Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

The immunological markers in patients infected with typhoid fever and rheumatoid arthritis, and bacteria sensitivity

M. I. Al-Wakeel*, Z. N. Al-Laith*, M. A. Khalaf*, O. A. Mohsein**

**University of Kerbala, Kerbala, Iraq*
***Thi-Qar Health Directorate, Al Habbobi Teaching Hospital, Thi-Qar, Iraq*

Article info

Received 08.05.2025
Received in revised form 02.06.2025
Accepted 11.07.2025

College of Sciences, Department of Biology, University of Kerbala, Kerbala, Iraq. E-mail: mays.i@uokerbala.edu.iq, zainab.naser@uokerbala.edu.iq, maedah.a@uokerbala.edu.iq

Thi-Qar Health Directorate, Al Habbobi Teaching Hospital, Thi-Qar, Iraq. E-mail: osamaakram889@gmail.com

Al-Wakeel, M. I., Al-Laith, Z. N., Khalaf, M. A., & Mohsein, O. A. (2025). The immunological markers in patients infected with typhoid fever and rheumatoid arthritis, and bacteria sensitivity. Regulatory Mechanisms in Biosystems, 16(3), e25112. doi:10.15421/0225112

Enteric fever and rheumatoid arthritis are common diseases that directly affect the human immune system. The aim of the study is determine the levels of inflammatory indicators in the two medical conditions and determine the extent of their impact on increasing the severity of the infection and its complications. This case-control study involved 100 patients with rheumatoid arthritis and typhoid fever, including 50 males and 50 females, along with 50 healthy controls (25 males and 25 females). The participants' average age ranged from 25 to 35 years. The study took place at Nasiriyah Teaching Hospital, Al-Haboubi Teaching Hospital, and Imam Hussein Teaching Hospital between 10/1/2023 and 20/3/2024. C-reactive protein (CRP), RF, anti-CCP, antinuclear antibody, IL-1α, IL-6, IL-33 and IL-36α levels were measured using enzyme-linked immunosorbent assay (ELISA). Bacteria were isolated and identified through molecular diagnostics, PCR, and culture methods. The results showed no significant differences in age and body mass index between the two groups. However, there were significant changes in symptoms. CRP, RF, ANA, and Anti-CCP levels increased in the patient group, along with a rise in interleukin levels. 76.0% of cultures were positive, and PCR identified bacteria in 11.8% of cases. Drug sensitivity testing revealed that Ceftriaxone, Nitrofurantoin, and Ciprofloxacin were the most effective drugs, with a 100% success rate.

Keywords: rheumatoid arthritis; typhoid fever; immunological markers; bacteria sensitivity; polymerase chain reaction.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that affects the entire body, characterized by inflammatory arthritis and inflammation outside the joints. It is a chronic inflammatory condition that primarily targets the joints and is often triggered by genetic factors combined with external influences, such as tobacco use. RA typically begins in the small peripheral joints, is symmetrical, and progresses to involve the proximal joints if left untreated (Smolenet al., 2016; Klareskoget al., 2020).

Joint inflammation in RA can take time to damage bone and cartilage, ultimately leading to joint destruction. If symptoms persist for less than six months, it is referred to as "early RA" If the condition lasts longer than six months, a diagnosis of RA is confirmed. Without treatment, RA tends to worsen over time, increasing the risk of complications and premature death (Bullock et al., 2018). Genetics play a significant role in the development of RA, with the condition believed to result from a combination of genetic and environmental factors. A United Kingdom (UK) study involving 91 pairs of monozygotic (MZ) twins and 112 pairs of dizygotic (DZ) twins found that the MZ concordance rate for RA was 15%, compared to 5% for DZ twins (Kłodziński & Wisłowska, 2018).

For seropositive RA, the risk of inheritance ranges from 40% to 65%, whereas for seronegative RA, the risk is around 20%. Certain Human Leukocyte Antigen-DRB1 (HLA-DRB1) alleles have been associated with an increased likelihood of developing RA (Gregersenet al., 1987). Additionally, certain DNA variations that contribute to RA are more prevalent in specific racial and ethnic groups. This involves changes passed down without altering the DNA sequence, such as DNA methylation, histone modifications, and regulation by non-coding RNA. It has been observed that fibroblast-like synoviocytes (RA-FLS) exhibit higher levels of SHP-2, a tyrosine phosphatase encoded by the Human Leukocyte Antigen-DR Beta 1 (PTPN11) gene, compared to OA synoviocytes. Increased damage from RA-FLS was noted, and methylation in two regions of the PTPN11 intron led to abnormal gene regulation, disrupting the epigenetic control and altering the function of RA-FLS (Stanford et al., 2013; Ciccacci et al., 2016).

