**Pacific Journal of Medical and Health Sciences**
ISSN: 2456-7450 | Volume10, Issue 1, January to March 2025, pp - 87 - 93

PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

**Review**

# Scopic Review on Rheumatoid Arthritis

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**Received** : 24 February 2025
**Revised** : 08 March 2025
**Accepted** : 20 March 2025

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## ABSTRACT

*Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder that primarily affects synovial joints, which causes persistent pain, swelling, and if not treated promptly leads to joint deformities. This disorder is characterised by an immune system dysfunction that causes inflammation of synovial, cartilage degradation, and bone deformities and erosion. Genetic predisposition, environmental factors , and immune system dysfunction play significant roles in RA pathogenesis. Early diagnosis and detection are crucial, with clinical symptoms, serological markers, and imaging techniques. Treatment is mainly focused on reducing inflammation, reducing symptoms, and preventing joint damage and deformity. Disease-modifying antirheumatic drugs (DMARDs), biologics, and Janus kinase (JAK) inhibitors are common therapeutic options, with methotrexate being the standard first-line treatment. Recent advances in targeted therapies have improved disease outcomes and quality of life , offering hope for long-term remission.*

**KEYWORDS:** Rheumatoid arthritis, EULAR, DMARDs, Biologics, JAK inhibitors

## INTRODUCTION

Rheumatoid arthritis (RA) is a persistent autoimmune condition associated with inflammation of the body that mainly targets its synovial joints which ultimately results in deterioration, discomfort, and disability of the joints. It results as a product of consistent synovitis, systemic inflammation and autoimmune reactions such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Polyarthritis typically occurs symmetrically, but may also impact other areas like the lungs, heart, and eyes.

Globally, RA impacts around 0.5% to 1% of the population with more cases being reported amongst women and those aged 30 to 60 years old. While its specific cause is unidentified, a combination of environmental triggers with immune system disorders and genetic factors is believed to have a hand in its development. Diagnosis along with intervention plays an important role in halting the damage

done to the joints and enhancing the outcomes in the long run. Using disease-modifying anti rheumatic drugs (DMARD), biologic and Janus kinase (JAK) inhibitors along with DMARD reduces inflammation, relieves the symptoms, slows the deterioration of the condition, and improves the overall quality of life.

Given the high prevalence and long-term benefits of early detection and timely therapeutic intervention, whether the diagnosis is beyond doubt or uncertain, it is important that physicians are aware of this disorder and timely intervention by referral to specialist.

## PATHOLOGY

Extensive genomic studies of single nucleotide polymorphisms (SNPs) in individuals with rheumatoid arthritis (RA) have identified human leukocyte antigen D-related B1 (HLA-DRB1) as a key genetic factor associated with the disease. Additionally, several other genes have been found to contribute to susceptibility, including protein tyrosine phosphatase non-receptor type 22 (PTPN22), cytotoxic T-lymphocyte antigen-4 (CTLA4), signal transducer and activator of transcription 4 (STAT4), TNF alpha-induced protein 3 (TNFAIP3), C-C motif chemokine ligand 21 (CCL21), and peptidyl arginine deiminase 4 (PADI4).

In Japanese populations, two distinct PADI4 gene haplotypes have been identified — one linked to increased disease susceptibility and the other to resistance. Research suggests that messenger RNA transcribed from the disease-susceptible PADI4 variant exhibits greater stability. Additionally, anti-cyclic citrullinated peptide (anti-CCP) antibodies serve as highly specific markers for RA, and individuals who test positive for these antibodies are at a greater risk of experiencing cartilage and bone destruction.

Beyond genetic factors, environmental influences such as smoking, gingivitis, and alterations in gut microbiota can trigger epigenetic modifications. These changes involve histone and DNA demethylation, leading to increased expression of proinflammatory cytokines. Although a specific autoantigen for RA has not been conclusively identified, interactions between genetic predisposition and environmental factors—combined with citrullination of extracellular matrix proteins like filaggrin and fibrinogen—are believed to drive epigenetic alterations, disrupt immune tolerance, and promote autoimmunity[1-3].

