

ORIGINAL ARTICLE

**FACTORS ASSOCIATED WITH TUBERCULOSIS AMONG
CHILDREN AND ADOLESCENTS IN KELANTAN:
A CROSS-SECTIONAL STUDY**

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Abstract

Objectives: This study aimed to estimate the proportion of tuberculosis patients among children and adolescents, to describe the socio-demography and clinical factors for tuberculosis infection among children and adolescents in Kelantan from 2012 until 2015. **Methods:** This study was a retrospective cross-sectional study between tuberculosis and non-tuberculosis cases among children and adolescents using Tuberculosis Information System as a source population. All notified cases that fulfilled the inclusion and exclusion criteria were included in the study. Descriptive statistics, simple and multiple logistic regressions were used for data analysis. **Results:** Out of 5412 tuberculosis cases, 8.4% were children and adolescents group with mean age of 15. Among 322 children and adolescents with tuberculosis, majority of them were Malay (91.2%), 7.5% illiterate and 79.6% resided in non-urban area. By clinical factors, 2.8% were Human Immunodeficiency Virus (HIV) positive and 14.6% were cigarettes smokers. Older age, cigarettes smoking, female gender, Malay ethnicity, good education level and non-urban residence were the significant associated factors for tuberculosis infection among children and adolescents with AOR 1.41 (95%CI: 1.29,1.54; p<0.001), 3.35 (95% CI: 1.86, 6.01; p<0.001), 1.88 (95% CI: 1.33, 2.65; p<0.001), 0.17 (95%CI: 0.07,0.44; p<0.001), 0.20 (95%CI: 0.12,0.33; p<0.001) and 1.92 (95% CI: 1.33, 2.79; p=0.001) respectively. **Conclusion:** The study provides important criteria of children and adolescents to be prioritized for tuberculosis screening, early diagnosis and prompt treatment, and might as well mitigate the dynamic transmission of tuberculosis in the community.

Keywords: Tuberculosis, Associated Factors, Children and Adolescents

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Introduction

Malaysia is a country located in the South-East Asia region and recognized as an upper middle-income country with 31 million people. The state of Kelantan is located in the northeast of Peninsular Malaysia and its people is made up of majorly Malay population (95.7%) [1]. The Western Pacific Region, of which Malaysia is part of it, accounted for nearly 60% of the world's tuberculosis cases in 2012. Our adjacent neighbours Indonesia, the Philippines and Thailand were the three of the 22 countries with the world's highest tuberculosis burden [2,3].

The World Health Organization (WHO) reported that in 2015, there were 1 million children and adolescents infected with tuberculosis around the world, and more than 136,000 die annually [2]. Recent report from Malaysian Ministry of Health (MOH) depicted that the proportion of tuberculosis cases among children and adolescents in Malaysia range between 17% until 20% out of total tuberculosis cases with increasing trend from year 2010 until 2015 [4]. Meanwhile, exclusively for Kelantan state, the proportion of tuberculosis cases among children and adolescents range from 1% to 3.01% out of total cases from year 2000 to 2015 also with increasing trend as well [5].

A retrospective cohort study of all patients registered in the 2012 Malaysian National Tuberculosis Surveillance Database showed that 1824 cases of tuberculosis were children and adolescents which comprised about 8.5% out of total tuberculosis cases [3]. Meanwhile, an analysis study of Malaysia tuberculosis surveillance data in 2000 found that the proportion of tuberculosis cases by age groups were 2.8% (<14 year old), 67.7% (14-54 year old) and 29.5% (>54 year old)

[6]. A cohort study in Sabah in year 2001 found that 3908 patients were infected with tuberculosis. Out of these cases, 512 (13%) cases were children and adolescents and majority of the cases (59%) among children and adolescents were from the age strata of 15-19 year old [7].

Proportion of tuberculosis cases among children and adolescents globally varies from 6.6% to 39.2% [8-14]. According to the WHO regions, the proportion was higher in African region (16.0% to 39.2%), followed by Eastern Mediterranean region (35.0%), South East Asia region (20.0%), Region of the Americas (6.6% to 17.3%) and Western Pacific region (8.5%) [2].

