PREVALENCE OF METABOLIC SYNDROME IN NON-ALCOHOLIC FATTY LIVER DISEASE AND ITS TREATMENT APPROACHES

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Abstract: Metabolic syndrome is a clustering of risk factors that greatly increases an individual’s probability for developing atherosclerotic cardiovascular disease, type 2 diabetes mellitus and chronic kidney disease. Primary aim of this study is to estimate the prevalence of metabolic syndrome in Non-alcoholic fatty liver disease patients and classifying the level of steatosis based on the ultrasound. The subjects screened for study participation came from Department of Master Health checkup, Sri Ramachandra Medical Centre - Chennai. Sample size was calculated using Epi software and the confidence interval 95%. Totally 136 patients participated in this study with the duration of 6-months. Metabolic syndrome was present in 106 patients which satisfy National Cholesterol Education Program, Adult Treatment Panel-III criteria. The association between development of metabolic syndrome and non-alcoholic fatty liver disease is statistically significant (p<0.05). Finding shows that males (71) are more prone to metabolic syndrome when compared to the females (35). Metabolic syndrome was found to be more prevalent in non alcoholic fatty liver disease patients. Prevalence of metabolic syndrome is significantly higher in male patients when compared to female patients. When the separate components of metabolic syndrome were analyzed, it was found that non alcoholic fatty liver disease is closely associated with marked metabolic derangements.

Keywords: Metabolic syndrome, Obesity, Triglycerides, Blood glucose, Non-alcoholic fatty liver disease

INTRODUCTION
Metabolic syndrome is a cluster of risk factors that raises the possibility of developing atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and chronic kidney disease. Abdominal obesity, dyslipidemia, hypertension, increased plasma glucose, a prothrombotic condition, and a pro-inflammatory state appear to be the most common underlying risk factors. NAFLD is rapidly becoming a major public health concern across the world, with an estimated incidence of 20%-30% in Western countries and 90% in morbidly obese people. NAFLD is defined as the accumulation of more than 5% liver fat per liver weight along with a daily alcohol consumption of 10 g. The significance of early NAFLD identification cannot be emphasised, since it can lead to cirrhosis, portal hypertension, and liver-related mortality in early adulthood. NAFLD is associated to MetS, obesity, type 2 diabetes, hyperlipidemia, and even an increased likelihood of mortality from any cause. The majority of NAFLD patients do not exhibit abnormal symptoms, especially in the early stages, limiting early diagnosis and prevention of NAFLD. As a result, early diagnosis and intervention for NAFLD are critical; moreover, there is an urgent need for sensitive and specific biochemical markers for NAFLD, as serial measurements of aspartate transaminase (AST) and alanine aminotransferase (ALT) can be misleading and cannot accurately predict the severity or outcome. Although a liver biopsy is necessary to diagnose NAFLD, noninvasive techniques have been developed that demonstrate sufficient concordance with histological results. They include ultrasonography (US), computed tomography (CT), magnetic resonance spectroscopy (MRS), and other indexes such as the fatty liver index (FLI).

