psychological. As an example, RA patients will tend to experience anxiety and depression, which could exacerbate the disease. In line with these, holistic care through medical intervention and psychological assistance (e.g., promoting engagement with mental health specialists, or access to RA patient support groups) should be suggested [17]. The presence of RA in women is partially a complicated mix of hormonal changes in females, hereditary inclinations, and exposure to the environment. In the prevention strategies, they can be based on knowledge and alterations of certain hormonal components. In other countries like Pakistan, further studies are justified to comprehend the effects of socioeconomic factors, individual factors (e.g., demographic attributes like race, gender, and age), environmental exposures, dietary exposures, and treatment on the experiences and outcomes of people with RA. Despite the extensive research on rheumatoid arthritis, very few studies have been conducted to find the prevalence of the disease and the risk factors of the

disease among women in the Sahiwal region. These local trends should be understood to aid in the early detection of the disease and to aid intervention programs that have the potential to enhance patient care and outcomes within this community.

Rheumatoid arthritis (RA) is a chronic autoimmune disease that disproportionately affects women and poses a substantial public health burden due to its impact on physical function, quality of life, and socioeconomic productivity. Although global evidence highlights the role of demographic, hormonal, lifestyle, and socioeconomic factors in the development and progression of RA, there remains a paucity of region-specific data from Pakistan, particularly from semi-urban districts such as Sahiwal. Most existing national studies focus on urban populations or lack comprehensive evaluation of hormonal, metabolic, and lifestyle-related comorbidities among women. This gap limits the development of contextually relevant prevention and management strategies. Therefore, the present study aimed to determine the prevalence of rheumatoid arthritis among women in the Sahiwal District of Pakistan and to investigate associated demographic, socioeconomic, clinical, hormonal, and lifestyle-related risk factors to provide localized evidence for improved disease recognition and targeted interventions.

## METHODS

The cross-sectional study was conducted at several hospitals in the Sahiwal District. A convenience sampling method was used to recruit the participants. The research was conducted between April 27, 2024, and October 27, 2024. Permission to conduct the study was sought and given by the Medical Superintendent of District Headquarter Hospital, Sahiwal (Diary No. 2870). Informed consent was given by all participants in writing, and they were assured that their details would be kept confidential. A hierarchical questionnaire was employed in the study to study demographics, clinical symptoms, diagnostic evaluation, prevalence, and risk determinants of rheumatoid arthritis (RA) in the context of hormones and reproductive health. Ultrasound, MRI, and blood test evidence to be used in diagnosis were also examined. The preliminary results indicated that arthritis is rampant in the community, yet no detailed examination of the occurrence of RA and its risk factors had been done. Therefore, this research was conducted in order to determine the prevalence and possible contributory factors. A total of 288 subjects were enrolled in the study; the majority of them were enrolled in the study at hospitals located in Sahiwal, with the District Headquarters (DHQ) Hospital being the primary recruitment site. The recruitment plan was aimed at recruiting individuals with diverse medical and

