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Correlation Between Maternal Serum Concentrations of Mannose-Binding Lectin and The Risk of Shorter Duration of Pregnancy and Lower Birth Weight

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Abstract
Background: Preterm birth is the delivery of a baby before 37 completed weeks' gestation.
Aim of the study: The aim of this study is to investigate whether serum concentrations of MBL correlate with the incidence of preterm birth and low birth weight in a cohort of women with signs of threatened preterm birth
Materials and methods: This cross-sectional study was conducted in Salah Al-din General Hospital from January 2019 to of August 2019. **(**The study included 100 patients who presented with regular contractions and/or short cervix between 24 to 32 weeks of gestation and 50 healthy controls who had no pregnancy complications and delivered at term). The cervical length was measured using vaginal ultrasound by one certified sonographer. Four ml of blood was collected from each patient enrolled in this study for determination of MBL by Enzyme linked immunosorbent assay (ELISA) technique and hs-C-Reactive protein by immunofluorescence.
Results: The study showed that the rate of regular contractions was 40% in patients group while no one of the control group was with regular contractions (P<0.01). The study demonstrated that the lowest mean of cervical length and birth Wight were found in group with preterm labor as compared with the control group. The study also revealed that 36% of women with preterm labor was delivered before 34 weeks, 40% were delivered between 34-37 weeks and 24% were delivered after 37 weeks (term delivery) compared with 100% of control group who delivered after 37 weeks, the difference was statistically significant at P. value <0.01. The study revealed that the mean of MBL was reduced significantly in women with preterm delivery (35.16±11.51 pg/ml) as compared with the control group (51.77±16.23 pg/ml) at P. value <0.01. The study revealed that the mean of Hs-CRP was elevated significantly in women with preterm delivery (6.12±0.55 mg/dl) as compared with the control group (5.91±0.51 mg/dl) at P. value <0.05. In this study, 36 of 100 of study cases delivered preterm (< 34 weeks). In this subgroup, 12 mothers had histologically proven evidence of Chorioamnionitis, and 5 of these patients additionally tested positive for funisitis. It is interesting to note that the levels of MBL in these 5 patients who tested positive for both Chorioamnionitis and funisitis were significantly reduced. The study found that, infants born to study cases with MBL deficiency (n = 38, MBL < 10 ng/mL) had significantly lower birth weights, compared to those born to preterm women with normal MBL serum concentrations (p< 0.01).
Conclusions: It was concluded that there was a role of the immune system in the pathogenesis of preterm labor and a strong association between MBL deficiency and preterm delivery, and associated low birth weight.

Keywords: Mannose-Binding Lectin; Preterm labor; Lower Birth Weight

Introduction

Preterm birth is the delivery of a baby before 37 completed weeks' gestation. Most mortality and morbidity affects "very preterm" infants (those born before 32 weeks' gestation), and especially "extremely preterm" infants (those born before 28 weeks of gestation) [(1)]. Over the past 20-30 years advances in perinatal care have improved outcomes for infants born after short gestations. The number of weeks of completed gestation that defines whether a birth is preterm rather than a fetal loss has become smaller[(2)]. These changes influence the structures of the collagen and glycosaminoglycans that make up cervical tissue. Estrogen stimulates collagen degradation whereas progesterone inhibits it. Therefore, progesterone is used to

