



## Research Article

# Circulating Interleukin-23 Levels in Rheumatoid Arthritis and its Relationship to Disease Activity: a Systematic Review with Meta-Analysis

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## ABSTRACT

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**Keywords:** Interleukin-23, IL-23, Rheumatoid arthritis, DAS28, Meta-analysis.



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**Background:** Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease that is characterized by severe synovial inflammation, cartilage erosion, bone loss, and generalized vasculopathy. Although the immunologic mechanism of RA is still unclear, it is now thought to be a primarily Th17-driven disease. Along with other factors, IL-23 stimulates the expansion of Th17 cells from naive CD4+ T cells.

**Objective:** The objective of this study is to assess the circulating levels of interleukin (IL)-23 in rheumatoid arthritis (RA) and determine the correlation between plasma/serum IL-23 levels and disease activity. So, we performed a systematic review with meta-analysis comparing plasma/serum IL-23 levels between patients with RA and controls and examined correlation coefficients between circulating IL-23 levels and disease activity

**Subjects and Methods:** Using the following keywords: lenterleukin-23, IL-23, and rheumatoid arthritis, a comprehensive literature search was carried out in the following databases: PubMed, Scopus, Google Scholar, and Web of Science. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards were followed, and the review was registered in the PROSPERO International prospective register of systematic reviews with registration number CRD42022345901. Results were reported as standardized mean differences (SMDs) with a 95% confidence interval. All statistical analysis was performed using StatsDirect statistical software version 3.0.0 (StatsDirect Ltd., Cheshire, UK). A sensitivity analysis was conducted using the leave-one-out approach to test the robustness of the results.

**Results:** The total sample size for the RA group included in our review was 408 cases, while

the control group sample size was 244 cases. The serum IL-23 level in the RA group was significantly higher than the control group (pooled SMD = 3.5, 95% CI; 2.1: 4.8,  $P < 0.0001$ ) as compared to the control group. There were 8 studies with a total sample size of 402 that reported the correlation between IL-23 and DAS28-based RA activity. According to our findings, a significantly positive correlation between IL-23 and DAS28-based RA activity was found, with a weighted mean correlation of 0.57 (95% CI; 0.4: 0.75,  $P < 0.0001$ ).

**Conclusion:** Our meta-analysis has shown that IL-23 circulatory levels are higher in RA patients and that there is a significant positive correlation between IL-23 and disease activity. Our findings emphasize the role that IL-23 may have in RA. More studies may be required to fully comprehend the involvement of IL-23 in RA.

## Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease. During the early stages of RA, both T and B cells are activated. Tumor necrosis factor (TNF), IL-1, and IL-17 are pro-inflammatory cytokines that cause inflammation as well as bone and cartilage damage (1). Several studies have found that immune cells such as cluster of differentiation 4 (CD4+) Th cells (CD4+ T cells, Th cells), macrophages, and B cells are involved in the pathogenesis of RA (2-5). The immunologic mechanism of RA, however, is still unclear. Although RA had long been classified as a Th1-mediated disease (6), it is now thought to be a primarily T helper 17 (Th17) - driven disease (7,8). Th17 cells differentiate upon exposure to TGF and IL-6, which causes the transcription factor retinoid-related orphan receptor (ROR)-t to be activated. (ROR)-t promotes the expression of IL-17A and the IL-23 receptor (IL-23R) (9,10). Subsequent exposure to IL-23 is necessary for the Th17 lineage to be maintained and expanded(11,12)and Th17 phenotype is lost in the absence of IL-23(11).

IL-23, a member of the IL-6/IL-12 superfamily, is a heterodimeric cytokine and is composed of the p40 subunit in common with IL-12 and with a unique p19 subunit (13). The inflammatory involvement of IL-23 in RA was first reported by Liu et al. (14). Indeed, the IL-23-IL-17 axis is involved in the pathophysiology of autoimmune diseases, including rheumatoid arthritis (15). In experimental models, studies revealed the involvement of IL-23 in joint inflammation and bone destruction. For instance, according to Yago et al., anti-IL-23 antibody treatment reduces collagen-induced arthritis (CIA) by preventing both synovial inflammation and bone destruction (16). In addition, a meta-analysis on associations between interleukin-23 receptor polymorphisms and susceptibility to rheumatoid arthritis revealed that IL-23R genes confer susceptibility to RA in the European population (17).

