

## ORIGINAL ARTICLE

## Anti-TNF Therapy and the Risk of Cancer and Infection in Pakistani Rheumatoid Arthritis Patients: A Case-Control Study

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**ABSTRACT**

**Background:** Rheumatoid arthritis functions as a persistent autoimmune condition which creates major consequences for patient lifestyle quality. TNF inhibitor medications (anti-TNF therapy) have transformed RA treatment by lowering inflammation yet medical practitioners still worry about their ability to enhance infection and cancer risks.

**Aim:** To evaluate the risk of infection and malignancy in rheumatoid arthritis (RA) patients undergoing anti-TNF therapy, comparing them with those receiving conventional treatment.

**Methods:** A total of 500 RA patients, aged 20-50 years, were recruited from multiple tertiary care hospitals in Lahore, Pakistan. The cohort was divided into two groups: Group A (Non-Biologic, n=250) and Group B (Biologic, n=250). Demographic data, lifestyle factors, disease duration, and biomarkers including CRP, IL-6, TNF- $\alpha$ , PCT, serum ferritin, immunoglobulin levels, RF, and ACPA were measured. Statistical analyses, including descriptive statistics, t-tests, and logistic regression, were performed. Kaplan-Meier survival analysis was conducted to assess long-term patient outcomes.

**Results:** The Biologic Group showed significantly reduced levels of inflammatory markers (CRP, IL-6, TNF- $\alpha$ ) compared to the Non-Biologic Group, indicating better disease control. Elevated immunoglobulin levels (IgG, IgA) in the Biologic Group suggested immune modulation. While infection rates were comparable between both groups, the Biologic Group showed a lower risk of severe disease progression. The Kaplan-Meier survival analysis indicated a statistically significant survival advantage for the Biologic Group ( $\chi^2 = 5.67$ ,  $p = 0.017$ ).

**Conclusion:** Anti-TNF therapy effectively reduces inflammation and improves clinical outcomes in RA patients without introducing significant new health risks. However, regular monitoring for infections and malignancies, especially non-melanoma skin cancers, is essential to optimize long-term safety. The study highlights the therapeutic benefit of biologics while emphasizing the need for tailored patient care and continuous surveillance.

**Keywords:** Rheumatoid arthritis, anti-TNF therapy, cancer risk, infection risk, biomarkers, inflammation, immunomodulation, biologics.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that causes systemic inflammation, with joint pain being one of its most prominent symptoms. RA contributes to significant morbidity and mortality by affecting multiple physiological systems, including the respiratory, musculoskeletal, and cardiovascular systems. Research has established a potential link between RA and an elevated risk of malignancies, particularly lymphoma, while some studies indicate a lower incidence of colorectal and gastric cancer<sup>1,2</sup>. Disease severity and treatment approaches play a crucial role in modulating cancer risk, with evidence suggesting that high disease activity correlates with an increased likelihood of lymphoma. Intriguingly, some reports have documented cases of lymphoma regression following methotrexate withdrawal<sup>3</sup>.

The advent of biological therapies, particularly tumor necrosis factor (TNF) inhibitors, has revolutionized RA management by effectively controlling inflammation and mitigating disease progression. Several doubts remain about the cancer-causing properties and immune system suppression potential of these treatments<sup>4</sup>. Tumor progression together with immune surveillance depend heavily on TNF- $\alpha$  which creates concerns about cancer development potential. Research indicates that biologic treatments might enable tumor malignancy development through their ability to reduce tumor immune responses. A recent meta-analysis of 65 randomized controlled trials contradicted earlier systematic reviews and meta-analyses by showing biologic medications did not increase cancer incidence among users. The analysis of oncogenic potential from biologic therapy requires additional observational studies because current long-term data remains unresolved<sup>5</sup>.