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prevent or delay ripening. Both hormones are implicated in regulating the gap-junction formation and the upregulation of connexin 43 proteins which contribute to parturition[3,4]. Additionally, contractions are an integral contributor to labor. The change from uncoordinated myometrial contractions to coordinated uterine contractions is attributed to neural control. Oxytocin plays an essential role in the circadian rhythm of these contractions. The degradation of the extracellular matrix is assessed by fetal fibronectin detection in cervicovaginal secretions and is also part of the parturition process. When detected between 22 and 37 weeks gestational age, it indicates the disruption of the decidual-chorionic interface and increased risk of preterm labor[5,6,7]. Spontaneous preterm births account for about two thirds of all preterm births. Following the framing of women's uteruses as muscles that respond to hormonal signals, the contemporary causal model for spontaneous preterm birth is that labor or membrane rupture before a pregnancy reaches term occurs when maternal hormones, similar if not the same as those that function during term labor, are triggered early[7,8]. The hypothesis that inflammation might play a role in preterm labor and thus shorter gestational age is supported by studies demonstrating that conditions involving increased inflammation, like infections, e.g. periodontitis and systemic autoimmune diseases, e.g. rheumatoid arthritis, are associated with shorter gestational age[9]. Maternal MBL serum levels are increased from the first trimester of pregnancy and onwards, suggesting a role of MBL in nidation, placentation and maintenance of pregnancy. This rise in MBL levels during pregnancy is strictly related to the maternal genotype. Multiple studies have described low maternal MBL levels (or low MBL production genotypes) in association with adverse pregnancy outcome [10,11]. The aim of this study is to investigate whether serum concentrations of MBL correlated with the incidence of preterm birth and low birth weight in women with signs of threatened preterm birth.

Patients and methods

This cross-sectional study was conducted in Salah Al-din General Hospital from January 2019 to of August 2019. Study included 100 patients who presented with regular contractions and/or short cervix between 24 to 32 weeks of gestation and 50 healthy controls who had no pregnancy complications and delivered at term.

Inclusion criteria:

1. Gestational age: 24 to 32 weeks
2. Singleton pregnancy
3. Women with regular uterine contractions
4. Women with short cervix, defined as a cervical length ≤ 25 mm.

Methods

The following clinical outcomes were recorded:
i) delivery before 34 wk gestation.
ii) Term delivery (> 37 wk).
iii) Chorioamnionitis (confirmed histologically after delivery).
iv) Funisitis (confirmed histologically after delivery).

Cervical length measurement

The cervical length was measured using vaginal ultrasound (by one certified sonographer.

Blood collection

Four ml of blood was collected by vein puncture from each patient enrolled in this study. Blood samples were placed in plane tubes left for 30 minutes at 37°C then were centrifuged at 3000 rpm for 15 minutes then the clot removed and the remain re- centrifuged at 3000 rpm for 10 min and the obtained sera were then aspirated using automatic micropipette and transferred into two clean test tubes , one for determination of MBL by Enzyme linked immunosorbent assay (ELISA) technique and hs-C-Reactive protein by immunofluorescence. The blood samples were obtained during admission in group A, or during prenatal care in group B to match the gestational age of the time of collection in both groups

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Results

Table 1 shows demographic and clinical characteristics of the study population **Table 3.1: General characteristics of the studied groups**

Variables	Preterm Labor (n:100)	Control group (n:50)	P. value
Age (Mean±SD)	33.5±3.9	32.5±3.8	NS
BMI	25.4±4.1	26.1±5.1	NS
Parity, median (Range)	2 (1–5)	2 (1–4)	NS
Residence (rural)	60%	62%	NS

The study also revealed that 36% of women with preterm labor were delivered before 34 weeks, 40% were delivered between 34-37 weeks and 24% were delivered after 37 weeks (term delivery) compared with 100% of control group who delivered after 37 weeks, the difference was statistically significant at P. value <0.01 (Figure 1)