Several investigations comparing the levels of circulating IL-23 in RA patients and healthy controls have associated interleukin-23 with rheumatoid arthritis disease activity. We thus carried out a meta-analysis to overcome the shortcomings of individual research and to address the discrepancies in their conclusions.

## Subjects and Methods

### Search strategy

Using the following keywords: interleukin-23, IL-23, rheumatoid arthritis, RA a comprehensive literature search was carried out in the following databases: PubMed, Scopus, Google

Scholar, and Web of Science. Using Zotero version 6, search findings were combined, and duplicates were eliminated. Only original publications published in English were included in the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards were followed in the selection of the eligible articles (18). The review was registered in the PROSPERO International prospective register of systematic reviews, with registration number CRD42022345901.

### Inclusion and exclusion criteria

Two independent reviewers (H.K and S.A.B) selected the included studies based on the inclusion and exclusion criteria and crosschecked by N.R, A.A and A.Az.

Any study that fulfilled one of the following criteria was included:

1. Studies that compared levels of interleukin 23 in healthy and rheumatoid arthritis patients.
2. Studies that associate interleukin 23 with rheumatoid arthritis disease activity.

Only primary studies that were published in English were included.

### Exclusion criteria:

Studies were excluded if they had any of the following: studies published in languages other than English; full-text not available; case report studies; review articles; or conference abstracts; The data cannot be extracted.

Any discrepancies were settled by discussion between the authors.

### Quality assessment

Two independent reviewers (M.s.M and A.Az) evaluated the study quality of each article based on Newcastle–Ottawa-Scale (NOS) criteria for the assessment of the quality of nonrandomized studies in meta-analyses (19). The NOS criteria are composed of three assessing aspects, namely selection, comparability and outcome assessment with a highest score of nine.

### Data extraction:

From each included study, the following information was extracted by S.S and M.S and crosschecked by H.K and S.A.B: The first author's last name; year of publication; country; number of participants; mean and standard deviation (SD) of IL-23 level; disease duration; IL-23 detection method; and coefficients of

correlation between IL-23 levels and RA. Any discrepancies were settled by discussion between the authors.

### Data synthesis

I-squared and Q-test were used to measure the heterogeneity between the studies and based on the random effects model, results were reported as standardized mean differences (SMDs) with a 95% confidence interval (CI). Publication bias testing was not performed when the number of studies was less than ten. All statistical analysis was performed using StatsDirect statistical software version (Version 3.0.0, StatsDirect Ltd, Cheshire UK). SMD values of 0.2-0.5 are considered small, values of 0.5-0.8 are considered medium, and values > 0.8 are considered large.

For correlation coefficients, the published Spearman correlation coefficient ( $r$ ) values were converted to Pearson correlation coefficient ( $r$ ) values, which were used for the meta-analysis (20). Sensitivity analysis was conducted using leave-one-out approach to test the robustness of the results.

## Results

### Studies included in the meta-analysis

As depicted (Fig. 1), four separate databases were searched, yielding a total of 1206 results. 351 duplicates were removed, and 855 articles were irrelevant by title and abstract. The remaining 13 publications were then evaluated by reading the full-text, and three publications were eliminated. In the end, a total of 11 studies fulfilled our inclusion and exclusion criteria and were included in our review (21-31). Seven reports compared the circulating IL-23 level in RA and controls (21-27) (Table 1). Of those, four studies also reported the correlation between circulating IL-23 level and disease activity of RA (22,23,26,27). Another four studies also reported the correlation between circulating IL-23 levels and the disease activity of RA (28-31).

The characteristics of included studies that associated interleukin 23 with Rheumatoid arthritis disease activity based on DAS-28 are presented in Table 2. The PRISMA checklist is presented in Table S.1.

### Meta-analysis comparing the circulating IL-23 level in RA and controls

The total sample size (SZ) for RA group included in our review was 408 cases while control group sample size was 244 cases. There was a high heterogeneity between studies evident by  $I^2$  (inconsistency) = 97.4%. The RA group was significantly higher than the control group (Pooled SMD= 3.5; 95% CI; 2.1: 4.8,  $P < 0.0001$ ) (Fig.2) as compared to the control group.