INDIAN SCENARIO
An increase in obesity, hypertension, and diabetes mellitus has resulted in an increased incidence and prevalence of NAFLD in India over the years. The ICMR Indian Diabetes Study (ICMR-INDIAB) has revealed the prevalence of Diabetes mellitus (DM) (both known and newly diagnosed) in four Indian states: 10.4% in Tamil Nadu, 8.4% in Maharashtra, 5.3% in Jharkhand, and 13.6% in Chandigarh (Union Territory). The overall number of diabetics in India in 2011 was 62.4 million, which was corroborated by the IDF Diabetes Atlas (5th edition), which put the figure at 61.3 million, between the ages of 20 and 79. In India, studies have shown an increasing trend in the prevalence of hypertension in urban adults; in Jaipur (1995), 30% of men and 33% of women had hypertension; in Mumbai (1999), men 44% and women 45% had hypertension; in Thiruvananthapuram (2000), men 31% and women 36% had hypertension; in Jaipur (2002), men 36% and women 37% had hypertension; and in Chennai (2001), 14% of women had hypertension. In Rajasthan (1994), HTN prevalence was 24% in males and 17% in women in rural populations. In South India, the Chennai Urban Rural Epidemiology Study (CURES) found a prevalence of HTN of 23.2% among males and 17.1% among women. In India, hypertension is responsible for 57% of all stroke deaths and 24% of all coronary artery disease (CAD) deaths. Obesity prevalence varies mostly by region, gender, and socioeconomic status. Urban locations have a higher frequency, as do higher socioeconomic stratum and women. Although while metropolitan regions have a larger prevalence and a quickly increasing incidence of obesity, rural Asian-Indians are also displaying an increase in obesity. Overweight and obesity are becoming increasingly common among youngsters. Indians' Insulin Resistance and Other Risk Factors Indians have greater IR and higher hepatic triglycerides (HTGs) than other races, implying that they are more prone to developing NAFLD. Insulin resistance is associated with NAFLD regardless of obesity. With Asian-Indians living in India, the prevalence of IR ranges from 7% to 55%. Because insulin resistance and the metabolic syndrome are common in Asian-Indians, it is fair to assume that NAFLD is as well; however, data are limited. According to current studies, Asian-Indians have about double the amount of hepatic fat as white
Caucasians for the same body mass index (BMI). Insulin resistance in children and adolescents has also been documented. The high prevalence of IR and metabolic syndrome in Asian-Indians is most likely attributable to a combination of variables. It is noteworthy to highlight that all of the NAFLD connections, excess body fat, abdominal obesity (truncal subcutaneous fat and intra-abdominal fat), diabetes, hypertriglyceridaemia, and IR are particularly prevalent in urban Asian-Indians and may play a role in NAFLD pathogenesis. Nevertheless, the interrelationships of NAFLD, IR, and MS in Asian-Indians have not received much attention.

NON-ALCOHOLIC FATTY LIVER DISEASE
NAFLD is defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (providing a reasonable approximation of the volume fraction of fatty material in the liver) >5.6% assessed by proton magnetic resonance spectroscopy (1H MRS) or quantitative fat/water selective magnetic resonance imaging (QFWMRI) (MRI). NAFLD is comprised of two pathologically separate disorders with unique prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter encompasses a broad range of disease severity, including fibrosis, cirrhosis, and hepatocellular cancer (HCC). The diagnosis of NAFLD necessitates the elimination of both secondary causes as well as a daily alcohol intake of more than 30g for males and more than 20g for women. Excessive alcohol consumption implies alcoholic liver disease. Because the association between alcohol and liver damage is affected by various cofactors (kind of alcoholic beverage, drinking habits, duration of exposure, individual/genetic vulnerability), simple quantitative limits are at best arbitrary. Patients who drink moderate amounts of alcohol may be predisposed to NAFLD if they have metabolic risk factors. In these patients, the total influence of metabolic risk factors on the incidence of steatosis appears to be greater than that of alcohol. NAFLD is classified as being either primary or secondary based on the underlying aetiology. Primary NAFLD is associated with insulin resistance and metabolic syndrome. Other conditions associated with NAFLD are total parenteral nutrition, acute starvation, abdominal surgery (e.g., extensive small bowel resection, biliopancreatic diversion, and jejunal bypass), use of several drugs (e.g., amiodarone, tamoxifen, glucocorticoids, synthetic estrogens, diltiazem, aspirin, methotrexate, highly active antiretroviral therapy). It is also associated with hepatitis C, HIV and metabolic disorders i.e. hypobetalipoproteinemia, lipodystrophy, hypopituitarism, hypothalamic obesity, Weber-Christian syndrome, acute fatty liver of pregnancy, Reyes syndrome and Mauriacsyndrome. Studies indicate that occupational exposure to organic solvents may play a role in the development of NAFLD and that women with polycystic ovary syndrome may have an increased prevalence of non-alcoholic fatty liver disease.

DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER DISEASE
NAFLD is typically asymptomatic, diagnosed only by abnormal liver function or imaging findings at health screening or during follow-up for other conditions. Patients with persistent elevations of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and fatty change on ultrasonography (US) or computed tomography (CT) and no history of habitual drug/ethanol intake or positive hepatitis virus markers or autoantibodies can be suspected of having NAFLD. NAFLD/NASH can follow primary or secondary basis due to the influence of metabolic risk factors on the incidence of steatosis approximating >5% of hepatocytes. Insulin resistance in children and adolescents has also been documented. The high prevalence of IR and metabolic syndrome in Asian-Indians is most likely attributable to a combination of variables. It is noteworthy to highlight that all of the NAFLD connections, excess body fat, abdominal obesity (truncal subcutaneous fat and intra-abdominal fat), diabetes, hypertriglyceridaemia, and IR are particularly prevalent in urban Asian-Indians and may play a role in NAFLD pathogenesis. Nevertheless, the interrelationships of NAFLD, IR, and MS in Asian-Indians have not received much attention.