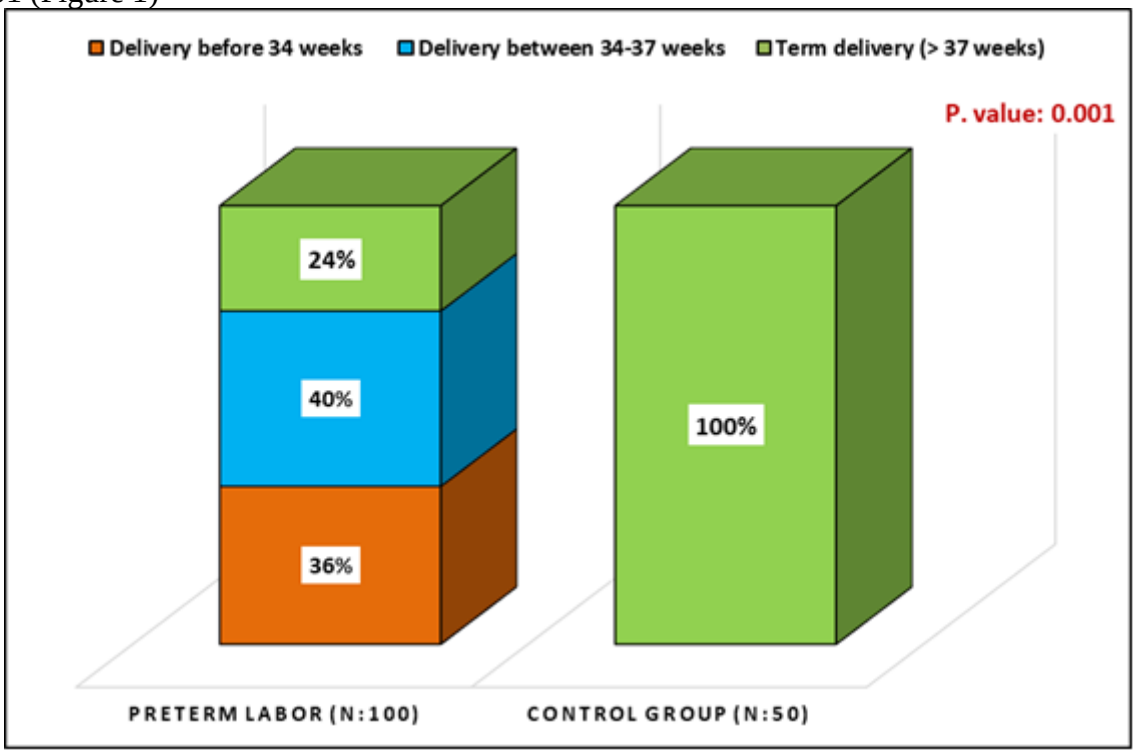

Figure 1: Time of delivery of the study groups

The study revealed that the mean of MBL was reduced significantly in women with preterm delivery (35.16±11.51 pg/ml) as compared with the control group (51.77±16.23 pg/ml) at P. value <0.01 and the study found that 38% of cases were with decreased MBL level (<10 pg/ml) compared to control group (0%), Table 2.

Table 2: Relation of mannose binding lectin with preterm delivery

MBL level	Preterm delivery group	Control group
Mean	35.16	51.77
SD	11.51	16.23

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No.	100	50
MBL below 10 pg/ml	38 of 100	0 of 50

T. test: 7.23 P. value: 0.0008

The study revealed that the mean of Hs-CRP was elevated significantly in women with preterm delivery (6.12±0.55 mg/dl) as compared with the control group (5.91±0.51 mg/dl) at P. value <0.05 (Table 3).

Table 3: Level of high sensitive C-reactive protein in preterm delivery women and the control group

Hs-CRP level	Preterm delivery group	Control group
Mean	6.12	5.91
SD	0.55	0.51
No.	100	50

T. test: 2.68 P. value: 0.048

The study showed that the concentration of MBL was significantly reduced in patients who experienced uterine contractions (n:40) compared to those who did not (n: 60) (P< 0.05) while Hs-CRP wasn't differed significantly between them (Figure 2).