demographic backgrounds and representative of the healthcare-seeking population in the local setting. Patients and their families were different in their clinical condition to reflect a picture of the community's health. The necessary size of the sample was calculated through the formula of cross-sectional studies:  $n = z^2 \cdot p(1-p) / d^2$ , where  $Z = 1.96$  critical value of a 95% interval,  $p =$  expected prevalence of rheumatoid arthritis (20% of the studies by the region), and  $d = 0.05$ , the level of error. Based on these values, a minimum of 246 participants was determined to be the minimum sample size. A total of 288 participants were eventually recruited to guarantee a robust study, as well as to take into consideration the potential non-response. The recruitment was done predominantly in Sahiwal, and the District Headquarters (DHQ) Hospital was the main location. The sample of this study entails female participants aged 25–60 years having moderate to severe rheumatoid arthritis and having abnormality due to hormonal factors. A particular population was chosen in order to measure the interplay between hormonal factors and RA and identify the particular issues the patients face in managing the disease. This population facilitated this research to narrow down and generate evidence that can be used to develop effective interventions that can be used in controlling RA and hormonal factors associated with it. Explicit exclusion criteria were used in the study to minimize bias and conflicting information. Women aged below 19 years and above 60 years were not included. Women who had a previous diagnosis of tuberculosis, who are hypersensitive to any medication, or who have any allergy were also excluded. Overall, individuals who had a previous infection diagnosis, including HIV or Hepatitis B or C, or whose immunity was compromised, were excluded without an indication of exclusion, since these factors can or cannot influence the conclusion of the research study. Certified raters, through a standardized and validated questionnaire, collected data [18]. The instrument consisted of four major parts: (1) Demographics, age, body mass index, family history of disease, and past medical history; (2) Socioeconomic Background, including the household setting, education, occupation, income, use of medication, and self-reported physical activity, and (3) Dietary Assessment, measuring the number of meals per day, eating habits, and consumption of fruits and vegetables; and (4) Laboratory Tests, which included clinical assessment of factors such as complete blood count, rheumatoid factor and erythrocyte sedimentation rate. This was a systematic method of collecting data that was complete and dependable to the study. The analysis of the data was done with SPSS version 25.0. A descriptive analysis was undertaken in order to summarize numerical variables, and cross-tabulations were generated to determine ratios of the dependent variable. Statistical

tests were performed through chi-square to find out statistical associations between independent variables (that can affect the dependent variable) with respect to the prevalence of rheumatoid arthritis. To further investigate the predictors that are linked to rheumatoid arthritis (RA), the binary logistic regression was used. The research design was aimed at developing the comprehension of aspects concerning the occurrence and treatment of rheumatoid arthritis among this specific group of people.

## RESULTS

The sample described the demographic and clinical features of the patients with the background of rheumatoid arthritis (RA). The factors that were included were polycystic ovary syndrome (PCOS), family history, socioeconomic status, medications, physical activity, menopause status, and obesity. The study of 288 patients showed that RA progressed significantly with age, and the highest prevalence rate was found in the group of patients aged between 43-48 years, showing 110 cases (38.2%), which depicts a risk presented in middle age. The highest prevalence was recorded in the cohort between 49-54 years of age and had 54 cases (18.8%), as the second-highest prevalence. Prevalence was lower in younger age groups, where the cohort of age between 37-42 years gave a threshold of 39 cases (13.5%), the cohort of age between 55 and 60; prevalence further declined in persons aged between 25-30 years, with total cases of 17 cases (5.9%). Cumulative percentages are based on percentage of the proportion of participants with RA at each age group, not on incidence over time. Furthermore, the researchers determined the prevalence of Polycystic Ovary Syndrome (PCOS) among the RA patients and concluded that 184 (63.9%) of them had no PCOS, and the other 104 (36.1%) had PCOS, which appears to be an interesting correlation between RA and PCOS. Also, 140 patients (48.6%) indicated that they had a family history of autoimmune diseases, whereas 148 patients (51.4%) did not. The given statistic stressed the relevance of the family in the case of RA because a considerable number of them can be predisposed to autoimmune diseases (Table 1).

**Table 1:** Frequency of RA According to Age, Frequency of PCOS, Family Disease History

Valid	Frequency (%)	Cumulative Percent
<b>Age</b>		
25-30	17 (5.9%)	5.9%
31-36	29 (10.1%)	16.0%
37-42	39 (13.5%)	29.5%
43-48	110 (38.2%)	67.7%
49-54	54 (18.8%)	86.5%
55-60	39 (13.5%)	100.0%
Total	288 (100.0%)	—

<b>Frequency of PCOS</b>		
No	184 (63.9%)	63.9%
Yes	104 (36.1%)	100.0%
Total	288 (100.0%)	—
<b>Family Disease History</b>		
No	148 (51.4%)	51.4%
Yes	140 (32.8%)	100.0%
Total	288 (100.0%)	—