AIM AND OBJECTIVES
The primary goal of the study is to explore the prevalence of metabolic syndrome in non-alcoholic fatty liver disease and its treatment approaches.

1. To estimate the prevalence of metabolic syndrome in non-alcoholic fatty liver disease and its treatment approaches.
2. Classification of the degree of steatosis as mild, moderate or severe based on the ultrasound criteria.
3. To analyze the prescribing pattern of treatment.

METHODOLOGY
The data were collected from the medical health checkup record of each patient: age, sex, height, weight, family history, personal history, past medication history, past medical history, fasting blood sugar, waist circumference, blood pressure, triglycerides and high-density lipoprotein and, imaging result (ultrasonography).

SITE OF THE STUDY
Sri Ramachandra Institute of higher education and research (deemed to be university) Chennai, India.

PERIOD OF THE STUDY
6-Months

SAMPLE SIZE
Sample size was determined based on literature using Epi software and the confidence interval, 95%. The calculated sample was 128 patients. Hence with 10% of attrition rate [128×10%=13.6]. The sample size was found to be 136.

INCLUSION CRITERIA
- Patients who are belongs to the age group of 18-65 years old in both genders.
- No or low alcohol consumption (<20 g/day in women and <30 g/day for men) proven and tested.
- Ultrasonography impression showing fatty liver.
- Normal or altered liver function tests, not due to viral hepatitis or other hepatobiliary or systemic diseases, nor due to drug causes (glucocorticoids, synthetic estrogens, amiodarone, aspirin ...).

**EXCLUSION CRITERIA**
- Patients who are below 18 years of age.
- Alcohol consumption (>20 g/day in women and >30 g/day for men).
- Altered liver function tests, due to viral hepatitis or other hepatobiliary or systemic diseases, chronic liver diseases (including autoimmune, drug-induced, vascular and inherited hemochromatosis and Wilson disease) or due to drug causes (glucocorticoids, synthetic estrogens, amiodarone, aspirin ...).
- Active illicit drug users.
- Pregnant women.
- Seropositive for HIV.
- Patients who are dyslipidemic taking lipid lowering agents.

**ETHICS APPROVAL**
The study began after the Institutional Ethics Committee of Sri Ramachandra Medical College and Research Institute approved it (Deemed to be University).

**SCREENING OF SUBJECTS**
The patients screened for study participation were from the master health checkup department at Sri Ramachandra Medical College and Research Institute (Deemed to be University), and their eligibility was confirmed by a review of the applicable inclusion and exclusion criteria.

**DATA COLLECTION**
Subjects who fulfilled the requirements for eligibility were requested to sign an informed consent form in their native language for their convenience. Following consent, data was collected using a specially designed study proforma. Data were collected from 136 individuals who participated in the Master Health Checkup. For these participants, complete anthropometric and laboratory measurements, as well as abdominal ultrasonography, will be conducted to test for NAFLD and its grade. MetS was determined in all individuals using the Adult Treatment Panel III (2001) of the National Cholesterol Education Program (NCEP/ATP-III).

**METABOLIC SYNDROME DETECTION**
ATP-III criteria of three or more of the following was used to define metabolic syndrome.
1. Abdominal obesity: circumference >102 cm in men and >88 cm in women.
2. Hypertriglyceridermia: ≥ 150 mg/dL.
3. HDL cholesterol < 40 mg/dL in men and <50 mg/dL in women.
4. Hypertension: ≥ 130/85 mmHg.
5. Basal glucose: ≥ 110 mg/dL.

**DATA ANALYSIS:**
The collected data were statistically analyzed using SPSS software (Statistical Package for Social Sciences) version 17.0. Descriptive statistics was performed and data presented as mean (SD). The chi square test was used to determine the relationship between NAFLD and metabolic syndrome. For the outcome variable, Metabolic syndrome, stratified analysis was performed based on age, gender, and illness duration. The Chi square test with a 5% significance level was performed to examine the relationship between the outcome variable and the independent variables such as age, gender, and illness duration.