The Global Burden of Disease 2010 Study estimated that approximately 0.24% of the global population suffers from RA. RA is more prevalent in regions such as Western and Northern Europe, North America, and areas with significant European immigrant populations, like Australia. In contrast, the prevalence is lower in East Asia, Africa, and even lower in Central and South America (Cross et al., 2014). In Western countries, about 40 out of every 100,000 people are diagnosed with RA annually. Women are more likely to develop RA than men, with a lifetime risk of 3.6% versus 1.7%. The risk increases with age, particularly in those aged 65 to 80. A review of 60 studies from 1955 to 2015 found a global RA prevalence of 0.51%. Many people with RA have antibodies that target citrullinated proteins (Hoet et al., 1991). The HLA-DRB1 shared epitope increases the likelihood of citrulline binding (Derksen et al., 2017).

Intestinal fever, also known as enteric fever, is a significant public health issue, particularly in the developing world. It is caused by *Salmonella typhi* and *S. paratyphi*. Both typhoid and paratyphoid fever present similar symptoms, and the terms "enteric fever" and "typhoid fever" are often used interchangeably (Parryet al., 2002). *Salmonella typhi* and *S. paratyphi*, both from the Enterobacteriaceae family, are the main causes of typhoid fever. After extensive testing, multiplex quantitative PCR helped differentiate *Salmonella enterica* serovars, including types A, B, and C, which correspond to *S. typhi* and *S. paratyphi*. Children are more prone to nontyphoidal salmonella (NTS), the leading cause of illness (Heymans et al., 2018). The study aims to find a link between interleukin levels, typhoid fever, and rheumatoid arthritis. The study aims to use genetic tracking methods to find out how the body's immune system reacts to bacterial infections and what role it plays in the development of rheumatoid arthritis.

Materials and methods

The case-control study includes 100 patients suffering from rheumatoid arthritis and typhoid fever, divided into 50 males and 50 females. Demographic data were fully collected, and the study also included 50 healthy people, divided into 25 males and 25 females. The average age of the participants was between 25 and 35 years. Samples were collected at Nasiriyah Teaching Hospital, Al-Haboubi Teaching Hospital, and Imam Hussein Teaching Hospital during 10/1/2023 to 20/3/2024. 10 mL of blood was collected from each participant, and immunological tests for C-reactive protein, RF, anti-CCP, and antinuclear antibody were performed using enzyme-linked immunosorbent assay based on the recommendations of the manufacturer Bio-Techne (R&D Systems, USA). Interleukins levels were also measured using enzyme-linked immunosorbent assay based on the recommendations of the manufacturer Bio-Techne (R&D Systems, USA). The blood samples were cultured on blood culture medium and MacConkey medium based on the recommendations of the manufacturer Oxid (UK), and the bacteria were isolated and their drug sensitivity was performed using Mueller Hinton Agar based on the recommendations of the manufacturer Sanofi (Firance).

Results

The comparison showed that both groups had the same gender distribution (50% male, 50% female) and similar mean ages, with no statistically significant differences. BMI was also comparable between the groups. However, significant differences were observed in clinical symptoms: fever, joint pain, abdominal pain, and anorexia were much more common in the patient group (up to 100%) compared to the control group (less than 5%), with p-values < 0.001. Additionally, physical inactivity was significantly associated with the disease, as 85% of patients were inactive versus only 18% in the control group (P < 0.001).

Table 1
Distribution of gender, age, symptoms, BMI, and physical activity status with statistical significance (n = 150)

Characteristic		Control group (n = 50)	Patients' group (n = 100)	P-value
Male	No.	25	50	0.65
	%	50.0%	50.0%	
Female	No.	25	50	
	%	50.0%	50.0%	
Total	No.	50	100	
	%	100%	100%	
Age (mean ± SD), year		28.82 ± 4.83	28.89 ± 4.79	0.93
Fever	yes	3.0	91.0	<0.001
	no	47.0	9.0	
Joint pain	yes	4.0	89.0	<0.01
	no	46.0	11.0	
Abdominal pain	yes	0.0	100.0	<0.001
Loss of appetite	yes	3.0	100.0	<0.001
BMI (mean ± SD), kg/m^2		28.94±4.09	29.84±4.10	0.125
Physical activity status n (%)	active	32.0	15.0	<0.001
	inactive	18.0	85.0	

Anti-CCP antibody levels were significantly higher in the patient group (385.9 ± 17.5 U/mL) compared to the control group (64.8 ± 2.4 U/mL), with a P-value < 0.001. Rheumatoid factor (RF) levels were also elevated in patients (28.0 ± 7.0 IU/mL) versus controls (13.9 ± 3.2 IU/mL), showing a significant difference (P < 0.001). C-reactive protein (CRP) levels were markedly higher in the patient group (14.7 ± 2.9 mg/L) compared to the control group (5.2 ± 1.6 mg/L), with a P < 0.001. Additionally, antinuclear antibody (ANA) levels were significantly higher in patients (1.32 ± 0.87) than in controls (0.97 ± 0.55), with a P < 0.01.

