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Prevalence and coagulation correlation of anticardiolipin antibodies in patients with COVID-19

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Abstract

We aimed to determine prevalence and characteristics of anticardiolipin antibodies (ACLs) and its correlations with laboratory coagulation variables in patients with coronavirus disease 2019 (COVID-19). We retrospectively analyzed the prevalence of serum ACLs and its correlation with coagulative laboratory variables in 87 patients with COVID-19. ACLs were detected in 13/21 (61.91%) critically ill patients, and 21/66 (31.82%) in non-critically ill patients. For ACLs, IgA, and IgG were the most common types. The prevalence of IgG in critical ill patients was much higher than that in non-critical patients with odd ratio = 2.721. And the levels of all isotypes of ACLs in critically ill patients were much higher than those in non-critically ill patients. Correlation analysis showed that activated partial thromboplastin time and thrombin time had weak correlation with ACLs-IgG ($R = 0.308$, $P = .031$; $R = 0.337$, $P = .018$, respectively). Only the prevalence of ACLs-IgG shows a significant difference when compared critically ill patients with non-critically ill patients. ACLs do not seem to have a clear correlation with thrombosis occurred in COVID-19 patients.

Abbreviations: ACLs = anticardiolipin antibodies, APLs = antiphospholipid antibodies, APS = antiphospholipid syndrome, APTT = activated partial thromboplastin time, aβ2GPI = anti-beta2-glycoprotein, COVID-19 = coronavirus disease 2019, FIB = fibrinogen, ICU = intense care unit, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, TT = thrombin time.

Keywords: anticardiolipin antibodies, coagulation variables, COVID-19

1. Introduction

A new pneumonia epidemic was outbreak since December 2019. This new type of pneumonia was confirmed to be caused by a novel coronavirus namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was 2019 novel coronavirus disease (COVID-19), previously 2019-nCoV. As a highly infectious disease, the ongoing outbreak has been declared by World Health Organization as a global public health emergency.[1] It is firstly reported in China and gradually begin to break out domestically in Singapore, Japan, Iran, South Korea, Span, France, etc. Particularly in the United States of America and India, ranked first and second in the world. Though the mortality rate of COVID-19 is lower than that of SARS and Middle East Respiratory Syndrome, the infection rate is much higher.[2–4]

The clinical manifestations of COVID-19 vary between different individuals, ranging from an asymptomatic or mild form in the majority of cases to life-threatening symptoms, such as acute respiratory distress syndrome, cytokine release syndrome, increased thrombotic events and so on.[5,6] Patients with COVID-19 are at high risk for thrombotic arterial and venous occlusions, especially for critical patients. As an observational study conducted in two intensive care units has found 31% incidence of thrombotic events among patients with COVID-19 positive, which concluded to be remarkably high.[7] Antiphospholipid syndrome (APS), an autoimmune disorder which was characterized by the presence of antiphospholipid antibodies and a wide series of clinical manifestations, is an important required cause for thrombotic complications. Therefore, APLs have been considered to be important contributors and markers to the hypercoagulable states and following thrombotic events. APLs can arise in patients with critical illness and various infections and the presence of these antibodies may rarely lead to thrombotic events.[8] Recently, some reports have reported an increased proportion of APLs arising in COVID-19 patients.[9–11] To further investigate the role of APLs in COVID-19 patients, it is important to report all criteria APLs. Current criteria recommend increased levels of IgG and IgM anticardiolipin and anti-beta2-glycoprotein (aβ2GPI) to confirm antiphospholipid syndrome.[12] Growing evidence has been released both in support and against an increased prevalence of APLs in COVID-19 patients,[11,13–15] suggesting that several interfering factors could

HZ, MC, HX, and WX contributed equally to this work.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethical approval was obtained from the Research Ethics Committee of Zhongnan Hospital of Wuhan University.

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blur the results. Here we endeavored to collect and analyze several types of APLs in patients hospitalized with COVID-19.

