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# The impact of eosinophilia on treatment duration in patients with newly diagnosed drug-sensitive pulmonary tuberculosis

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## Abstract:

**BACKGROUND AND AIM:** Eosinophilia, defined by an absolute eosinophil count (AEC)  $\geq 500$  cells/ $\mu$ L, is a common finding associated with various conditions, including mycobacterial infections, and can rarely be induced by standard anti-tuberculosis (TB) drugs such as isoniazid, ethambutol, and rifampin. While in vitro studies suggest that eosinophil products, such as eosinophil peroxidase, possess mycobactericidal activity, the clinical impact of eosinophilia on TB outcomes is unknown. This study aimed to analyze the association between eosinophilia development during treatment and the duration of therapy in a retrospective cohort of patients newly diagnosed with drug-sensitive pulmonary TB.

**METHODS:** This was a retrospective cohort study conducted at a tertiary center. A total of 6,045 patients with drug-sensitive pulmonary TB treated between 2017 and 2022 were screened. Patients were excluded if they had conditions that could confound eosinophilia or treatment duration, including allergic diseases, drug-resistant TB, severe comorbidities, and an AEC  $\geq 1500$  cells/ $\mu$ L. The final cohort included 121 contemporary non-eosinophilic controls (Group 1) and 119 patients who developed eosinophilia with no identifiable cause (Group 2).

**RESULTS:** The median age was comparable between Group 1 (43 years, range: 18–82) and Group 2 (45 years, range: 18–84;  $p=0.485$ ). A statistically significant difference was observed in the duration of anti-TB treatment ( $p=0.013$ ). The median treatment duration for the control group (Group 1) was 7 months (range: 6–9 months), whereas the median duration for the eosinophilia group (Group 2) was 6 months (range: 6–9 months). Logistic regression analysis confirmed that eosinophilia was significantly associated with treatment duration (odds ratio: 2.06, (95% confidence interval: 1.14–3.71;  $p=0.017$ ).

**CONCLUSIONS:** The development of eosinophilia during treatment for drug-sensitive pulmonary TB was associated with a significantly shorter treatment duration. Conversely, the absence of eosinophilia is an independent risk factor for prolonged therapy. These findings suggest that eosinophils may contribute to a more effective host immune response against Mycobacterium tuberculosis, serving as a potential positive prognostic indicator in clinical practice.

## Keywords:

Eosinophilia, treatment duration, tuberculosis

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## Introduction

Tuberculosis (TB) is a significant global infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB). According to the World Health Organization (WHO), an estimated 10.6 million people developed TB in 2022, continuing an upward trend compared to incidence rates in 2020 and 2021.<sup>[1]</sup> Despite the development and testing of various therapeutic alternatives, the 6-month regimen remains the standard of care worldwide, comprising isoniazid (H), rifampin (R), ethambutol (E), and pyrazinamide (Z).<sup>[2]</sup> Numerous studies have identified factors that negatively affect TB treatment success, including, but not limited to male sex, human immunodeficiency virus (HIV) co-infection, poor nutritional status, drug resistance, advanced age, alcohol consumption, smoking, and sputum smear non-conversion at two months.<sup>[3,4]</sup> However, the potential effect of eosinophil count on TB treatment success has not been explored in the current literature.

Eosinophilia is generally defined by an absolute eosinophil count (AEC)  $\geq 500$  cells/ $\mu\text{L}$ .<sup>[3]</sup> Use of the AEC is preferred over the eosinophil percentage (which is typically  $< 5\%$  in healthy individuals) because the latter is influenced by variations in the total white blood cell (WBC) count and the proportions of other leukocytes, such as lymphocytes and neutrophils.<sup>[5]</sup> Eosinophilia is a frequent clinical finding associated with a broad spectrum of disorders, including allergic, infectious, neoplastic, and idiopathic disease processes.<sup>[6]</sup> While some mycobacterial infections may induce eosinophilia, and certain standard treatments (e.g., H-E-R) have been rarely associated with it,<sup>[7]</sup> the precise causes and effects of this condition in the context of TB remain largely unknown. Eosinophils are known to release various mediators, including proteins, growth factors, and interleukins. While the full range of effects of all these released mediators is not fully established, evidence suggests that eosinophil cationic proteins (ECP) possess both mycobactericidal and lytic properties. In vitro studies have further demonstrated that human eosinophil peroxidase (EPO) can induce surface alterations and subsequent lysis of MTB. Furthermore, macrophages containing EPO have exhibited potent antimycobacterial activity.<sup>[8,9]</sup>