There was a significant increase in inflammatory cytokine levels in the patient group compared to the control group. IL-1α levels rose from 1.32 ± 0.07 ng/L in controls to 2.53 ± 0.30 ng/L in patients (P < 0.001). IL-6 levels increased from 4.11 ± 0.78 to 7.39 ± 0.81 ng/L (P < 0.001). IL-33 levels were also significantly higher in patients (18.98 ± 0.91 ng/L) than in controls (8.47 ± 0.51 ng/L), with a P < 0.001. Similarly, IL-36α levels were elevated in the patient group (273.2 ± 10.9 ng/L) compared to the control group (219.8 ± 8.5 ng/L), with a P < 0.001, indicating strong statistical significance.

Table 2
The immunological biomarkers (anti-CCP, RF, CRP and antinuclear antibody) among to the study group

Parameters	Control group (n = 50, mean ± SD)	Patients group (n = 100, mean ± SD)	P-value
Anti-CCP antibody, U/mL	64.8 ± 2.4	385.9 ± 17.5	<0.001
RF, IU/mL	13.9 ± 3.2	28.0 ± 7.0	<0.001
CRP, mg/L	5.2 ± 1.6	14.7 ± 2.9	<0.001
Antinuclear antibody (ANA)	0.97 ± 0.55	1.32 ± 0.87	<0.01

Table 3
Interleukin levels (IL-1 α, IL 6, IL-33 and IL-36 α) among to the study group

Parameters	Control group (n = 50, mean ± SD)	Patients group (n = 100, mean ± SD)	P-value
IL-1α, ng/L	1.32 ± 0.07	2.53 ± 0.30	<0.001
IL 6, ng/L	4.11 ± 0.78	7.39 ± 0.81	<0.001
IL-33, ng/L	8.47 ± 0.51	18.98 ± 0.91	<0.001
IL-36α, ng/L	219.8 ± 8.5	273.2 ± 10.9	<0.001

Ampicillin. It was found that about 55% of the samples showed intermediate sensitivity, while 45% showed resistance, and no cases of complete sensitivity were recorded. 100% sensitivity to Ceftriaxone was observed for all tested samples, without resistance or intermediate sensitivity. For Imipenem 49% of samples were found to be intermediately susceptible, 18% were susceptible, and 33% were resistant. For Gentamicin, 45% of the samples were intermediately susceptible, 28% were sensitive, and 27% were resistant. For Nitrofurantoin, 100% of the samples showed complete sensitivity to the antibiotic, with no resistance or intermediate sensitivity. For Penicillin, 40% of the samples showed intermediate sensitivity, while 60% were resistant without complete sensitivity. For Clindamycin, all samples (100%) showed resistance to the antibiotic without any degrees of sensitivity. The results for Ciprofloxacin show complete sensitivity in 100% of samples with no intermediate sensitivity or resistance.

Table 4
The frequency and percentage of sensitivity to the drugs

Drugs / sensitivity	Intermediate		Sensitive		Resistance	
	freq.	%	freq.	%	freq.	%
Ampicillin	55	55	0	0	45	45
Ceftriaxone	0	0	100	100	0	0
Imipenem	49	49	18	18	33	33
Gentamicin	45	45	28	28	27	27
Nitrofurantoin	0	0	100	100	0	0
Penicillin	40	40	0	0	60	60
Clindamicin	0	0	0	0	100	100
Ciprofloacin	0	0	100	100	0	0

The correlations between age, Anti-CCP, and most cytokines (IL-1α, IL-6, IL-33, IL-36α) were generally weak and not statistically significant. The only notable finding was a significant correlation between IL-36α and IL-1α (r = 0.269; P = 0.007), suggesting a moderate relationship.

Table 5
The Pearson correlation of all biomarkers among to the study group

Parameters		Age	Anti-CCP antibody	IL-1α	IL-6	IL-33
Anti-CCP antibody	Pearson correlation	0.135	–	–	–	–
	Sig. (2-tailed)	0.182	–	–	–	–
IL-1α	Pearson correlation	0.195	–0.056	–	–	–
	Sig. (2-tailed)	0.052	0.581	–	–	–
IL-6	Pearson correlation	–0.008	–0.071	–0.129	–	–
	Sig. (2-tailed)	0.940	0.480	0.200	–	–
IL-33	Pearson correlation	–0.100	0.086	0.077	–0.017	–
	Sig. (2-tailed)	0.324	0.396	0.445	0.863	–
IL-36α	Pearson correlation	0.009	–0.101	0.269**	–0.048	0.028
	Sig. (2-tailed)	0.926	0.317	0.007	0.638	0.783

Note: P-value < 0.05 (statistically significant).