The socioeconomic background of the patients revealed that most of them are within the low-income bracket, with 152 patients (52.8%). It might mean that socioeconomic conditions might contribute to the control and the course of RA, since a lower socioeconomic background is traditionally linked to the inability to access health care resources. A large proportion of patients with RA (252 or 87.5%) were using medication to manage their disease, with only 36 patients (12.5%) not doing so. This highlights the chronicity of RA and the need to have continued medical care in the majority of patients. Additional research will provide the data on physical activity, and it was found that 156 patients (54.2%) were sedentary, 93 patients (32.3%) were involved in limited physical activity, and only 39 (13.5%) people were moderately active in their physical activity. This implies that a high percentage of RA patients are possibly not exercising enough, which is essential to handle the symptoms and enhance quality of life. The status of the patients in terms of menopause indicates that 133 (46.2%) of the patients were postmenopausal and 155 (53.8%) were not. This data was pertinent because menopause hormone transformation may alter the course of RA and its intensity. Obesity has been a major issue among the RA patients, and 125 (43.4%) patients were found to be obese as opposed to 163 (56.6%) who were not. Obesity is prevalent in this population and may also make management of RA more challenging, as well as worse. The data analysis of the information obtained from RA patients showed some considerable data about the demographic features, health status, and lifestyle of the patients. Most of the RA patients are in a rural setting, where 178 (61.8%) of the respondents live in rural settings, with 110 (38.2%) in urban settings. The distribution of RA shows that there is a significant prevalence of this condition among people living in rural environments (Table 2).

**Table 2:** Frequency of Socioeconomic Status, Taking Medicine, Physical Activity, Post Menopause, Obesity, and Area of Residence with RA patients

Valid	Frequency (%)	Cumulative Percent
<b>Socioeconomic Status</b>		
High	46 (16%)	16.0%
Low	152 (52.8%)	68.8%
Middle	90 (31.3%)	100.0%

Total	288(100.0%)	–
<b>Taking Medicine</b>		
No	36(12.5%)	12.5%
Yes	252(87.5%)	100.0%
Total	288(100.0%)	–
<b>Physical Activity</b>		
Little	93(32.3%)	32.3%
Moderate	39(13.5%)	45.8%
Sedentary	156(54.2%)	100.0%
Total	288(100.0%)	–
<b>Post Menopause</b>		
No	155(53.8%)	53.8%
Yes	133(46.2%)	100.0%
Total	288(100.0%)	–
<b>Obesity</b>		
No	163(56.6%)	56.6%
Yes	125(43.4%)	100.0%
Total	288(100.0%)	–
<b>Area of Residence</b>		
Rural	178(61.8%)	61.8%
Urban	110(38.2%)	100.0%
Total	288(100.0%)	–

A huge percentage of 199 (69.1%) of the participants claimed that they are facing insomnia, and only 89(30.9) of them do not experience insomnia. This implies that one of the typical comorbidities in people with RA is insomnia. The dietary habits of the RA patients revealed that a big percentage of the sample population eats twice a day, with 143(49.7%) constituting the percentage. In the meantime, 57(19.8%) indicated that they ate once a day, and 88(30.6%) were eating thrice a day. Such a distribution implies inconsistency in the frequency of meals, which can influence the general well-being and treatment of RA. The correlation between RA and thyroid diseases showed that 212 (73.6%) of RA patients did not have a thyroid disease, whereas 76 (6.4%) had a thyroid disease. It indicates that although thyroid diseases do exist in a significant proportion of patients with RA, they are not the most common one. The incidence of diabetes is interesting among patients with RA. 175 (60.8%) of the respondents had no diabetes diagnosis as compared to 113(39.2%) who had a diagnosis of diabetes. This suggests that diabetes is a major prevalence in the RA patients. The infection rate of the autoimmune connective tissue disease (ACD) among the RA patients suggested that 153 (53.1%) of the respondents have ACD, and 135 (46.9%) do not. This brings out a significant overlap between ACD and RA (Table 3).

