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# Thiol-disulfide homeostasis in irritable bowel syndrome

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**Abstract. – OBJECTIVE: The etiopathogenesis and pathophysiological mechanism of irritable bowel syndrome (IBS) is not fully known. In this study, evaluating dynamic thiol-disulfide homeostasis (TDH) in patients with IBS was aimed.**

**SUBJECTS AND METHODS: A total of 92 people, 46 IBS patients and 46 healthy sex and aged-matched volunteers, were included in the study. Thiol/disulfide parameters in serum were measured in all cases, and the two groups were compared.**

**RESULTS: Disulfide levels (21.9 ± 5.0 µmol/L *vs.* 19.4 ± 4.2 µmol/L, respectively; $p < 0.001$), disulfide/native thiol (5.7% ± 1.2% *vs.* 4.9% ± 0.8%, $p < 0.001$, respectively) and disulfide/total thiol ratio (5.1% ± 0.9% *vs.* 4.5% ± 0.7%, respectively, $p < 0.001$) were found to be higher in IBS patients, and native thiol/total thiol ratio (89.8% ± 1.9%, 90.6% ± 1.9%, $p < 0.001$, respectively) was found to be lower in IBS patients.**

**CONCLUSIONS: In our study, it was shown that TDH is impaired in IBS, which is an important result supporting studies showing that oxidative stress plays a role in IBS. On the other hand, it is thought that this study will contribute to the literature in terms of being the first study evaluating TDH in adult IBS.**

*Key Words:*
Irritable bowel syndrome, Oxidative stress, Thiol-disulfide homeostasis.

## Introduction

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by recurrent abdominal pain, associated with defecation or changes in intestinal habits in the absence of detectable structural and biochemical abnormalities. For diagnosis, the onset of symptoms should occur at least 6 months ago and should last for the last 3 months[1]. It is a common functional disease that generates a significant burden on the healthcare system and can adversely affect the quality of life of the patients. The prevalence of subjects with severe IBS is widely variable, ranging from 8.4% to 55% and depending on countries and methods of evaluation. The etiopathogenesis and pathophysiological mechanism of IBS are not fully known[2-4]. Life stressors, infections, food intolerance, visceral hypersensitivity, increased mucosal immune activation, impaired intestinal permeability and altered brain-gut interaction are considered responsible factors. However, these factors were not sufficient to explain the etiology of IBS[5].

Oxidative stress is defined as an imbalance between the generation of ROS within cells and tissues and endogenous detoxification mechanisms, such as superoxide dismutase, catalase, and glutathione peroxidase[6]. Recent research[7,8] has suggested that reactive oxygen species (ROS) and antioxidant system imbalance may occupy a role in the development of IBS. Much of our knowledge about the role of oxidative stress (OS) in the IBS etiology comes from experimental research. IBS patients have been shown to have increased oxidants, while antioxidants have decreased, compared with healthy subjects in human studies[9]. OS is the result of the imbalance between pro-oxidants, oxidants and antioxidants in the body and plays a role in several physiological conditions. Recent studies[10-13] have shown the relationship between increased inflammation, oxidative stress, and thiol metabolism. This pathological pathway has been studied in studies involving psychiatric, neurological, and gastrointestinal diseases. Thiols contribute to the total antioxidants in the organism and are important

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molecules in defense against OS. At the same time, thiols play an important role in the regulation of programmed cell death, cellular enzymatic activity, and detoxification[14]. Thiols are organic compounds with a sulfhydryl group (-SH) on their active region. Under oxidative stress, thiol sulfhydryl groups oxidize and form disulfide bonds. As a result, they protect the tissue from oxidative damage. This reaction is reversible, and the disulfide bonds return to their original state. The dynamic thiol-disulfide homeostasis (TDH) is thus maintained, which is essential for cellular redox balance[15]. Until recently, only one side (thiol) of the thiol/disulfide balance could be measured, while today, both sides of the equilibrium can be determined using the latest test methods, and the thiol/disulfide balance can be completely evaluated[16]. Dynamic thiol-disulfide measurement was first begun with a new automatic method developed by Erel and Neselioglu[11]. Many diseases of unknown etiology have been associated with impaired TDH[17-19]. There are few studies in the literature investigating the OS status in IBS by evaluating the thiol-disulfide balance in adult patients with IBS. It is aimed to evaluate the oxidative status of patients with IBS by TDH parameters in this study.