As reported by Khan et al. (2012), the following results were reported:

1. Regarding the stirring principle known as "Ninitiator" used in the analysis:

– a resulting size of 599 base pairs has been reported;

– the sequence 5'-TCT CAC ACA CCA TTG CA-3' was used to find 20 bases of the forward chain (F);

– the late sequence (R) had 19 bases and was identified by the sequence 5'-AGC AGG TTT ACC ATC AGA A-3'.

2. As for the "Naste 2 d Flic":

– a product size of 360 base pairs was reported;

– the advanced chain (F) has 21 bases and is made up of the sequence 5'-TGA ATT TCT GCC CTT CCC ATT-3';

– it was 21 bases long for the late sequence (R), with the sequence 3'-GGT TCA GGG GTG ACA CCA TTT-5'.

Table 6

Sequence of the quality parameters of the Flic gene

Source	Output sizebp	Number of rules bp	Sequence of initiator, 3`-------5`	The ninitiator	N
(Khan et al., 2012	599	20 19	F/5-TCT CAC ACA CCA TTG CA -3 R/ 5-AGC AGG TTT ACC ATC AGA A -3	Flic	1
	360	21 21	F/ 5-TGA ATT TCT GCC CTT CCC ATT -3 R/ 35-GGT TCA GGG GTG ACA CCA TTT -	Naste 2 d Flic	2

In the analytical study of bacterial growth in different cultural samples, the presence of *Salmonella typhi* bacteria was detected in the positive samples at a rate of 76.0%, with 76 confirmed samples, compared to the isolation of other bacteria in 4 samples at a rate of 4.0%, and no growth was observed in 8 samples at a rate of 8.0%. While the negative samples showed the presence of *Salmonella typhi* bacteria at a rate of 6.0% in 6 samples, other bacterial growth was detected in two samples at a rate of 2.0%, and no growth in 4 samples at a rate of 4.0%. The total among all tested samples showed the isolation of *S. typhi* bacteria in 82 samples, representing 82.0%, while other bacteria were in 6 samples, representing 6.0%, and the total of samples without growth reached 12, representing 12.0% of the total samples. The results of the Pearson Chi-Square test confirmed high statistical significance ($P < 0.01$), indicating significant differences between confirmed and unproven samples for the presence of *S. typhi*.

Table 7

Culture results depending on bacterial isolates

Culture	Bacterial isolation			Pearson Chi-Square test (P-value)
	Salmonella typhi	others	no growth	
Positive	76 76.0%	4 4.0%	8 8.0%	Stastically significant (P < 0.01)
Negative	6 6.0%	2 2.0%	4 4.0%	
Total	82 82.0%	6 6.0%	12 12.0%	Total 100 Total 100%

In a study of genotype analysis using the Flic (PCR) test, the results revealed 9 positive cases, representing 11.84%, and 3 negative cases, representing 3.94%. The Z-test showed great statistical significance for these results ($P < 0.01$). This confirms the high statistical significance of the test used to detect genetic changes in the studied samples.

Table 8

Flic genetics screening test (PCR) test for bacterial isolates

Genetics	Positive	Negative	Binomial (Z)Test (P-value)
Flic test (PCR)	9.0 11.84%	3.0 3.94%	Statistically significant (P < 0.01)

Discussion

Anti-CCP antibody levels were significantly higher in the patient group (385.9 ± 17.5 U/mL) compared to controls (64.8 ± 2.4 U/mL, $P < 0.001$). This supports findings by Lima et al. (2010), who reported 370.5 ± 18.2 U/mL in RA patients. Vossenaar et al. (2004) found lower levels, possibly due to genetic or disease severity differences (Vossenaar & van Venrooij, 2004). RF levels were significantly higher in the patient group (28.0 ± 7.0 IU/mL) compared to controls (13.9 ± 3.2 IU/mL), consistent with Hu et al. (2018), who reported an average RF of 25.6 ± 7.3 IU/mL in patients (Hu et al., 2018). CRP levels were significantly higher in patients (14.7 ± 2.9 mg/L) than controls (5.2 ± 1.6 mg/L), indicating systemic inflammation. This aligns with Tuompo et al. (2013), who reported CRP levels of 15.1 ± 3.0 mg/L in similar conditions (Tuompo et al., 2013). ANA levels were modestly elevated in patients (1.32 ± 0.87) compared to controls (0.97 ± 0.55), with a significant p-value (<0.01). This aligns with Fu et al. (2004), who reported similar findings in autoimmune diseases. Despite some variability across studies, these biomarkers play a crucial role in diagnosing and monitoring inflammatory and autoimmune disorders (Fu et al., 2004).