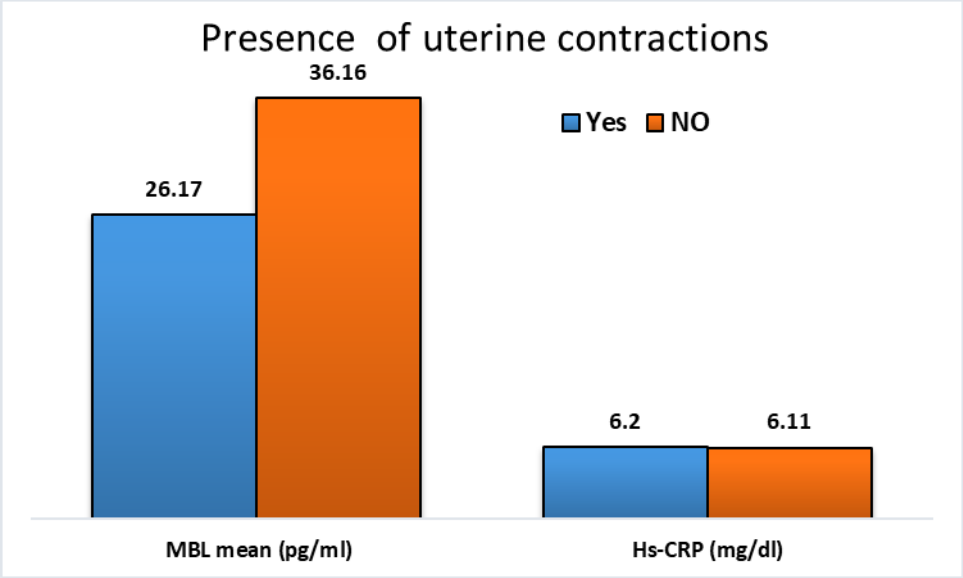

Figure 2: Levels of MBL and Hs-CRP in women who experienced uterine contractions

In this study, 30 of 100 preterm labor women were with severe short cervical length (< 15 mm) and MBL was significantly reduced in patients with severe cervical shortening (< 15 mm) (P = 0.031) while no statistically significant differences were recorded regarding Hs-CRP concentrations between the two groups of patients (Figure 3)

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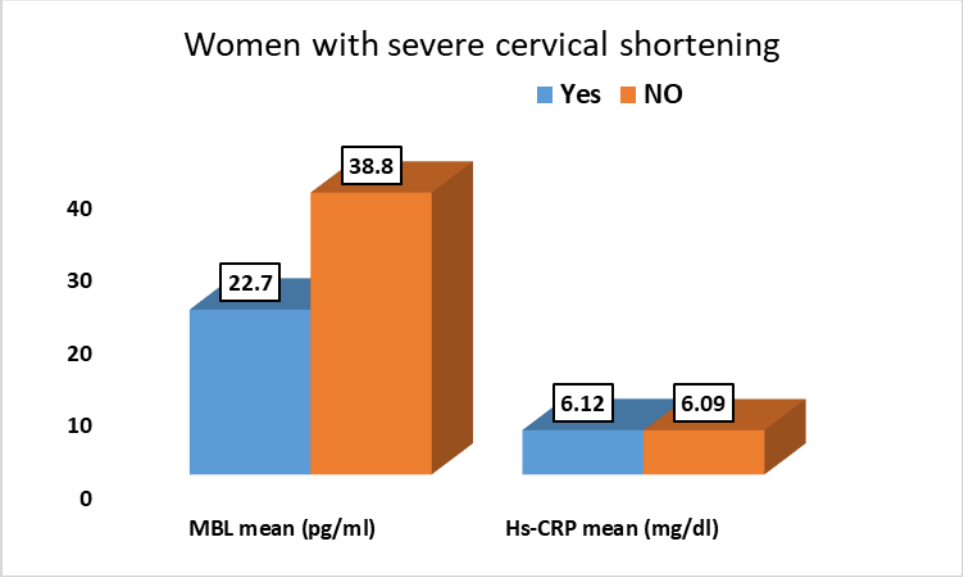

Figure 3: Levels of MBL and Hs-CRP in women severe short cervical length

In this study, 36 of 100 of study cases delivered preterm (< 34 weeks). In this subgroup, 12 mothers had histologically proven evidence of chorioamnionitis, and 5 of these patients additionally tested positive for funisitis. It is interesting to note that the levels of MBL in these 5 patients who tested positive for both Chorioamnionitis and funisitis were significantly reduced; (Figure 4).