### Meta-analysis of the correlation between circulating IL-23 level and disease activity of RA

There were 8 studies with a total sample size of 402 that reported the correlation between circulating IL-23 level and disease activity of RA based on DAS28. There was a high heterogeneity between studies ( $I^2 = 95.7\%$ ).

The meta-analysis of correlation revealed a significant positive correlation between IL-23 and DAS28-based RA activity, with a weighted mean correlation of 0.57 (95% CI; 0.4: 0.75,  $P 0.0001$ ) (Fig.2).

### Sensitivity analysis

The sensitivity analyses by removing each one study and cumulative analysis were done on overall analysis. The omission of study 7 (Abu Al Fadl et al.) (27) Seems to have a relatively larger influence (when compared with other studies) on the estimation of the overall effect size. Omitting study 7 causes the overall SMD to decrease by roughly 1.6 (Fig.2).

## Discussion

Rheumatoid arthritis (RA), a chronic and systemic autoimmune disease, is characterized by severe synovial inflammation, cartilage erosion, bone loss, and generalized vasculopathy (32-34). TNF- $\alpha$ , interleukin (IL)-1, and IL-6 are among the pro-inflammatory cytokines implicated in the RA disease process. Indeed, indeed, all three of those cytokines have been found to be higher in the synovial fluid of RA patients compared to controls (35-37). TNF- $\alpha$ , IL-1, and IL-6 have thus been specifically targeted and anti-TNF- $\alpha$ , anti-IL-1, and anti-IL-6 drugs are available for the treatment of RA(38-40). RA is now thought to be a primarily Th17-driven disease(7,8). Along with other factors, IL-23, stimulates the expansion of Th17 cells from naive CD4+ T cells (12). Therefore, additional work into the potential function that IL-23 may have in RA is required.

According to the current review, there is combined evidence for higher circulating IL-23 levels in the RA group compared to the control group and a correlation between plasma or serum IL-23 and disease activity. The results of the meta-analysis revealed that circulating IL-23 may have a role in the pathogenesis of RA.

A randomized phase II study, however, evaluated the efficacy and safety of Ustekinumab and Guselkumab (anti-IL-23 antibodies) and revealed a non-substantial improvement in the signs and symptoms of RA patients. Both antibodies failed to meet the objective (ACR20 at week 28)(41).

The unfavorable findings of anti-IL-23 antibodies in rheumatoid arthritis studies raise the issue of whether blocking the IL-23/IL-17 axis synergistically other biologics and might lead to treatment outcomes.

Rheumatoid arthritis disease activity was evaluated by disease activity score-28 (DAS-28)(42). Disease activity was graded as high ( $DAS28 > 5.1$ ); moderate ( $3.2 < DAS28 \leq 5.1$ ), low ( $DAS28 \leq 3.2$ ) and remission ( $DAS28 < 2.6$ ) (43). The significant positive relationship between IL-23 levels and DAS 28 ( $r = 0.59$ ,  $P 0.0001$ ) is one of the study's main findings. Thus, higher IL-23 levels may reflect higher disease activity in RA. In contrast, Zaky and El-Nahrery(21)There was no correlation between IL-23 and activity in RA patients (DAS-28 score). Rasmussen et al. found a non-significant correlation between any of the IL-23 and DAS28 at the time of diagnosis or at 3 months after diagnosis (28). In both cases the correlation coefficient was not reported.

In addition to the positive correlation between DAS28 and IL-23 several studies reported a positive significant correlation between IL-23 and biologic markers that aid in diagnosis of rheumatoid arthritis such as rheumatoid factors (RF) c-reactive protein (CRP) erythrocyte sedimentation rate (ESR) Anti-cyclic citrullinated peptide (Anti CCP) (22,23,28,30) as shown in Table 3. In contrast Kageyama et al. found a non a significant correlation with RF,CRP and ESR(31).

Furthermore, a significant correlation between IL-23 and the degree of disability in RA patients was reported according to the health assessment questionnaire (HAQ)(22,23,30).