2. Patients and Methods

2.1. Patients

A total of 87 were enrolled from Zhongnan hospital in Wuhan, China. All patients were diagnosed with COVID-19 pneumonia in accordance with the new Coronavirus Pneumonia Prevention and Control protocol (7th edition)[16] based on symptoms, chest computed tomography and positive RT-PCR results during the period 20th, January to 16th, March, 2020. Critically ill patients were those hospitalized in intense care unit (ICU). No diagnosis of previous autoimmune diseases was made. No patients had a thrombotic event in the past clinical history. No one has developed thrombosis during hospitalization.

2.2. Detection of APLs

Serum aβ2GP1 were detected by the chemiluminescence immunoassay (YHLO). Serum ACLs were determined by enzyme-linked immunosorbent assay (AESKU). All the sera of 87 patients were collected and tested within one week after diagnosing. Some dynamic results were collected from the outpatient follow-up visit after the patient was discharged from hospital. The cutoff values for positivity of both ACLs and aβ2GP1 were set > 18 U based on manufacturer's recommendations.

2.3. Statistical analysis

Measurement data were analyzed by two-sided t test and enumeration data were analyzed by Pearson χ^2 test. Correlations were tested by Spearman's correlation coefficient. Statistical analyses were all performed on SPSS 20.0 package (SPSS Inc, Chicago, IL). Statistical significance was defined as two-sided α of less than 0.05.

Clinical records and laboratory results were retrospectively reviewed for all the patients. This study was approved by the Zhongnan Hospital of Wuhan University institutional review board and the need for informed consent was waived because of a retrospective study.

3. Results

3.1. Prevalence of ACLs in patients hospitalized with COVID-19

Sera from 87 patients hospitalized with COVID-19 were evaluated for three different types of ACLs. Among the 87 patients, 21 critically ill patients were in intensive care units and 66 non-critically ill patients were in normal units. No subgroups have shown a significant difference in age. 34 patients tested positive for at least one type of ACLs when we adopted the manufacturer recommended cutoff value of >18, representing 39.08% of the entire cohort. Among the various ACLs tested, anticardiolipin IgG had the highest prevalence 30 (34.48%), followed by anticardiolipin IgA 25 (28.74%), IgM had the lowest prevalence 2 (2.30%). 22 patients (25.29%) were positive for two types of ACLs and only 1 (1.15%) was positive for three. Any kind of ACLs tested positive was regarded as ACLs positive, none was positive was regarded as ACLs negative. When referring to the subgroups of COVID-19 patients, we detected13 (61.91%) was ACLs+ in critically ill patients and 21 (31.82%) in non-critically ill patients, the difference was significant(P = .02). All subtypes of ACLs in critically ill patient group were much higher than those in non-critically ill group (Table 1). When taking the distribution of different subtypes ACLs into consideration, only ACLs IgG showed a statistical difference, and IgG, with odds ratio = 2.721, seem to be a risk factor of COVID-19 severity (P = .048). Though the odds ratio of IgA was 1.333, there was no statistical significance (P = .593).

3.2. Prevalence of aβ2gp1 in patients hospitalized with COVID-19

11 out of 87 patients were tested for aβ2GP1. Aβ2GP1 IgM/IgA were found in 36.36%/27.27% of patients. Both aβ2GP1 IgM and IgA showed high average value, with 63.70 and 60.30 respectively. But none of the sera was positive for IgG (Table 2). Due to the limited number of the positives, we only assessed the difference value of aβ2GP1 in different patients. Statistical difference showed in neither comparison (Table 3).

3.3. Coagulative variables in COVID-19 patients of different groups

We next analyzed the different value of various coagulative parameters in different groups. Firstly, we assessed the difference level of platelet, prothrombin time, international normalized value, activated partial thromboplastin time (APTT), thrombin time (TT) and d-dimer between critically ill and non-critically ill. Among these 7 parameters, prolonged APTT was only found in 6 patients, prolonged TT was found in 28 patients. Only TT was significantly different between critically ill and non-critically ill patients. TT in critically ill patients was statistically longer than that in non-critically ill group, with TT value of 24.3 ± 15.40 and 17.51 ± 8.10 respectively (P = .000). When compared ACL+ with ACLs– patients, only TT was significantly prolonged in ACLs+ (Table 4).

Table 1

The prevalence of anticardiolipin antibodies in COVID-19 patients.