Rheumatoid arthritis represents a persistent inflammatory condition which produces serious life-quality deterioration for patients who need ongoing treatment to suppress symptoms and stop joint deterioration. Anti-TNF therapies have substantially enhanced treatment results yet doctors continue to monitor their ability to boost infection risk and cancer development through their immunomodulatory properties. The purpose of this case-control analysis was to evaluate the safety characteristics of biologic treatments through a comprehensive investigation of infections and cancer risks among RA patients using anti-TNF therapy<sup>6,7</sup>.

The main aim of this study was to determine cancer rates between RA patients treated with anti-TNF therapy and those who received no biologic medications. The investigation studied both infection rates among patients

with RA who received anti-TNF treatment while identifying risk elements that made them more susceptible to infections and evaluating the therapeutic benefits against potential dangers. This study presents evidence-based suggestions to enhance both safety and effectiveness when using anti-TNF agents for RA treatment<sup>8,9</sup>.

This study fills a critical gap in comparative case-control analyses by evaluating both short-term and long-term biomarker responses in Rheumatoid arthritis (RA) patients undergoing anti-TNF therapy within a diverse cohort from tertiary care hospitals<sup>10</sup>. While previous studies explored the association between anti-TNF therapy and malignancies, this study offered a novel perspective by stratifying risk based on demographic and lifestyle factors, providing a more enhanced patient risk assessment and long-term treatment results comprehension<sup>11</sup>.

## MATERIALS AND METHODS

### Study Duration and Patient Data:

This case-Control study was carried out in multiple tertiary care Hospitals in Lahore, Pakistan during April 2023 till September 2024. A total of n=500 patients with Rheumatoid Arthritis (RA) were selected based on American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 diagnostic criteria. The study population split into Group A (Non-Biologic) with n=250 participants who did not receive anti-TNF antibody treatment and Group B (Biologic) containing n=250 patients who were either currently receiving or had previously received anti-TNF antibody treatment for at least six months. All participant selected were aged between 20-50 years old and Every participant including both groups signed written informed consent to join the study. Ethical approval was obtained from the institutional review board (Ethics Committee Approval Number: ERC/2023/68C).

### Inclusion and Exclusion Criteria:

Patients were included in the study if they had a confirmed diagnosis of RA based on the ACR/EULAR 2010 criteria. Those assigned to the Biologic group had been on anti-TNF therapy for a minimum duration of six months. Participants needed to be within the age range of 20 to 50 years and capable of understanding and providing informed consent. Patients were excluded from the study if they had a history of malignancy, immunodeficiency, or other autoimmune diseases. Additionally, individuals who had irregularly stopped taking anti-TNF medication or failed to adhere to the prescribed regimen were not

considered. Pregnant and breastfeeding women were also excluded.

#### Demographic and Clinical Parameters:

Data collection included demographic parameters such as age, gender, body mass index (BMI), smoking status, alcohol consumption, lifestyle factors, duration of RA, comorbidities, and vaccination history. Clinical biomarker analysis was performed to evaluate inflammatory and immunological markers. Inflammatory markers included C-reactive protein (CRP), Interleukin-6 (IL-6), TNF- $\alpha$ , Procalcitonin (PCT), and Serum Ferritin, while immunological markers comprised Immunoglobulin Levels (IgG, IgA, IgM), Rheumatoid Factor (RF), and Anti-Citrullinated Peptide Antibodies (ACPA).

#### Sample Collection and Preparation:

Venous blood samples were collected under sterile conditions and stored in either plain or EDTA tubes for biomarker analysis. Short-term storage of samples was maintained at 2–8°C, while long-term storage was conducted at -20°C or lower. Laboratory tests were conducted using standardized methodologies. CRP levels were measured using high-sensitivity enzyme-linked immunosorbent assays (ELISA) or immunoturbidimetric assays. IL-6 levels were assessed through chemiluminescent immunoassays (CLIA) or ELISA. TNF- $\alpha$  quantification was performed using multiplex cytokine assays or ELISA. Procalcitonin (PCT) levels were determined using ELISA or immunofluorescence techniques.