Within the synovial tissues of RA patients, autoreactive T and B cells accumulate. Normally, T cells exhibit tolerance to self-antigens; however, when this tolerance is compromised, autoreactive T cells become activated, stimulating B cells to generate autoantibodies. These autoantibodies form immune complexes with their respective antigens, which then deposit in tissues, triggering complement activation and immune-mediated damage (Type III hypersensitivity reaction). Synovitis—a key feature of RA—is marked by angiogenesis, synoviocyte proliferation, and infiltration of lymphocytes. In cases of diffuse inflammation, memory T and B cells aggregate, potentially forming lymphoid follicle-like or germinal center-like structures. Within these sites, proinflammatory cytokines and costimulatory molecules are highly expressed, facilitating interactions among immune cells[1-3].

In synovitis lesions, inflammatory cytokines such as TNF, interleukin (IL)-1, and IL-6 are produced by synoviocytes and lymphocytes, fueling inflammation. This contributes to both systemic symptoms (e.g., low-grade fever, fatigue) and extra-articular manifestations (e.g., keratoconjunctivitis sicca, sialadenitis, interstitial pneumonia). Additionally, cytokine-activated synoviocytes secrete matrix metalloproteinases (MMPs), which degrade cartilage when released into the synovial fluid. Furthermore, synoviocytes and lymphocytes express receptor activator of nuclear factor kappa B ligand (RANKL), which promotes osteoclast differentiation and activity, leading to bone resorption. Over time, inflammatory granulation tissue—comprising proliferative synoviocytes—progresses to areas of direct bone contact, where multinucleated osteoclasts mediate bone degradation, ultimately driving joint destruction[1-5].

## CLINICAL FEATURES

Rheumatoid arthritis (RA) is characterised by morning stiffness and pain affecting multiple joints. Many individuals experience stiffness in their fingers upon waking, often making it difficult to form a fist. Joint pain (arthralgia) is frequently accompanied by swelling and limited movement, primarily affecting the joints in the hands, feet, knees, elbows, and cervical spine. However, the distal interphalangeal joints are rarely the first to be affected.

Additional symptoms often include fatigue, malaise, and fever. Some patients also experience dry eyes due to keratoconjunctivitis sicca (about 45%), dry mouth caused by sialadenitis (40%), subcutaneous rheumatoid nodules on the forearm's extensor surface (35%), and numbness in the hands and feet due to nerve compression (25%). In some cases, interstitial pneumonia can lead to shortness of breath or a dry cough (15%).

## EXAMINATION AND DIAGNOSIS

Physical examinations often reveal tenderness, joint swelling, and synovial fluid accumulation. Affected joints typically show inflammation, which may include redness, warmth, and swelling. RA commonly affects multiple joints symmetrically and bilaterally. As the disease progresses, joint deformities may develop, such as boutonnière and swan-neck deformities in the fingers. Cervical spine involvement, particularly atlantoaxial subluxation, can cause occipital headaches and hand numbness. When inflammation spreads to the tendons,

patients may develop carpal tunnel syndrome, often leading to wrist swelling and trigger finger.

Laboratory tests play a key role in diagnosing RA. Approximately 80% of patients test positive for rheumatoid factor (RF); however, RF can also be detected in healthy individuals and those with liver disease. Anti-cyclic citrullinated peptide (anti-CCP) antibodies have a sensitivity and specificity of 90% or higher, often appearing before symptoms develop. Patients with high levels of anti-CCP antibodies or RF tend to experience rapid joint destruction. Inflammatory markers such as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly observed, along with increased white blood cell counts and normocytic hypochromic anemia. Matrix metalloproteinase-3 (MMP-3), a protease produced in synovial tissues, is associated with joint damage progression.

## IMAGING AND DISEASE PROGRESSION

Radiographic imaging is essential for diagnosing and monitoring RA. Early signs include periarticular osteopenia, while localised bone erosion serves as a key diagnostic indicator. Joint destruction is quantitatively assessed through radiographic scoring methods. The Sharp score, calculated from images of the wrists, hands, and feet, helps evaluate disease severity. This scoring system measures joint space narrowing (indicating cartilage loss) and bone erosion, with annual changes reflecting disease progression and treatment response.