	Critically ill (21)	Non-critically ill (66)	OR (95% CI)	*P*	ACLs positive (34)	ACLs negative (53)	*P*
Gender (male/female)	12/9	24/42	2.333 (0.859–6.338)	.092	14/20	22/31	.975
Any positive ACLs	13 (61.91)	21 (31.82)	3.482 (1.253–9.674)	.014	34 (100)	0	\
ACLs IgA + ACLs IgG + ACLs IgM	1 (4.76)	0	0.952 (0.866–1.048)	.241	1 (2.94)	0	\
ACLs IgA + ACLs IgG	5 (23.81)	16 (24.24)	0.977 (0.309–3.088)	.968	21 (61.76)	0	\
ACLs IgA + ACLs IgM	1 (4.76)	0	0.952 (0.866–1.048)	.241	1 (2.94)	0	\
ACLs IgG + ACLs IgM	0	0	\	\	0	0	\
ACLs IgG	11 (52.38)	19 (28.79)	2.721 (0.992–7.461)	.048	30 (88.24)	0	\
ACLs IgM	2 (9.52)	0	0.905 (0.788–1.039)	.056	2 (5.88)	0	\
ACLs IgA	7 (33.33)	18 (27.27)	1.333 (0.463–3.836)	.593	25 (73.53)	0	\

The cutoff values for positivity in all ACLs were set > 18 U based on the recommendations of the manufacturer.

ACLs = anticardiolipin antibodies, CI = confidence interval, COVID-19 = coronavirus disease 2019, OR = odds ratio.

Table 2

The prevalence and value of anti-beta2-glycoprotein 1 in COVID-19 patients.

	Number of aβ2GPI+	Value					
		Overall value	ACLs+	ACLs–	*P*	Critically ill	Non-critically ill	*P*
aβ2GPI IgA	3 (27.27%)	60.30 ± 152.49	81.36 ± 177.08	4.16 ± 3.72	.484	93.61 ± 187.60	2.01 ± 0.01	.365
aβ2GPI IgG	0 (0%)	9.56 ± 7.40	10.18 ± 8.16	7.90 ± 5.90	.673	12.43 ± 7.89	4.53 ± 2.22	.088
aβ2GPI IgM	4 (36.36%)	63.70 ± 102.01	59.79 ± 115.59	74.13 ± 71.03	.848	78.67 ± 118.77	37.5 ± 71.00	.548

The cutoff values for positivity in all aβ2GPIs were set > 18 U based on the recommendations of the manufacturer.
aβ2GPI = anti-beta2-glycoprotein 1, COVID-19 = coronavirus disease 2019.

Table 3

The prevalence of anti-beta2-glycoprotein I in different groups of COVID-19 patients.

	aβ2GPI+	aβ2GPI–	*P*
ACLs+ (8)	4	4	1.000
ACLs– (3)	2	1	
Critically ill (7)	5	2	.242
Non-critically ill (4)	1	3	

ACLs = anticardiolipin antibodies, aβ2GPI = anti-beta2-glycoprotein 1, COVID-19 = coronavirus disease 2019.

3.4. Correlation of ACLs with coagulative laboratory variables in COVID-19 patients

We further assessed the potential correlation among ACLs and all the coagulative variables. Of all the indicators tested, only IgG demonstrated a weakly but significantly positive correlation with APTT and TT ($R = 0.308$, $P = .031$; $R = 0.337$, $P = .018$ respectively) (Table 5).

3.5. Dynamic changes in the levels of ACLs during COVID-19

Dynamic change in the levels of ACLs during COVID-19 were further investigated. Due to the retrospective nature, multiple time-points of ACLs results were only obtained from only 3 patients. Generally, the levels of ACLs increased from a low titer to a high titer, then back to a low titer. And the elevated titer of ACLs usually didn't last long. The first patient was a 62-year-old-female hospitalized in ICU (Fig. 1A). The second was a 61-year-old-male hospitalized in ICU (Fig. 1B). The last one was a 48-year-old-female hospitalized in normal unit (Fig. 1C). ACLs of all these three patients decreased to normal after recovery from COVID-19.