**Table 3:** Frequency of Insomnia, Taking Meals, Thyroid Disorder, Diabetes, and ACD in RA Patients

Valid	Frequency (%)	Cumulative Percent
<b>Insomnia</b>		
No	89(30.9%)	30.9%

Yes	199(69.1%)	100.0%
Total	288(100.0%)	–
<b>Taking Meals</b>		
1 Time	57(19.8%)	19.8%
2 Times	143(49.7%)	69.4%
3 Times	88(30.6%)	100.0%
Total	288(100.0%)	–
<b>Thyroid Disorder</b>		
No	212(73.6%)	73.6%
Yes	76(26.4%)	100.0%
Total	288(100.0%)	–
<b>Diabetes</b>		
No	175(60.8%)	60.8%
Yes	113(39.2%)	100.0%
Total	288(100.0%)	–
<b>ACD</b>		
No	135(46.9%)	46.9%
Yes	153(53.1%)	100.0%
Total	288(100.0%)	–

The given results of erythrocyte sedimentation rate (ESR) in the patients with RA demonstrate that an impressive 238 (82.6%) of them had high positive ESR, and 50 (17.4%) had moderate positive levels. This indicates that there is a high inflammatory reaction in most RA patients. Another important result is that the percentage of participants with abnormal anti-CCP levels is rather high (273, or 94.8%), which means that the correlation between such antibodies and RA is strong, and 15 (5.2%) participants have normal levels (Table 4).

**Table 4:** Frequency of ESR and Anti-CCP in RA Patients

Valid	Frequency (%)	Cumulative Percent
<b>ESR</b>		
High Positive	238(82.6%)	82.6%
Moderate Positive	50(17.4%)	100.0%
Total	288(100.0%)	–
<b>Anti-CCP</b>		
Abnormal	273(94.8%)	94.8%
Normal	15(5.2%)	100.0%
Total	288(100.0%)	–

## DISCUSSION

Rheumatoid arthritis (RA) is a long-term autoimmune disease, which is marked by inflammation of the joints resulting in serious morbidity and loss of quality of life. The purpose of the discussion is to place the results of the present study on the prevalence of RA and the risk factors related to it in the environment of the existing literature to indicate the epidemiological patterns, socioeconomic determinants, comorbidities, and implications of research on healthcare. It was significantly age-related, and rheumatoid arthritis (RA) was common, with the highest prevalence occurring between the ages of 43 and 48. The

same trends have been observed in Pakistan, where RA was observed mostly in middle-aged women. Research has indicated that RA was observed more in women compared to men across the globe, usually between the ages of 40-60 years as a result of hormonal and genetic effects [1]. In this study, it was indicated that RA was 29.5% at the age of 42 and at its highest by the age of 60, which was 100. Thus, age is a significant factor that determines the disease onset and outcome. The financial condition of the RA patients in Sahiwal identified that the majority of the patients belonged to low-income families. It is common to associate the socioeconomic position with ill health and inaccessibility to health services [3]. Health infrastructure has its threshold in Pakistan, and the patients who have limited resources will find it harder to deal with the conditions that are related to RA. The majority of the participants were generally poorly educated, and this could be a constraint on their knowledge of the disease and the capacity to comply with medications. Although 87.5 percent of the participants had been taking medicine, more than half (54.2%) respondents said they were of a sedentary lifestyle, indicating how lacking awareness of the disease and self-management is. The comorbid conditions among patients in the study were also of great burden, with 43.4, 39.2, and 69.1 being obesity, diabetes, and insomnia, respectively. The current literature has also shown similar tendencies in which it is possible to complicate treatment and thus impair health outcomes when multiple co-existing conditions are involved [11]. The insomnia prevalence rates are also additional examples of why the integrative care approaches should be considered to cover both physical care and mental care. Hormonal factors - especially in women were also checked in connection with RA. A high percentage of RA patients were stated to experience polycystic ovary syndrome (36.1%), and therefore, there might be a relation between hormonal factors and autoimmune diseases. Previous studies have shown that hormonal changes affect immune performance and predispose to autoimmune or autoimmune diseases such as RA [7]. These are also key factors to include hormonal wellness in RA treatment, especially among women. The studies also indicated that there was an urgent demand for healthcare provision tailored to the region, in this case, Sahiwal, Pakistan, and other regions that are located in a similar location. RA and other risk factors are also a huge burden, and the healthcare system should note the need to evaluate the disease timely, the comprehensive method of care in the disease and the patient, and the requirements linked to the socioeconomic and mental effects of the disease, but not only the physical effects. Education and awareness programs may be an important part of making patients more adherent to the treatment process in order to improve the quality of life of people with