This study was designed to investigate the effect of eosinophilia development on treatment duration in patients newly diagnosed with drug-sensitive pulmonary TB. The potential implications of our findings are sig-

nificant, as they may inform a more efficient and effective treatment approach for TB management.

## Materials and Methods

This was a retrospective cohort study involving patients with TB managed at our center. Our institution, designated as one of four national TB centers, provides comprehensive care for both outpatients and inpatients with TB, including those with drug-resistant disease. A total of 6,045 patients treated for pulmonary TB between 2017 and 2022 were screened for inclusion in this study. All patients diagnosed with TB in our region are managed and followed at our center. Patient follow-up involves monthly chest radiographs and sputum cultures. Treatment termination decisions are made by the center's physicians based on these findings and clinical assessment. In compliance with national regulations, the follow-up process and all patient data are meticulously recorded. The study protocol received approval from Izmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2023/38-39, Date: 21.06.2023).

### Study design, inclusion, and exclusion criteria

We planned to divide patients who met the inclusion and main exclusion criteria, based on AEC, into the control group (Group 1, no eosinophilia) and the study group (Group 2, eosinophilia). Eosinophilia was defined as an AEC  $\geq 500$  cells/ $\mu\text{L}$ .<sup>[3]</sup> We screened a total of 6,045 patients who were treated between 2017 and 2022.

Patients were included in the study if they presented as new cases of TB with simultaneous evidence of TB-compatible lesions on chest imaging (evaluated by both chest X-ray and thoracic computed tomography) and microbiological confirmation of MTB infection, defined by positive acid-fast bacilli (AFB) identification and either polymerase chain reaction (PCR) positivity or culture positivity in sputum or bronchoscopic samples.

We excluded patients with coexisting conditions such as immunologic and hematologic diseases; other pre-existing lung diseases, including asthma or chronic obstructive pulmonary disease (COPD) (based on prior diagnosis in the national database); human immunodeficiency virus (HIV) positivity (routinely checked); thyroid diseases (thyroid-stimulating hormone [TSH] is regularly checked); diagnosed or suspected malignancy; liver or

renal disorders identified at baseline or during follow-up; discontinuation of anti-TB medication(s) for any reason; a smoking history exceeding 10 pack-years (PY); and age under 18 years. These exclusion criteria were applied to the entire study population.

We applied rigorous exclusion criteria to control for confounding factors. A large number of patients were systematically excluded due to confounding factors: 21 cases of HIV; 1,334 with liver dysfunction; 498 with renal dysfunction; 977 with COPD; 136 with asthma; 401 with immunologic/hematologic diseases; 1,241 with a smoking history >10 PY; 391 with malignancy; 127 with thyroid disease; 91 with multi-drug resistance (MDR); 8 with extensive drug-resistance (XDR); 5 with pre-XDR; 186 treatment failures; 96 relapses; 91 treatment withdrawals; 101 deaths; 90 with drug discontinuation for reasons such as gastrointestinal symptoms without elevated liver function tests; and 6 with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Furthermore, a total of 508 cases that were consulted with the Department of Allergy and Immunology were excluded following definitive diagnoses of drug allergy, urticaria, allergic asthma, or idiopathic/immunologic diseases.

To isolate the effect of severe eosinophilia on treatment duration in patients with eosinophilia, the exclusion criteria included an AEC  $\geq 1500$  cells/ $\mu\text{L}$ , and 5 patients with severe eosinophilia (AEC  $\geq 1500$  cells/ $\mu\text{L}$ ) were excluded from the study group. The AEC was routinely monitored in the blood of all screened patients, both at baseline (before treatment) and during follow-up.

