Eradication of Helicobacter Pylori *Infections and GERD: A systematic review and meta-analysis*

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ABSTRACT

Background/Aims: *This study evaluates the association between the eradication of* Helicobacter pylori (H. pylori) *and gastroesophageal reflux disease (GERD).*

Materials and Methods: *Relevant studies were identified by conducting literature search in PubMed, Cochrane, Embase, CNKI, VANFUN, and VIP databases. The prevalence rates of gastroesophageal reflux, heartburn, epigastric pain, and nausea were extracted from the identified research articles and were used in meta-analysis of relative risks (RR) to achieve an overall effect size of the relationship between* H. pylori *eradication and GERD.*

Results: *A total of 19 randomized controlled trials were included in this meta-analysis. The prevalence of gastroesophageal reflux was significantly higher in patients with* H. pylori *eradication compared with patients without it (RR: 1.54, 95% CI: 1.06-2.24; p=0.02). A subgroup analysis did not identify any significant difference in GERD prevalence in studies conducted outside China (RR: 1.62, 95% CI: 0.98-2.68) or in China (RR: 1.30, 95% CI: 0.76-2.22). There were no significant differences in heartburn (RR: 1.03, 95% CI: 0.88-1.20), epigastric pain (RR: 0.98, 95% CI: 0.13-7.56), or nausea (RR: 0.44, 95% CI: 0.07-2.72) risk between patients with and without* H. pylori *eradication.*

Conclusion: *Eradication of* H. pylori *infection is found to be associated with GERD, although regional differences may exist in the prevalence. Well-designed studies especially those with stratification of patients' basic conditions are needed to seek refined evidence of the association between* H. pylori *eradication and the GERD.*

Keywords: Helicobacter pylori*, eradication, gastroesophageal reflux disease, randomized controlled trial, meta-analysis*

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which gastric or gastroduodenal contents flow back into the esophagus to the pharynx, larynx, or respiratory tract, thereby causing reflux acid, heartburn, chest pain, and dysphagia associated with mucosal inflammatory surge (1). Various factors, including the destruction of esophageal anti-reflux barrier and the weakening of esophageal acid scavenging play an important role in the pathogenesis of GERD. *Helicobacter pylori* (*H. pylori*) infection has been accepted as a major cause of acute/chronic gastritis and peptic ulcer disease and is an established etiological factor for gastric cancer (2, 3). Therefore, *H. pylori* infection should be eradicated especially in patients with peptic ulcer disease or a family history of gastric cancer (4).

In recent years, the eradication of *H. pylori* has become a preferable clinical practice for reducing the risk of stomach cancer and possibly of the Alzheimer's disease (5,6) but at the same time, its possible adverse effects such as GERD have garnered significant attention of physicians. Many studies have found that the eradication of *H. pylori* may cause or worsen GERD, but others found no obvious association or even noted an inverse correlation (7–10).

This study aims to examine the relationship between the eradication of *H. pylori* and GERD by performing a meta-analysis of the GERD prevalence rate data available from randomized controlled trials (RCTs) to update the evidence of this association.

MATERIALS AND METHODS

Search Strategy

To identify the studies that attempted to seek a link between treatment-mediated *H. pylori* eradication and GERD, the Cochrane, PubMed, Embase, CNKI, VANFUN, and VIP databases were searched for the identification of relevant articles. Search terms used were: Helicobacter pylori, H. pylori, gastroesophageal reflux disease, GERD,

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reflux, gastroesophageal reflux, esophageal reflux, randomized controlled trial, and RCT. We also screened the references lists of all identified articles to search for additional studies.

Study Selection Criteria

Studies to be included in this meta-analysis had to fulfill the following criteria: (1) had to be RCTs, (2) recruited patients in *H. pylori* eradication group and standard therapy (without medication for *H. pylori* eradication) group, and 3) published in English or Chinese language.

Studies were excluded for reasons including: (1) articles with repeated data or secondary analyses, (2) case reports, case-control studies, theoretical research, conference reports, systematic reviews, meta-analyses, and other forms of research or comments, and (3) qualitative studies.