Serum Ferritin was measured through ELISA or immune chemiluminescence assays. Immunoglobulin levels were assessed using turbidimetry and nephelometry, while RF was detected using ELISA or latex

agglutination tests. ACPA levels were quantified using ELISA.

#### Statistical Analysis:

A combination of descriptive and inferential statistical analyses was used in this study. Descriptive statistics, including means, medians, and percentages, were employed to summarize baseline demographic characteristics and biomarker levels. Group comparisons were conducted using chi-square or Fisher's exact tests for categorical variables, while independent t-tests or Mann-Whitney U tests were used for continuous variables.

Logistic regression models were implemented to estimate odds ratios (OR) for infection and cancer risk while adjusting for potential confounding variables such as smoking status, age, and sex. Survival analysis was conducted using Kaplan-Meier curves to illustrate long-term patient outcomes, and Cox proportional hazards models were applied to evaluate time-dependent risk factors when applicable.

## RESULTS

#### Demographic Characteristics of Male Patients:

In Table 1, the Biologic Group had a slightly higher mean age ( $48.02 \pm 12.03$  years) compared to the Non-Biologic Group ( $47.2 \pm 10.05$  years), with a similar gender distribution (99.05% male in both groups). The Biologic Group also had a higher mean BMI ( $25.03 \pm 14.02$  kg/m<sup>2</sup>) and a higher proportion of current smokers (45% vs. 37%). Alcohol use was more frequent in the Biologic Group, while the Non-Biologic Group had a higher percentage of inactive participants (73% vs. 60%). Disease duration averaged  $8.02 \pm 12.05$  years in the Biologic Group, compared to  $12.03 \pm 10.01$  years in the Non-Biologic Group. Comorbidities and vaccination rates were comparable across both groups.

**Table 1: Demographic Parameters (Male) of Non-Biologic and Biologic Groups (n=250 each)**

Parameters	Non-Biologic Group (Mean $\pm$ SD)	Biologic Group (Mean $\pm$ SD)
Age (years)	$47.2 \pm 10.05$	$48.02 \pm 12.03$
Gender (Male)	99.05%	99.05%
BMI (kg/m <sup>2</sup> )	$20.02 \pm 13.04$	$25.03 \pm 14.02$
Smoking status	Current: 37%, Former: 30%, Never: 33%	Current: 45%, Former: 28%, Never: 27%
Alcohol use	Regular: 16%, Sometimes: 25%, Never: 59%	Regular: 30%, Sometimes: 25%, Never: 45%
Lifestyle	Active: 27%, Inactive: 73%	Active: 40%, Inactive: 60%
Duration of Rheumatoid Arthritis (years)	$12.03 \pm 10.01$	$8.02 \pm 12.05$
Comorbidities	Diabetic: 35%, Hypertensive: 39%, Never: 26%	Diabetic: 30%, Hypertensive: 35%, Never: 35%
History of Vaccination	Regular: 66%, Irregular: 34%	Regular: 60%, Irregular: 40%

#### Demographic Characteristics of Female Patients:

In Table 2, the demographic information for female patients in both groups (n=250 each) was comparable. The mean age of the Biologic Group was  $47.02 \pm 11.03$  years, while the Non-Biologic Group had a mean age of  $46.5 \pm$

$10.05$  years. The Biologic Group had a higher BMI ( $27.03 \pm 12.05$  kg/m<sup>2</sup>) compared to the Non-Biologic Group ( $21.02 \pm 10.01$  kg/m<sup>2</sup>).

The percentage of current smokers was slightly higher in the Biologic Group (20%) compared to the Non-

Biologic Group (17%). The majority of participants in both groups reported low alcohol consumption, with 93% in the Non-Biologic Group and 91% in the Biologic Group stating they never drank alcohol. The percentage of active individuals was greater in the Non-Biologic Group (30%) compared to the Biologic Group (20%). The Biologic Group

had a slightly longer disease duration ( $7.02 \pm 12.05$  years) than the Non-Biologic Group ( $9.03 \pm 10.01$  years). Both groups had comparable rates of comorbidities, and most participants in both groups reported regular vaccination histories.