Following these rigorous exclusions, particularly the exclusion of patients with allergic causes of eosinophilia, 240 eligible patients were ultimately included in the final analysis, ensuring a robust sample size. Of these, 121 contemporary patients meeting all inclusion and main exclusion criteria were assigned to the control group (Group 1, no eosinophilia,  $< 500$  cells/ $\mu\text{L}$ ), and 119 patients in whom eosinophilia was present but no underlying cause could be identified after specialized consultation were designated as the study group (Group 2, eosinophilia,  $\geq 500$  cells/ $\mu\text{L}$ ).

Treatment duration was calculated as the total calendar time, in months, from initiation of the anti-TB regimen to the final decision of treatment completion by the center's physician.

### Sample size

The study sample size was calculated using a multiple regression approach with G\*Power version 3.1.9.7. Accordingly, it was estimated that approximately ten predictors that could affect treatment duration would be included in the model. The minimum number of subjects to be included in the study for the model, which was predicted to have a maximum of 10 independent predictors with Cohen's medium effect ( $f=0.15$ ), type I error of 0.05, and 0.80 power, was calculated as 118 subjects.

### Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 28; IBM Corp., Armonk, New York, USA). Nominal variables were presented as frequencies and compared using the chi-square test. Continuous variables were presented as median, minimum, and maximum values, as they were not normally distributed. Comparisons between groups were performed using the Mann-Whitney U test.

For multivariate analysis, the continuous variable "treatment duration" was dichotomized into two categories: standard treatment duration ( $\leq 6$  months) and prolonged treatment duration ( $> 6$  months). Binary logistic regression analysis was then performed to determine the independent effects of comorbidities and eosinophilia on the likelihood of prolonged treatment. Odds ratios (OR) and 95% confidence intervals (95% CI) were reported. The probability of a type I error was set at  $\alpha=0.05$ , and all statistical tests were two-sided. A p-value  $< 0.05$  was considered statistically significant.

## Results

A total of 240 patients were included in the final analysis, divided into two groups: the control group (Group 1, no eosinophilia) with 121 patients and the study group (Group 2, eosinophilia) with 119 patients. A statistically significant difference in gender distribution was observed between the two groups ( $p=0.001$ ), with Group 1 comprising 85 males (70.2%) and Group 2 comprising 106 males (89.1%). Regarding the clinical setting, significantly more patients in Group 2 were managed as inpatients (26 patients) compared to Group 1 (11 patients), and this difference was statistically significant ( $p=0.011$ ). Analysis of common comorbidities revealed no statistically significant differences in the prevalence of diabetes mellitus (DM) (23 patients in Group 1 vs. 16 in Group

**Table 1: Demographic and laboratory characteristics of the patients**

Variables	Group 1 (No Eosinophilia)	Group 2 (Eosinophilia)	p
Age (years)	43 (18–82)	45 (18–84)	0.485
ALT (unit/L)	24 (9–31)	23 (17–32)	0.431
AST (unit/L)	28 (11–40)	28 (12–33)	0.191
Creatinine (mg/dL)	0.9 (0.2–1.2)	0.8 (0.7–1.1)	0.340
Eosinophils (cells/ $\mu$ L) (baseline)	100 (0–400)	200 (0–500)	<0.001
Eosinophils (%) (baseline)	1 (0–5)	2 (0–6)	<0.001
Eosinophils (cells/ $\mu$ L) (1 <sup>st</sup> month)	200 (0–500)	500 (0–1400)	<0.001
Eosinophils (%) (1 <sup>st</sup> month)	2 (0–5)	6 (0–19)	<0.001
Eosinophils (cells/ $\mu$ L) (2 <sup>nd</sup> month)	100 (0–400)	400 (0–1400)	<0.001
Eosinophils (%) (2 <sup>nd</sup> month)	2 (0–6)	4 (0–13)	<0.001
Peak eosinophils (cells/ $\mu$ L)	200 (40–500)	600 (300–1450)	<0.001
Peak eosinophils (%)	3 (0–6)	8 (3–28)	<0.001
Eosinophils (cells/ $\mu$ L) (end of treatment)	100 (0–400)	300 (0–1450)	<0.001
Eosinophils (%) (end of treatment)	2 (0–6)	5 (1–28)	<0.001
Treatment duration (months)	7 (6–9)	6 (6–9)	0.013

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

2;  $p=0.321$ ) or hypertension (HT) (8 patients in Group 1 vs. 9 in Group 2;  $p=0.972$ ). Other cardiac comorbidities, such as heart failure (one patient) and coronary artery disease (three patients), were infrequent and observed exclusively in Group 2.