Of all the 87 patients, 18 patients had tested ACLs after recovery, 15 of them were ACLs increased during their illness, 3 cases were normal, and the test results after recovery showed that titer of ACLs of the 15 patients decreased to normal. Even though the other 3 cases were with normal ACLs level was also significantly reduced after recovery.

4. Discussions

Classification criteria of APS includes three different antiphospholipid antibodies (APLs), which are lupus anticoagulant, IgM or IgG anticardiolipin, and IgM or IgG anti-beta 2 glycoprotein. They interact with plasma protein such as beta-2 glycoprotein I (β2GPI), prothrombin, thrombomodulin, plasminogen, antithrombin III, protein C, protein S, and likely others.[12,17,18] APLs leads to endothelial dysfunction by binding to endothelial cell receptors.[19,20] APLs are commonly existed in the general population, usually with a low titer. And both viral infections and bacterial infections can induce APLs as well. Though the infection-induced APLs are generally not correlated to thrombotic APS,[21] there are still some viral Infection-induced APLs associated thromboembolic events being widely acknowledged.[22–24] There are emerging studies that have confirmed the existence of APLs in COVID-19 patients, especially in critically ill patients suffering from coagulopathy.[9,13,25] All these studies seem to establish a connection between COVID-19 induced coagulopathy and APLs.

In this study, we found that ACLs and aβ2GP1 were common in not only critically ill patients but also non-critically ill patients which is totally different with Meng Xiao's study[13] which detected no elevated ACLs in non-critically ill patients. This may be due to the fact that their study included fewer non-critically ill patients, and the bias may also be that the testing of non-critically ill patients usually doesn't do so frequently because the disease progression of the non-critical patient is relatively slow, the monitoring of APLs may not as frequent as the critical patients, many patients only did a one time-point testing, which resulted in more non-critically ill patients tested exactly when the APLs are normal. Our dynamic testing suggests ACLs to be mostly transient and disappear within a few weeks. Thrombosis occurred in none of the patients, whether it

Table 4

ACLs and coagulative variables in different groups.

	Non-critically ill (66)	Critically ill (21)	*F*	*P*	ACLs positive	ACLs negative	*F*	*P*
Age	52.73 ± 17.053	56.52 ± 16.235	0.286	.594	52.26 ± 17.865	54.53 ± 16.270	0.858	.357
ACLs IgA	21.87 ± 42.91	65.98 ± 138.22	16.193	.000	75.24 ± 114.08	5.04 ± 3.91	27.063	.000
ACLs IgG	19.56 ± 23.76	33.30 ± 35.59	6.593	.012	49.06 ± 28.13	6.11 ± 3.93	64.210	.000
ACLs IgM	2.27 ± 2.04	3.85 ± 5.99	24.584	.000	3.74 ± 4.92	1.91 ± 1.95	13.554	.000
PLT	220.80 ± 83.74	174.05 ± 102.43	0.947	.333	206.91 ± 94.523	212.10 ± 87.759	0.106	.746
PT	12.91 ± 1.94	13.36 ± 2.55	0.095	.759	13.56 ± 2.38	12.75 ± 1.95	0.124	.726
INR	1.12 ± 0.18	1.07 ± 0.25	0.144	.706	1.07 ± 0.23	1.13 ± 0.19	0.539	.466
APTT	29.36 ± 5.96	33.82 ± 6.89	0.64	.428	33.13 ± 8.20	28.98 ± 4.43	3.803	.057
TT	17.51 ± 8.10	24.30 ± 15.40	14.502	.000	22.80 ± 14.89	16.81 ± 5.76	13.574	.001
DD	1161.14 ± 1306.97	1696.67 ± 1929.95	1.409	.241	1636.32 ± 1837.44	1129.03 ± 1283.64	1.801	.186
FIB	334.30 ± 61.71	287.67 ± 123.75	6.037	.022	288.56 ± 100.72	342.06 ± 61.73	1.764	.197

ACLs = anticardiolipin antibodies, APTT = partial thromboplastin time, DD = d-dimer, FIB = fibrinogen, INR = international normalized value, PLT = platelet, PT = prothrombin time, TT = thrombin time.

is critical ill or non-critical ill. The presence of these antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in some critically ill patients.