rheumatoid arthritis (RA) [20]. The noted relationships between rheumatoid arthritis and PCOS, menopause, obesity, SES, diabetes, and insomnia are descriptive. These cannot be taken as causal relationships because no regression analysis was done to ascertain. These relationships have to be verified in future analytical research. The results of our studies on the relationship between RA and age, gender, and hormonal factors agree with those done previously. As an example, Koller-Smith *et al.* and Bullock *et al.* found women to be higher in midlife, which is in line with the fact that the majority of cases were identified in women aged 40-55 years in our case [1, 2]. On the same note, our study findings that found an obesity and RA relationship are similar to Tanaka's findings, although our group association was stronger, perhaps because of dietary and lifestyle factors within the region [9]. Nevertheless, the findings of our study were in contrast to those of Tobone *et al.* who discussed the effects of environmental triggers, because there was no significant effect of SES on the prevalence of RA in our study, implying that local population characteristics might alter the known risk factors [3]. These comparisons draw similarities and differences, and it is important to have context-specific studies that would inform prevention and management strategies. The results are descriptive, and they point to the noticeable trends in the population of the study. The only inferential analysis that was not done included logistic regression and others; therefore, associations are supposed to be taken with care. Multivariate models should be used in future studies to establish the independent and causal influence of these factors.

This study has certain limitations that should be acknowledged. The cross-sectional design restricts causal inference between identified risk factors and the development or progression of rheumatoid arthritis. The use of convenience sampling and recruitment from hospital-based settings may limit the generalizability of findings to the wider community, including undiagnosed or untreated individuals. Additionally, the absence of multivariate regression analysis limits the ability to determine independent predictors of RA, and reliance on self-reported data may introduce recall or reporting bias. Future studies should employ longitudinal and community-based designs with probability sampling to better assess causal relationships and disease progression. Incorporating multivariate analytical models and exploring genetic, environmental, and psychosocial determinants would further strengthen understanding. Such research could support the development of targeted screening, early intervention, and comprehensive management programs tailored to women in resource-limited and semi-urban settings of Pakistan.

## CONCLUSIONS

The findings of this study indicate that the occurrence rate of rheumatoid arthritis (RA) in females residing in Sahiwal, Pakistan, is very high, and the most vulnerable group is middle-aged individuals, with a range of 43 to 48 years. The research results also showed that age, socioeconomic disadvantage, less education, and sedentary lifestyle are the risk factors that are linked to RA, as well as the fact that the environmental and personal variables are at times confounding in the development and progression of the disease. Similarly, common obesity, diabetes, insomnia, and other comorbidities contributed specifically to the difficulty in managing the disease and reminding them of their necessity of comprehensive care. The role of hormones, especially polycystic ovary syndrome (PCOS), was observed among a significant proportion of patients, and consequently, there has been speculation as to the link that exists between the endocrine and the autoimmune functions.

## Authors' Contribution

Conceptualization: SA

Methodology: KR, MAN, J, A, TI

Formal analysis: MS

Writing and Drafting: AI, TI

Review and Editing: SA, KR, MAN, J, A, TI, MS, AI

All authors approved the final manuscript and take responsibility for the integrity of the work.

## Conflicts of Interest

The authors declare no conflict of interest.

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