## Subjects and Methods

### Study Population

The study was carried out prospectively at Harran University Hospital between December 2020 and December 2021. Patients diagnosed with IBS according to Rome IV criteria and other organic causes excluded by routine diagnostic studies were included1. The number of patients was determined by G power analysis. The study included total 92 people, sex and age matched 46 patients with IBS and 46 healthy volunteers. Patients under the age of 18, pregnant women, patients with additional gastrointestinal disease, and cancer patients were excluded from the study. Demographic and clinical characteristics (age, gender, marital status) and laboratory results (hemogram, vitamin D, vitamin B12, folic acid, ferritin, total thiols, native thiols and dynamic disulfide) were recorded.

### Biochemical Parameters

Venous blood samples were taken from all participants for TDH tests. Blood samples were centrifuged for 10 minutes at 4000 rpm, and stored at -80°C. Then, parameters were studied in the same session and in all serum samples. Other laboratory parameters of the participants were the routine parameters at the time of enrollment and were recorded from the patient files.

### Thiol-Disulphide Homoeostasis

Total thiol, native thiol, and disulfide levels were evaluated using a new and fully automated test developed by Erel and Neselioglu[11]. The total thiol content was determined by using Ellman's reagent. Next, the native thiol levels were subtracted from the total thiol levels, and 50% of this difference revealed the amount of disulphide bonds. To measure the amount of native thiol and disulphide, an automated clinical chemistry analyser Cobas 501 (Roche, Mannheim, Germany) was used. Serum thiol and disulfide values were measured as μmol/L.

### Statistical Analysis

A pilot study was conducted with a control and a patient group who applied to the center, each consisting of 10 people. The mean value of the total thiol was 90.66 ± 1.09 for the patient group and 91.27 ± 1.01 for the control group. In the G power analysis, it was seen that with 95% power and 5% margin of error, the sample size was sufficient for both groups. In the study, analyses were made using the SPSS 20 statistical package program (IBM Corp. Armonk, NY, USA). Categorical variables were shown as numbers and percentages. The Kolmogorov-Smirnov test was used to evaluate the suitability of the data to normal distribution. The distribution of continuous variables was shown with mean and standard deviation. Mann Whitney U and correlation analysis (Pearson and Spearman) were performed for univariate analyses. The significance level was accepted as $p < 0.05$.

## Results

A total of 92 people, 46 patients with IBS and 46 healthy volunteers were included in the study. There were 22 (47.8%) women and 24 (52.2%) men in the IBS group, with a mean age of 39.0 ± 11.9 years. In the control group, there were 29 (63.0%) women and 17 (37.0%) men, and their mean age was 40.8 ± 10.1 years. The two groups were similar in terms of age and gender. The mean vitamin B12 levels was significantly higher in the IBS group than the control group (350.1 ± 114.8 pg/ml *vs.* 279.8 ± 71.4 pg/ml, respectively, $p < 0.05$). The socio-demographic characteristics and laboratory findings of the two groups are summarized in Table I.

**Table I.** Socio-demographic characteristics and laboratory.

| | IBS group | Control group | *p*-value |
|---|---|---|---|
| Gender (male), n (%) | 24 (52.2) | 17 (37.0) | 0.14 |
| Age (year) | 39.0 ± 11.9 | 40.8 ± 10.1 | 0.48 |
| Marital status (married), n (%) | 32 (71.1) | 37 (80.4) | 0.29 |
| Additional disease, n (%) | 3 (6.5) | 0 (0.0) | 0.24 |
| Cigarette, n (%) | 14 (31.1) | 9 (19.6) | 0.20 |
| Alcohol, n (%) | 2 (4.4) | 1 (2.2) | 0.61 |
| Vitamin D (µg/L) | 16.31 ± 10.10 | 16.65 ± 14.09 | 0.63 |
| Vitamin B12 (pg/mL) | 350.1 ± 114.8 | 279.8 ± 71.4 | 0.01 |
| Folate (ng/mL) | 10.95 ± 16.82 | 8.35 ± 2.79 | 0.56 |
| Ferritin | 60.83 ± 59.17 | 73.34 ± 136.39 | 0.40 |
| Hemoglobin (10e3/uL) | 14.30 ± 1.99 | 13.62 ± 2.41 | 0.24 |
| Hematocrit (%) | 44.21 ± 5.28 | 42.78 ± 6.04 | 0.26 |
| MCV (fL) | 83.32 ± 6.79 | 82.84 ± 8.02 | 0.54 |
| Neutrophil (10e3/uL) | 2.03 ± 0.75 | 2.22 ± 1.04 | 0.39 |
| Lymphocyte (10e3/uL) | 2.56 ± 1.12 | 2.16 ± 0.71 | 0.05* |
| Platelet (10e3/uL) | 314.93 ± 80.13 | 262.13 ± 67.62 | < 0.001 |