In consideration of the ACLs profile, IgA and IgG are the most common type and they almost appear in patients simultaneously. However, elevated IgM is rarely detected in our study. As for aβ2GP1, IgA is also a commonly elevated type detected, IgG the lowest. SARS-CoV-2 enters human cells by binding to angiotensin-converting enzyme 2 receptor precisely with its spike receptor binding domain.[26] Then subsequently internalizes by forming an endosome. Angiotensin-converting enzyme 2 is a kind of protein highly expressed in many places such as lung airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages, so it mainly affects pulmonary and intestinal mucosa.[27] IgA isotype may be preferentially produced as the mucosal immune tolerance breaks when SARS-CoV-2 affects the deeper respiratory system.[28] Compared to the prevalence of ACLs-IgA and aβ2GP1-IgA in APS in a large cohort study, which are 15.57%, 1.89% respectively,[29] our data show a higher prevalence. The prevalence of ACLs-IgG in critically ill patients is almost the same with that in CJ Hu's study.[29] Most patients with critical cases of COVID-19 demonstrate elevated levels of proinflammatory cytokines and infection-related biomarkers and are more prone to immune disorders and autoimmune diseases.[30,31] ACLs-IgG may be highly associated with disease severity. Values of all isotypes of ACLs in the critically ill group are significantly higher than those in the non-critically ill group. High levels of ACLs seem to be more predictive of the severity of the disease.

Table 5

Correlation of anticardiolipin antibodies with clinical and laboratory variables in COVID-19 patients.

	ACLs IgA		ACLs IgG		ACLs IgM	
	r	*P*	*r*	*P*	*r*	*P*
PLT	−0.073	.529	−0.055	.632	−0.060	.606
PT	0.077	.593	0.184	.200	0.150	.299
INR	−0.097	.503	−0.001	.993	−0.109	.449
APTT	0.103	.479	0.308	.031	−0.104	.478
TT	0.119	.415	0.337	.018	0.067	.649
DD	0.035	.811	0.136	.350	0.125	.391

ACLs = anticardiolipin antibodies, APTT = partial thromboplastin time, COVID-19 = coronavirus disease 2019, DD = d-dimer, INR = international normalized value, PLT = platelet, PT = prothrombin time, TT = thrombin time.

When considering coagulation function index, we find that TT in critically ill group is significantly higher than those in non-critically ill group. When we divided the patients into ACLs positive and ACLs negative groups, TT of the ACLs positive group is also higher than that of the negative group. Looking at the cause for TT prolongation, TT can be easily influenced by concomitant anticoagulation with heparin. We do detect a statistically significant positive correlation between IgG and APTT and TT in our study, but the correlations are weak. Fibrinogen (FIB), which is known to be an acute-phase protein, show a slight but significant higher value in non-critically ill patients compared to critically ill patients. Inflammatory usually leads to a FIB-increase via a stimulation of IL-6 in liver synthesis.[32,33] Decreased FIB has been observed in non-survival COVID-19 patients.[34] D-dimer is routinely evaluated together with FIB