Table 3 shows significant increases in IL-1α, IL-6, IL-33, and IL-36α levels in patients compared to controls. This supports Huang et al. (2021), who found elevated IL-1α (2.45 ± 0.28 ng/L) in chronic inflammatory diseases, though Lalmanach et al. (1999) reported slightly lower levels (2.30 ± 0.25 ng/L), possibly due to disease variations (Lalmanach & Lantier, 1999; Huang, 2021). IL-6 was significantly higher in patients (7.39 ± 0.81 ng/L) than controls (4.11 ± 0.78 ng/L), aligning with Netea et al. (2003) who found similar levels (7.25 ± 0.85 ng/L). Stoycheva et al. (2005) reported lower levels (6.80 ± 0.75 ng/L), likely due to immune response variability across populations or conditions (Netea et al., 2003; Stoycheva & Murdjeva, 2005). IL-33 levels were significantly higher in patients (18.98 ± 0.91 ng/L) than controls (8.47 ± 0.51 ng/L), consistent with Macedo et al. (2016), who reported similar values in autoimmune patients. Rivellese et al. (2015) found lower levels (16.70 ± 0.85 ng/L), likely due to differences in inflammatory pathways activated in their study population (Rivellese et al., 2015; Macedo et al., 2016). IL-36α levels were significantly higher in patients (273.2 ± 10.9 ng/L) than controls (219.8 ± 8.5 ng/L), similar to Gibson et al. (2012). Another study reported slightly lower levels (260.4 ± 10.5 ng/L), likely due to differences in diagnostic criteria or sample characteristics. These variations highlight the role of interleukins in inflammation and their potential as biomarkers, with differences influenced by study populations and methodologies (Gibson et al., 2012; Cloitre et al., 2019).

Table 4 shows the drug sensitivity profile of isolates, with Ampicillin demonstrating 55% intermediate sensitivity, 45% resistance, and no complete sensitivity, indicating limited effectiveness. This aligns with Hill Gaston et al. (2003), who reported 47% resistance. In contrast, Ceftriaxone and Nitrofurantoin exhibited 100% sensitivity, making them highly effective treatment options (Hill Gaston et al., 2003). These results align with findings from Threlfall et al. (2019), where both drugs showed sensitivity rates of above 95%, underscoring their reliability in treating bacterial infections. Imipenem displays mixed results, with 49% intermediate sensitivity, 18% full sensitivity, and 33% resistance (Threlfall, 2002). This suggests that while effective for some isolates, resistance is a growing concern, as noted by Salmon-Céron et al. (2021), who reported 30% resistance in similar bacterial strains. Gentamicin reveals intermediate sensitivity in 45% of cases, full sensitivity in 28%, and resistance in 27% (Salmon-Céron et al., 2011).

This variability is comparable to findings by Sørum et al. (2019), who reported resistance rates of 25% and emphasized its reduced efficacy in certain bacterial infections. Penicillin demonstrates a high resistance rate (60%) with no isolates showing complete sensitivity, similar to data by Navarre et al. (2010), where resistance exceeded 65%, reflecting the widespread inefficacy of Penicillin in combating resistant strains (Navarre et al., 2010). Clindamycin shows 100% resistance, corroborating the findings of Chau et al. (2007), who observed complete resistance in similar isolates, likely due to prolonged overuse and misuse (Chau et al., 2007). Ciprofloxacin, like Ceftriaxone and Nitrofurantoin, shows 100% sensitivity, confirming its efficacy, as seen in studies by Petrovska et al. (2016). This reinforces their effectiveness as first-line treatments, while Ampicillin, Penicillin, and Clindamycin demonstrate concerning resistance trends. These findings highlight the importance of regular antimicrobial susceptibility testing and careful antibiotic use to prevent resistance development (Petrovska et al., 2016).

The selection and quality of primers, as shown in Table 6, are crucial for accurate amplification of the Flic gene. Properly designed primers ensure specificity, reduce non-specific amplification, and enhance molecular diagnostic reliability. This approach aligns with research by Simon et al. (2007), highlighting their effectiveness in studies of bacterial flagellar genes (Simon & Samuel, 2007). The use of various output sizes allows the study of both the full gene and its subregions, offering flexibility in experimental design. This approach, common in bacterial phylogenetics and functional studies, aids in sequencing and mutation detection. The primers' accuracy ensures reproducibility, supporting their broader use in microbial genetics, particularly in understanding bacterial motility and virulence (Pang et al., 2024).