MCV: Mean Corpuscular Volume.

Total thiol (428.9 ± 72.9 µmol/L *vs.* 433.4 ± 80.8, $p = 0.90$) and native thiol (385.0 ± 67.3 µmol/L *vs.* 394.5 ± 75.4 µmol/L, $p = 0.65$) levels were found to be lower in the IBS group compared to the control group, but this difference was not statistically significant (Figure 1). In contrast, disulfide levels (21.9 ± 5.0 µmol/L *vs.* 19.4 ± 4.2 µmol/L, respectively; $p < 0.001$), disulfide/native thiol (5.7% ± 1.2% *vs.* 4.9% ± 0.8%, $p < 0.001$, respectively) (Figure 2) and disulfide/total thiol ratio (5.1% ± 0.9% *vs.* 4.5% ± 0.7%, respectively, $p < 0.001$) was found to be significantly higher and more native in IBS patients compared to the control group, and thiol/total thiol ratios (89.8 ± 1.9 %, 90.6 ± 1.9 %, $p < 0.001$, respectively) were found to be significantly lower (Figure 3). The thiol and derivatives findings of the IBS and control group are shown in Table II in detail. The relationship between IBS subtype and thiol derivatives levels of the IBS group was not significant (Table III).

## Discussion

The most common reason for referral to gastroenterologists in clinical practice is IBS. It is defined by symptoms such as abdominal pain and bloating, discomfort, and abnormal bowel