**RESULTS**

![Figure 1: Age wise distribution](image1)

![Figure 2: Gender wise distribution](image2)
Table 1: Distribution of patients based on fasting blood sugar level

<table>
<thead>
<tr>
<th>Fasting blood sugar</th>
<th>GENDER</th>
<th>Overall percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Normal (&lt;100mg/dl)</td>
<td>17(34.6%)</td>
<td>22(25.27%)</td>
</tr>
<tr>
<td>Abnormal (≥100mg/dl)</td>
<td>32(65%)</td>
<td>65(74.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>49(100%)</td>
<td>87(100%)</td>
</tr>
</tbody>
</table>

Table 2: Distribution of patients based on Blood pressure

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>GENDER</th>
<th>Overall percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Normal (≤130/≤85mmHg)</td>
<td>21(42.8%)</td>
<td>34(39%)</td>
</tr>
<tr>
<td>Abnormal (≥130/≥85mmHg)</td>
<td>28(57.1%)</td>
<td>53(60.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>49(100%)</td>
<td>87(100%)</td>
</tr>
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</table>

Table 3: Distribution of patients based on high density lipoprotein

<table>
<thead>
<tr>
<th>High density lipoprotein</th>
<th>GENDER</th>
<th>Overall percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female(&lt;50mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male(&lt;40mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8(16.3%)</td>
<td>24(27.5%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>41(83.6%)</td>
<td>63(72.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>49(100%)</td>
<td>87(100%)</td>
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</table>

Table 4: Distribution of patients based on Triglycerides
<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>GENDER</th>
<th>Overall percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Normal (≤150mg/dl)</td>
<td>31(63.2%)</td>
<td>42(48.2%)</td>
</tr>
<tr>
<td>Abnormal (≥150mg/dl)</td>
<td>18(36.7%)</td>
<td>45(51.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49(100%)</td>
<td>87(100%)</td>
</tr>
</tbody>
</table>

Table 5: Distribution of patients based on Fatty liver grade

<table>
<thead>
<tr>
<th>GRADING</th>
<th>GENDER</th>
<th>Overall percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Normal</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>37(77.5%)</td>
<td>64(73.5%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>11(22.4%)</td>
<td>23(26.4%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>1(2%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49(100%)</td>
<td>87(100%)</td>
</tr>
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</table>

Table 6: Distribution of patients based on waist circumference

<table>
<thead>
<tr>
<th>Waist circumference</th>
<th>GENDER</th>
<th>Overall percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Normal</td>
<td>1(2%)</td>
<td>20(22.9%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>48(97.9%)</td>
<td>67(77%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49(100%)</td>
<td>87(100%)</td>
</tr>
</tbody>
</table>

Table 7: Prevalence of metabolic syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patient fulfilling NCEP/ATP-III criteria</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Four criteria (4/5)</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>Three criteria (3/5)</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Five criteria (5/5)</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>
Figure 3: Distribution of metabolic syndrome

Distribution of metabolic syndrome parameter in NAFLD patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>With MetS</th>
<th>Without MetS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist</td>
<td>115</td>
<td>71</td>
<td>44</td>
</tr>
<tr>
<td>HDL</td>
<td>104</td>
<td>35</td>
<td>69</td>
</tr>
<tr>
<td>FBS</td>
<td>97</td>
<td>14</td>
<td>83</td>
</tr>
<tr>
<td>BP</td>
<td>78</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td>TG</td>
<td>63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4: Frequency of metabolic syndrome

Frequency of metabolic syndrome

<table>
<thead>
<tr>
<th>Sex</th>
<th>Total</th>
<th>With MetS</th>
<th>Without MetS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>71</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 5: Drugs prescribed for the study population
DISCUSSION

This study assessed the prevalence of MetS with its associated components in NAFLD. In this study of 136 NAFLD patient’s data were collected using NCEP/ATP III criteria. The respondents had a mean age of 48.2 years, similar to the study by Imam S K et al. 77 where the mean age was 49.9 years conducted in Karachi. 77 On breaking down the age wise distribution we observed that higher percentage of patients with metabolic syndrome were people who are >50 years group, 73 which was similar to the study conducted by Ford E S et al. 74 This denotes that age is one of the main risk factor of metabolic syndrome. The sample size showed a higher percentage of males with metabolic syndrome when compared with females. The study conducted by M. Srinivas et al. 78 have explained that male gender was commonly associated with fatty liver compared to women in their study, similar to previous reports from India, a larger community-based study in Asian subjects reported that peak prevalence of NAFLD occurred a decade earlier in men (40-49 years) compared to women (>50 years). 79 This study showed that males (71) are more prone to have metabolic syndrome when compared to females (35).