## PROGNOSIS AND ASSOCIATED RISKS

The life expectancy of individuals with RA is typically reduced by about ten years due to complications such as physical disability, organ dysfunction, and adverse reactions to medications. In some populations, respiratory disease, kidney failure, and infections are common causes of RA-related mortality. Extra-articular organ involvement, particularly interstitial pneumonia, significantly impacts prognosis.

## DIAGNOSIS

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) established rheumatoid arthritis (RA) classification criteria in 2010 to improve diagnostic accuracy [6]. These criteria aim to distinguish RA from other forms of arthritis at an early stage, enabling timely treatment with disease-modifying antirheumatic drugs (DMARDs).

**Diagnostic Process**:

The diagnostic process involves two key steps:

1. Exclusion of Other Conditions: Physicians first rule out alternative diseases that may present with arthritis, such as connective tissue diseases, osteoarthritis, spondyloarthritis, and crystal-induced arthritis.
2. Scoring System: Patients are then evaluated based on four weighted criteria:
    - Joint Involvement: Swelling in small or intermediate/large joints.
    - Serologic Tests: Presence of Rheumatoid Factor (RF) and anti-cyclic Citrullinated Peptide (anti-CCP) antibodies.
    - Symptom Duration: Persistent symptoms lasting 6 weeks or longer.
    - Acute-Phase Reactants: Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

A combined score of 6 out of 10 confirms a diagnosis of definite RA.

Alternatively, the diagnosis of rheumatoid arthritis can be made if one or more affected joints present with typical bone erosion, regardless of the score.

## DISEASE ACTIVITY ASSESSMENT

Assessing disease activity is crucial for treatment planning. The following tools are widely used:

- 28-joint Disease Activity Score (DAS28): Calculated using the number of tender/swollen joints, ESR results, and the patient's global assessment of disease activity.
    - > 5.1: High Disease Activity
    - 3.2 - 5.1: Moderate Disease Activity
    - < 3.2: Low Disease Activity
    - < 2.6: Rémission
- Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are also common tools for evaluating disease severity.

### Functional Assessment

The Health Assessment Questionnaire Disability Index (HAQ-DI) is widely employed to evaluate physical dysfunction. This tool includes 20 questions covering 8 categories of daily living activities, helping clinicians track the patient's physical abilities.