A child or adolescent get infected with tuberculosis in the exact pattern as an adult, which is through inhalation of droplets of tuberculosis bacteria in the air deriving from person with active tuberculosis. The infection source for children and adolescents is usually a person living in the same house who has active tuberculosis and persistently cough. Besides that, children and adolescents can get infected in a communal setting such as nurseries, kindergartens, schools and colleges [15]. The risk of progression to tuberculosis disease is highest when the child age is less than four years old, and to a lesser extent when they are less than ten years old. There is also a higher risk of progression in children and adolescents who are immune-compromised, for instance Human Immunodeficiency Virus (HIV) positive individuals [15].

Children and adolescents comprises nearly 30% of total Malaysia population [1]. At the same time, tuberculosis cases among children and adolescents in Malaysia is increasing in number with almost 20% of tuberculosis cases in Malaysia are of

children and adolescents group [4]. And yet, there is no well-published local study in Malaysia to determine the associated factors for tuberculosis infection among children and adolescents. Therefore, this study aimed to estimate the proportion of tuberculosis patients among children and adolescents and tried to explore the associated factors for tuberculosis infection among children and adolescents particularly among Kelantan population. Among the known socio-demographic factors from existing literatures contributing to tuberculosis infection among children and adolescents are older children [12,16,17], Malay ethnicity [3,18,19], male gender [10,17], low education level [10,11] and resident of rural area [8]. Whereas the known clinical factors associated with tuberculosis infection included cigarette smoking [3,10] and positive HIV status [3,17,20]. We expect that the findings of our study could have a significant impact on the principles and practices of tuberculosis detection and control management in the local setting, and may help other National Tuberculosis Programs to review their criteria of detection with similar statistics.

Methods

Study design and participants

This study applied a retrospective cross-sectional study design and was conducted within three months period starting from January until March 2017 in Tuberculosis and Leprosy Control Unit, Kelantan State Health Department.

The reference populations were all children and adolescent tuberculosis patients in Kelantan and the study samples were children and adolescent with tuberculosis and non-tuberculosis in Kelantan registered

in Tuberculosis Information System (TBIS) from 2012 to 2015 who fulfilled study inclusion and exclusion criteria. In this study, the inclusion criteria were confirmed cases of tuberculosis who were notified to respective District Health Offices in Kelantan and registered in TBIS from 1st January 2012 to 31st December 2015. Non-tuberculosis cases were tuberculosis contacts who have no symptom, negative Mantoux test, no chest radiograph abnormality and registered in TBIS from 1st January 2012 to 31st December 2015. Both cases and non-tuberculosis cases must be of 1 year old till 19 year old of age.

The sample size was calculated for each variable of associated factors for tuberculosis infection among children and adolescent using Power and Sample Size calculation software as well to compare two independent proportions. The largest estimated sample for each group was 322 using the proportion of non-tuberculosis children and adolescents by factor of urban residence 0.61 [21]. The estimated proportion of 0.49, 5% type 1 error, 80% power and additional 20% missing data. We used simple random sampling method to obtain 322 study samples from respective sampling frames for each comparison group between tuberculosis and non-tuberculosis.