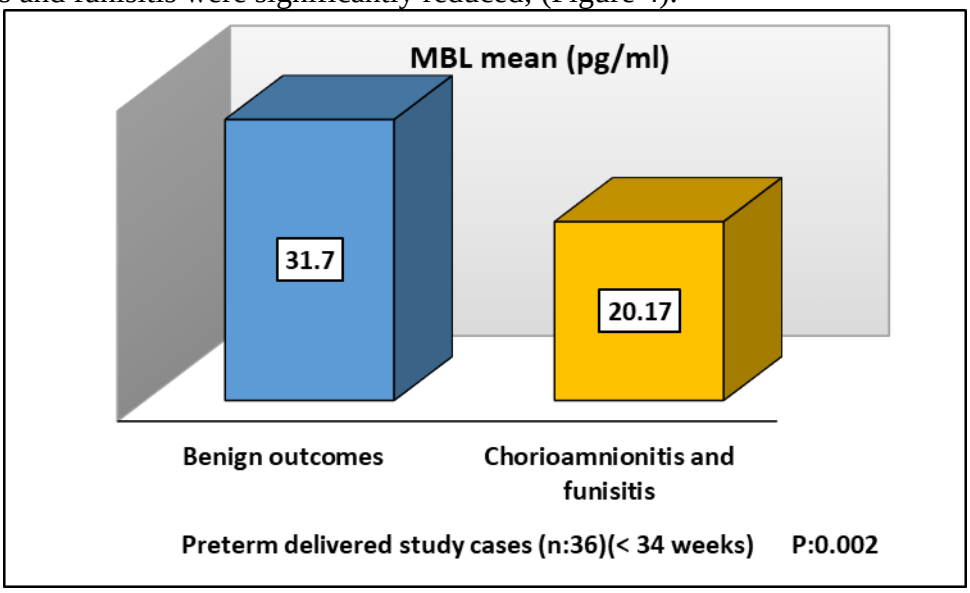

Figure 4: MBL serum levels and pregnancy outcomes

The study found that, infants born to study cases with MBL deficiency (n = 38, MBL < 10 ng/mL) had significantly lower birth weights, compared to those born to preterm women with normal MBL serum concentrations ($p < 0.01$), Figure 5.

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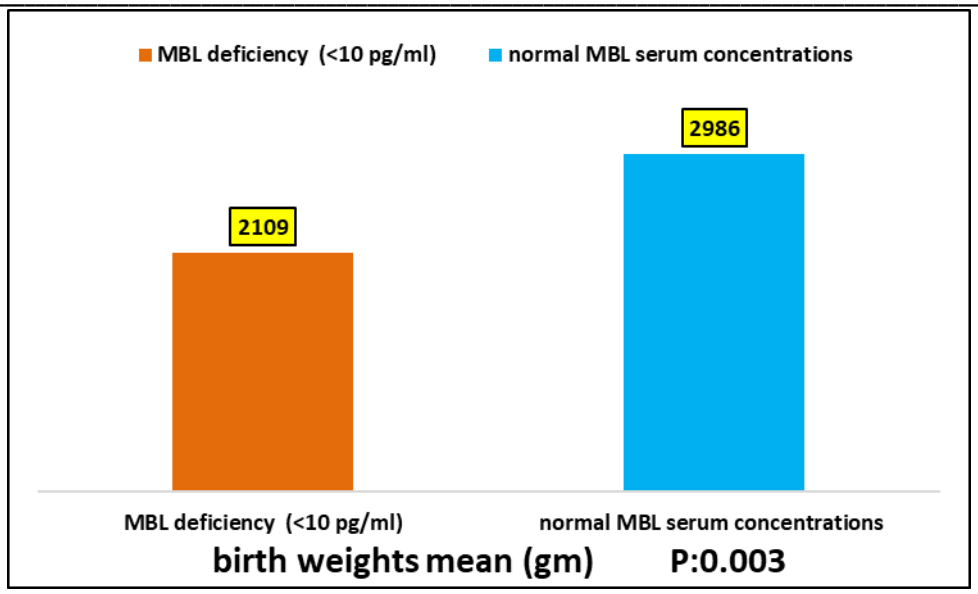