The median age of the control group (Group 1) was 43 years (range: 18–82 years), which was comparable to the study group (Group 2), with a median age of 45 years (range: 18–84 years), indicating no statistically significant difference between the groups ( $p=0.485$ ). Furthermore, baseline liver and renal function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and creatinine, showed no significant differences between the groups. Importantly, a statistically significant difference was observed in the duration of anti-tuberculosis treatment between the groups ( $p=0.013$ ). Specifically, the median treatment duration for Group 1 was 7 months (range: 6–9 months), whereas the median duration for Group 2 was 6 months (range: 6–9 months). The detailed characteristics of the patients are summarized in Table 1.

To determine the independent factors affecting TB treatment duration, logistic regression analysis was performed using the dichotomized outcome of standard ( $\leq 6$  months) versus prolonged ( $>6$  months) treatment. The model examined the effects of comorbidities, age, gender, and eosinophilia.

In the univariate analysis, no statistically significant associations were observed for age ( $p=0.438$ ), gender ( $p=0.699$ ),

or hypertension ( $p=0.414$ ). In contrast, statistically significant associations were found for DM and eosinophilia.

In the multivariate model, variables were entered in a stepwise manner to identify independent predictors. Age was excluded from the final multivariate model because it was evenly distributed between the study groups and showed no significant association with the outcome in univariate analysis. The multivariate model revealed that DM was strongly associated with an increased likelihood of prolonged treatment (OR: 3.20; 95% CI: 1.57–6.52;  $p=0.001$ ). Regarding eosinophilia, the analysis indicated that the absence of eosinophilia (Group 1) was significantly associated with an increased likelihood of prolonged treatment, with an odds ratio of 2.06 (95% CI: 1.14–3.71;  $p=0.017$ ). In other words, patients who developed eosinophilia were significantly less likely to require prolonged treatment compared to those who did not. These results are presented in detail in Table 2.

## Discussion

Our primary finding demonstrates that TB patients who developed eosinophilia during treatment experienced a significantly shorter treatment duration compared to the non-eosinophilia control group. This primary outcome, observed after rigorously excluding allergic and secondary causes, suggests a potential beneficial role of eosinophilia in the host response to TB. As widely accepted, the AEC is the most reliable metric for defining

**Table 2: Multivariate logistic regression analysis**

Step	Variables	B	SE	Wald value	p	OR (CI: Lower-Upper)
Step 1	HT (Present/Absent)	0.14	0.56	0.06	0.797	1.15 (0.38-3.47)
	DM (Present/Absent)	1.11	0.38	8.45	0.004	3.03 (1.43-6.41)
	Sex (Male/Female)	0.36	0.37	0.96	0.328	1.44 (0.69-2.97)
	Group (No eosinophilia/Eosinophilia)	0.72	0.30	5.80	0.016	2.06 (1.14-3.71)
	Constant	-1.52	0.42	13.3	<0.001	0.22
Step 2	DM (Present/Absent)	1.14	0.37	9.65	0.002	3.12 (1.52-6.39)
	Sex (Male/Female)	0.35	0.37	0.91	0.340	1.42 (0.69-2.91)
	Group (No eosinophilia/Eosinophilia)	0.72	0.30	5.77	0.016	2.05 (1.41-3.70)
	Constant	-1.50	0.41	13.4	<0.001	0.22
Step 3	DM (Present/Absent)	1.16	0.36	10.2	0.001	3.20 (1.57-6.52)
	Group (No eosinophilia/Eosinophilia)	0.63	0.28	4.9	0.017	2.06 (1.14-3.71)
	Constant	-1.18	0.23	26.9	<0.001	0.31

SE: Standard error, OR: Odds ratio, CI: Confidence interval, HT: Hypertension, DM: Diabetes mellitus.

eosinophilia rather than the percentage threshold, as the latter depends on the total white blood cell count.<sup>[3]</sup> Consistent with standard definitions, we used an AEC of up to 500 cells/μL as the normal upper limit and applied this cut-off value in peripheral blood for group assignment.