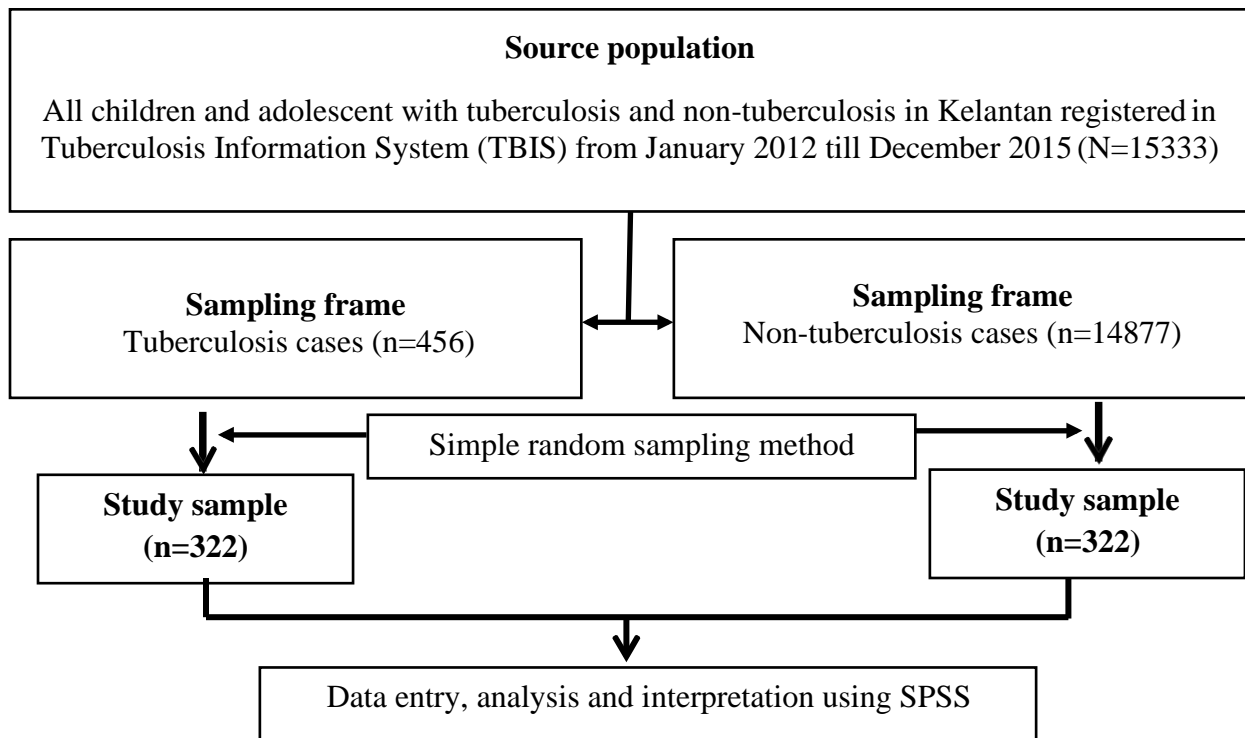
Data were collected from Kelantan TBIS. TBIS is an online registry set up by the Ministry of Health for surveillance purpose of tuberculosis disease in Malaysia. The retrieved information includes data on socio-demography (age, ethnicity, gender, location of residence and education level) and clinical factors (HIV and cigarettes smoking status).

From Kelantan TBIS, we found a total of 15333 tuberculosis cases and tuberculosis

contacts among children and adolescents from 2012 till 2015. Then we subdivided them into tuberculosis cases and non-tuberculosis cases sampling frames. From

each sampling frame, we used simple random sampling method to obtain 322 study samples for each group. The flowchart for this study is shown in Figure 1.

Figure 1. Flowchart of the study for factors associated with tuberculosis infection among children and adolescents in Kelantan



The study was approved by the Human Research and Ethics Committee, Universiti Sains Malaysia USM/JEPeM/16120592 and the Medical Review and Ethical Committee from National Institute of Health, Ministry of Health Malaysia NMRR-16-2348-33521 (IIR).

Operational definitions

In this study, good education level is defined as those above 10 years old who were attending or had attended school [22]. As for location of residence, urban areas are

defined as gazetted areas which have a combined population of 10000 or more. Meanwhile, rural areas are defined as gazetted areas which have a combined population of less than 10000 [23].

Statistical analysis

Statistical Package for Social Science (SPSS) version 22.0 statistical software was used for data entry and analysis. Descriptive statistics with mean and standard deviation (SD), frequency and percentages were calculated. Simple and multiple logistic

regression analysis were used to determine factors associated with tuberculosis infection among children and adolescents. A *p*-value of less than 0.05 was considered statistically significant.

Results

There were 5412 tuberculosis cases and 36356 tuberculosis contacts notified and registered in Kelantan TBIS during the four

year period (2012-2015). All tuberculosis cases were included to determine the proportion of tuberculosis cases among the studied population. The proportion of children and adolescents with tuberculosis out of total tuberculosis cases ranged between 8% to 9% annually between 2012 until 2015. Details regarding the proportion of tuberculosis patients among children and adolescents in Kelantan from 2012 till 2015 were shown in Table 1.