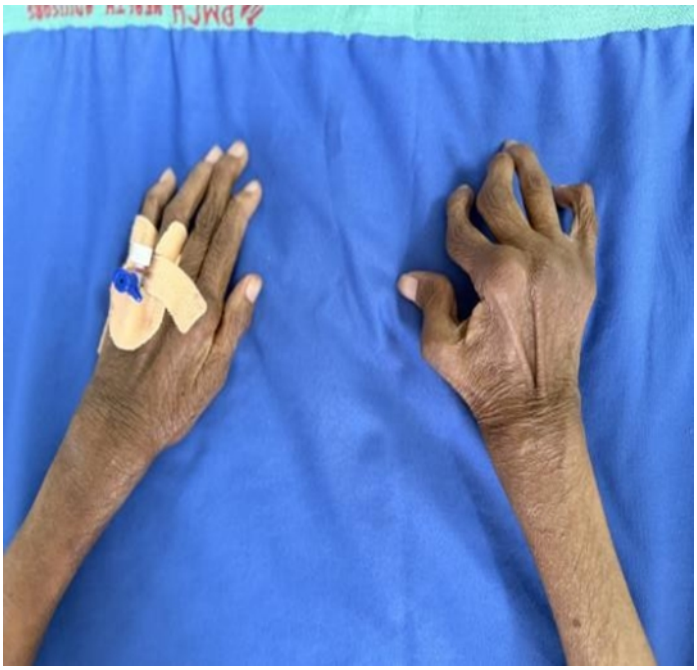

**Figure 1**

**Figure 2**

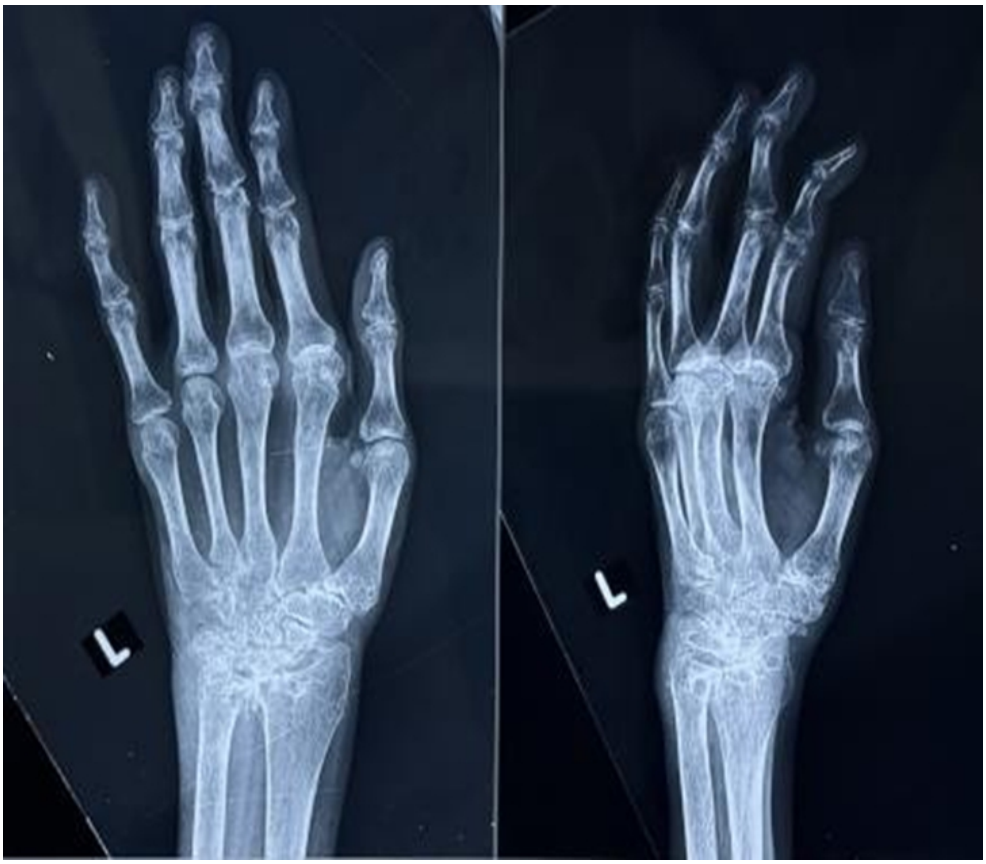

**Figure 3**

**Figures 1 & 2**: Showing Joint Deformities like Piano Key Deformity and Boutonnière Deformity

**Figure 3**: Showing X-ray of Hand featuring Loss of Joint Space and Periarticular Osteopenia, Characteristic of Rheumatoid Arthritis

## EXTRA-ARTICULAR INVOLVEMENT AND COMPLICATIONS

RA is often associated with systemic complications that impact prognosis. Common extra-articular manifestations include:

- Lungs: Interstitial pneumonia, chronic obstructive pulmonary disease (COPD), pleurisy, pulmonary hemorrhage, and bronchiectasis
- Eyes: Keratoconjunctivitis sicca
- Heart: Pericarditis and myocarditis
- Skin: Rheumatoid nodules
- Nervous System : Mono-neuritis multiplex
- Blood and Immune System: Anemia, lymphoproliferative disorders, and autoimmune conditions like Hashimoto's thyroiditis or secondary Sjögren's syndrome

### Imaging and Prognostic Assessment

Chest computed tomography (CT) scans are commonly used to assess lung complications in RA patients, with approximately:

- 50% showing nonspecific lung changes;
- 30% presenting interstitial pneumonia;
- 20% displaying chronic infection or COPD-related changes.

Patients with advanced RA may experience severe complications such as rheumatoid vasculitis, characterised by systemic inflammation affecting multiple organs.

Differentiating RA from other autoimmune and infectious conditions is essential for effective management and improved patient outcomes.