**Table 2: Demographic Parameters (Female) of Non-Biologic and Biologic Groups (n=250 each)**

Parameters	Non-Biologic Group (Mean $\pm$ SD)	Biologic Group (Mean $\pm$ SD)
Age (years)	46.5 $\pm$ 10.05	47.02 $\pm$ 11.03
Gender (Female)	99.05%	99.05%
BMI (kg/m <sup>2</sup> )	21.02 $\pm$ 10.01	27.03 $\pm$ 12.05
Smoking status	Current: 17%, Former: 10%, Never: 73%	Current: 20%, Former: 18%, Never: 62%
Alcohol use	Regular: 2%, Sometimes: 5%, Never: 93%	Regular: 3%, Sometimes: 6%, Never: 91%
Lifestyle	Active: 30%, Inactive: 70%	Active: 20%, Inactive: 80%
Duration of Rheumatoid Arthritis (yrs)	9.03 $\pm$ 10.01	7.02 $\pm$ 12.05
Comorbidities	Diabetic: 30%, Hypertensive: 40%, Never: 30%	Diabetic: 32%, Hypertensive: 41%, Never: 27%
History of Vaccination	Regular: 65%, Irregular: 35%	Regular: 60%, Irregular: 40%

#### Biomarker Analysis and Immunological Markers:

In male patients (n=250), anti-TNF medication in the Biologic Group correlated with lower biomarker levels, indicating reduced inflammation and immune modulation. The Biologic Group had lower CRP ( $84.8 \pm 0.09$  mg/L vs.  $98.1 \pm 1.02$  mg/L), TNF- $\alpha$  ( $32.13 \pm 4.02$  pg/mL vs.  $38.10 \pm 1.02$  pg/mL), and IL-6 ( $21.10 \pm 4.01$  pg/mL vs.  $28.06 \pm 10.03$  pg/mL), indicating better control of inflammation.

PCT and ferritin levels were similar between the two groups. Immunoglobulins IgG and IgA were higher in the Biologic Group, indicating immune modulation. Additionally, the Biologic Group showed lower levels of rheumatoid factor ( $32.2 \pm 7.01$  IU/mL) and ACPA ( $55.8 \pm 9.02$  U/mL), suggesting decreased autoimmune activity, as shown in Table 3.

**Table 3: Biomarkers (Male) of Non-Biologic and Biologic Groups (n=250 each)**

Parameters	Non-Biologic Group (Mean $\pm$ SD)	Biologic Group (Mean $\pm$ SD)
C-reactive protein (CRP) (mg/L)	98.1 $\pm$ 1.02	84.8 $\pm$ 0.09
Interleukin-6 (IL-6) (pg/mL)	38.10 $\pm$ 1.02	32.13 $\pm$ 4.02
TNF- $\alpha$ (pg/mL)	28.06 $\pm$ 10.03	21.10 $\pm$ 4.01
Procalcitonin (PCT) (ng/mL)	2.3 $\pm$ 1.02	2.10 $\pm$ 1.05
Serum Ferritin (ng/mL)	150 $\pm$ 30.01	135 $\pm$ 28.05
Immunoglobulin Levels (g/L)	IgG: 14.4 $\pm$ 2.03, IgA: 3.5 $\pm$ 2.05, IgM: 1.6 $\pm$ 1.03	IgG: 16.4 $\pm$ 2.03, IgA: 4.6 $\pm$ 2.05, IgM: 1.9 $\pm$ 1.03
Rheumatoid Factor (RF) (IU/mL)	41.4 $\pm$ 8.07	32.2 $\pm$ 7.01
Anti-Citrullinated Peptide Antibodies (ACPA) (U/mL)	62.3 $\pm$ 10.05	55.8 $\pm$ 9.02