Table 1. Proportion of tuberculosis patients among children and adolescents in Kelantan 2012-2015 (N=5412)

Year	Total tuberculosis cases (N=5412)	Tuberculosis among children and adolescents (n=456)	Proportion (95%CI)
2012	1411	116	0.08 (0.07,0.10)
2013	1402	123	0.09 (0.07,0.10)
2014	1366	118	0.09 (0.07,0.10)
2015	1233	99	0.08 (0.07,0.10)
Summative	5412	456	0.08 (0.08,0.09)

A total of 644 samples were included in this study with 322 samples for each group of tuberculosis and non-tuberculosis cases. The mean age of children and adolescents with tuberculosis was higher as compared to those with non-tuberculosis. For both groups, Malay was the predominant ethnicity and female gender slightly predominated the study. Tuberculosis cases showed higher percentage for residing in non-urban area and being educated as

compared to non-tuberculosis cases. Higher percentage of cigarette smokers was observed among tuberculosis cases as nearly all non-tuberculosis cases were non-smoker. HIV status showed small discrepancy between these two groups with majority of them had negative HIV status. Details regarding socio-demographic and clinical characteristics of children and adolescents registered in Kelantan TBIS were shown in Table 2.

Table 2. Socio-demographic and clinical characteristics among children and adolescents registered in Kelantan TBIS 2012-2015 (n=644)

Patients characteristic	Frequency (%)	
	Tuberculosis cases (n=322)	Non-tuberculosis cases (n=322)
Age*	15.98 (3.74)	12.54 (5.14)
Gender		
Male	207 (45.4)	7408 (49.8)
Female	249 (54.6)	7469 (50.2)
Ethnicity		
Malay	416 (91.2)	14137 (95.0)
Others	40 (8.8)	740 (5.0)
Education		
Good	422 (92.5)	10866 (73.0)
Poor	34 (7.5)	4011 (27.0)
Location		
Non-urban	363 (79.6)	12399 (83.3)
Urban	93 (6.4)	2478 (16.7)
Smoking		
No	275 (85.4)	302 (93.8)
Yes	47 (14.6)	20 (6.2)
HIV status		
Negative	313 (97.2)	321 (99.7)
Positive	9 (2.8)	1 (0.3)

*Mean (SD)

Simple and multiple logistic regression analysis were used to determine the significant associated factors. Age, gender, education level, location of residence and

smoking status were the significant associated factors for tuberculosis infection among children and adolescents and the details were shown in Table 3.

Table 3. Factors associated with tuberculosis infection among children and adolescents in Kelantan 2012-2015 by multiple logistic regression (n=644)

Factors	Crude OR^a (95% CI)	Adjusted OR^b (95% CI)	Wald statistics^b (df)	p-value^b
Age	1.23 (1.17,1.29)	1.41 (1.29,1.54)	60.56 (1)	<0.001
Gender				
Male	1.00	1.00		
Female	1.29 (0.95,1.77)	1.88 (1.33,2.65)	12.90 (1)	<0.001
Ethnicity				
Others	1.00	1.00		
Malay	0.22 (0.09,0.50)	0.17 (0.07,0.44)	13.35 (1)	<0.001
Education				
Good	1.00	1.00		
Poor	0.24 (0.15,0.38)	0.20 (0.12,0.33)	39.32 (1)	<0.001
Location				
Urban	1.00	1.00		
Non-urban	1.82 (1.28,2.61)	1.92 (1.33,2.79)	11.90 (1)	0.001
Smoking				
No	1.00	1.00		
Yes	2.58 (1.49,4.47)	3.35 (1.86,6.01)	16.33 (1)	<0.001
HIV infection				
No	1.00	1.00		
Yes	9.23 (1.16,73.28)	6.76 (0.83,54.77)	3.20 (1)	0.073

^aSimple logistic regression, ^bMultiple logistic regression

Forward LR method applied

No multicollinearity and no interaction found

Classification table 74.5% correctly classified

Area under Receiver Operating Characteristics (ROC) curve was 79.5%

Discussions

Based on the findings of this study, the annual tuberculosis cases in children and adolescents in Kelantan was 8.0% (95% CI 0.08,0.09). Our finding is slightly lower than

the national data study where children and adolescents comprised about 8.5% out of total tuberculosis cases nationwide [3]. The discrepancy in the findings could be attributed to the number of children and adolescents that get tuberculosis in Kelantan

were possibly underestimated from the true incidence numbers which led to underreporting. The reasons for the underestimated numbers are poor accessibility to tuberculosis diagnosis and treatment, similarities in the clinical pictures with other typical childhood illnesses and inadequate routine recording and reporting of childhood and adolescents tuberculosis cases [24].