**Table 1:** Characteristics of included studies that compared levels interleukin 23 in healthy and Rheumatoid Arthritis patients

| Authors (publication time)(citation) | Country  | disease duration | case |       |              |              |       | control |       |             |        |       | method | quality |
|--------------------------------------|----------|------------------|------|-------|--------------|--------------|-------|---------|-------|-------------|--------|-------|--------|---------|
|                                      |          |                  | SZ   | M/F   | Age          | Mean (pg/ml) | SD    | SZ      | M/F   | Age         | Mean   | SD    |        |         |
| Zaky(2016) (21)                      | Egypt    | 2-20 Y           | 77   | -     | 46.5 ± 10.5  | 78.92        | 52.47 | 25      | -     | 44.6 ± 10   | 33.34  | 3.99  | ELISA  | 7       |
| Al-Sheikh(2018)(22)                  | Egypt    | 4.98 ± 4.1Y      | 40   | 3/37  | 43.3 ± 10.4  | 67.5         | 39.2  | 40      | 8/32  | 39.5 ± 12.7 | 37.7   | 15.64 | ELISA  | 8       |
| Fadda (2017)(23)                     | Egypt    | 25–31 M          | 100  | 20/80 | 25-55        | 19.12        | 13.45 | 50      | 10/40 | 21-51       | 0.9    | 0.63  | ELISA  | 7       |
| Dalila (2014)(24)                    | Malaysia | 10.75 ± 4.79 Y   | 45   | 5/40  | 54.78 ± 7.07 | 24.5         | 13.98 | 45      | 5/40  | 54.00 ± 7.4 | 5.98   | 3.4   | ELISA  | 7       |
| Wendling(2015)(25)                   | France   | -                | 27   | -     | 55±12        | 22.7         | 25.9  | 24      | -     | 54±13       | 5.1    | 7.9   | ELISA  | 8       |
| GUO(2013)(26)                        | china    | 68.2±50.2(M)     | 59   | 20/39 | 49.56±15.3   | 370.7*       | 25.7  | 30      | -     | -           | 248.5* | 20.1  | ELISA  | 6       |
| Abu Al Fadl (2013)(27)               | Egypt    | 10 ± 2 Y         | 60   | 16/44 | 40(20- 60)   | 420*         | 15.3  | 30      | -     | 8/22        | 135*   | 12    | ELISA  | 5       |

Abbreviations: sample size/F: Male/Female, SD: standard deviation

\*ng/ml

**Table2:** Characteristics of included studies that associated interleukin 23 with Rheumatoid arthritis

| Authors(publication time)(citation) | Country | disease duration | Sample size | M/F   | Age (year)  | Correlation coefficients(r) | Statistical analysis | Pearson's r estimated form spearman's r | quality |
|-------------------------------------|---------|------------------|-------------|-------|-------------|-----------------------------|----------------------|---|---------|
| Al Sheikh (2018)(22)                | Egypt   | 4.98 ± 4.1Y      | 40          | 3/37  | 43.3 ± 10.4 | 0.35                        | spearman's r         | 0.36                                    | 8       |
| Fadda(2017) (23)                    | Egypt   | 25–31 M          | 100         | 20/80 | 25-55       | 0.967                       | Pearson's r          | 0.967                                   | 7       |
| Rasmussen (2010)(28)                | Denmark | > 8 Y            | 40          | -     | 52–69       | 0.443                       | spearman's r         | 0.44                                    | 8       |
| Zaky(2014)(29)                      | Egypt   | 2-20 Y           | 35          | -     | 46.5± 10.5  | 0.109                       | spearman's r         | 0.12                                    | 7       |
| Melis(2009)(30)                     | Belgium | 8.91±2.02 Y      | 22          | 6/16  | 56.14±2.78  | 0.627                       | spearman's r         | 0.65                                    | 7       |
| Kagyama(2009)(31)                   | Japan   | 17.6 ± 6.0 Y     | 26          | 3/23  | 61.4 ± 10.6 | 0.263                       | Pearson's r          | 0.263                                   | 8       |
| GUO(2013)(26)                       | china   | 68.2±50.2M       | 59          | 20/39 | 49.56±15.3  | 0.461                       | Pearson's r          | 0.461                                   | 6       |
| Abu Al Fadl(2013)(27)               | Egypt   | 10 ± 2 Y         | 60          | 16/44 | 40(20- 60)  | 0.683                       | Pearson's r          | 0.683                                   | 5       |
| Kagyama(2007)(32)                   | Japan   | 15.3 ± 7.4       | 22          | 2/22  | 61.8 ± 9.0  | 0.429                       | Pearson's r          | 0.429                                   | 7       |