The literature survey and the observation of eligibility criteria were performed by two investigators independently who unified their outputs, and disagreements were resolved either with mutual discussions or by involving a third author.

Data Extraction and Quality Assessment

For each of the included studies, data were extracted as basic information and primary study outcomes. Basic information relevant to this meta-analysis included: author names, year of publication, disease information, therapeutic strategy for *H. pylori* eradication, sample size, follow-up period, and Jadad score. Primary clinical outcomes for the meta-analysis were the dichotomous data to be used for the calculation of relative risk of gastroesophageal reflux, heartburn, epigastric pain, or nausea between *H. pylori* eradication and non-*H. pylori* eradication patients.

Study quality was assessed with Jadad scale which appraises following criteria: studies included a specific statement regarding randomization, the method used to randomize patients was appropriate, the study was conducted in a double-blinded manner, the approach to double-blinding was described appropriately, and information on any patients that withdrew from or dropped out of the study was provided. A Jadad score <3 was deemed to indicate a study of low-quality depicting a substantial risk of bias. This data extraction was performed independently by two investigators who unified their outputs with the involvement of a third researcher for resolving any disagreement/s.

Statistical Analysis

Stata software (version 10, Texas, USA) was used for all analyses. Heterogeneity in study results were estimated using chi squared and I^2 indices. A chi-squared with $p \leq 0.05$ and an $I^2 > 50\%$ of the outcomes was considered high heterogeneity. The dichotomous outcomes of the prevalence of gastroesophageal reflux, heartburn, epigastric pain, and nausea between *H. pylori* eradication and non-*H. pylori* eradication patients were used to calculate relative risks which were then subjected to meta-analyses for generating inverse-variance weighted overall effect size/s.

RESULTS

Overview of Included Studies

We screened a total of 1375 articles identified during literature search of which 1282 were excluded after title/abstract review. The remaining 93 articles were subjected to full-text reprint retrieval and assessment which led to the exclusion of 74 articles for failing to meet study inclusion criteria. We ultimately identified a total of 19 RCTs (11-29) that fulfilled the inclusion criteria. Study screening and selection process is outlined in Figure 1. Overall, these studies recruited 3285 patients in the *H. pylori* eradication group and 4148 in control group. Table 1 summarizes the basic information for each study.

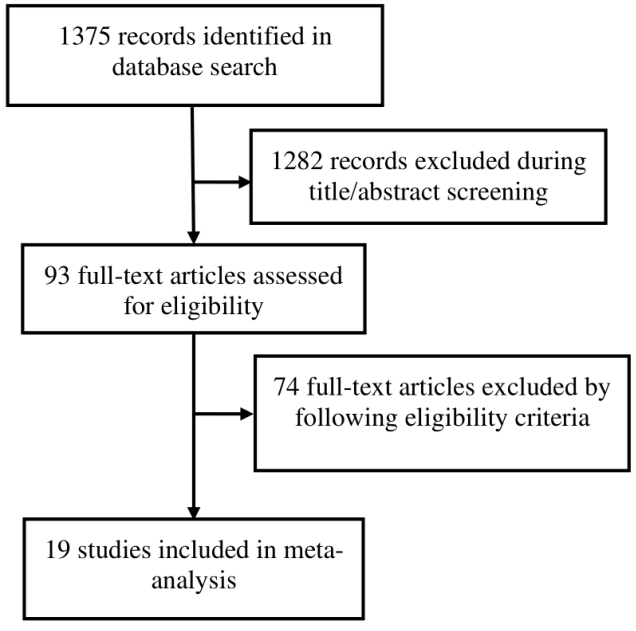

Figure 1. A flowchart of the study screening and selection strategy.

Table 1. The basic characteristics description of included studies.