In Malaysia, high tuberculosis incidence of children and adolescents was seen among age strata of 10 to 19 year old [3]. The finding was consistent with the present study for Kelantan where the mean (SD) age for tuberculosis infection was 15.98 (3.74) years old. The finding was almost similar to a matched case-control study in Brazil to analyze the risk factor for tuberculosis infection among older children that identified the mean age of the enrolled patients was 14.4 years [10]. Another study on prevalence of tuberculosis among adolescents in Western Kenya also reported similar finding of mean (SD) age of infected adolescents with tuberculosis, reported as 14.4 (1.90) years [8].

In our study, age has been found to be a significant factor associated with tuberculosis infection. A person with an increase of one year of age has a 1.41 times the odds to get tuberculosis similar to the findings in a cohort study in South Africa among adolescents tuberculosis patients [16]. Possible explanation is that older age is associated with engaging in multiple health risk behaviors among adolescents hence exposing to various disease risks including tuberculosis [25].

We found significant association between gender and tuberculosis infection through this study. More than half of patients were

female (54.6%) as compared to male (45.4%), and being female children and adolescents were almost two times more likely to get tuberculosis infection, compared with male group. Findings of this study are in line with three other different studies conducted among children and adolescents with tuberculosis in Uganda, Pakistan and South Africa. All of these studies showed that female children and adolescents had higher odds of getting tuberculosis infection [11,12,16]. Some worldwide studies have shown that male has higher risk factors like smoking, alcoholism, drug addiction and HIV infection to acquire tuberculosis compared to female, thus the sex difference in tuberculosis prevalence was attributable by all these factors [26,27]. However, there is possible explanation for the shift of notification rate towards female group. It is possible that female adolescents are simply more likely to use health services during their reproductive years. A study in United States reported that different health seeking behaviour by female group would increase their chance of being diagnosed should they have symptoms of tuberculosis [28].

The result of our study also showed significant association between other socio-demographic determinants such as ethnicity and education level with tuberculosis infection among children and adolescents. From this study, it is reported that Malay population in Kelantan is less likely to get infected with tuberculosis (AOR 0.17; 95%CI: 0.07,0.44). However, Malay people comprised the majority of the studied patients compared to other races such as Chinese, Indian and Siamese, most probably due to enormous Malay population (95.7%) in Kelantan [1]. Conclusion of tuberculosis was prevalent among Malay children and adolescents cannot be made because there

were few non-Malay samples in this study. Therefore the variable cannot be used to test the causal hypothesis. Nevertheless, other studies in Malaysia pointed out that tuberculosis is prevalent among Malay population. A retrospective cohort study of all patients registered in the 2012 Malaysian National TB Surveillance Database reported that 50.8% of patients were of Malay ethnicity [3]. Another study by Hooi (1994) on tuberculosis patients visiting Chest Clinic, Penang Hospital reported that 59.3% of patients were Malay people [18] whereas Nissapatorn et al. (2004) reported that 49.2% of total patients with extrapulmonary tuberculosis diagnosed at the National Tuberculosis Center, Kuala Lumpur were of Malay ethnicity [19].

Study by Liew et al. (2015) showed that patients without any formal education were 1.94 fold more likely to develop tuberculosis infection compared to educated group, contradicting with this current study [3]. Our study revealed that educated children and adolescents were more prone to get infected with tuberculosis. This finding is supported by previous study in Brazil which reported that there is evidence indicating the lack of knowledge and misinformation about tuberculosis among educated group could expose them to the same risk of getting tuberculosis as the uneducated ones [29]. Possible reasons could be due to lack of tuberculosis awareness or education programmes that focused among educated group. There are many issues that contributed to the lack of tuberculosis awareness or education programmes in Malaysia. Among the issues was the community's reluctance to take ownership of health issues as educated people are more reluctant to participate in health activities [30].