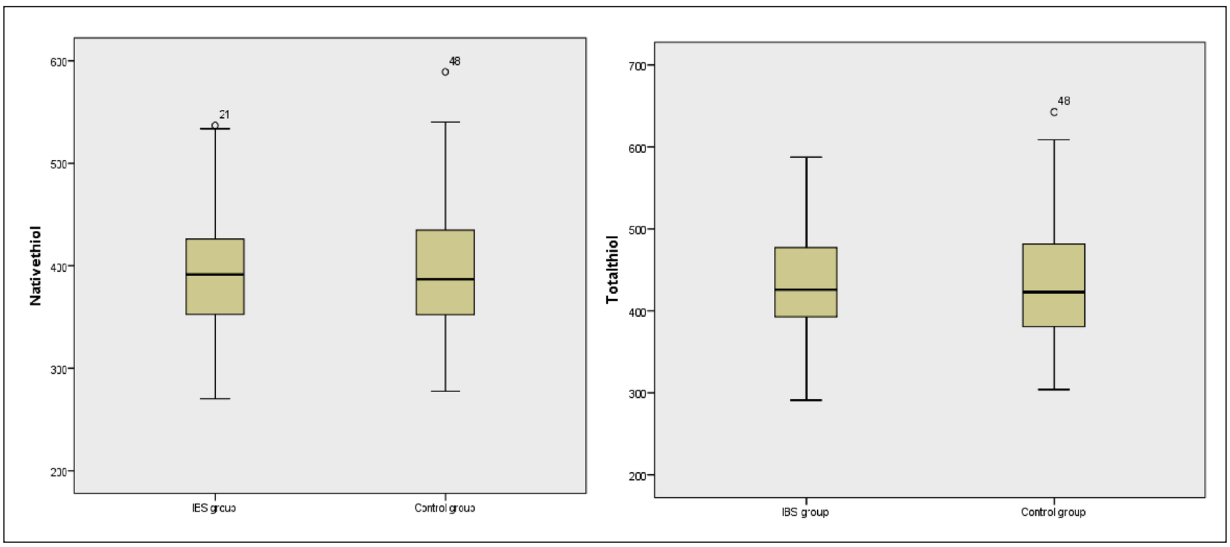


**Figure 1.** Comparison of native thiol and total thiol levels in the IBS group and control group.

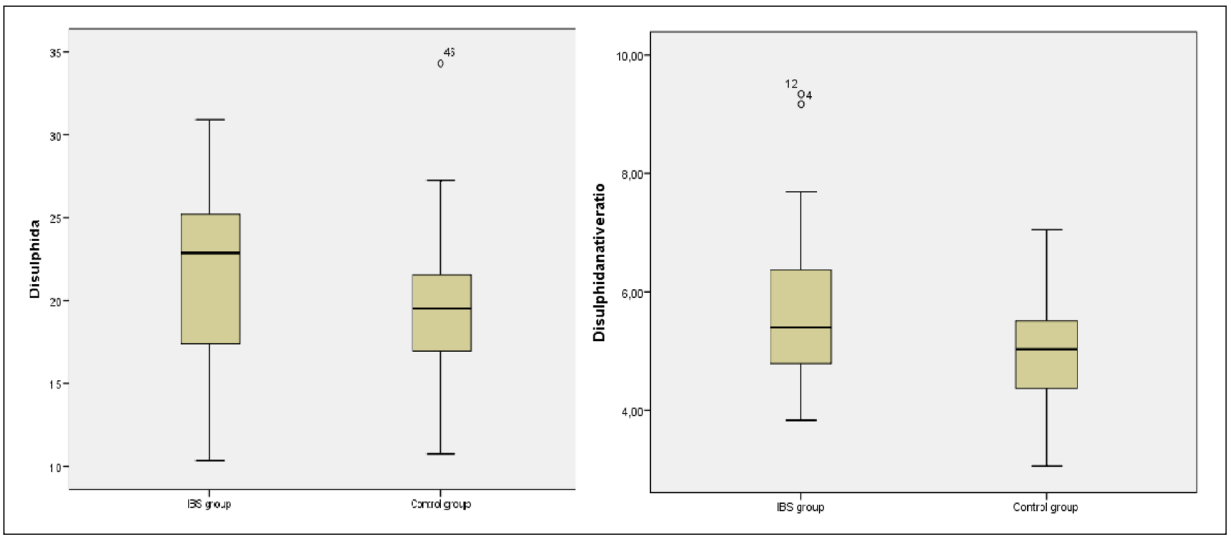


**Figure 2.** Comparison of disulfide levels and disulfide/native thiol ratio in the IBS group and control group.

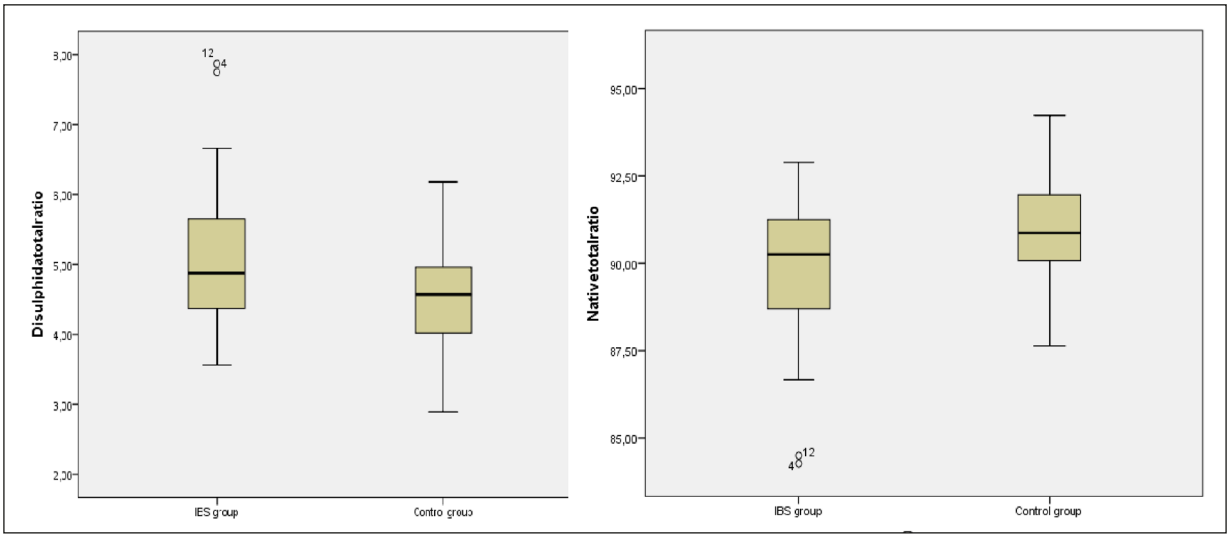


**Figure 3.** Comparison of disulfide/total thiol ratio and native thiol/total thiol ratio in the IBS group and control group.

**Table II.** Thiol and derivatives levels of the study population.

| | IBS group | Control group | *p*-value |
|---|---|---|---|
| Native thiol (µmol/L) | 385.0 ± 67.3 | 394.5 ± 75.4 | 0.65 |
| Total thiol (µmol/L) | 428.9 ± 72.9 | 433.4 ± 80.8 | 0.90 |
| Disulphide (µmol/L) | 21.9 ± 5.0 | 19.4 ± 4.2 | < 0.001 |
| Disulphide/native thiol (%) | 5.7 ± 1.2 | 4.9 ± 0.8 | < 0.001 |
| Disulphide/total thiol (%) | 5.1 ± 0.9 | 4.5 ± 0.7 | < 0.001 |
| Native thiol/total thiol (%) | 89.8 ± 1.9 | 90.9 ± 1.4 | < 0.001 |

habits. Although the pathophysiology of IBS is not fully understood, the features are associated with miscommunication between the neural, endocrine, and immune systems, inflammation and oxidative systems. Reactive oxygen species and free oxygen radicals are continuously produced in the body and eliminated by antioxidant mechanisms. They are the main molecules that cause oxidative damage to

**Table III.** Relationship between IBS subtypes and thiol derivatives levels.

| | Constipation | Diarrhea | p |
|---|---|---|---|
| Native thiol (μmol/L) | 391.64 ± 66.90 | 347.61 ± 61.80 | 0.13 |
| Total thiol (μmol/L) | 434.59 ± 80.38 | 388.52 ± 69.17 | 0.13 |
| Disulphide (μmol/L) | 22.23 ± 4.86 | 20.46 ± 6.4 | 0.45 |
| Disulphide/native thiol (%) | 5.72 ± 1.21 | 5.88 ± 1.59 | 0.77 |
| Disulphide/total thiol (%) | 5.11 ± 0.95 | 5.23 ± 1.24 | 0.76 |