Study	Region	No. of patients		Basic Disease	Drugs used for eradicating *Helicobacter pylori*	Follow-up (months)	Jadad score
		Treated	Control				
Befrits, 2000	Sweden	79	66	DU	O+A	24	4
Bytzer, 2000	Denmark	139	137	DU	O+A+M	24	3
Chen, 2001	China	74	53	DU	A+B+M	-	2
Fallone, 2000	Canada	63	24	DU	A+B+M	12	3
Hamada, 2000	Japan	286	286	Gastritis/PUD	O+A+C	12	4
Harvey, 2004	England	787	771	RS	R+C+B	24	4
Jonaitis, 2010	Lithuania	119	31	DU	R+A+M/O+A+C/O+A+M	12	3
Kim, 2001	Korea	233	144	Gastritis/PUD	A+C/P+P+I	24	3
Malfertheiner, 2002	Multicenter	162	107	DU/GU	O+A+C/O+M+C	6	4
Moayyedi, 2001	Germany	85	93	GERD	C+O+T	10	4
Nam, 2010	Korea	548	1635	Health population	O+A+C	24	5
Ott, 2005	BRAZIL	73	60	dyspepsia	L+A+C	12	4
Pilotto, 2006	Italy	31	30	RS	P+A+C	8	5
Vakil, 2000	America	64	178	DU	R+B+A+C	6	3
Wang, 2010	China	74	74	Barrett esophagus	O	-	2
Wu, 2003	China	53	51	GERD	O+A+C	12	4
Xue, 2015	China	92	84	reflux esophagitis	E	120	3
Yan, 2008	China	276	276	GERD	C+O	120	3
Zheng, 2018	China	47	48	PU	A+C+O	-	2

A: amoxicillin; B: bismuth agent; C: clarithromycin; DU: duodenal ulcer; E: Esomeprazole; GERD: Gastroesophageal Reflux Disease; GU: gastric ulcer; L: lansoprazole; M: metronidazole; N: Nexium; N/A: undefined; O: omeprazole; P: pantoprazole; PU; peptic ulcer; R: ranitidine; RS: reflux symptom; T: tinidazole

Risk of Gastroesophageal Reflux

In total, 18 studies reported the outcomes of 3221 patients in the *H. pylori* eradication group and 3970 in control group with regards to the prevalence of gastroesophageal reflux. A random-effects meta-analysis revealed that the prevalence of gastroesophageal reflux was higher in the *H. pylori* eradication group than in the control group (RR: 1.54, 95% CI: 1.06–2.24; p=0.02; I^2=64.7%, Figure 2).

Twelve studies which reported on GERD prevalence with 2478 patients in the eradication group and 3288 in control group were conducted outside China. A random-effects meta-analysis revealed an RR of 1.62 (95% CI: 0.98–2.68; I^2=73.1%; Figure 2). Among the studies conducted in China, 6 studies with 616 patients in the *H. pylori* eradication group and 586 in control patients reported on gastroesophageal reflux prevalence. A meta-analysis of these studies revealed an RR of 1.30 (95% CI: 0.76–2.22; I^2=32%; Figure 2).

Risks of Heartburn, Epigastric Pain, and Nausea

A meta-analysis of 4 studies which reported on the prevalence of heartburn in 955 patients in *H. pylori* eradication group and 1039 in control group revealed an RR of 1.03 (95% CI: 0.88–1.20; I^2=0.0%; Figure 3).

A meta-analysis of 2 studies which reported the prevalence of epigastric pain (95 patients in *H. pylori* eradication group and 208 in control group) revealed an RR of 0.98 (95% CI: 0.13–7.56; I^2=53.3%; Figure 3).