Abbreviation: M/F: Male/Female

**Table3:** Characteristics of included studies that associated interleukin 23 with Rheumatoid arthritis biological markers

| Authors(publication time)(citation) | Sample size | Biological marker | Correlation coefficients(r) | Statistical analysis |
|-------------------------------------|-------------|-------------------|-----------------------------|----------------------|
| Al Sheikh (2018) (22)               | 40          | RF                | 0.48                        | spearman's r         |
|                                     |             | CRP               | 0.39                        |                      |
|                                     |             | ESR               | 0.45                        |                      |
|                                     |             | Anti CCP          | 0.35                        |                      |
| Fadda (2017) (23)                   | 100         | RF                | 0.917                       | Pearson's r          |
|                                     |             | CRP               | 0.954                       |                      |
|                                     |             | ESR               | 0.950                       |                      |
| Melis (2009) (30)                   | 22          | CRP               | 0.578                       | spearman's r         |
|                                     |             | ESR               | 0.665                       |                      |
|                                     |             | CRP               | 0.28                        |                      |
| Rasmussen (2010)(28)                | 40          | ESR               | 0.50                        | spearman's r         |

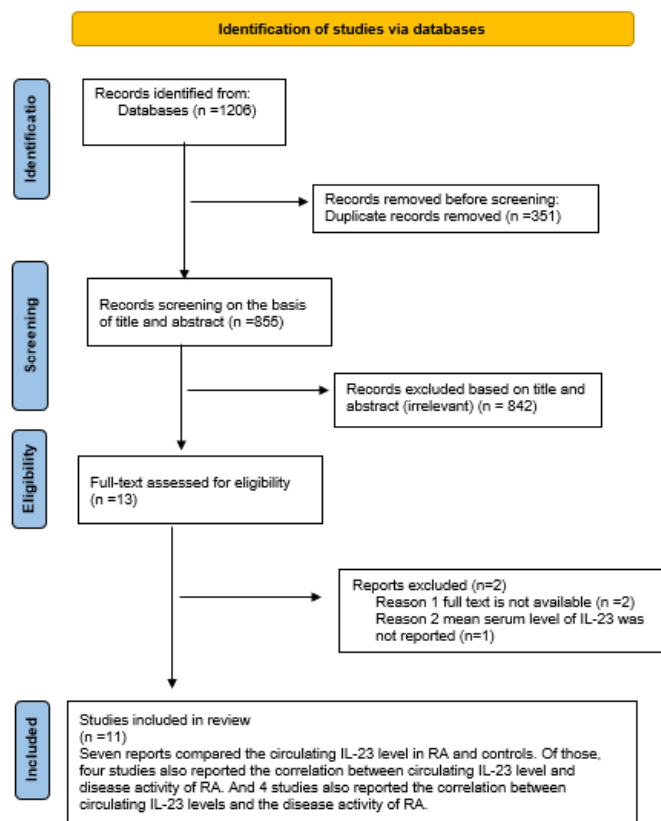


Figure1: Flow chart depicting the selection of publications

This analysis has some limitations that need to be carefully considered. First the small sample size of some studies. Second, the majority of studies were reported from Egypt, with a paucity of studies from other regions of the world. Therefore, the meta-analysis can be underpowered. Third the studies may have employed various generations of screening kits, and there may have been differences in sensitivity and specificity, which might explain the discrepancy in SMD between studies. Nevertheless, our meta-analysis is the first to provide cumulative evidence for IL-23 status in patients with RA. Due to the enhanced statistical power and clarity of the findings of separate analytic procedures, our findings on the link between IL-23 levels and RA were more precisely measured than in individual studies.