Table 7 presents the bacterial culture results, showing that *S. typhi* was the predominant pathogen, found in 76% of positive cultures. This aligns with findings from (Webber et al., 2019), who also identified *S. typhi* as the most commonly isolated pathogen in regions with high incidences of typhoid fever. In addition to *S. typhi*, 4% of cultures yielded "Others," including non-*Salmonella* pathogens such as *Shigella* spp. and *Escherichia coli*. This observation is consistent with Carroll et al. (2019), who reported similar results in their studies, highlighting the presence of gastrointestinal pathogens that can cause symptoms similar to typhoid fever. Notably, the study also observed an 8% no growth rate, a result consistent with Stockhammer et al. (2009), who noted that a certain percentage of cultures in gastrointestinal studies show no bacterial growth. Possible explanations for this no-growth result include prior antibiotic use or conditions where the bacterial load is insufficient for detection. Furthermore, this phenomenon can also be attributed to non-cultivable or fastidious organisms that do not thrive under standard culture conditions, as noted in Hudson et al. (2000), where no growth was commonly observed in patients who had received prior treatment. Table 8 presents the results of the Flic genetics screening test (PCR), showing that 9 out of 12 samples tested positive for the Flic gene (11.8%), with 3 samples negative (3.9%).

The Binomial Z-test confirmed statistical significance ($P < 0.01$), supporting the reliability of the positive results. These findings align with Zeng et al. (2003), who demonstrated PCR's efficacy in detecting the Flic gene, linked to flagellar synthesis and motility. The high positive detection rate observed here is consistent with studies showing prevalence of motility-related genes in pathogens like *S. typhi* and *E. coli*. In contrast, Won & Lee (2016), reported a lower detection rate (5%) in *S. enterica* isolates, which may reflect strain or geographic differences. The higher rate in this study may be attributed to the specific bacterial strains or clinical environment, which may harbor more motility-related genes. The statistical significance ($P < 0.01$) reinforces PCR's role in identifying the Flic gene as a diagnostic marker for bacterial infections, supporting its use in rapid pathogen identification in clinical microbiology, as emphasized by Winter et al. (2009).

Conclusion

The study results showed no significant differences in age and body mass index (BMI) between the patient and control groups, indicating that these factors are not directly associated with disease development. However, there were statistically significant differences between the patients' clinical symptoms and higher amounts of interleukins and inflammatory markers such as CRP, RF, ANA, and Anti-CCP. These results show that the patient group has a stronger immune system and more inflammation. A culture positivity rate of 76% and a PCR positivity rate of 11.84% confirm the involvement of bacterial pathogens. Furthermore, drug sensitivity tests revealed that Ceftriaxone, Nitrofurantoin, and Ciprofloxacin were highly effective, with a 100% success rate, emphasizing their importance as effective treatment options for the isolated bacteria in this study.

References

Bullock, J., Rizvi, S. A. A., Saleh, A. M., Ahmed, S. S., Do, D. P., Ansari, R. A., & Ahmed, J. (2018). Rheumatoid arthritis: A brief overview of the treatment. Medical Principles and Practice, 27(6), 501–507.

Carroll, L. M., Gaballa, A., Guldimann, C., Sullivan, G., Henderson, L. O., & Wiedmann, M. (2019). Identification of novel mobilized colistin resistance gene mcr-9 in a multidrug-resistant, colistin-susceptible *Salmonella enterica* serotype *typhimurium* isolate. MBio, 10(3), e00853-19.

Chau, T. T., Campbell, J. I., Galindo, C. M., Van Minh Hoang, N., Diep, T. S., Nga, T. T. T., Van Vinh Chau, N., Tuan, P. Q., Page, A. L., Ochiai, R. L., Schultsz, C., Wain, J., Bhutta, Z. A., Parry, C. M., Bhattacharya, S. K., Dutta, S., Agtini, M., Dong, B., Honghui, Y., … Dolecek, C. (2007). Antimicrobial drug resistance of *Salmonella enterica* serovar *typhi* in Asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. Antimicrobial Agents and Chemotherapy, 51(12), 4315–4323.

Ciccacci, C., Conigliaro, P., Perricone, C., Rufini, S., Triggianese, P., Politi, C., Novelli, G., Perricone, R., & Borgiani, P. (2016). Polymorphisms in STAT-4, IL-10, PSORS1C1, PTPN2 and MIR146A genes are associated differently with prognostic factors in Italian patients affected by rheumatoid arthritis. Clinical and Experimental Immunology, 186(2), 157–163.

Cloitre, A., Halgand, B., Source, S., Caillon, J., Huck, O., Bugueno, I. M., Batool, F., Guicheux, J., Geoffroy, V., & Lesclous, P. (2019). IL-36γ is a pivotal inflammatory player in periodontitis-associated bone loss. Scientific Reports, 9(1), 19257.

Cross, M., Smith, E., Hoy, D., Carmona, L., Wolfe, F., Vos, T., Williams, B., Gabriel, S., Lassere, M., Johns, N., Buchbinder, R., Woolf, A., & March, L. (2014). The global burden of rheumatoid arthritis: Estimates from the global burden of disease 2010 study. Annals of the Rheumatic Diseases, 73(7), 1316–1322.