The present report further highlights the association of NAFLD with features of the metabolic syndrome. Obesity, diabetes, hypertension, and hyperlipidaemia have been repeatedly reported in NAFLD, but their simultaneous presence significantly increases the risk of more severe stages of liver disease. This association is maintained also in the present group of patients without overt diabetes, where the very high prevalence of the metabolic syndrome might blur the relationship. In this study the use of the sole waist circumference identifies a larger proportion of women (a total of 49(34%) female, only one person shows normal and remaining 48 were abnormal), in contrast with the common belief linking abdominal adiposity to the male sex (a total of 87(64%), 20 were normal and 67 were abnormal). Therefore, the prevalence was high in women (98%) when compared to males (77%). Similar data were reported by Ford et al. 73 in their survey of a U.S. population. In selected groups, a lower cut off point of 94 cm for waist circumference was suggested by ATPIII. 71 Such a limit would increase the prevalence of the metabolic syndrome in male population from 31% to 38% and the overall prevalence from 36% to 42%. 73 This denotes according to south Asian population waist circumference is the one major risk factor of metabolic syndrome and its more observed among women when compared with men. Waist circumference (98%) and high-density lipoprotein (83.6%) were strong evident factors for females and triglycerides (52%), FBS (75%) and BP (61%) for males. In the total NAFLD patients increased waist circumference is the commonest component in metabolic syndrome. Bhattarai S, et al. 78 have explained that increased waist circumference and increased waist/hip ratio prevalent in female when compared with male. 78 Presence of four criteria (33.8%) was found to be higher when compared to five (16.9%) and three (25%) criteria. Kennedy N Jet al 84 have reported a higher assessment of, abdominal obesity (61%) and hypertension (77.2%) are the most prevalent parameters for the cause of metabolic syndrome. 74 However this study shows more number of patients with increased waist circumference (84.5%) and dyslipidaemia (76.4%).

The other risk factors identified in this study were high FBS and TG levels, increased BP levels and low HDL profile, which is associated with high risk for steatosis, diabetes and other cardio -vascular complications. A study conducted by Kuen Cheh Yang et al. 86 have stated that a simple, standardized liver US scoring system may assist in future research regarding whether the severity of NAFLD should be incorporated into the MetS criteria and whether it can be used clinically to diagnose MetS. The liver is the site of the production of glucose and very low-density lipoproteins (VLDLs) that contain the majority of triglycerides. This involvement means that MetS and NAFLD share the same risk profiles. However, NAFLD can develop independently of insulin action in the liver. Increase in hepatic fat in insulin-resistant subjects arising because of dietary fat and adipocyte lipolysis without invoking insulin-driven de novo hepatic lipogenesis. Hepatic fat is the most important predictor of hepatic insulin resistance. 86
CONCLUSION

Metabolic syndrome was found to be more frequent in people with non-alcoholic fatty liver disease. Despite the study's larger male sample, the prevalence of metabolic syndrome is considerably greater in male patients than in female patients. When the individual components of metabolic syndrome were examined, it was discovered that non-alcoholic fatty liver disease is closely associated with significant metabolic derangements, primarily obesity in women and triglyceridemia, both of which are important determinants of type 2 diabetes mellitus and cardiovascular disease. Obesity, sedentary lifestyle, unhealthy eating patterns, and metabolic syndrome have all increased the prevalence of nonalcoholic fatty liver disease. A multidisciplinary approach involving not only the hepatologist but also the endocrinologist and the cardiologist could be beneficial in the treatment of individuals with non-alcoholic fatty liver disease. A personalised approach to lifestyle changes based on a comprehensive assessment of individual metabolic and nutritional condition is suggested. Patient motivation, which leads to greater lifestyle adherence, is an important element in reducing metabolic syndrome components. These aspects can be improved by active collaboration with the health-care system. The advent and expansion of point-of-care technology, allowing pharmacists to independently assess patient risk factors at the time of a clinic visit, will further increase the pharmacist’s role in this area.

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