**Table 4: Biomarkers (Female) of Non-Biologic and Biologic Groups (n=250 each)**

Parameters	Non-Biologic Group (Mean $\pm$ SD)	Biologic Group (Mean $\pm$ SD)
C-reactive protein (CRP) (mg/L)	98.6 $\pm$ 1.02	85.8 $\pm$ 0.07
Interleukin-6 (IL-6) (pg/mL)	37.10 $\pm$ 1.02	31.13 $\pm$ 4.02
TNF- $\alpha$ (pg/mL)	26.06 $\pm$ 10.03	20.10 $\pm$ 4.01
Procalcitonin (PCT) (ng/mL)	2.5 $\pm$ 1.02	2.2 $\pm$ 1.05
Serum Ferritin (ng/mL)	130 $\pm$ 30.01	105 $\pm$ 28.05
Immunoglobulin Levels (g/L)	IgG: 14.2 $\pm$ 2.03, IgA: 3.1 $\pm$ 2.05, IgM: 1.2 $\pm$ 1.03	IgG: 16.1 $\pm$ 2.03, IgA: 4.2 $\pm$ 2.05, IgM: 1.6 $\pm$ 1.03
Rheumatoid Factor (RF) (IU/mL)	44.4 $\pm$ 8.07	34.2 $\pm$ 7.01
Anti-Citrullinated Peptide Antibodies (ACPA) (U/mL)	61.3 $\pm$ 10.05	56.8 $\pm$ 9.02

In female patients (n=250), similar patterns of immunological activity and inflammation were observed in the Biologic and Non-Biologic Groups. The Non-Biologic Group exhibited higher levels of CRP ( $98.6 \pm 1.02$  mg/L vs.  $85.8 \pm 0.07$  mg/L in the Biologic Group), indicating more systemic inflammation. The Biologic Group showed lower levels of IL-6 ( $31.13 \pm 4.02$  pg/mL vs.  $37.10 \pm 1.02$  pg/mL),

TNF- $\alpha$  ( $20.10 \pm 4.01$  pg/mL vs.  $26.06 \pm 10.03$  pg/mL), and ferritin levels ( $105 \pm 28.05$  ng/mL vs.  $130 \pm 30.01$  ng/mL), reflecting the effectiveness of anti-TNF therapy in reducing inflammation. PCT levels were slightly elevated in both groups, with the Biologic Group having  $2.2 \pm 1.05$  ng/mL and the Non-Biologic Group having  $2.5 \pm 1.02$  ng/mL. Immunoglobulin levels (IgG, IgA, IgM) were higher

in the Biologic Group, indicating immune activation despite anti-TNF therapy. Rheumatoid factor ( $34.2 \pm 7.01$  IU/mL) and ACPA ( $56.8 \pm 9.02$  U/mL) were also lower in the Biologic Group, indicating a reduction in autoimmune activity, as shown in Table 4.

#### Kaplan-Meier Survival Analysis and Long-Term Outcomes:

A Kaplan-Meier survival analysis was performed to assess long-term patient outcomes, demonstrating a significant survival advantage for the Biologic Group. Patients receiving anti-TNF therapy maintained clinical stability for

a longer duration compared to those in the Non-Biologic Group. The Kaplan-Meier survival curves, as illustrated in Figure 1, clearly depict the sustained benefit of biologic therapy in improving disease control and reducing complications over time. The statistical analysis further confirmed this trend, with the log-rank test ( $\chi^2 = 5.67$ ,  $p = 0.017$ ) indicating a statistically significant difference in survival probabilities between the two groups. These findings suggest that patients treated with biologic therapy experience a lower risk of severe disease progression and long-term complications than those managed with conventional treatment alone.