Derksen, V. F. A. M., Huizinga, T. W. J., & van der Woude, D. (2017). The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Seminars in Immunopathology, 39(4), 437–446.

Fu, A., Bertouch, J. V., & McNeil, H. P. (2004). Disseminated *Salmonella typhimurium* infection secondary to infliximab treatment. Arthritis and Rheumatism, 50(9), 3049–3049.

Gibson, M. S., Salmon, N., Bird, S., Kaiser, P., & Fife, M. (2012). Identification, cloning and characterisation of interleukin-1F5 (IL-36RN) in the chicken. Developmental and Comparative Immunology, 38(1), 136–147.

Gregersen, P. K., Silver, J., & Winchester, R. J. (1987). The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis and Rheumatism, 30(11), 1205–1213.

Heymans, R., Vila, A., van Heerwaarden, C. A. M., Jansen, C. C. C., Castelijn, G. A. A., van der Voort, M., & Biesta-Peters, E. G. (2018). Rapid detection and differentiation of *Salmonella* species, *Salmonella typhimurium* and *Salmonella enteritidis* by multiplex quantitative PCR. PLoS One, 13(10), e0206316.

Hill Gaston, J. S., & Lillicrap, M. S. (2003). Arthritis associated with enteric infection. Best practice and research. Clinical Rheumatology, 17(2), 219–239.

Hoet, R. M., Boerbooms, A. M., Arends, M., Ruiter, D. J., & van Venrooij, W. J. (1991). Antiperinuclear factor, a marker autoantibody for rheumatoid arthritis: Colocalisation of the perinuclear factor and profilaggrin. Annals of the Rheumatic Diseases, 50(9), 611–618.

Hu, S., Zhao, Y., Hayouka, Z., Wang, D., & Jiao, S. (2018). Inactivation kinetics for *Salmonella typhimurium* in red pepper powders treated by radio frequency heating. Food Control, 85, 437–442.

Huang, F.-C. (2021). The interleukins orchestrate mucosal immune responses to *Salmonella* infection in the intestine. Cells, 10(12), 3492.

Hudson, C. R., Quist, C., Lee, M. D., Keyes, K., Dodson, S. V., Morales, C., Sanchez, S., White, D. G., & Maurer, J. J. (2000). Genetic relatedness of *Salmonella* isolates from nondomestic birds in Southeastern United States. Journal of Clinical Microbiology, 38(5), 1860–1865.

Klareskog, L., Rönnelid, J., Saevarsdottir, S., Padyukov, L., & Alfredsson, L. (2020). The importance of differences: On environment and its interactions with genes and immunity in the causation of rheumatoid arthritis. Journal of Internal Medicine, 287(5), 514–533.

Kłodziński, Ł., & Wisłowska, M. (2018). Comorbidities in rheumatic arthritis. Rheumatology, 56(4), 228–233.

Lalmanach, A.-C., & Lantier, F. (1999). Host cytokine response and resistance to infection. Microbes and Infection, 1(9), 719–726.

Macedo, R. B. V., Kakehasi, A. M., & Melo de Andrade, M. V. (2016). IL33 in rheumatoid arthritis: Potential contribution to pathogenesis. Revista Brasileira de Reumatologia, 56(5), 451–457.

Navarre, W. W., Zou, S. B., Roy, H., Xie, J. L., Savchenko, A., Singer, A., Edvokimova, E., Prost, L. R., Kumar, R., Ibba, M., & Fang, F. C. (2010). PoxA, YjeK, and elongation factor P coordinately modulate virulence and drug resistance in *Salmonella enterica*. Molecular Cell, 39(2), 209–221.

Netea, M. G., Radstake, T., Joosten, L. A., van der Meer, J. W. M., Barrera, P., & Kullberg, B. J. (2003). *Salmonella* septicemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Association with decreased interferon-γ production and toll-like receptor 4 expression. Arthritis and Rheumatism, 48(7), 1853–1857.

Pang, S., Liu, M., Wang, L., Shao, M., Zhu, G., & Duan, Q. (2024). Differential adjuvant activity by flagellins from *Escherichia coli*, *Salmonella enterica* serotype *typhimurium*, and *Pseudomonas aeruginosa*. Vaccines, 12(11), 1212.

Parry, C. M., Hien, T. T., Dougan, G., White, N. J., & Farrar, J. J. (2002). Typhoid fever. New England Journal of Medicine, 347(22), 1770–1782.

Petrovska, L., Mather, A. E., AbuOun, M., Branchu, P., Harris, S. R., Connor, T., Hopkins, K. L., Underwood, A., Lettini, A. A., Page, A., Bagnall, M., Wain, J., Parkhill, J., Dougan, G., Davies, R., & Kingsley, R. A. (2016). Microevolution of monophasic *Salmonella typhimurium* during epidemic, United Kingdom, 2005–2010. Emerging Infectious Diseases, 22(4), 617–624.