In our multivariate analysis, DM emerged as a strong independent predictor of prolonged treatment duration (OR: 3.20; 95% CI: 1.57–6.52). This finding within our cohort aligns with the well-documented association between DM and susceptibility to MTB infection.<sup>[10]</sup> Individuals with DM typically experience a state of chronic, subclinical inflammation that impairs overall immune function, often necessitating longer or more complex treatment courses. This negative prognostic impact of DM stands in stark contrast to the protective association observed with eosinophilia in our study. While metabolic comorbidities such as DM appear to hinder rapid clearance, the development of eosinophilia correlates with a shortened treatment duration, suggesting that these two factors may represent opposing immunological influences on TB treatment outcomes.

The shorter treatment duration observed in our eosinophilia group aligns with in vitro evidence suggesting a direct antimycobacterial role for eosinophil products. Specifically, a study by Borelli et al.<sup>[8]</sup> demonstrated that EPO, released from eosinophils, can strongly disrupt the cell wall of MTB, ultimately leading to the organism lysis. Although no previous human study has investigated the direct link between eosinophilia development during TB treatment and treatment duration, the substantial disruptive effect of EPO on the MTB cell wall may contribute to the observed more rapid clinical

recovery. However, contrasting evidence exists, as a separate study conducted in guinea pigs infected with MTB failed to show any direct interaction between eosinophils and mycobacteria within infection lesions.<sup>[11]</sup>

Previous literature, primarily consisting of case reports, suggests an interaction between TB and eosinophilia, with TB potentially acting as an underlying cause of increased eosinophil counts. For instance, Garg et al.<sup>[12]</sup> presented a case of a 68-year-old female diagnosed with TB after other causes of marked eosinophilia (total leukocyte count  $12 \times 10^9$  cells/L with an eosinophil percentage of 32%) were excluded. Similarly, two pediatric case reports described patients with pulmonary and hepatic TB presenting with striking eosinophilia (eosinophil percentages of 72% and 50%, respectively).<sup>[13,14]</sup> The magnitude of eosinophilia reported in these cases was considerably higher than the levels observed in our study population, given our strict exclusion of patients with an AEC  $\geq 1500$  cells/μL. Although a definitive epidemiological association between eosinophilia and TB has not been established, and the impact of eosinophilia on the TB treatment process has not been previously investigated, our robust findings indicate that patients who developed eosinophilia during treatment required a shorter treatment duration. To strengthen the validity of this finding and minimize confounding factors, our study applied strict exclusion criteria, systematically ruling out numerous conditions known to affect both treatment duration and eosinophil count.

The prognostic significance and functional role of eosinophils have also been investigated in other infectious contexts, particularly viral diseases. For instance,

in patients with Coronavirus Disease 2019 (COVID-19), the development of eosinopenia within nine days of onset has been identified as a predictor of poor prognosis, suggesting that eosinophils may provide a protective benefit, possibly by modulating neutrophil-induced inflammation.<sup>[15]</sup> While the traditional focus has often been on the potentially harmful proinflammatory functions of eosinophils, emerging evidence highlights their specific antiviral capabilities. This is particularly evident in respiratory syncytial virus (RSV) infection, where eosinophils demonstrate antiviral activity through the release of granule proteins such as eosinophil-derived neurotoxin (EDN) and ECP. Furthermore, eosinophils are capable of generating nitric oxide (NO) via the NO synthase pathway, a mechanism that has demonstrated antiviral efficacy against both parainfluenza virus and RSV.<sup>[16–18]</sup>