Moreover, tuberculosis awareness among public in Malaysia is still low due to lack of health education or promotion focusing on tuberculosis issue. Currently, tuberculosis awareness programmes are not being promoted aggressively since tuberculosis is no longer the number one killer disease in Malaysia and also due to the emergence of new outbreaks such as rabies, leptospirosis and others. Thus, the concentration on addressing tuberculosis in Malaysia has become less. Additionally, dengue fever cases keep burgeoning every year and this indirectly changes the priority of Ministry of Health to overcome the disease accordingly [31].

We also found that there was significant association between area of residence and tuberculosis infection among children and adolescents. Children and adolescents residing in rural area had 1.92 times higher odds of getting tuberculosis, compared to those in urban area. The result was in line with a study in Western Kenya which reported that rural children were more likely to get tuberculosis, which accounted for 87% of total case load [8]. The prevalent of tuberculosis among rural residents are majorly due to lack of knowledge regarding the disease itself. It is reported through a study in a northern rural area of Vietnam that knowledge of causes, transmission routes, symptoms and curability of tuberculosis was low among rural people. They reported that, 82% of the women and 74% of the men resided in rural area did not know that tuberculosis is caused by bacteria. A large proportion reported that tuberculosis is caused by hard work or it is a hereditary disease [32]. In contrast to the finding of our study, a nationwide study in Malaysia reported that patients residing in urban area were more likely to get tuberculosis as

compared to those residing in rural area (OR 1.22; 95%CI 1.14,1.30; $p<0.001$) [3].

The result of this study showed that children and adolescents who smoke cigarette were three times more likely to develop tuberculosis infection, compared to non-smoking group. Findings of this study are in line with another study conducted among older children in Brazil which showed that tobacco smoking has a significant impact on tuberculosis infection [10]. Similarly, a local study conducted in Penang and Kuala Lumpur reported that cigarette smoking was a substantial determinant in 817 of 943 new cases of tuberculosis [33]. A case-control study on association between tobacco smoke and tuberculosis among children in Thailand revealed that children who were also exposed to tobacco smoke were almost four times more likely to get tuberculosis infection compared to unexposed group [34]. Smokers were more likely to develop tuberculosis due to pathophysiological changes in their respiratory pathway. Smoking not only induces local anatomical disruption, it also elicits a complex immunological response among smokers [35]. Eventually, the natural lung defense mechanisms against mycobacterium or its elimination among smokers will be impaired, hence explain how smoking could increase the probability to contract tuberculosis [36].

Multivariable analysis showed no significant association between HIV status and tuberculosis infection among children and adolescents, after controlling potential confounding factors. This finding was in agreement with study in rural Eastern Uganda which also projected there was no significant association between HIV status and tuberculosis infection among children and adolescents [17]. However, it is well-

known that tuberculosis is among the commonest opportunistic infection in HIV infected patients [37]. HIV positive people are about 20-30 times more likely than HIV negative people to develop tuberculosis in countries with a generalized HIV epidemic. Liew et al (2015) reported that HIV positive patients in Malaysia were 5 times more likely to get tuberculosis infection as compared to HIV negative patients (AOR 5.01; 95%CI 4.27,5.88; $p<0.001$) [3].

Tuberculosis is also a major cause of morbidity in HIV infected children, with HIV infected children having a 20–25-fold higher incidence of tuberculosis than HIV uninfected children, with an overall tuberculosis incidence in South African HIV infected children of 9.2% (95%CI:0.14–0.97) [38].

Small sample size for HIV positive patients was one of the limitations of this study because small sample size would limit the findings on its association with tuberculosis infection. There was also a limitation to identify ethnicity as one of possible associated factors for tuberculosis infection owing to Kelantan population are made up mainly of Malay ethnicity. Conclusion of Malay ethnicity being the highly prevalent group for tuberculosis infection certainly inappropriate as there were few non Malays recruited in this study.

This study had demonstrated that the significant associated factors for tuberculosis infection among children and adolescents in Kelantan were older age, female gender, good education level, rural residence and cigarettes smoking. By delineating these possible significant risk factors for tuberculosis infection, it will assist and guide health authorities to design a better and comprehensive plan for the national tuberculosis control programme,

focusing more attention towards children and adolescents group without marginalizing them. Consequently, dynamic transmission of tuberculosis in our community would be mitigated.

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Conflict of interest

The authors have no conflicts of interest associated with the material presented in this paper.

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