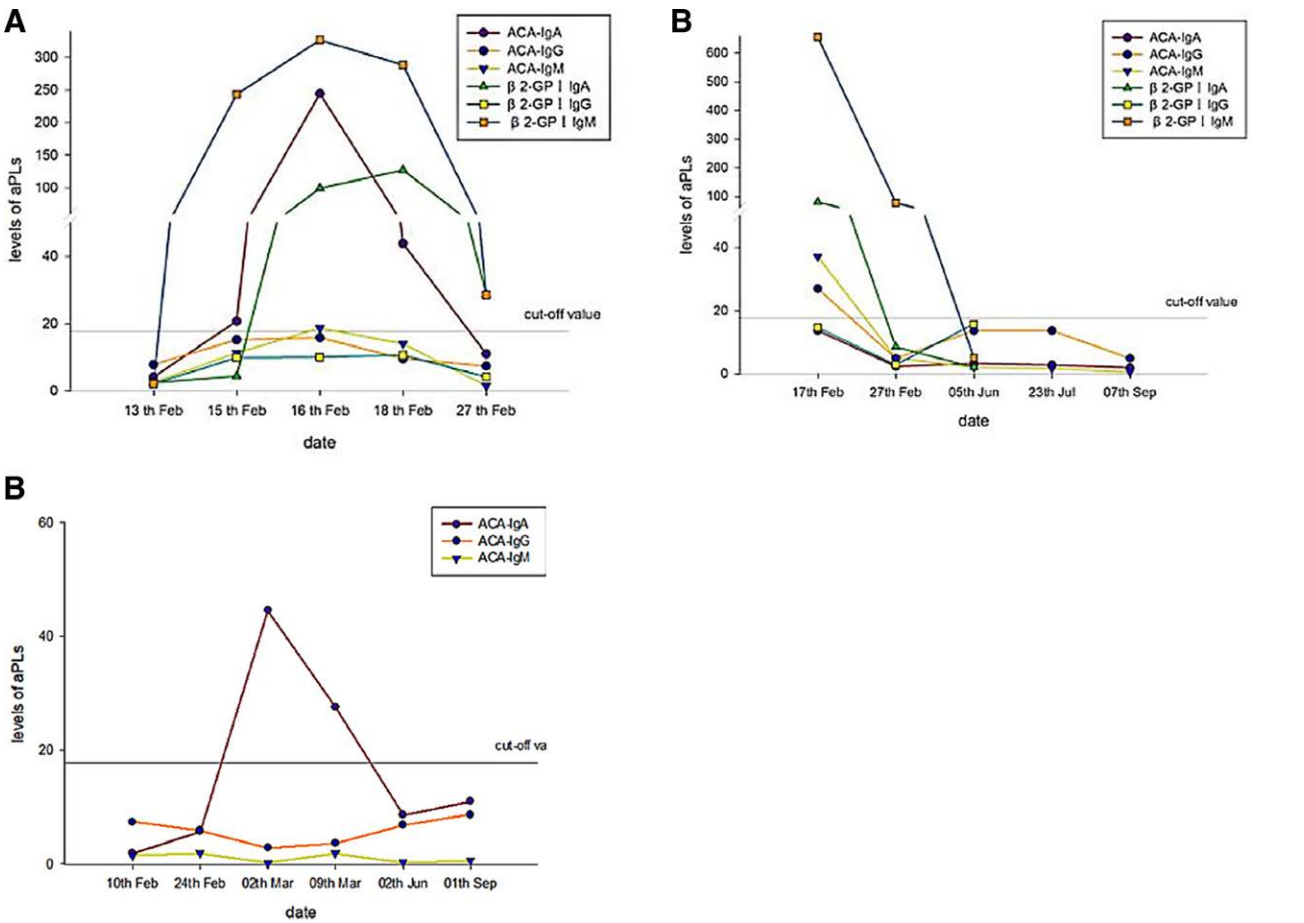

Figure 1. Dynamic changes in the levels of APLs during COVID-19. APLs = antiphospholipid antibodies, COVID-19 = coronavirus disease 2019.

in diagnosing DIC. High value of D-dimer is associated with adverse outcomes.[35,36] But the value of D-dimer in our study presented no significant difference between critically illness and non-critically illness. In Daniel Bertin's study,[37] ACLs-IgG is highly and independently associated with disease severity. In our dynamic monitoring, we found that the duration of antibody elevation is not long-term, but relatively short. A systematic review showed that one-third of individuals with thrombotic events and APLs associated with viral infections have a persistent positivity of these APLs for at least a few months, meeting the APS classification criteria.[12] This may be one of the reasons why blood coagulation does not occur in our patients, and perhaps only the long-term presence of antibodies is easier for thrombotic complications. Transient APLs may not have prothrombotic potential.

In conclusion, ACLs and aβ2GP1 can occasionally arise in COVID-19 patients no matter they are critically ill or non-critically ill. ACLs are not clearly related to thrombotic complications. The presence of ACLs in COVID-19 patients should be cautiously interpreted. But patients with high ACLs titers and the presence of IgG are more likely to develop into a serious state. Thus, ACLs detection especially ACLs-IgG detection could obviously provide an important reference to help stratify patients with COVID-19 and to manage the therapeutic decision.

Author contributions

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