## TREATMENT

The primary goal of treatment of rheumatoid arthritis is prompt intervention after the diagnosis has been made to limit the disability, prevent joint destruction, subdue arthritis and to induce remission.

Therapeutic plan should be based on disease activity after taking into account ,the comprehensive assessment of disease activity (SDAI, CDAI, and DAS are used to evaluate disease activity), radiological findings, complications and co-morbidities[7].

The main goal of treatment is to induce remission, limit joint destruction and reduce physical disability.

Standard Initial treatment after establishment of diagnosis of rheumatoid arthritis is methotrexate DMARD should be used (contraindication should be ruled out first)[8,9].

However, if there is no improvement within 3months or there is failure to achieve remission in 6 months, in spite giving the full dose of methotrexate, the addition of biological DMAR Ds

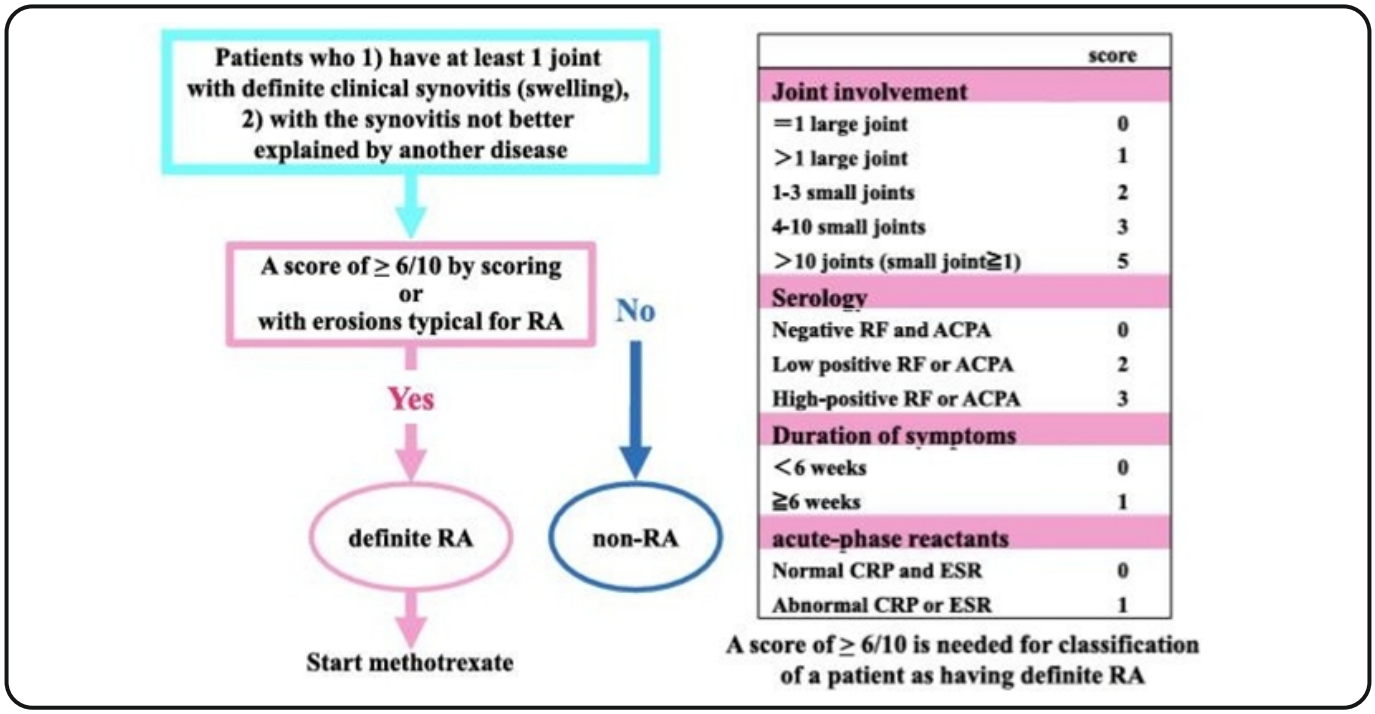


**Figure 4**: The Rheumatoid Arthritis Classification Criteria Published by the ACR/EULAR in 2010.
*Modified from Reference 6*

or Janus kinase (JAK) inhibitors is recommended. If treatment goal is still not achieved, other DMARDs or JAK inhibitors should be added to approximately 3–6 months later.