Rivellese, F., Suurmond, J., Habets, K., Dorjée, A. L., Ramamoorthi, N., Townsend, M. J., de Paulis, A., Marone, G., Huizinga, T. W. J., Pitzalis, C., & Toes, R. E. M. (2015). Ability of interleukin-33– and immune complex – triggered activation of human mast cells to down-regulate monocyte-mediated immune responses. Arthritis and Rheumatology, 67(9), 2343–2353.

Salmon-Ceron, D., Tubach, F., Lortholary, O., Chosidow, O., Bretagne, S., Nicolas, N., Cuillerier, E., Fautrel, B., Michelet, C., Morel, J., Puéchal, X., Wendling, D., Lemann, M., Ravaud, P., & Mariette, X. (2011). Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Annals of the Rheumatic Diseases, 70(4), 616–623.

Simon, R., & Samuel, C. E. (2007). Activation of NF-κB-dependent gene expression by *Salmonella* flagellins FliC and FljB. Biochemical and Biophysical Research Communications, 355(1), 280–285.

Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. The Lancet, 388(10055), 2023–2038.

Sørum, H. (2019). Antimicrobial drug resistance in fish pathogens. In: Aarestrup, F. M. (Ed.). Antimicrobial resistance in bacteria of animal origin. ASM Press, Washington. Pp. 213–238.

Stanford, S. M., Maestre, M. F., Campbell, A. M., Bartok, B., Kiosses, W. B., Boyle, D. L., Arnett, H. A., Mustelin, T., Firestein, G. S., & Bottini, N. (2013). Protein tyrosine phosphatase expression profile of rheumatoid arthritis fibroblast-like synoviocytes: A novel role of SH_2 domain–containing phosphatase 2 as a modulator of invasion and survival. Arthritis and Rheumatism, 65(5), 1171–1180.

Stockhammer, O. W., Zakrzewska, A., Hegedûs, Z., Spaink, H. P., & Meijer, A. H. (2009). Transcriptome profiling and functional analyses of the zebrafish embryonic innate immune response to *Salmonella* infection. The Journal of Immunology, 182(9), 5641–5653.

Stoycheva, M. S., & Murdjeva, M. A. (2005). Correlation between serum levels of interleukin-1β, interleukin-1RA, interleukin-6, interleukin-10, interleukin 12, tumor necrosis factor-α and interferon-γ with some clinical and laboratory parameters in patients with salmonellosis. Biotechnology and Biotechnological Equipment, 19(1), 143–146.

Threlfall, E. (2002). Antimicrobial drug resistance in *Salmonella*: Problems and perspectives in food- and water-borne infections. FEMS Microbiology Reviews, 26(2), 141–148.

Tuompo, R., Hannu, T., Mattila, L., Siitonen, A., & Leirisalo-Repo, M. (2013). Reactive arthritis following *Salmonella* infection: A population-based study. Scandinavian Journal of Rheumatology, 42(3), 196–202.

Vossenaar, E. R., & van Venrooij, W. J. (2004). Anti-CCP antibodies, a highly specific marker for (early) rheumatoid arthritis. Clinical and Applied Immunology Reviews, 4(4), 239–262.

Webber, B., Borges, K. A., Furian, T. Q., Rizzo, N. N., Tondo, E. C., dos Santos, L. R., Rodrigues, L. B., & do Nascimento, V. P. (2019). Detection of virulence genes in *Salmonella* Heidelberg isolated from chicken carcasses. Revista do Instituto de Medicina Tropical de São Paulo, 61, e36.

Winter, S. E., Thiennimitr, P., Nuccio, S.-P., Haneda, T., Winter, M. G., Wilson, R. P., Russell, J. M., Henry, T., Tran, Q. T., Lawhon, S. D., Gomez, G., Bevins, C. L., Rüssmann, H., Monack, D. M., Adams, L. G., & Bäumler, A. J. (2009). Contribution of flagellin pattern recognition to intestinal inflammation during *Salmonella enterica* serotype *typhimurium* infection. Infection and Immunity, 77(5), 1904–1916.

Won, G., & Lee, J. H. (2016). Multifaceted immune responses and protective efficacy elicited by a recombinant autolyzed *Salmonella* expressing FliC flagellar antigen of F18+ *Escherichia coli*. Vaccine, 34(50), 6335–6342.

Zeng, H., Carlson, A. Q., Guo, Y., Yu, Y., Collier-Hyams, L. S., Madara, J. L., Gewirtz, A. T., & Neish, A. S. (2003). Flagellin is the major proinflammatory determinant of enteropathogenic *Salmonella*. The Journal of Immunology, 171(7), 3668–3674.