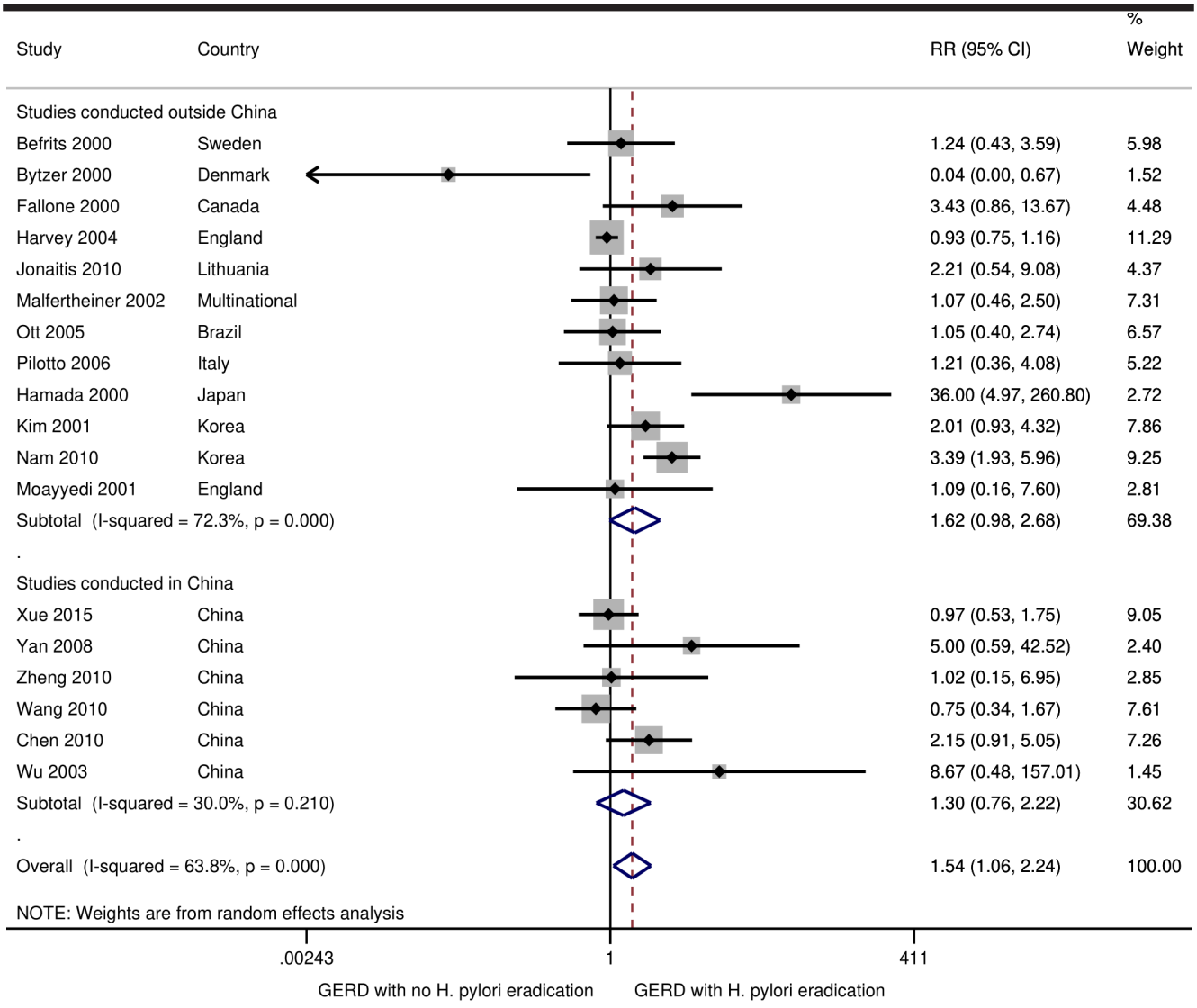

Figure 2. A forest plot showing the overall relative risk of esophageal reflux prevalence between *H. pylori* eradication and control groups and the subgroup effect sizes for the studies conducted in China and outside China.

Two studies (95 patients in *H. pylori* eradication group and 208 in control group) reported the prevalence of nausea and were subjected to a meta-analysis which yielded an RR of 0.44 (95% CI: 0.07-2.72; I^2=53.4%; Figure 3).