Meanwhile, steroids are for temporary use for up to 3 months as concomitant therapy to reduce pain and swelling at the time of relapse or initiation of therapy.

Methotrexate is a mainstay drug in the treatment of rheumatoid arthritis and other autoimmune conditions. It is classified as a conventional synthetic Disease-Modifying Antirheumatic Drug (csDMARD). Its therapeutic effects are primarily achieved through the following mechanisms :

1. Inhibition of Dihydrofolate Reductase (DHFR):MTX acts as a folate antagonist, inhibiting the enzyme dihydrofolate reductase. This blocks the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF), which is essential for purine and thymidylate synthesis. By limiting nucleotide production, MTX reduces the proliferation of rapidly dividing cells, particularly immune cells such as T and B lymphocytes, which are central to RA pathogenesis.
2. Inhibition of AICAR Transformylase: MTX increases the intracellular concentration of adenosine, a potent anti-inflammatory mediator. Adenosine suppresses inflammatory pathways by down-regulating cytokines such as TNF-α, IL-6, and IL-8, which are key drivers of synovial inflammation in RA.

Side Effects of Methotrexate: While effective, MTX can cause various adverse effects that require monitoring. These may range from mild to severe.

Common Side Effects: Gastrointestinal Disturbances — Stomatitis, Nausea, Vomiting, Diarrhea, and Abdominal discomfort are common.

Hematologic Side Effects: Myelosuppression — May lead to Leukopenia, Thrombocytopenia, or Anemia.

Hepatotoxicity: Elevated Liver Enzymes and, in rare cases, Liver Fibrosis or Cirrhosis may occur.

Pulmonary Side Effects: Interstitial Pneumonitis is a rare but potentially serious side effect, often presenting with Cough, Dyspnea, and Fever. Prompt discontinuation of MTX is crucial if this develops.

Co-administration of Folic acid is useful in reducing an preventing adverse reactions.

Biological DMARDs are prescribed when synthetic DMARDs fail to provide an adequate therapeutic response. Combining biological DMARDs with methotrexate has been found to induce remission in nearly half of the cases. These drugs are effective in preventing bone destruction and preserving joint function over extended periods[10].

Janus Kinase (JAK) inhibitors fall under the category of targeted synthetic DMARDs. Medications such as Tofacitinib, Baricitinib, Peficitinib, Upadacitinib, and Filgotinib are commonly used to manage rheumatoid arthritis. These inhibitors can be administered either as monotherapy or alongside methotrexate[11-15].

In some studies where biological DMARDs were used to treat rheumatoid arthritis, post-marketing surveillance was required to verify their safety[16,17].

Patients at risk of tuberculosis are advised to take prophylactic isoniazid, while pneumococcal vaccination is recommended for those vulnerable to pneumonia.

## CONCLUSION

Rheumatoid arthritis is chronic autoimmune inflammatory disease features mainly synovitis and further joint destruction if not intervened timely with DMARDS and Biologics. Joint deformity is irreversible and causes physical dysfunction. Therefore, early diagnosis and treatment is necessary. For treatment, DMARDs are used to suppress immune abnormalities and control disease activity. DMARDs are classified into conventional synthetic DMARDs (e.g., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine), targeted synthetic DMARDs (e.g., JAK inhibitors), and biologic DMARDs. Appropriate treatment with these drugs has allowed clinicians to aim for remission in rheumatoid arthritis patients. These drug classes have been demonstrated to prevent structural damage to the joints and to prevent the progression of physical dysfunction. The advent of molecular-targeted drugs, such as biological drugs and JAK inhibitors, has allowed for the use of targeted therapies based on pathological mechanisms and the management of autoimmune inflammatory diseases, which were previously considered to be intractable. This can be regarded as revolutionary progress. In the future, safer and more effective treatments, therapeutic strategies aiming at cure, and the introduction of precision medicine are expected.

**CONFLICT OF INTEREST**: None

**FINANCIAL SUPPORT**: None

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