| Native thiol/total thiol (%) | 89.76 ± 1.91 | 89.54 ± 2.48 | 0.77 |

various cellular and tissue structures. In this study, plasma native, total thiol levels and native thiol/total thiol percentage declined, whereas disulfide levels, disulfide/total thiol and disulfide/native thiol percentages increased significantly in the IBS group over the control group. It was shown that TDH was impaired in IBS, which supports studies showing that oxidative stress plays a role in IBS.

The involvement of OS in many common physiological pathways, as well as in common pathologies such as gastrointestinal, neurological and psychiatric diseases, and nutritional problems has been investigated for a long time[20-22]. A study[8] in animal models of IBS have reported that increased inflammation, visceral hypersensitivity, epithelial permeability, and altered brain-gut interactions may be important in the etiopathogenesis. However, it has been concluded that it is not sufficient to determine the exact cause of the disease or effective treatment approaches in humans[23]. Mete et al[24] reported a decrease in serum glutathione peroxidase, superoxide dismutase, and catalase antioxidant enzyme activities and an increase in adenosine deaminase and xanthine oxidase activities in patients with IBS. Thus, they showed that OS increased[24]. In another study[25], it was reported that IBS and OS are associated with microinflammatory processes, and OS in patients with IBS is associated with antioxidant defenses. In our study, similar to other studies, OS of IBS patients was shown to be impaired. Unlike other studies, TDH an important part of the antioxidant system, was used to evaluate oxidative stress in IBS. Evaluation of OS with TDH parameters may provide new assumptions in the pathogenesis of IBS.