Eosinophils are known to express Toll-like receptors (TLRs), specifically TLR-3, TLR-7, and TLR-9, which are typically activated during viral recognition.<sup>[19–21]</sup> These receptors play a pivotal role in the innate immune response and the subsequent initiation of adaptive immunity against various infectious agents.<sup>[22,23]</sup> Upon activation, TLRs regulate the transcription of key proinflammatory cytokines (including interleukin-1 beta [IL-1 $\beta$ ], tumor necrosis factor-alpha [TNF- $\alpha$ ], and IL-6) which are fundamental for the recruitment of immune cells to the site of infection and the effective control of MTB.<sup>[24]</sup> The importance of this pathway is underscored by murine studies demonstrating that TLR-2 and TLR-4 are essential for recognizing MTB pathogen-associated molecular patterns (PAMPs), and that mice deficient in TLR-2 or TLR-8 genes fail to control the infection and succumb to the disease.<sup>[25,26]</sup> Furthermore, activation of TLR-2 by bacterial lipoprotein (19-kD) in macrophages has been shown to trigger mycobactericidal activity; however, unlike findings in viral models, some studies indicate that this specific pathway may not involve nitric oxide production.<sup>[27,28]</sup> Consequently, eosinophils appear to significantly influence the immunopathology of MTB infection; however, their protective effect is likely multifactorial, potentially involving not only TLR activation but also other distinct pathways that remain to be fully established in the literature.

This study is subject to several limitations inherent to its design. First, as a retrospective cohort analysis, despite mandatory and rigorous data registration in our

national system, the study is subject to potential selection bias and cannot establish a causal relationship between eosinophilia and shortened treatment duration. Second, the study was conducted at a single tertiary center, which may restrict the generalizability of our findings to other settings. Third, a significant limitation is the absence of data regarding cavitory lesions on baseline chest imaging, a well-established determinant of treatment duration in TB, which was not recorded in our database and may represent a residual confounder. Fourth, we did not specifically analyze the prognostic impact of the timing of eosinophilia onset (e.g., early vs. late development). Fifth, the strict exclusion criteria—necessary to isolate idiopathic eosinophilia—significantly reduced our sample size and resulted in the exclusion of patients with common comorbidities. Additionally, we observed a significant male predominance in the eosinophilia group compared to controls; however, multivariate regression analysis included gender as a covariate and found no significant association between sex and treatment duration, suggesting that this disparity likely did not skew the primary outcome. Finally, we relied on peripheral blood counts and did not quantify specific eosinophil-derived mediators (e.g., ECP or EPO), therefore, the precise biological mechanisms remain speculative.

## Conclusion

The immunopathology of TB is intricate and remains a subject of ongoing investigation. The precise function of eosinophils in many disease contexts, including TB infection, is only partially understood. Our study demonstrates that the development of eosinophilia during treatment of drug-susceptible pulmonary tuberculosis is associated with a significantly shorter duration of therapy. Conversely, the absence of eosinophilia emerged as an independent predictor for prolonged treatment duration, highlighting the potential prognostic value of eosinophil kinetics in clinical practice. These findings suggest that eosinophils may play a protective role in the host immune response against MTB, rather than merely representing an allergic drug reaction. While the retrospective nature of this study warrants caution, our results provide a clinical foundation for further prospective investigation into the use of eosinophil counts as a novel, accessible biomarker to guide and potentially personalize TB treatment management.

### Ethics Committee Approval

The study was approved by the Izmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (No: 2023/38-39, Date: 21/06/2023).

### Informed Consent

Written informed consent was not required due to the retrospective nature of this study.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

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### Use of AI for Writing Assistance

No use of AI-assisted technologies was declared by the authors.

### Author Contributions

Concept – S.Y., S.D.; Design – S.D.; Supervision – S.D., O.K.; Resource – S.Y., O.K., G.V.Ş.; Materials – S.Y., O.K., G.V.Ş.; Data Collection and/or Processing – S.Y., O.K., G.V.Ş.; Analysis and/or Interpretation – S.Y., S.D.; Literature Review – S.Y., G.V.Ş.; Writing – S.Y., S.D.; Critical Review – S.D., O.K.

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Externally peer-reviewed.

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