Quality and Bias Assessment

A mean Jadad score for the included studies was 3.42 which led us to consider the overall quality of the included studies adequate for analysis. The symmetry in the log RR funnel plot for the relative risk of gastroesophageal reflux for these studies suggested a lack of publication bias (Figure 4). The Begg and Mazumdar rank test (p=0.380) and Egger's test (p=0.899) also endorsed that there was no significant publication bias.

DISCUSSION

In this meta-analysis, we found that the prevalence of esophageal reflux is higher in *H. pylori* eradication group than in the non-*H. pylori* eradication (control) group. The prevalence of heartburn, epigastric pain, and nausea were similar between the groups, although less data was available for these meta-analyses.

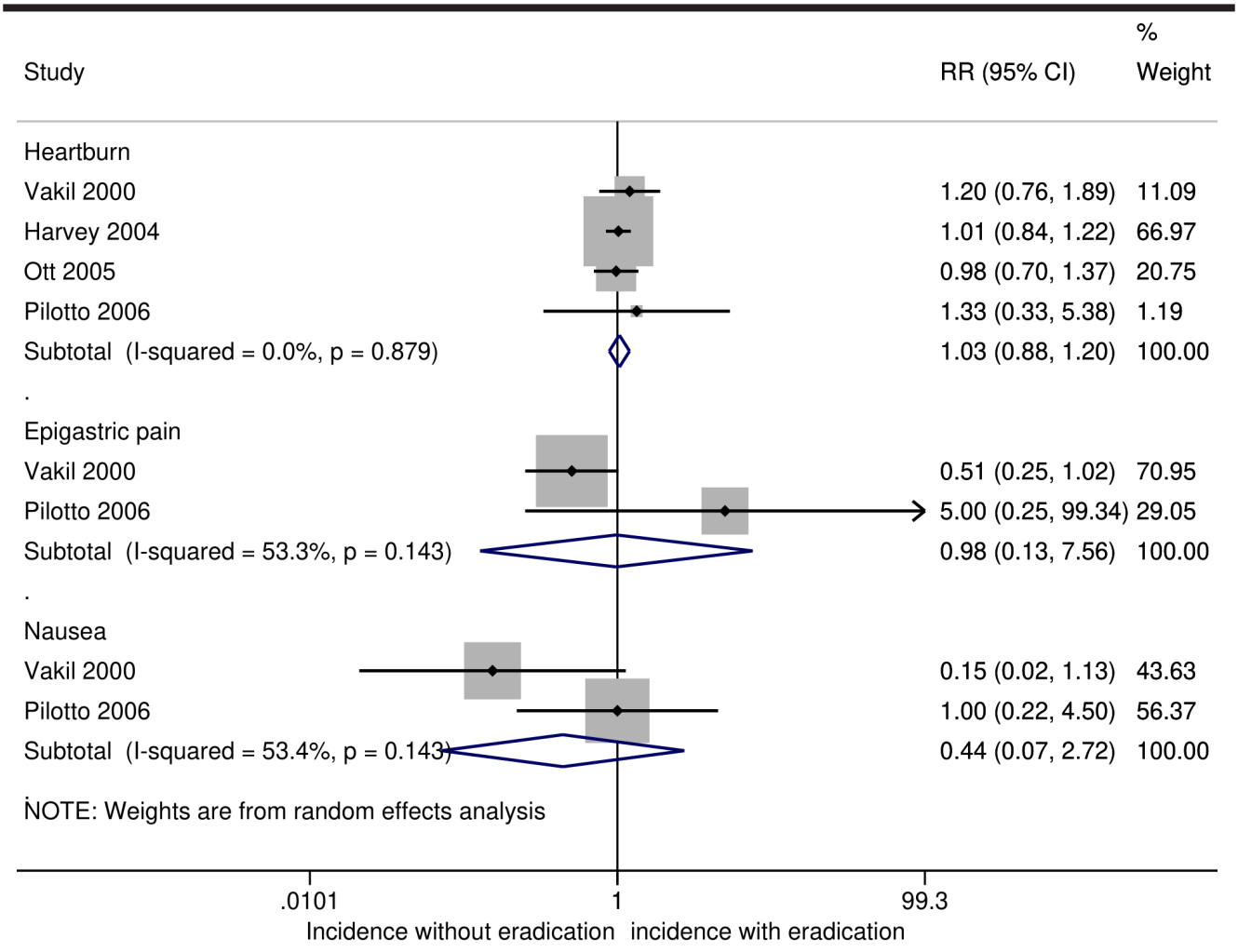

Figure 3. A forest plot showing the pooled analysis of the risk ratio of heartburn, epigastric pain, and nausea prevalence between *H. pylori* eradication and control groups.

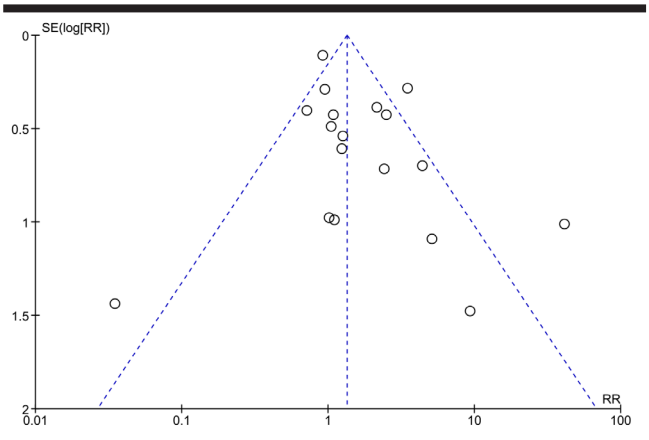

Figure 4. A funnel plot of log RR of esophageal reflux showing the absence of publication bias.

A previous meta-analysis by Qian et al. (30) that included 11 articles did not detect any significant association between *H. pylori* eradication and the development of endoscopically diagnosed GERD relative to patients with chronic *H. pylori* infections regardless of study location or follow-up duration, and the association was not affected by patient underlying disease status. Another meta-analysis of 43 studies performed by Xie et al. (31) found that in cohort studies, there was increased GERD prevalence in patients successfully treated for *H. pylori*. In this analysis, RCTs also suggested that *H. pylori* eradication was linked to elevated GERD risk, with this being particularly true for studies conducted in Asian countries.

Whether eradicating *H. pylori* infections can drive the development of GERD has been a topic of intensive re-