Choghakhori et al[26] reported that methylmalonic acid levels increased and total oxidant capacity decreased in IBS patients. OS and inflammation seem to be inevitably linked. Another study[27] confirmed the relationship between oxidative stress and inflammation in IBS. In our study, it was thought that the change in inflammatory hematological parameters might be related to this. Vitamin B12 functions as a ROS scavenger, and it is known as a redox-active cofactor. Several studies reported unclear results regarding vitamin B12 status and OS. The antioxidant properties of vitamin B12 have been demonstrated by many studies[28,29]. In our study, vitamin B12 level was found to be significantly higher in the IBS group. This situation was interpreted as compensation to increase the antioxidant effect on increased OS.

TDH has been widely measured in recent years to evaluate OS and has only just begun to be understood more precisely. It has been shown that TDH plays a role in various diseases. These results can determine the pathogenic mechanisms, diagnosis, prognosis or treatment planning of the IBS. Total thiol levels reflect the sum of both oxidized and unoxidized thiols. Native thiols are molecules containing unreduced functional thiol groups and decrease when OS increases. They are highly potent antioxidants that protect an organism from the harmful effects of OS[30-32]. As known, thiols are a class of organic compounds containing a sulfhydryl group (-SH) consisting of hydrogen and a sulfur atom attached to a carbon atom. These disulfide bonds can be reduced to thiol groups; in this way, TDH is preserved. TDH is very important for the organism. OS increases when the equilibrium shifts towards disulphide[33-35]. It is known that abnormal TDH plays a role in the pathogenesis of acute and chronic disease. It has been shown to be impaired in many diseases such as skin diseases, vitamin D deficiency, autism, adult attention deficit hyperactivity disorder, celiac disease, acute pancreatitis, and cancer[36-40]. Recently, in a study evaluating TDH in children with IBS[41], it was observed that plasma native and total thiol levels decreased, and disulfide levels increased, the percentage of disulfide/total thiol was higher, and the percentage of natural thiol/total thiol decreased in the IBS group compared to healthy children. Similar results in this study suggested that OS may be one of the causes of the disease, and this could be focused on treatment planning. Among the IBS subtypes, antioxidants were lower in the diarrhea group than in the constipation subtype.

Oxidants were higher in the constipation group than in the diarrhea subtype. However, these findings were not statistically significant. It was thought that this can be due to the difference in patient distribution between the subgroups in the study and the low number of patients. To investigate whether OS status differs among IBS subtypes, more comprehensive, well-designed studies involving larger patient groups may be conducted.

### Limitations

The main limitation of this study is its single-center design, which makes it difficult to generalize the research results. And there were relatively few patients in the IBS subgroups, particularly the diarrhea-predominant type group, which may not be sufficient to assess OS among the IBS subgroups. It may be more informative to evaluate the relationship between IBS and TDH in a larger patient population.

## Conclusions

In conclusion, this study showed that TDH balance was impaired in IBS, especially due to a decrease in antioxidant mechanism. Impaired antioxidant status may be a critical key factor in pathogenesis or may occur during the course of illness. In addition, supportive therapy with antioxidants may be beneficial in IBS. We believe that this study will contribute to further studies on this subject.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Informed Consent

Written informed consent was obtained from the participants of the study.

### Ethics Approval

The study was approved by the Ethics Committee of Harran University, Faculty of Medicine (approval No. 76244175-050.04.04 and dated 23.11.2020).

### Availability of Data and Materials

The data presented and supporting the findings of this study are available upon reasonable request from the corresponding author (Ç.C.).

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### Authors' Contribution

Conceptualization: Ç.C., and A.U.; data curation: S.S., M.Ö.; formal analysis: Ç.C., A.U., and M.A.E.; methodology: Ç.C., and A.U.; supervision: Ö.E., and A.U.; softwares and validation: Ç.C., A.U., S.S., and M.Ö.; writing-original draft: Ç.C., and A.U.; writing-review and editing: Ç.C., and A.U. All authors have read and agreed to the published version of the manuscript in ERMPS.

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