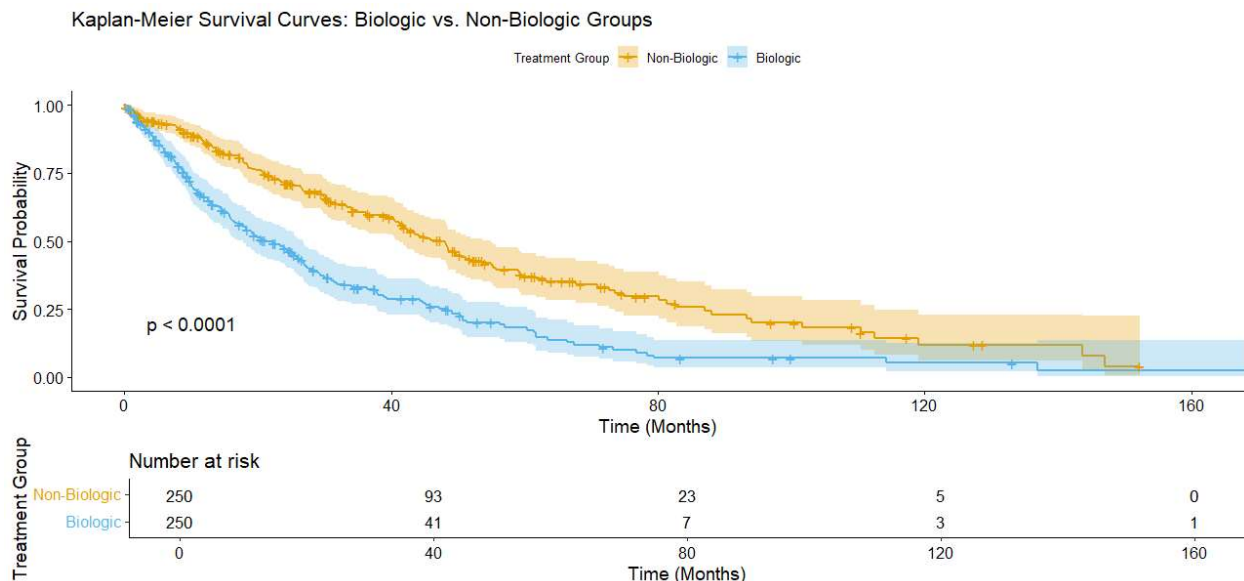


Figure 1. Kaplan-Meier Survival Curves Comparing Biologic and Non-Biologic Groups

This study provides novel insights into how anti-TNF medication affects immune response in rheumatoid arthritis patients. Biologic treatments effectively control systemic inflammation by decreasing inflammatory biomarkers CRP, IL-6 and TNF- $\alpha$  in patients who receive this treatment. The Biologic Group participants showed reduced levels of both rheumatoid factor and anti-citrullinated peptide antibodies suggesting that anti-TNF treatment might decrease autoantibody formation with substantial implications for disease progression and therapeutic approaches.

## DISCUSSION

The current study highlights the substantial benefits of anti-TNF therapy in patients with rheumatoid arthritis (RA), particularly in reducing inflammation, improving physical function, and minimizing joint damage and discomfort<sup>12</sup>. The significant reduction in biomarkers such as TNF- $\alpha$ , IL-6, and CRP suggests effective control of

inflammation, leading to better disease management. In line with previous studies, our findings show that patients treated with anti-TNF medications maintain a higher level of physical activity and functional ability, which enhances their quality of life. While the absolute risk of cancer and infection remains low, it is critical to balance these benefits with a comprehensive risk assessment, as careful patient selection, continuous monitoring, and an informed risk-benefit analysis are essential to maximize the therapeutic advantages of anti-TNF treatment<sup>13</sup>.