search focus in recent years (32), and yet results remain controversial with respect to this research question. Many studies have found different results which may in part be due to differences in patient populations including those suffering from peptic ulcers, GERD, and dyspepsia, complicating the interpretation of individual studies. GERD, as an acid reflux-related disease, is closely related to gastric acid secretion and reflux. In recent years, it has been pointed out that the influence of *H. pylori* on gastric acid secretion depends on the type and degree of related gastritis and therefore, in order to establish whether *H. pylori* infection has a protective effect on GERD, and different types of *H. pylori* infection-related gastritis need to be taken into account. Moreover, a variety of factors including the study area, basic diseases, follow-up time, average age, and type of gastritis may affect the final results. Therefore, it is necessary to provide the corresponding treatment plan according to the basic conditions of the corresponding population.

There are some limitations of this study which may have an impact on the outcomes. These include: (1) only RCTs that qualitatively ranged from 2 to 5 score on Jadad scale were included, (2) individual studies had variations in exclusion/inclusion criteria, (3) treatments for *H. pylori* eradication varied between studies, (4) GERD conditions in patients varied between studies, and (5) individual patient data were not available.

We conducted this meta-analysis with the goal of comprehensively exploring the link between *H. pylori* eradication and GERD. Our results indicate that eradication of *H. pylori* infection is associated with gastroesophageal reflux. However, regional differences in the prevalence may occur. The choice of *H. pylori* eradication treatment should be decided by considering the basic conditions of patients.

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Conflict of Interest: The authors have no conflict of interest to declare.

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