Figure 5: Relation of MBL serum levels and birth weight

Discussion

The study revealed that the mean of MBL was reduced significantly in women with preterm delivery 38% of cases was with decreased MBL level (<10 pg/ml) compared to control group (0%). In agreement with these finding, Koucký *et al* [11] found that MBL level was significantly reduced in women with preterm birth as compared with term pregnant women (P<0.01). There is no clear consensus in the literature regarding the association between MBL levels and preterm birth. Our results are in agreement with those of Calkavur *et al* [12] who showed increased incidence of preterm birth and spontaneous abortions in women with MBL deficit (defined as serum concentrations <10 pg/ml). The concentrations of MBL are dependent on individual's genotype and MBL2 polymorphism. MBL deficiency has been defined as serum levels < 10 pg/ml (severe deficiency, occurs in ~ 5% population) [65]. MBL deficiency has been associated with a large and heterogeneous group of disease processes. However, subnormal levels are also found in healthy people. There is, therefore, no consensus on the clinical relevance of MBL deficiency or its treatment. It is yet unclear how MBL deficiency could lead to abnormal pregnancy outcomes [9,10]. The role of native immunity has been discussed in the pathogenesis of preterm birth. There are complex pathways at the maternofetal interface between fetal trophoblast cells and maternally-derived cells, which are biased in favor of Th2-type responses. This microenvironment creates a tolerogenic niche to facilitate the development of the semiallogeneic fetus. Perturbations in the fetomaternal immune cross-talk seem to play a role in pregnancy complications [13,14]. MBL and other collectins, which are present in gestational tissues during pregnancy, are likely to be important regulators of fetomaternal interactions as they can alter mother's immune response to the allogenic fetus. Pregnancy is thus affected by the native maternal immune system and its interactions with the fetus [11]. There is not much information available regarding the levels of MBL during physiological pregnancy. Van de Geijn reported increased serum MBL concentrations during pregnancy, compared to pre-pregnant levels [12]. It is interesting to note that the levels of MBL in these 5 patients who tested positive for both Chorioamnionitis and funisitis were significantly reduced. Koucký *et al* [11] also found that low levels of MBL were associated with a lower birth weight, which is likely a consequence of the increased incidence of preterm delivery in these patients. In addition, low levels of MBL were associated with a high risk of chorioamnionitis and funisitis. Histological presence of funisitis is a feature of fetal inflammatory response, which is associated with increased neonatal morbidity[15]. In addition, recent studies suggest that the fetus does not develop in a completely sterile environment, and the pregnancy outcome is thus dependent on the interaction between the maternal immune system, the fetoplacental unit and the maternal microbiome in the womb and other tissues [16,17,18]. We speculate that the association between low levels of MBL and the incidence of prematurity can be related to the maternal microbial colonisation of the birth canal. The pregnancy outcome may thus depend on individual interactions of maternal and fetal immune system with these microorganisms. Kindinger *et al* [19] reported that the dominance of *Lactobacillus iners* in the vaginal

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microbiota at 16 weeks of gestation is a risk factor for preterm birth, whereas *L. crispatus* dominance is protective against preterm birth. In agreement with our finding, Pitiphat *et al* [20] found that high levels of maternal plasma CRP in early pregnancy were associated with increased risk of preterm delivery. Compared with women with normal CRP levels, those with elevated CRP levels (≥8 mg/liter) had a greater than twofold higher odds of preterm delivery. The association was stronger for cases who experienced spontaneous preterm delivery versus indicated preterm delivery. These findings suggest that inflammation, as represented by elevated CRP levels, could lead to the physiologic changes that result in preterm delivery. In another study of women who provided blood at 15–18 weeks' gestation, women who delivered spontaneously before 34 weeks had slightly higher median CRP levels (0.6; range, 0–5.6 mg/dl; $n = 10$) than those who delivered at term (0.5; range, 0–2.6 mg/dl; $n = 280$) [21,22]; however, the difference was not statistically significant. A recent, small study also reported a higher median level of serum CRP in women who subsequently delivered at 36 weeks or less (8.26 mg/liter, $n = 30$) compared with those who delivered at more than 36 weeks. However, it is not clear at which stage of gestation the blood was collected [23,24].

Conclusions

1. Preterm birth affects a high proportion of the population world-wide.
2. There is a role of the immune system in the pathogenesis of preterm labor.
3. There is a strong association between MBL deficiency and preterm delivery, and associated low birth weight.
4. There is a high risk of Chorioamnionitis and funisitis in MBL deficient patients. MBL deficiency could thus be considered an important risk factor for preterm birth.

Recommendations

1- Future studies are required to clarify relation of maternal immune system and how this can lead to preterm labor, particularly in the presence of underlying abnormalities of the native or acquired immune system.

2- We speculate that future studies will explore the interactions between maternal immune system and disorders before and after pregnancy.

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