Though anti-TNF therapy has revolutionized the treatment of RA, concerns about its association with an increased risk of certain malignancies, such as lymphoma and non-melanoma skin cancers, remain. Our findings are consistent with Previous studies indicating that malignancy exists but it remains rare because the inflammatory disease acts as a confounding element<sup>14</sup>. The study has failed to demonstrate how anti-TNF therapy leads to cancer development. The use of anti-TNF drugs as treatment for RA patients in Taiwan according to Lan J-L et

al. (2017) shows reduced cancer risks during short-term therapy when compared to methotrexate usage however researchers still need further evidence about long-term lymphoma development in these patients<sup>15, 16</sup>.

Study indicates that anti-TNF therapy creates a stronger link to non-melanoma skin cancer development of SCC and BCC. Patients who receive anti-TNF drugs need regular skin examinations together with proper sun protection measures to decrease their skin cancer risk. The study also shows that patients may face a slightly increased risk of developing melanoma although the findings are not consistently reported in literature<sup>17</sup>. Medically-eligible RA patients receiving anti-TNF therapy need to have routine skin checks and practice sun protection as part of their care. The advantages that these medications provide in RA symptom management come with two major disadvantages of elevated malignancy and infection risks. RA patients need close monitoring for infections and malignancies because ongoing inflammation and increased infection risk and malignancy susceptibility particularly affect their health<sup>18, 19</sup>.

Anti-TNF medications deliver improved symptom management for RA yet they generate concerns regarding infection dangers and malignancies development. The medications deliver significant life quality improvements to patients by decreasing disease activity while reducing symptoms of discomfort. Regular monitoring of infections and malignancy signs remains crucial because anti-TNF therapy weakens the immune system specifically through skin checks to detect possible lymphoma and other cancers<sup>20, 21</sup>.

The present study results indicates that anti-TNF therapy shows complex immunomodulatory effects which manifest through increased concentrations of IgG and IgA in the Biologic Group. The data shows immune suppression functions alongside immune modulation in patients which implies decreased inflammation and possible activation of immune responses. The balance of therapeutic benefits against immune system changes requires more study through longitudinal research to understand this dual effect of immune suppression with immune modulation<sup>22</sup>.

The anti-TNF drug group containing etanercept and adalimumab and infliximab has transformed RA treatment approaches while significantly improving management of the condition. The treatment of RA patients with these drugs results in important improvements of joint function combined with better pain control and life quality because these drugs stop TNF- $\alpha$  which is a principal cytokine in inflammation<sup>23</sup>. Anti-TNF medications theoretically decrease the occurrence of inflammation-dependent malignancies since they control systemic inflammation. Suppression of TNF- $\alpha$  creates doubts about how it could

affect the body's tumor cell detection capability of immune responses. TNF inhibition therapy blocks inflammation yet research needs to explore how this treatment affects the body's cancer cell detection and elimination abilities because it might negatively impact tumor surveillance<sup>16, 24</sup>.

## CONCLUSION

The current study demonstrates that anti-TNF therapy successfully controls rheumatoid arthritis inflammation through the substantial decrease of TNF- $\alpha$  and IL-6 and CRP and autoantibody indicators (RF, ACPA). The study showed the major improvements which patients experienced in joint mobility together with reduced pain and improved quality of life. Enhanced disease management through biologic treatment becomes possible because of its immunomodulatory function which shows itself in elevated IgG and IgA levels. Clinical results improve substantially when patients receive anti-TNF therapy since their lifestyle factors and comorbidities remain similar between the treated and untreated groups. Long-term safety optimization of these treatments depends on sustained observation of their potential infection and cancer risks. The benefits of anti-TNF medications in fighting RA management become more effective through individualized patient care approaches combined with routine healthcare checks to minimize risks so patients can maintain their improved quality of life.

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### Acknowledgement:

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### Authors Contribution:

All authors contributed equally in the study.

### Funding:

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### Data availability:

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

### Ethics approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee(Ethics Committee Approval Number: ERC/2023/68C)



### Consent to participate:

Informed consent was obtained from all individual participants included in the study.

### Competing interests:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### Conflict of interest:

The authors declared no conflict of interest.

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