**Conclusion**

Our meta-analysis has shown that IL-23 circulatory levels are higher in RA patients and that there is a significant positive correlation between IL-23 and disease activity. Our findings emphasize the role that IL-23 may have in RA. More studies may be required to fully comprehend the involvement of IL-23 in RA.

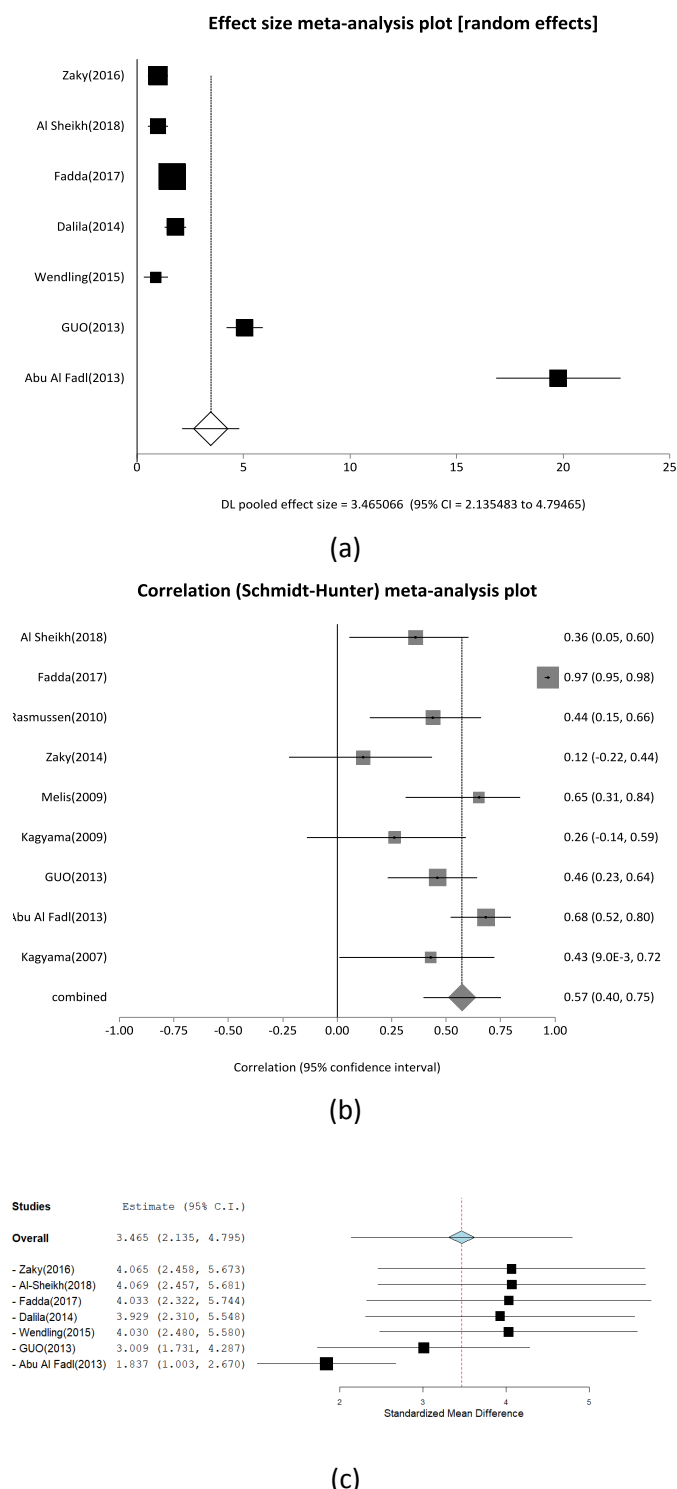


Figure 2: Forest plot of the circulating IL-23 level in RA and controls. (A): standardized mean difference (SMD) of the circulating IL-23 level in RA and controls. (B): correlation coefficients between interleukin-23 levels and the activity of rheumatoid arthritis based on DAS28. (C): leave-one-out meta-analysis with random effect for standard mean difference in serum or plasma IL-23 levels in the rheumatoid patients vs. controls

**Ethics approval and consent to participate**

Not applicable

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**Conflict of Interest**

No conflict of interest

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